

# Chapter 11

## CYANIDE POISONING

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## INTRODUCTION

Cyanide has been used as a poison for thousands of years. In World War I, however, possibly because of inefficient delivery, cyanide was not highly successful as a chemical warfare agent. The effects of high-dose cyanide are quick, and death occurs within minutes. Antidotes are effective if administered in time (although antidotes are unlikely to be available in time with high-dose exposures).

Cyanide is ubiquitous. It is present in some foods

and in the products of combustion of synthetic materials, and it is widely used in industry. The cyanides of military interest are the volatile liquids hydrocyanic acid (or hydrogen cyanide [HCN], North Atlantic Treaty Organization [NATO] designation: AC) and cyanogen chloride (NATO designation: CK); however, a great number of cyanide compounds actually release active cyanide. Cyanides are stored and used in either liquid form or as solid salts (Table 11-1).

## HISTORICAL USE

### Discovery and Ancient Use of Cyanide

Since the time of ancient Egypt, plants containing cyanide derivatives, such as bitter almonds, cherry laurel leaves, peach pits, and cassava, have been used as

lethal poisons.<sup>1,2</sup> Peach pits used in judicial executions by the ancient Egyptians are on display in the Louvre Museum, Paris, and an Egyptian papyrus refers to the "penalty of the peach."<sup>2</sup> The Romans used cherry laurel leaves as a method of execution (also known

TABLE 11-1

CHEMICAL, PHYSICAL, ENVIRONMENTAL, AND BIOLOGICAL PROPERTIES OF CYANIDES

Properties	Hydrogen Cyanide (AC)	Cyanogen Chloride (CK)
<b>Chemical and Physical</b>		
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	NA	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>5</sup> mg/m <sup>3</sup> at 12.9°C
Appearance and Odor	Gas: Odor of bitter almonds or peach kernels	Bitter almonds scent; colorless gas or liquid; irritating to upper airway, eyes
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)
<b>Environmental and Biological</b>		
Detection	ICAD; M254A1 kit	M256A1 kit
Persistence		
In soil	< 1 h	Nonpersistent
On material	Low	Nonpersistent
Skin Decontamination	Water; soap and water	Water; soap and water
Biologically Effective Amount		
Vapor (mg•min/m <sup>3</sup> )	LC <sub>t</sub> : 2,500–5,000 (time-dependent)	LC <sub>t</sub> : 11,000
Liquid (mg/kg)	LD <sub>50</sub> (skin): 100	LD <sub>50</sub> (skin): 100

ICAD: individual chemical agent detector

LC<sub>t50</sub>: the vapor or aerosol exposure (concentration • time) lethal to 50% of the exposed population

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

NA: not applicable

as “the cherry death”), and the Roman emperor Nero used cherry laurel water to poison members of his family and others who displeased him. Dioscorides, a Greek physician who served in Nero’s army, compiled information on more than 600 species of plants with medicinal value in the five books titled *De Materia Medica*, recognizing the poisonous properties of bitter almonds. Napoleon III proposed the use of cyanides to enhance the effectiveness of his soldiers’ bayonets during the Franco–Prussian War; it has also been suggested that Napoleon died from cyanide.<sup>3</sup>

The first description of cyanide poisoning, by Wepfer in 1679, dealt with the effects of extract of bitter almond administration.<sup>2</sup> In 1731 Maddern demonstrated that cherry laurel water given orally, into the rectum, or by injection, rapidly killed dogs.<sup>4</sup> Although substances containing cyanide have been used for centuries as poisons, cyanide was not identified until 1782, when Swedish pharmacist and chemist Carl Wilhelm Scheele<sup>2</sup> isolated cyanide by heating the dye Prussian Blue with dilute sulfuric acid, obtaining a flammable gas (hydrogen cyanide) that was water soluble and acidic. Scheele called this new acid Berlin blue acid, which later became known as prussic acid and today is known as cyanide (from the Greek word “kyanos,” meaning “blue”). Scheele’s discovery may have cost him his life several years later, from either engaging in unsafe experimental practices such as taste testing and smelling HCN, or accidentally breaking a vial of the poison. A better understanding of the cyanides was achieved in 1815 by the French chemist Joseph Louis Gay-Lussac.<sup>2</sup> Gay-Lussac identified a colorless, poisonous gas called cyanogen, which had an almond-like flavor and considerable thermal stability. His work on acids, including HCN, led to the realization that acids do not need to contain oxygen, and that the cyanogen moiety could be shifted from compound to compound without separating the individual carbon and nitrogen atoms.

### Terrorist and Military Uses

Although ancient civilizations used plants containing cyanides to kill, it was not until World War I, in late 1915 and early 1916, that cyanide was produced expressly for the purpose of killing. France started the large-scale use of cyanide as a chemical weapon, producing approximately 8 million pounds of HCN by distilling a concentrated solution of potassium cyanide (KCN) with dilute sulfuric acid. Even though HCN had quick-kill properties and was not readily absorbed on charcoal (allowing penetration through enemy gas masks), its use provided no tactical advantage. This was due, in part, to small payload munitions and the

high volatility of cyanide with no cumulative effects (cyanide is lighter than air, persisting for only a few minutes in the open air). Concentrations sufficient to incapacitate or kill were not achieved. In addition, Germany learned of its use and equipped its troops with masks capable of filtering out the gas.

In September 1916, France tried another cyanide-based poison, cyanogen chloride, which is heavier and less volatile than HCN and had a cumulative effect on its victims. Cyanogen chloride was produced by chlorinating a saturated solution of KCN at 0°C (32°F). Its toxicity was similar to that of HCN, but cyanogen chloride was more effective at low concentrations because it irritated the eyes and lungs. Cyanogen chloride also had a delayed toxic effect similar to lung irritants such as chlorine and phosgene. At the same time that France launched cyanogen chloride, Austria introduced a poisonous gas derived from KCN and bromine. The resulting cyanogen bromide was still highly volatile, yet it had only a quarter of the volatility of HCN and was less toxic. Cyanogen bromide had a strong irritating effect on the conjunctiva and 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>5</sup>

During World War II, the Nazis employed HCN adsorbed onto a dispersible pharmaceutical base (Zyklon B) to exterminate millions of civilians and enemy soldiers in the death camps. Cyanide was detected in the walls of crematoria almost 50 years later.<sup>6,7</sup> Zyklon B was also used as a fumigant and rodenticide to rid ships of rodents by the United States and other countries. Japan allegedly used cyanide against China before and during the war.

In the late 1980s, reports indicated that cyanide-like agents may have been used against the inhabitants of the Syrian city of Hama,<sup>8</sup> the Kurdish city of Halabja, Iraq,<sup>9</sup> and possibly Shahabad, Iran, during the Iran-Iraq War.<sup>10</sup> In addition to military operations, cyanide has been used by individuals and terrorist organizations. One notorious incident was the poisoning of Tylenol (acetaminophen, manufactured by McNeill Consumer Products Co, Fort Washington, Pa) in the Chicago area in 1982, which killed seven people.<sup>11</sup> 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 the city in March 1995.<sup>12</sup>

### Executions and Suicides

Cyanide has been the typical agent used in “gas chambers,” in which a cyanide salt is dropped into an acid to produce HCN. Gas chambers used in some

states to judicially execute murderers provide information on the effect of HCN. In US gas chambers HCN was usually released by dropping a bag of sodium cyanide into sulfuric acid. Unconsciousness was thought to be instant, with death following in 5 to 10 minutes. In 1994 District Judge Marilyn Hall Patel ruled that the gas chamber was an inhumane method of punishment and outlawed its practice in California. Two years later the 9th US Circuit Court of Appeals supported Patel's decision and ruled that gas chambers violated the Eighth Amendment to the Constitution because of the horrible pain observed for several minutes. However, in several states, death row inmates still have the right to choose the gas chamber over lethal injection, as Walter LeGrand did in Arizona in 1999.

Cyanide has often been used by individuals and groups to commit suicide.<sup>13</sup> One of the most notorious of such events happened in 1978 near Port Kaituma, Guyana, when the followers of Jim Jones drank a grape-flavored drink laced with cyanide, resulting in the deaths of more than 900 children and adults.<sup>14</sup>

### Cyanide Sources and Accidental Poisoning

Although there are many chemical forms of cyanide, HCN (or the cyanide anion  $\text{CN}^-$ ) is the primary toxic agent, regardless of its origin. Military personnel and civilians may be exposed to common natural and anthropogenic sources of cyanide through edible and nonedible plants, industrial operations, fires, and cigarette smoke. Ongoing low-level cyanide exposures are managed by the body through reaction pathways that detoxify amounts in excess of biological tolerances. Much of the medical information on cyanide poisoning has come from civilian experiences of poisoning, fires, and industrial accidents.

HCN is released into the atmosphere from volcanoes, plants, bacteria, and fungi.<sup>15-21</sup> However, the primary natural source of cyanide poisoning in humans and animals is from plants. Over 2,000 plant species, including edible fruits and vegetables, contain cyanogenic glycosides, which can release cyanide when ingested.<sup>18,22,23</sup> Rapid hydrolysis of cyanogenic glycosides and release of HCN occurs when the plant

cell structure is disrupted. Thus consumption of improperly processed plants with cyanogen-containing glycosides will release HCN and may result in illness or death. Some common cyanogenic edible plants reported to cause cyanide poisoning include cassava, sorghum, sweet potatoes, yams, maize, millet, bamboo, sugarcane, peas, lima beans, soybeans, almond kernels, lemons, limes, apples, pears, peach, chokecherries, apricots, prunes, and plums.<sup>18,22-30</sup> Cassava (manioc) and sorghum are staple foods for hundreds of millions of people in many tropical countries and are blamed in part for the high incidence of central and peripheral neuropathies in those areas.<sup>31</sup> Known cyanogenic glycosides in plants include amygdalin, linamarin, prunasin, dhurrin, lotaustralin, and taxiphyllin.

Worldwide manufacturing of cyanide to support industrial and agricultural demand is in the range of 2.5 million US tons annually. In industries using cyanide, occupational exposures occur primarily by the dermal and inhalation routes. Nonindustrial accidental exposures of clinical significance are typically associated with commercial fires involving the burning of plastics.<sup>32,33</sup>

Inhalation of tobacco smoke, another source of cyanide, has been associated with tobacco amblyopia, a syndrome of visual failure occurring in association with the use of tobacco, thought to result from nutritional or idiopathic deficiencies in certain detoxification mechanisms, particularly those that target the cyanide component of tobacco smoke.<sup>34</sup> Cyanide levels in smokers versus nonsmokers are often used as a sensitivity test in analytical methods for determination of cyanide or its metabolites in biological fluids.<sup>35</sup> HCN concentrations in inhaled smoke from US-manufactured cigarettes range from 10 to 400  $\mu\text{g}$  per cigarette. In non-US-manufactured cigarettes, cyanide concentrations range from 280 to 550  $\mu\text{g}$  per cigarette in inhaled smoke and from 53 to 111  $\mu\text{g}$  per cigarette in second-hand smoke.<sup>15,36-38</sup> Cyanide has also been found to be a metabolic product of certain pharmacological preparations such as laetrile, nitroprusside, and succinonitrile. Some of these formulations have caused cyanide poisoning, in some cases resulting in death.<sup>21, 39-43</sup>

## BIOCHEMICAL BASIS FOR POISONING

Cyanide is known to bind and inactivate several enzymes, particularly those containing iron in the ferric ( $\text{Fe}^{3+}$ ) state and cobalt. It is thought to exert its ultimate lethal effect of histotoxic anoxia by binding to the active site of cytochrome *c* oxidase, the terminal protein in the electron transport chain located within mitochondrial membranes (Figure 11-1). By this means,

cyanide prevents the transfer of electrons to molecular oxygen. Thus, despite the presence of oxygen in the blood, it cannot be utilized toward adenosine triphosphate (ATP) generation, thereby stopping aerobic cell metabolism.<sup>44,45</sup> Initially cells attempt to replenish the ATP energy source through glycolysis, but the replenishment is short lived, particularly in the metabolically

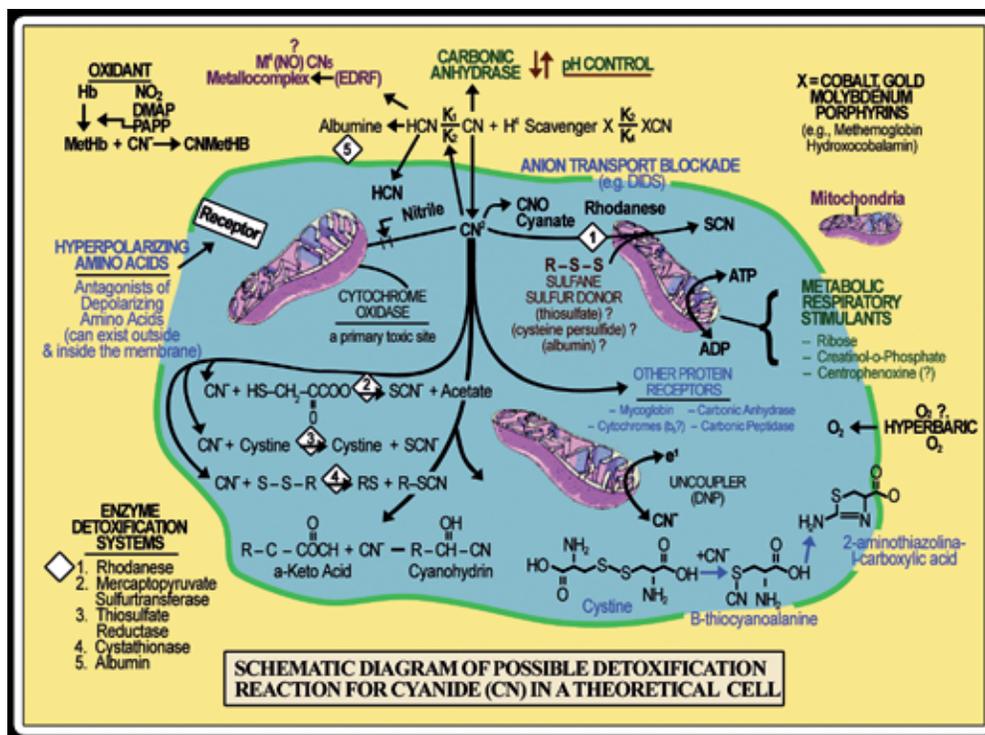


Fig. 11-1. Likely detoxification reactions for cyanide are shown for this hypothetical cell. The enzyme detoxification systems are as follows:

1. Rhodanese: an intramitochondrial liver enzyme that catalyzes the transfer of sulfur from a donor molecule to cyanide to form thiocyanate. Rhodanese is the major pathway for cyanide detoxification.
2. Mercaptopyruvate sulfurtransferases: a group of enzymes widely distributed in the body that catalyze the transfer of a sulfane sulfur atom from a donor molecule to a thiophilic acceptor substrate for the limitation of cyanide.
3. Thiosulfate reductase: enzymes found in the liver, kidney, heart, brain, intestine, and testis that use electrons from thiols, which in vivo probably use electrons from glutathione, to reduce the sulfane sulfur atoms of inorganic thiosulfate and organic thiosulfonate anions to the sulfide level. Sulfide production from these thiol-dependent reductases is thought to be used in the synthesis of Fe-S proteins.
4. Cystathionase: enzymes widely distributed in the body that can transfer sulfur from one cysteine to another, generating thiocysteine and pyruvate. Transamination of cysteine leads to the production of thiosulfate and the limitation of cyanide.
5. Albumin: molecules that act like an enzyme in the detoxification of cyanide. Albumin molecules contain sulfur sites that bind to and limit cyanide.

ADP: adenosine diphosphate

ATP: adenosine triphosphate

ATCA: 2-aminothiazoline-4-carboxylic acid

CN<sup>-</sup>: cyanide ion

CNMetHb: cyanomethemoglobin

CNO: cyanate

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

DMAP: dimethylaminophenol

DNP: deoxyribonucleoprotein

EDERF: endothelium-derived relaxing factor

Hb: hemoglobin

MetHb: methemoglobin

PAPP: p-aminopropiophenone

R: reduction factor

S: substrate

Drawing: Courtesy of Steven I Baskin, PhD, and Fred Sidell, PhD, US Army Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

active heart and brain. Binding to the cytochrome oxidase can occur in minutes.<sup>46</sup> A more rapid effect appears to occur on neuronal transmission. Cyanide is known to inhibit carbonic anhydrase,<sup>47</sup> and this enzyme interaction may prove to be an important contributor to the well-documented metabolic acidosis resulting from clinically significant cyanide intoxication.

Cyanide can be removed by several processes before it can enter cells. Cyanide may form a complex with endothelial-derived relaxing factor (thought to be nitric oxide). Heavy metals (eg, gold, molybdenum, or cobalt salts) or organic compounds with metal centers (eg, hydroxocobalamin) may scavenge cyanide, effectively removing it before it can enter the cell. Finally, albumin can exhibit enzyme-like behavior and use bound elemental sulfur<sup>48</sup> to detoxify cyanide.

Cyanide can be removed by several processes within cells. Perhaps of greatest importance is the formation of cyanomethemoglobin in red blood cells, which is produced when cyanide reacts with methemoglobin. At least four intracellular enzymes may be involved in cyanide detoxification. The generalized reactions of rhodanese, mercaptopyruvate sulfurtransferase, thiosulfate reductase, and cystathionase in the cell are shown in Figure 11-1. Cyanide also reacts with cystine to form 2-aminothiazoline-4-carboxylic acid (ATCA). Oxygen supplementation enhances recovery from cyanide intoxication, although the mechanism by which this happens is uncertain.<sup>49</sup>

Cyanide is readily diffusible through epithelium. This property contributes to its lethality after inhalation of HCN gas, 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 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>31</sup> Thiocyanate possesses a less inherent toxicological hazard than cyanide, cyanate ( $\text{CNO}^-$ ), 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>50</sup> and thiosulfate reductase (EC 2.8.1.3) (see Figure 11-1). The mechanisms of all three enzymes<sup>51</sup> as well as the pharmacokinetics of thiocyanate formation<sup>52,53</sup> have been studied. The enzymatic routes are efficient but constrained in situations of overwhelming acute overdose by insufficient sulfur donor substrate. 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.

The interaction of cystine and cyanide to form ATCA and its tautomer account for approximately 20% of cyanide metabolism.<sup>54</sup> This percentage increases with toxic doses of cyanide.<sup>55</sup> A minor route of metabolism, the exact extent of which is unknown, is the conversion of cyanide to cyanate.

Combined, these metabolic routes detoxify 0.017 mg of cyanide per kilogram of body weight per minute in the average human (1.19 mg/min in a 70-kg person).<sup>56,57</sup> 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>52</sup> The volume of distribution for cyanide appears to change as the blood levels of the chemical change,<sup>58</sup> but these alterations probably reflect the marked intracellular sequestration of the molecule. Animal studies<sup>59,60</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 exposure; 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>61</sup> and a marked increase in cerebral blood flow in dogs.<sup>62</sup>

Data from rodent studies suggest that a single, acute administration of a cyanide salt can result in death or complete recovery. Data from HCN inhalational studies in dogs, rabbits, monkeys, and humans suggest that death may be delayed for up to 8 days.<sup>63,64</sup> The neurological sequelae of cyanide intoxication may be delayed for up to a year.<sup>2</sup> These delayed changes in regional sensitivities of the brain are thought to be caused by hypoxic stress and are analogous to those seen following sublethal carbon monoxide poisoning.

## Toxicity

Although 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 HCN is generally stated to be 2,500 to 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  $\text{mg}\cdot\text{min}/\text{m}^3$ .)<sup>65</sup> The estimated intravenous dose of HCN for humans that is lethal to 50% of the exposed population ( $LD_{50}$ ) is approximately 1.0 mg/kg, and the estimated  $LD_{50}$  for liquid on the skin is about 100 mg/kg.

## DETECTION OF CYANIDE AND CYANIDE METABOLITES

The determination of cyanide, or its metabolites thiocyanate and ATCA, in biological fluids is often needed for forensics, clinical, research, or veterinary purposes. Although the detection of cyanide and cyanide compounds in other matrices is important to industrial, environmental, and research applications, it is not discussed in this chapter. This chapter will briefly discuss the available techniques and identify problems in cyanide analysis. Analytical methods for direct determination of cyanide and cyanide metabolites in biological samples have been reviewed.<sup>15,54,66,67</sup> Methods of analysis include spectrochemical absorption or luminescence methods,<sup>21,35,68–104</sup> electrochemical methods,<sup>68–76</sup> capillary electrophoresis,<sup>77,78</sup> and gas<sup>105–126</sup> or liquid chromatography techniques<sup>127–149</sup> coupled to a variety of detection techniques. The number of literature references (more than 200) that examine the detection of cyanide and cyanide metabolites in biological fluids can add to the difficulty in choosing a method. In addition, the numerous uncertainties and discrepancies in the literature have made comparison and selection of a method complicated for the novice. Obviously the first decision will be whether to choose cyanide, one of its metabolites, or both as the substance or substances to look for. Factors that influence this choice are cellular absorption and detoxification kinetics, sampling and analysis time, sample storage time and conditions, sample matrix, interferences, detection limits, available equipment and expertise, and budget allowances.

The analytical determination of cyanide and/or cyanide metabolites before antidotal treatment provides a more accurate assessment of the severity of poisoning and insight into antidote dose levels (especially because high doses of antidotes can also be toxic).<sup>19,79,80</sup> However, no available method is simple, accurate, and fast enough to justify waiting for test results before antidotal treatment is administered (ie, cyanide can kill faster than the analysis can be performed). Measurement of cyanide and its metabolites may have diagnostic or therapeutic value when sublethal; minimally or moderately symptomatic exposure is part of the differential diagnosis. In addition, biological samples

should be assessed for confirmation or refutation of a putative diagnosis of cyanide intoxication.

Blood has been the biological sample of choice when determining cyanide concentrations. However, cyanide is rapidly removed from blood by detoxification processes, binding to proteins and enzymes that contain metal centers or heme moieties, or sequestering in other favorable cellular entities.<sup>21,40,67,81–92</sup> Cyanide characteristics<sup>93,94</sup> suggest that a biological sample should be collected quickly, and analysis should be performed as soon as possible. If analysis of cyanide cannot be performed quickly, then the sampling and storage of biological samples for later testing should consider the following:

- **Cyanide resides mainly in erythrocytes rather than plasma.** Cyanide in blood primarily resides in erythrocytes (red blood cells)<sup>40,82,89–92,95</sup> by binding to methemoglobin, forming cyanomethemoglobin, but may also be present in plasma, especially if cyanide concentrations exceed erythrocyte concentrations.<sup>40,82,89</sup> Test results are improved by working with whole blood that is not coagulated. Heparinized vials should be used in the collection of the blood sample for determination of cyanide concentration. Containers that contain anticoagulants such as heparin and ethylenediaminetetraacetate (EDTA) help prevent clotting and also ensure efficient harvesting of plasma after the blood has been centrifuged. Lundquist et al demonstrated that the cyanide binding capacity of erythrocytes due to methemoglobin increased from 89,000 nM to 517,000 nM upon addition of sodium nitrite.<sup>82</sup>
- **Cyanide may evaporate because of HCN volatility at the physiological pH, and cyanide nucleophilic action should be reduced.** The next considerations should be reducing the evaporation and loss of cyanide from biological samples and preventing nucleophilic reactions. Using tightly sealed vials,

**TABLE 11-2**

**ANALYTICAL METHODS TO IDENTIFY CYANIDE AND ITS METABOLITES IN BIOLOGICAL FLUIDS\***

Analyte	Matrix Studied	Analytical Method	Detection Limit <sup>†</sup>		Estimated Time	Study
			nM	ng/mL		
<b>Gas Chromatography</b>						
HCN	Human blood (whole)	Headspace analysis GC-MS (internal standard: K <sup>13</sup> C <sup>15</sup> N)	300	8	~20	1
HCN	Human blood (whole)	Headspace analysis GC with NPD (also used SPME); calibration curve	519	14	~ 17 min	2
HCN	Human blood (whole)	Headspace analysis GC with NPD and cryogenic oven (internal standard: propionitrile)	74	2	~ 35 min	3
HCN	Human blood (whole)	HPLC-MS after derivatization (internal standard: K <sup>13</sup> C <sup>15</sup> N)	185	5	~ 45 min	4
HCN	Cow serum, rumen, liver	GCMS after derivatization (internal standard: bromocyclohexane in ethyl acetate)	700	18	~ 55 min	5
HCN, SCN <sup>-</sup>	Human blood (whole)	For HCN: GC-EC after derivatization; for SCN <sup>-</sup> : GC-EC after derivatization; (internal standard: 1,3,5 tribromobenzene in ethyl acetate)	10,000 3,000	270 174	~55 min	6
ATCA	Blood plasma, urine	GC-MS; (internal standard: ATCA-d <sub>2</sub> )	171.2	25	> 1 h	7
<b>Electrochemical</b>						
HCN	Human blood (whole)	Voltammetry with Ag RDE following trapping of HCN gas	1,000	27	> 50 min	8
SCN <sup>-</sup>	Human urine and saliva	Thiocyanate selective polymeric membrane electrode (electrode conditioning requires 24 h; pH range 5–10)	48	2.8	15 or 120 s for conditioned electrode	9
<b>Liquid Chromatography</b>						
HCN	Human blood (whole)	HPLC with fluorometric detection after derivatization	74	2	> 2 h	10
HCN, SCN <sup>-</sup>	Human blood (whole)	For HCN: IC with F detection after derivatization; for SCN <sup>-</sup> : IC with UV detection	3.8 86	0.10 5	~ 45 min	11
SCN <sup>-</sup>	Human urine	Ion interaction LC with UV detection	1,720	100	~ 10 min	12
SCN <sup>-</sup>	Human urine	IC with electrochemical detection	500	29	~ 15 min	13
SCN <sup>-</sup>	Human blood (whole)	HPLC with fluorometric detection after derivatization	0.165	0.0096	> 1 h	14
SCN <sup>-</sup>	Human plasma and urine	IC with spectrophotometric detection following chlorination	930	54	~ 25 min	15
ATCA	Human urine	HPLC with fluorometric detection after derivatization	300	44	> 3 h	16

(Table 11-2 continues)

Table 11-2 continued

Spectrochemical Absorption or Luminescence						
HCN	Human blood (whole)	Fluorometric	2,000	52	~ 17 min	17
HCN	Equine blood	Spectrophotometry following trapping of HCN gas	74	2	~ 16 h	18
HCN	Human blood (whole)	Spectrophotometry	1,000	27	~ 45 min	19
SCN <sup>-</sup>	Human blood serum, urine, saliva	Flame atomic absorption spectrometry; calibration	69	4	~ 20 min	20

\*This table is meant to give a general overview of analytical methods in this area and their detection limits. It is not meant to be all-inclusive. The 2004 US Department of Health and Human Services Agency for Toxic Substances and Disease Registry toxicology profile for cyanide also includes biological analytical methods not mentioned above and environmental analytical methods, including the US Environmental Protection Agency and National Institute for Occupational Safety and Health standard methods.<sup>21</sup>

<sup>†</sup>Conversion of units; figures are multiplied by the molecular weight of HCN, 27 g/mol.

EC: electron capture; GC: gas chromatography; GCMS: gas chromatography mass spectrometry; HCN: hydrogen cyanide; HPLC: high-performance liquid chromatography; IC: ion chromatography; LC: liquid chromatography; LCMS: liquid chromatography mass spectrometry; NPD: nitrogen phosphorous detector; RDE: rotating disk electrode; SPME: solid phase microextraction; SCN<sup>-</sup>: thiocyanate; UV: ultraviolet

Data sources: (1) Dumas P, Gingras G, LeBlanc A. Isotope dilution-mass spectrometry determination of blood cyanide by headspace gas chromatography. *J Anal Toxicol.* 2005;29:71–75. (2) Calafat AM, Stanfill SB. Rapid quantitation of cyanide in whole blood by automated headspace gas chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2002;772:131–137. (3) Ishii A, Seno H, Watanabe-Suzuki K, Suzuki O, Kumazawa T. Determination of cyanide in whole blood by capillary gas chromatography with cryogenic oven trapping. *Anal Chem.* 1998;70:4873–4876. (4) Tracqui A, Raul JS, Geraut A, Berthelon L, Ludes B. Determination of blood cyanide by HPLC-MS. *J Anal Toxicol.* 2002;26:144–148. (5) Meiser H, Hagedorn HW, Schultz R. Development of a method for determination of cyanide concentrations in serum and rumen fluid of cattle. *Am J Vet Res.* 2000;61:658–664. (6) Kage S, Nagata T, Kudo K. Determination of cyanide and thiocyanate in blood by gas chromatography and gas chromatography-mass spectrometry. *J Chromatogr B Biomed Appl.* 1996;675:27–32. (7) Logue BA, Kirschten NP, Petrikovics I, Moser MA, Rockwood GA, Baskin SI. Determination of the cyanide metabolite 2-aminothiazoline-4-carboxylic acid in urine and plasma by gas chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2005;819:237–244. (8) Westley AM, Westley J. Voltammetric determination of cyanide and thiocyanate in small biological samples. *Anal Biochem.* 1989;181:190–194. (9) Ganjali MR, Yousefi M, Javanbakht MJ, et al. Determination of SCN<sup>-</sup> in urine and saliva of smokers and non-smokers by SCN<sup>-</sup>-selective polymeric membrane containing a nickel(II)-azamacrocyclic complex coated on a graphite electrode. *Anal Sci.* 2002;18:887–892. (10) Felscher D, Wulfmeyer M. A new specific method to detect cyanide in body fluids, especially whole blood, by fluorimetry. *J Anal Toxicol.* 1998;22:363–366. (11) Chinaka S, Takayama N, Michigami Y, Ueda K. Simultaneous determination of cyanide and thiocyanate in blood by ion chromatography with fluorescence and ultraviolet detection. *J Chromatogr B Biomed Sci Appl.* 1998;713:353–359. (12) Connolly D, Barron L, Paull B. Determination of urinary thiocyanate and nitrate using fast ion-interaction chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2002;767:175–180. (13) Casella IG, Guascito MR, De Benedetto GE. Electrooxidation of thiocyanate on the copper-modified gold electrode and its amperometric determination by ion chromatography. *Analyst.* 1998;123:1359–1363. (14) Chen SH, Yang ZY, Wu HL, Kou HS, Lin SJ. Determination of thiocyanate anion by high-performance liquid chromatography with fluorimetric detection. *J Anal Toxicol.* 1996;20:38–42. (15) Lundquist P, Kagedal B, Nilsson L. An improved method for determination of thiocyanate in plasma and urine. *Eur J Clin Chem Clin Biochem.* 1995;33:343–349. (16) Lundquist P, Kagedal B, Nilsson L, Rosling H. Analysis of the cyanide metabolite 2-aminothiazoline-4-carboxylic acid in urine by high-performance liquid chromatography. *Anal Biochem.* 1995;228:27–34. (17) Groff WA, Stemler FW, Kaminskis A, Froehlich HL, Johnson RP. Plasma free cyanide and blood total cyanide: a rapid completely automated microdistillation assay. *J Toxicol Clin Toxicol.* 1985;23:133–163. (18) Hughes C, Lehner F, Dirikolu L, et al. A simple and highly sensitive spectrophotometric method for the determination of cyanide in equine blood. *Toxicol Mech Methods.* 2003;13:1–10. (19) Lundquist P, Sörbo B. Rapid determination of toxic cyanide concentrations in blood. *Clin Chem.* 1989;35:617–619. (20) Chattaraj S, Das AK. Indirect determination of thiocyanate in biological fluids using atomic absorption spectrometry. *Spectrochimica Acta.* 1992;47:675–680. (21) *Toxicological Profile for Cyanide.* Atlanta, Ga: US Department

low temperature, and preserving agents are common procedures used to prevent loss of cyanide. Rubber stoppers have been shown to adsorb or dissolve HCN when in contact with the gas, so use of rubber stoppers to seal vials should be avoided.<sup>95</sup> Storing samples at low temperatures to slow chemical reactions has been tested, and temperature studies for biological samples containing cyanide have been

performed. However, there are many temperature discrepancies in the literature.<sup>69,81,83,96,97</sup> The temperature study performed by Lundquist et al resulted in the following four determinations<sup>82</sup>: (1) cyanide in whole blood is reasonably stable at -20°C, and this stability decreased at the higher temperatures of 4°C and room temperature; (2) the addition of silver ions (silver sulfate) immediately after

collection appeared to stabilize cyanide at the higher temperatures; (3) the addition of the silver sulfate immediately after collection increased storage time of biological samples at 4°C for at least 2 weeks; and (4) the addition of silver sulfate also appeared to quench the reaction of cyanide and bovine serum albumin to form iminothiazolidine and cysteine residues in blood plasma. Forming other stable cyanide complexes, for example, by adding sodium nitrite to form methemoglobin or by adding hydroxocobalamin, has also been performed successfully.<sup>87,98</sup>

- **Cyanide may form during storage.** Artfactual formation of cyanide may also occur in biological samples depending on storage conditions.<sup>91,97,99-101</sup> It has been suggested that oxyhemoglobin,<sup>100</sup> thiocyanate oxidase,<sup>91,101</sup> and granulocytes (white blood cells)<sup>99</sup> may oxidize thiocyanate to cyanide and that these reactions are dependent on the temperature and pH of the sample. Lundquist's temperature dependence analysis was found to be different from earlier studies<sup>69,96,97</sup> and his use of silver ions may also improve thiocyanate stability.<sup>82</sup> Microorganisms are also responsible for cyanide production,<sup>101</sup> and low temperature storage helps to eliminate their growth.

These considerations, common to all the analytical methods, are a major source for the vast discrepancies in cyanide and cyanide metabolite levels reported from casualties. Because of the detoxification processes and cyanide's physical and nucleophilic properties, direct analysis of cyanide is not normally done with urine or saliva samples, although traces have been found in urine, saliva, and expired air. The cyanide metabolites thiocyanate and ATCA may be determined in urine, saliva, and blood plasma. Correlation of their concentrations to cyanide exposure have been examined.<sup>96,102-104,150-153</sup> Advantages to measuring thiocyanate are that appreciable concentrations may be found immediately after exposure, and that it is considered to be more stable than cyanide. However, the true concentration may also be difficult to determine because of its conversion back to cyanide during storage.<sup>153</sup> ATCA is stable in biological samples for months at freezing and ambient temperatures.<sup>154</sup> Based on determination of  $pK_a$  values (carboxylic acid: 2.03; amine: 8.48) and nuclear magnetic resonance studies,<sup>154</sup> ATCA forms a bipolar ion in solution and is therefore not volatile. It has been suggested that ATCA has lower initial concentrations than thiocyanate, but its stability and applicability to sensitive analytical techniques may

prove more beneficial. Disadvantages for both ATCA and thiocyanate, as with cyanide, include naturally occurring background levels that are different for each person, making it difficult to quantify low-level cyanide exposure without establishing baseline levels for an individual prior to exposure.<sup>96,155</sup> In addition, cyanide distribution and concentrations in organs differ depending on the route of administration and primate species type. Organ cyanide concentrations have also been used for blood cyanide intoxication levels in forensic cases; however, the postmortem production and transformation of cyanide must be considered in interpreting the results.<sup>85,86,92,156-159</sup>

The analytical determination of cyanide is not an easy task because of its volatility, nucleophilic properties, and lack of color. Although numerous methods have been developed, each must be used with precautions because of interferences and instrumentation capabilities. However, all the methods have helped in some way or another to provide insight into the detection of cyanide in biological fluids. When selecting an analytical method, several factors in addition to the detection limit and length of time needed (Table 11-2) must be considered:

- Does the method include consideration of preserving cyanide and its metabolites during storage?
- Does the method include correct storage of stock solutions<sup>95</sup> or use fresh preparations daily?
- Does the method include consideration of typical interferences found in blood?
- Does the method test for cyanide with and without clinically used antidotes present?
- Does the method include analysis procedures (eg, pH, heating, and acidification) that could result in the loss of cyanide? Are rubber stoppers or septums used?
- Are the chemicals used in the determination toxic or carcinogenic?
- Is the method precise, accurate, inexpensive, and practical?

The literature displays a great deal of inconsistency in reporting on how cyanide or thiocyanate analytical methods fared during storage, the validation of the method in the presence of antidotes, and timing of sample collection. Several authors strongly emphasize the importance of collection and storage of cyanide-contaminated biological samples.<sup>82,87,105-109,158-160</sup> Because no simple, fast, lightweight, sensitive, and accurate methods are currently available for detection of cyanide in biological fluids, none are appropriate for diagnostic

**TABLE 11-3**  
**ENDOGENOUS CYANIDE CONCENTRATIONS FOR SMOKERS AND NONSMOKERS\***

Subsample Size in Study	Cyanide							
	Nonsmokers				Smokers			
	Whole Blood (ng/mL)	Erythrocytes (ng/mL)	Plasma (ng/mL)	Saliva (ng/mL)	Whole Blood (ng/mL)	Erythrocytes (ng/mL)	Plasma (ng/mL)	Saliva (ng/mL)
n=20 <sup>1</sup>	4.4 ± 1.0			9.9 ± 6.8	7.0 ± 1.8			17.1 ±
n=5 smokers; n=10 nonsmokers <sup>2</sup>	3.5 ± 2.1	6.5 ± 5.9	0.54 ± 0.54		8.9 ± 3.2	18.0 ± 5.4	0.81 ± 0.54	13.5
n=10 nonsmokers <sup>3</sup>	51.3 ± 17.3							
	Thiocyanate							
	Whole Blood (ng/mL)	Plasma (ng/mL)	Urine (ng/mL)	Saliva (ng/mL)	Whole Blood (ng/mL)	Plasma (ng/mL)	Urine (ng/mL)	Saliva (ng/mL)
	n=20 <sup>1</sup>		1.94 ± 1.47		31.4 ± 23.5		6.54 ± 5.34	
	2-Aminothiazoline-4-carboxylic Acid							
	Whole Blood (ng/mL)	Plasma (ng/mL)	Urine (ng/mL)	Saliva (ng/mL)	Whole Blood (ng/mL)	Plasma (ng/mL)	Urine (ng/mL)	Saliva (ng/mL)
	n=19 smokers; n=21 nonsmokers <sup>4</sup>			85 ± 47				233 ± 237
n=27 smokers; n=27 nonsmokers <sup>5</sup>		11.8 ± 4.7				17.2 ± 5.2		

\*The nonsmoker averages 0.06 µg/mL of cyanide in blood, whereas the smoker averages 0.17 µg/mL.

Data sources: (1) Seto Y. False cyanide detection. *Anal Chem.* 2002;74:134A–141A. (2) Lundquist P, Rosling H, Sorbo B. Determination of cyanide in whole blood, erythrocytes and plasma. *Clin Chem.* 1985;31:591–595. (3) Lundquist P, Sörbo B. Rapid determination of toxic cyanide concentrations in blood. *Clin Chem.* 1989;35:617–619. (4) Logue BA, Kirschten NP, Petrikovics I, Moser MA, Rockwood GA, Baskin SI. Determination of the cyanide metabolite 2-aminothiazoline-4-carboxylic acid in urine and plasma by gas chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2005;819:237–244. (5) Maserek WK, Rockwood GA, Platoff GE, Baskin SI, Logue BA. Feasibility of using the cyanide metabolite 2-amino-2-thiazoline-4-carboxylic acid as a retrospective marker of cyanide exposure. *Toxicol Sci.* 2006;abstract 1918:392. (6) Clark CJ, Campbell D, Reid WH. Blood carboxyhaemoglobin and cyanide levels in fire survivors. *Lancet.* 1981;1:1332–1335.

use by first responders. Emergency personnel have to rely initially on the history and physical symptoms of the patient, rather than wait for laboratory results, recognizing that cyanide poisoning can have symptoms similar to other poisonings.<sup>101,110</sup> Blood and urine samples should be collected and analyzed as soon as possible for confirmation or refutation. Table 11-2 is a

method list, and Table 11-3 contains baseline concentrations (neither are intended to be all-inclusive). In addition, some of the methods listed have not been thoroughly examined against suggestions 1 through 5 above. When testing cannot be performed immediately, procedures such as those in Exhibit 11-1 should be used to collect and store samples for later analysis.

## CLINICAL PRESENTATION AND MANAGEMENT OF CASUALTIES

### Principles of Therapy

The effects of cyanide poisoning are those of progressive tissue hypoxia (Figure 11-2). Many cyanide compounds exist, but this chapter deals only with the toxicities of HCN. Additional signs and symptoms may occur as a result of the parent compound. For

example, cyanogen chloride also produces irritation of the eyes and mucous membranes similar to that produced by chlorine.

Lesser degrees of poisoning are survivable even in the absence of specific antidotal therapies. Acute, severe cyanide intoxication, however, is a life-threatening emergency. It is survivable with aggressive acute care

**EXHIBIT 11-1**

**PROCEDURES FOR COLLECTING AND STORING BLOOD SAMPLES FOR DELAYED CYANIDE ANALYSIS**

*Procedure 1*

- Step 1.** Collect a blood sample in a blood collection tube containing an anticoagulant (eg, EDTA, heparin, sodium citrate).
- Step 2.** Add 0.05 mL of 0.05 mol/L sodium nitrite per 1 mL of blood, cover, and let stand for 2 minutes.
- Step 3.** Store at -20 °C until analysis can be performed.<sup>1</sup>

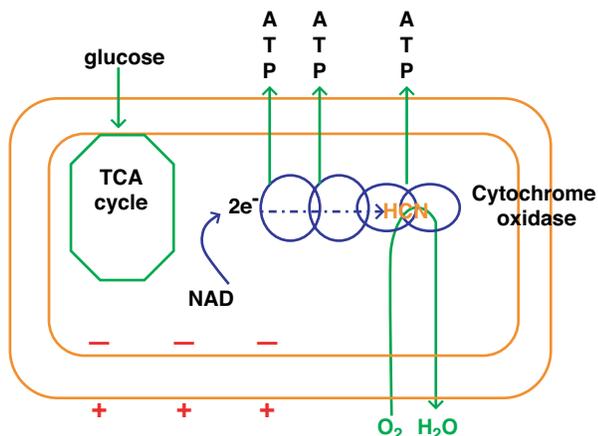
*Procedure 2*

- Step 1.** Prepare blood collection tubes containing the anticoagulant sodium citrate (~ 17 mg). Add 20 µL of 50% aqueous solution of sodium nitrite (~10 mg), and dry in vacuo over anhydrous calcium chloride.
- Step 2.** Collect a 5-mL blood sample.
- Step 3.** Store at 5°C.<sup>2</sup>

*Procedure 3*

- Step 1.** Collect a blood sample in a blood collection tube containing an anticoagulant (EDTA or heparin). Ensure that the top is not made of rubber.
- Step 2.** Add 1 mL of whole blood to 10 mL of the acid silver sulfate reagent (20 mmol in 0.5 mmol H<sub>2</sub>SO<sub>4</sub>).
- Step 3.** Store at -20°C until analysis can be performed.<sup>3</sup>

(1) Lundquist P, Sörbo B. Rapid determination of toxic cyanide concentrations in blood. *Clin Chem.* 1989;35:617–619. (2) Vesey CJ, Langford RM. Stabilization of blood cyanide. *J Anal Toxicol.* 1998; 22:176–178. (3) Lundquist P, Rosling H, Sorbo B. Determination of cyanide in whole blood, erythrocytes and plasma. *Clin Chem.* 1985;31:591–595.



**Fig. 11-2.** Cyanide binds the terminal enzyme of the cytochrome oxidase enzyme system. The enzyme system is located within the inner lamina of the mitochondria. The blockade interrupts the electron flow through the cytochrome oxidase system, thereby disrupting ATP production and both mitochondrial and cytoplasmic ionic balance.  
 ATP: adenosine triphosphate  
 HCN: cyanide  
 NADH: nicotinamide adenine dinucleotide  
 TCA: tricarboxylic acid cycle  
 2e<sup>-</sup>: two electrons

and support during recovery. Often, but not always, recovery is complete. In addition to medical therapeutics, it may be necessary for rescuers and providers to protect themselves from cyanide in the environment, on the casualty, or in exhaled air and vomitus. Once successful medical care begins, providers will need to support the casualty through neurological crisis including coma, seizures, and respiratory failure. They will need to manage cardiorespiratory crisis, including pulmonary edema, and they may need to manage other organ effects, such as toxic hepatitis and renal failure. After acute recovery, they need to prepare for psychiatric care and possible delayed neuropathology.

Cyanide is known to inhibit some 40 enzymes, including several metalloenzymes containing iron, copper, or molybdenum.<sup>125</sup> These reactions may well contribute to cyanide toxicity. The dominant effects of acute, high-dose exposure, however, result from cyanide's primary effect of inhibiting cytochrome c oxidase. This action impairs oxygen uptake and utilization, resulting over time in partial or complete cessation of oxidative metabolism, termed histotoxic anoxia. In massive cyanide poisoning, the mechanisms of toxicity appear to be more complex. In particular,

cyanide may cause both pulmonary arteriolar and/or coronary artery vasoconstriction, resulting in decreased cardiac output—a shock state unrelated to inhibition of the cytochrome-*c*-oxidase system.<sup>126</sup> Given its high dependency on oxidative metabolism and limited anaerobic capacity, central nervous system impairments unsurprisingly dominate the clinical picture of significantly exposed persons. Unless relieved, neuronal progression to cellular death occurs. The clinical record demonstrates that the single most important factor driving successful conversion of a potentially lethal exposure into full recovery is timeliness of rescue.

Cyanide is a rapidly acting poison with a steep dose-effect curve. A lethal dose of cyanide salts is generally considered to be approximately 300 mg or more.<sup>126,127</sup> Whole blood cyanide levels above 2.7 mg/L are potentially lethal.<sup>128</sup> Dysfunction of the central nervous system dominates the clinical picture. A severe, gapped metabolic acidosis, with a large anion gap is common due to overwhelming lactic acidosis. Cardiovascular instability is typical as the clinical course progresses. Differential diagnosis includes all other causes of rapid loss of consciousness and all other causes of lactic acidosis with anion gap. Chen and coworkers describe the usual findings (based on some 600 cyanide poisonings) as follows:

Clinically, the odor of bitter almond oil in breath is highly suggestive of cyanide poisoning. On the other hand, its absence does not rule out the possibility of cyanide poisoning. Other signs, while not specific or pathognomonic, consist of rapid respiration, later slow and gasping, accelerated pulse, vomiting, and convulsions which are followed by coma and cyanosis.<sup>129</sup>

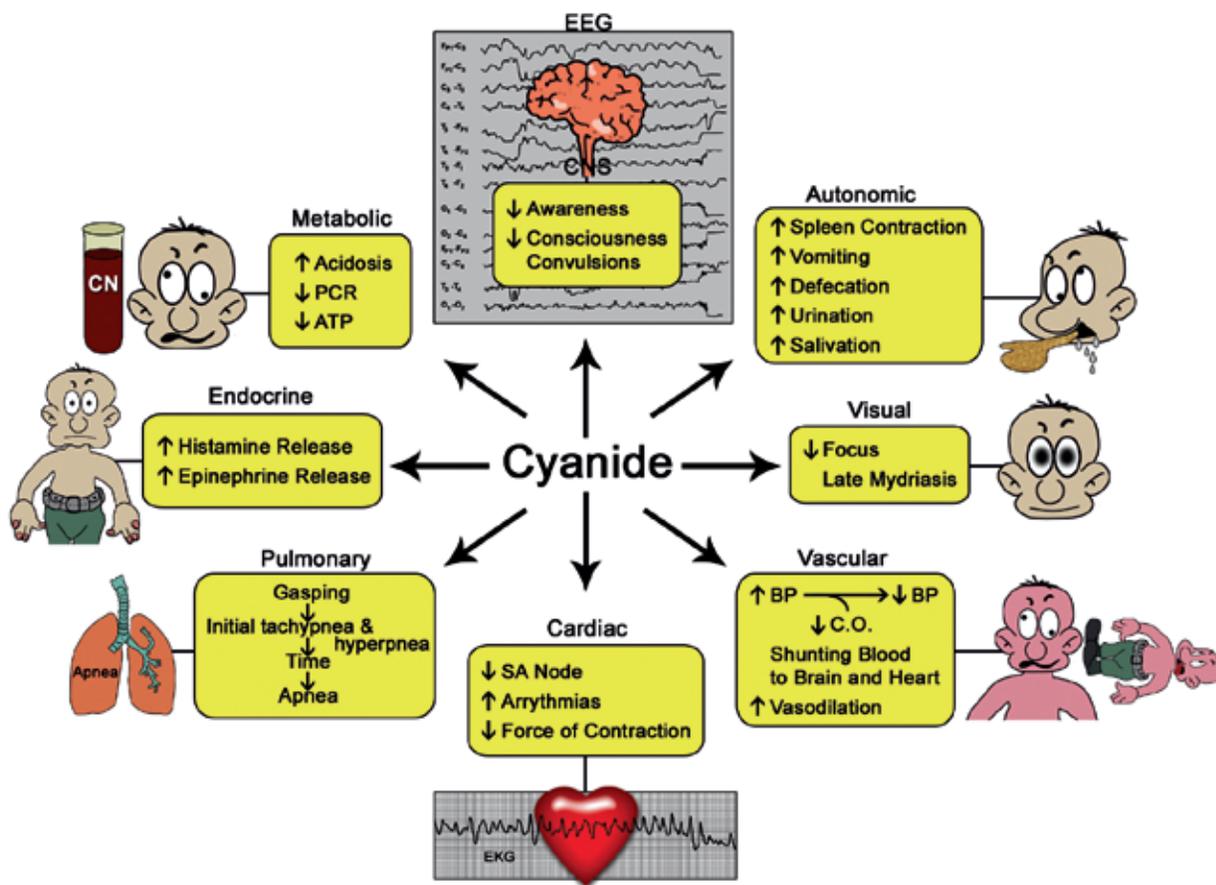
Common themes in case presentations (acute, severe) include rapid onset of coma; mydriasis with variable pupil reactivity; burnt/bitter/pungent almond scent; tachycardia; metabolic acidosis, often extreme; cyanosis of mucous membranes and/or flushed skin; absence of cyanosis despite respiratory failure; ECG showing the T wave originating high on the R (most severe); absence of focal neurological signs; distant heart sounds; an irregular pulse; and similar oxygen tension in both arterioles and venules (Figure 11-3). In a few cases of massive poisoning, pulmonary edema has been reported, likely a result of myocardial injury from the cyanide leading to temporary left heart failure and increased central venous pressure.<sup>130-132</sup> Another uncommonly reported acute complication is rhabdomyolysis.<sup>133</sup> Although patients in some reported cases received treatment with hemodialysis either to remove unknown toxins or to treat complications of

treatment, acute renal failure secondary to cyanide poisoning is not reported. Similarly, toxic hepatitis is not reported, presumably because few cyanide patients survive longer than the 6 hours of postcyanide shock usually necessary to induce toxic hepatitis.<sup>134</sup>

General supportive measures in the setting of acute reaction to moderate or high dose cyanide focus on assuring an airway, administering 100% oxygen, establishing intravenous (IV) access, ablating seizures, and monitoring vital signs and electrocardiograms (EKGs). Blood should be drawn (while noting its color) for a complete blood count, pH,  $PO_2$ ,  $PCO_2$ , electrolytes, glucose, and whole-blood cyanide. Additional studies may be indicated, particularly if the cause of illness is unknown. Subsequent interventions depend on clinical presentation, and the treatment team must be prepared to adjust therapies. Common adjuncts include pressor support; IV hydration; benzodiazapines; insulin; mannitol for pulmonary edema; antiarrhythmics; gastrointestinal clearance (lavage, activated charcoal, diarrheals); and sodium bicarbonate. In general, patients recovering from cyanide intoxication need 24 to 48 hours' observation to support early intervention in the event of acute complications and/or recurring intoxication from incompletely cleared cyanide.

Antidotal enhancement of cyanide excretion is a two-step process, represented in Figure 11-4. The first simplistically uses "scavengers" to restore aerobic energy production. The second prepares cyanide through sulfation for renal clearance from the body. The second step is required to eliminate the threat of re-intoxication. Nitrites and sodium thiosulfate have been used worldwide for many decades to treat cyanide intoxication. Thiosulfate, a sulfane donor, is the rate-limiting substrate for the sulfur transferase rhodanese. Rhodanese is the dominant system for clearing cyanide, working by converting cyanide into the renally excretable thiocyanate. Rhodanese is widely distributed, although most concentrated in the liver, and is intramitochondrial. Physiological reserves of thiosulfate are low, thereby limiting endogenous rhodanese activity. Excess thiosulfate is cleared through the kidneys. Experimental data indicate that thiosulfate and rhodanese effectively remove free HCN, resulting in restored cytochrome oxidase activity.<sup>135</sup> Although unrecorded as the sole therapeutic drug in human case history, sodium thiosulfate is likely a sufficient antidote for moderately severe poisonings, but insufficient for greater exposures.<sup>136</sup> Given its large safety margin, sodium thiosulfate may have particular value when clinicians are reluctant to apply more toxic or more complicated antidotes.

Nitrites available in the United States are amyl nitrite and sodium nitrite. Amyl nitrite (0.35 mL/crushable capsule) is considered a first aid inhalable form.

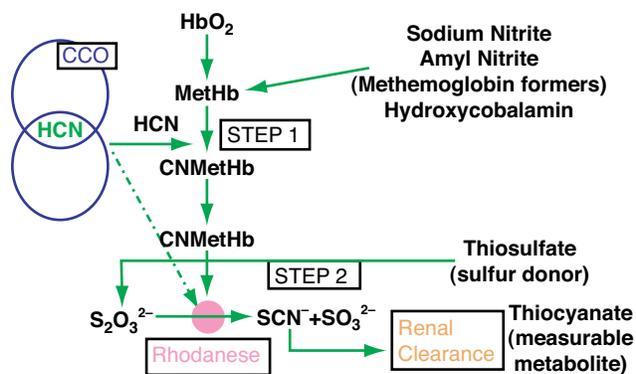


**Fig. 11-3.** Cyanide can affect the function of vascular, visual, pulmonary, central nervous, cardiac, autonomic, endocrine, and metabolic systems. The toxicodynamic effects can vary depending on the dose, route and speed of administration, chemical form (liquid, gas, solid) of the cyanide, and other 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 of 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 decreased capacity to focus, with late-onset mydriasis secondary to hypoxia. One of the first *pulmonary* effects from cyanide is a respiratory gasp, caused by stimulation of chemoreceptor bodies near the aortic bifurcation. Hyperventilation follows this response. Over time (the response is dose-dependent, occurring in 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 include 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 *c* oxidase.

ATP: adenosine triphosphate  
 CNS: central nervous system  
 CO: cardiac output  
 EEG: electroencephalogram  
 EKG: electrocardiogram  
 PCr: phosphocreatine

Sodium nitrite is the intravenous, definitive treatment form. Nitrite delivery increases endogenous methemoglobin, which binds cyanide but does not clear it from the body. Treatment with nitrites must be accompanied by treatment with sodium thiosulfate. Both amyl and

sodium nitrite are potent vasodilators, which may afford additional therapeutic advantage.<sup>137</sup> The value of combined intravenous sodium nitrite and sodium thiosulfate was recognized early and was summarized (as follows) by Chen et al:



**Fig. 11-4.** Fundamentals of cyanide antidote therapy. Clearance of excess cyanide is essentially a two-step process. The first step restores mitochondrial aerobic energy production by accelerating cyanide removal from cytochrome *c* oxidase. The second step enhances conversion of cyanide into a form suitable for renal clearance. It should be noted that the clearance process crosses multiple compartments and organ systems, and it works efficiently in the presence of adequate substrate and intact hepatic and renal function.

CCO: cytochrome *c* oxidase

HCN: cyanide

MetHb: methemoglobin

CNMetHb: cyanomethemoglobin

$S_2O_3^{2-}$ : thiosulfate ion

$SO_3^{2-}$ : sulfite

SCN<sup>-</sup>: thiocyanate

The two substances intravenously injected, one after the other, namely, the nitrite followed by the thiosulfate, are capable of detoxifying approximately twenty lethal doses of sodium cyanide in dogs, and are effective even after respiration has stopped. As long as the heart is still beating, the chances of recovery by this method of treatment are very good. Since dogs are more susceptible to the poison than man, these observations are especially significant. When sodium nitrite is used alone, about four lethal doses of the cyanide are detoxified. Sodium thiosulfate, when injected alone, nullifies about three lethal doses of the cyanide. Thus, there is not only a summation but a definite potentiation of action when the nitrite and the thiosulfate are administered together . . . . Another nitrite, namely amyl nitrite, by inhalation has the same detoxifying value as sodium nitrite by intravenous injection.<sup>129</sup>

More recent case experience confirms early reports.<sup>137</sup>

Because nitrite formers elevate methemoglobin levels and are powerful hypotensive agents, both methemoglobin levels and hypotension must be monitored during the course of therapy and nitrites withheld if necessary until recovery of acceptable blood pressure and treatment of methemoglobinemia.

Therapeutic levels of methemoglobin are usually well under 10% when measured, often 3% to 5%. Induced cyanomethemoglobin levels are usually unknown; available oxygen carrying capacity is always less than methemoglobin levels alone predict.

The two chief formations of cobalt antidotes are hydroxycobalamin and dicobalt edetate. Although cobalt EDTA is quite toxic, hydroxycobalamin appears to have a safety profile preferable to the nitrites, particularly in settings in which induction of methemoglobin is undesirable. No efficacy studies compare performance of nitrites against that of cobalts.

Oxygen is an important medicament for cyanide intoxication. It significantly enhances the antidotal value of nitrite plus thiosulfates, increasing the LD<sub>50</sub> dose 6-fold (drugs alone) to over 8-fold.<sup>49</sup> Oxygen's mechanisms of action are uncertain. The additional gain afforded by hyperbaric oxygen is uncertain, with some patients responding well and other attempts unsuccessful unless carbon monoxide intoxication coexists.<sup>138</sup> Patients should receive 100% humidified oxygen. If a mask is used, it should be a nonrebreathing mask to prevent rebreathing of exhaled cyanide.

Several case reports have been published in which full recovery occurred in the absence of specific antidotal therapy. In each case, indicated general supportive measures were otherwise provided.<sup>126,133,139,140</sup> Blood levels of cyanide in these individuals ranged from 2.14 to 7.7 mg/L. Levels exceeding 3 mg/L are usually considered potentially lethal, and levels exceeding 2 mg/L severe. These cases do not, however, justify withholding specific antidotal therapies if antidotes are available.<sup>56</sup> These survivors likely were more tolerant of the exposures than is typical. In addition, their postacute recovery statuses are not reported. Yen et al report the only published English language epidemiological case comparison between severe cyanide intoxications receiving nitrite/thiosulfate antidotes and those receiving supportive care alone.<sup>137</sup> In the absence of anoxic encephalopathy, administration of specific antidotes offered clear survival advantage.

Full treatment, including antidotes, should be administered to pregnant women who are seriously impaired by cyanide. Fetal effects other than methemoglobin induction have not been reported. Risks to the fetus from maternal incapacitation override concerns from possible fetal methemoglobin induction. In addition, the evidence suggesting the teratogenic risk of antidotes during pregnancy is very limited.<sup>141</sup> In a life-saving situation, therapies should not be modified as a consequence of pregnancy.

In summary, the fundamental principles of toxicologic therapies apply to treatment of cyanide-injured casualties. The first is to recognize the situation and

to protect those responding. The second is to rapidly intervene to avoid unnecessary complications. The third is to provide supportive measures according to the extent of injury. And the fourth is to provide specific antidotes even in the absence of confirmatory laboratory testing while controlling for undesirable side effects (Table 11-4). If these principles are followed, most persons arriving for medical care will recover within hours to days. Once discharged, all seriously affected persons should receive periodic follow-up to ensure that any underlying psychiatric problems or delayed neurological and other consequences are detected and managed (see below).

**Triage, Decontamination and Patient Transport (Evacuation)**

Triage is necessitated by the presence of overwhelming demands on the available medical system. It provides for a methodical and orderly approach to casualties. Triage, decontamination, and timely transport to prepared medical receivers depend on a trained, prepared, and well-integrated organizational system. A coordinated system is at least as critical to casualty survival as are specific antidotes.<sup>142</sup> The remainder of this discussion will assume reader awareness of general principles of casualty rescue: protection of workers from exposure; reduction of contamination by evacuation from the contamination source, undressing, and removal of obvious liquid cyanide; provision of general life support including seizure ablation; and, finally, medical decontamination and definitive medical care.

Triage of a cyanide mass casualty event focuses on identifying casualties who require emergent care to

survive with the least possible consequence to later function, including neurological function. Casualties absent of heart rate are termed expectant or black. Comatose, seizing, hypotensive, or hypopneic casualties are classified immediate or red. These patients must receive immediate respiratory support, oxygen, circulatory support, and antiseizure medications in addition to having obvious cyanide removed. As soon as possible, specific cyanide antidotes must be administered. Thiosulfate may be the preferred antidote in mass casualty situations because of its favorable safety profile. If personnel are available to monitor for nitrite-induced hypotension and to adjust the rate of administration, then the addition of nitrites will enhance recovery. Because their condition can be expected to deteriorate rapidly, persons who have ingested cyanide or who have liquid contamination should be considered for early intravenous access with possible initiation of thiosulfate infusion *even before overt signs develop*.

Remaining casualties are removed from further exposure and sorted into delayed (yellow) and minimal (green) categories. Minimal (green) is assigned to mildly affected, vapor-exposed persons. These casualties experience nausea and dizziness, and may be agitated or hyperventilating. They require only removal from exposure, a calming environment, and reassurance. Once recovered, they may be asked to provide assistance to the response effort, because they will sustain no injury from their exposure and may benefit from early return to useful activity. Delayed (yellow) casualties are those who have received initial treatment and are under observation during recovery. Casualties who are alive at the time of first medical contact should be expected to survive given full care.

Cyanide decontamination is straightforward. If

**TABLE 11-4**  
**US APPROACH TO CYANIDE ANTIDOTES**

Mechanism	Natural Process of Elimination	Treatment
Unload cyanide from cellular cytochrome oxidase	Use methemoglobin 1%–2% (Fe <sup>3+</sup> )	Amyl nitrite ampules (inhaled), sodium nitrite (300 mg IV), or hydroxocobalamin (5 g, diluted, IV)
Transfer CN <sup>-</sup> from stable, time-release depot to excretable molecule	Rhodanese conjugates CN <sup>-</sup> with thiocyanate ion → SCN <sup>-</sup> + sulfite	Sodium thiosulfate (50 mL of 25% solution, IV)
Remove from body	Renal excretion	Renal excretion
Potentiate effects of nitrite and thiosulfate	None	Supplemental oxygen (100% humidified)
Reduce burden of ingested cyanide	Vomit	Gastric lavage

CN<sup>-</sup>: cyanide anion  
SCN<sup>-</sup>: thiocyanate

cyanide has been ingested the gut should be decontaminated through gastric lavage and the administration of activated carbon. All cutaneous cyanide can be removed by washing with water or soap and water. Water temperature should be comfortably warm if possible, but decontamination should not be delayed while water is heated. Early decontamination definitely reduces the extent of illness by decreasing total body burden. Decontamination also protects emergency responders and healthcare personnel. Personnel conducting decontamination and any predecontamination care require appropriate personal protective equipment so that they themselves do not become casualties. Personnel conducting autopsy examinations on persons recently deceased from cyanide poisoning should also apply safety precautions. At the least, these include adequate ventilation to the outside, frequent breaks in uncontaminated spaces, and containment of heavily contaminated organs. Any personnel who become symptomatic should refrain from continued exposure. Documentation of postexposure blood cyanide levels can be considered.<sup>143</sup>

Transport of cyanide-intoxicated casualties to definitive care facilities should be done as rapidly as possible unless general supportive care and antidotes can be delivered by emergency responders. In the event of a suicide attempt, this could be at the home or workplace or in the ambulance en route to the hospital. In the event of an urban release, initial stabilization could occur in the warm zone (decontamination corridor). In the event of a military situation, initial stabilization would probably occur in the dirty side of the patient decontamination station. In any case, stabilization of critically ill casualties must be done before complete decontamination. Transport vehicles and personnel should be prepared to provide oxygen (100% if possible), intravenous lines, cardiopulmonary resuscitation, and antiseizure medications. Ideally they will also be equipped to initiate specific antidotal therapy, particularly with amyl nitrite and thiosulfate. Because of its side-effect profile, sodium nitrite should not be administered unless the care providers are equipped to monitor blood pressure closely and to adjust rates of administration.

### Laboratory Findings

Serious cyanide toxicity is characterized by obstruction of aerobic metabolism and forced anaerobic metabolism. These conditions cause lactic acidosis, manifesting as metabolic acidosis with anion gap and lactic acidemia, and reduced arteriovenous oxygen content difference. A lactate level measurement refines the more general impression of metabolic acidosis;

depending on the results, renal insufficiency would be a less likely cause of anion gapped metabolic acidosis. In the setting of severe and potentially fatal cyanide poisoning, pulse oximetry correctly demonstrates the high blood oxygen content. It will not, however, correctly reflect deficient oxygen delivery and uptake at tissue level.

As therapy proceeds and cellular respiration resumes, venous oxygen levels will drop, lactic acid levels will return to normal, and pH will move towards neutral.<sup>144-148</sup> Estimation of oxygen saturation by pulse oximetry will remain misleading, however, because of the presence of methemoglobin as a consequence of nitrite therapy.<sup>149</sup> Hemoximetry (in vitro multiwavelength cooximetry) can quantify the deficit in functional saturation resulting from methemoglobin and carboxyhemoglobin but does not account for additional, and likely significant, decrements caused by cyanomethemoglobin (unless newer machines capable of directly measuring cyanomethemoglobin are used).<sup>161</sup> Measured methemoglobin levels after administration of a 300-mg ampule of sodium nitrite will likely not exceed 7% to 10% and may be lower; the remaining oxygen carrying capacity will be something less than 90% to 93%, depending on the degree of dyshemoglobinemia present.

Interpretation of cyanide levels for clinical management is unreliable. Cyanide is continually eliminated from the body as long as the person remains alive. Cyanide can be measured in either plasma or whole blood. Whole blood levels more accurately reflect the total body burden because most cyanide is rapidly bound into red blood cells, but plasma levels may more correctly predict cellular exposure.<sup>144</sup> Blood cyanide levels do not reliably predict severity of illness. In addition, most centers are unable to receive test results quickly enough to support diagnostic use. Therefore, blood or plasma cyanide levels currently have limited value in the acute care setting outside of research hospitals. They remain valuable for confirmatory testing and forensic purposes. In the near future, the cyanide metabolite ATCA may prove to be a useful additional biomarker of excessive cyanide exposure because of its stability over time.<sup>151</sup>

### Long-Term Effects

Comparatively few persons survive acute, high-dose exposures to cyanide. Survivors typically either receive early aggressive medical support or represent the subpopulation with increased resistance to the poison. One other subgroup is those with gastric acidity. They tolerate large amounts of cyanide salts, apart from local erosions.<sup>162</sup> The understanding of the health

impacts of survival of otherwise lethal cyanide intoxications is necessarily framed by the few published case reports that follow survivors over time.<sup>127,162-170</sup> These reports indicate that the major system resulting in clinically relevant pathology is the central nervous system, particularly the brain, but also to some extent the spinal cord.<sup>171</sup>

Cyanide does not uniformly affect all brain cells. For example, CA1 neurons in the hippocampus are more susceptible than CA3 cells to metabolic inhibition by cyanide.<sup>172</sup> Nearly all long-term neurological sequelae of acute high-dose exposure result from damage to the basal ganglia and sensorimotor cortex, with additional defects referencing cerebellar Purkinje neurons. Cell death occurs slowly after brief ischemia. Current theory favors cellular apoptosis as the mechanism of demise as opposed to necrotic death.<sup>163,167</sup> Casualties with long-term effects manifest parkinsonian-like conditions and akinetic rigid syndromes, typically after intervals of weeks to months. Usually lacking are tremor, pathological reflexes, disorders of sensitivity, or intellectual deficits. Occasionally, the clinical picture partially improves over time. Some patients demonstrate partial improvement with medication. The following eight case synopses address the neuroanatomical pathology of survivors of large cyanide doses, with brief summaries of overall presentation and radiological/histopathologic features. (Note that advancing technologies allow gradually improved understanding of functional as well as anatomical consequences of survival from potentially lethal cyanide intoxications.)

**Case Study 11-1.** An 18-year-old male survived a 975- to 1,300-mg KCN ingestion.<sup>176</sup> He developed parkinsonian syndrome, characterized primarily by akinesia and rigidity, and died 19 months later. The autopsy revealed major destructive changes in the globus pallidus and putamin. The substantia nigra was intact.

**Case Study 11-2.** A 29-year-old male survived a 500-mg KCN ingestion.<sup>162</sup> Within 3 weeks he developed slowed and cumbersome speech and impaired swallowing. Within 4 weeks he overshot his trunk movements with postural change and had stiff gait, flat facies, hypokinesia, unmodulated speech, dyscoordination of speech, cogwheel phenomenon, severe bradydiadochokinesia, brisk monosynaptic reflexes, and absence of pathologic reflexes. T2-weighted magnetic resonance imaging (MRI) showed symmetrical signal elevation in both putamina. By 5 months, his clinical status was improved, although slow speech and pronounced bradydiadochokinesia of upper limbs

persisted. The putamina were hypodense on MRI.

**Case Study 11-3.** A 46-year-old male survived a 1,500-mg KCN ingestion.<sup>167</sup> Within 3 days he had mild difficulty with tandem gait and halting speech. Examination 3 weeks after recovery revealed marked bradykinesia; masked facies; slow, shuffling gait; mild rigidity; and weak dysphonic voice. Little tremor was present. MRI 12 months after ingestion revealed multiple, bilaterally symmetrical areas of high-signal intensity in the globus pallidus and posterior putamen on T2-weighted images. A 6-fluorodopa positron emission tomography revealed diffuse decreased activity in fluoridopa in the basal ganglia and markedly decreased activity in the posterior regions of the basal ganglia, similar to patients with parkinsonism.

**Case Study 11-4.** A 28-year-old male survived a 800-mg KCN ingestion.<sup>164</sup> Within several weeks he developed extrapyramidal signs including marked drooling, profound micrographia, masked facies, mild intention tremor, and cogwheel rigidity. MRI 3 months after poisoning demonstrated wedge-shaped areas of increased signal intensity in the T2-weighted images, particularly in the globus pallidi. Repeat scanning 12 months later disclosed no change in the extent of basal ganglial abnormality but showed the development of mild cerebellar atrophy.

**Case Study 11-5.** A 31-year-old male with epilepsy recovered fully after ingesting 20 to 40 gm KCN dissolved in milk.<sup>166</sup> As long as 1.5 years after the poisoning, he showed no signs or symptoms. His temporal lobe epilepsy was unchanged. Memory and intelligence were unaffected. T1-weighted images on MRI at day 51 demonstrated bilaterally symmetrical high-signal intensity in both putamina. Both regions became isointense to white matter by day 146 and remained so by day 286.

**Case Study 11-6.** A 27-year-old female survived a 300-mg KCN ingestion.<sup>165</sup> Over the next 2 months she developed gradually progressive stiffness and weakness of all four limbs, along with unclear speech, severe hyperkinetic dysarthria due to dystonia, mild left facial weakness, generalized lead pipe rigidity, and bradykinesia. She also demonstrated hemiplegic dystonia with bilateral involvement characterized by flexed upper limbs, extended lower limbs, and normal deep tendon reflexes with flexor plantar responses. Her upper limbs were flexed and supinated, with fingers tightly flexed and thumb strongly opposed. Her neck and spine were rigidly extended. She showed no tendency to spontaneous improvement. Cranial com-

puted tomography scan showed bilateral putaminal hypodensities, which were seen to be hyperintense on MRI T2-weighted images. Multimodal evoked potentials were normal.

**Case Study 11-7.** A 19-year-old female survived inhalational exposure of a large dose (the exact amount was unknown) as an intended victim of homicide.<sup>173</sup> During trial proceedings 8 months after the poisoning, she was noted to be fully recovered with the exception of a mild dragging of one leg. No imaging studies were reported.

**Case Study 11-8.** A 35-year-old female survived a usually lethal ingestion of KCN.<sup>163</sup> By day 5 she displayed agitation and choreoathetotic movements of all four extremities and the trunk, which was suppressed while she was communicating. Deep tendon reflexes were brisk, and both plantar responses were positive. By week 3, the choreoathetotic movements abated to a state of akinetic mutism with loss of power, resembling generalized dystonia. She was dysarthric and had limited swallowing. An electroencephalogram (EEG) revealed diffuse, abnormal beta activity, more pronounced in frontal and front-temporal regions, but no focal epileptic activity. Serial evoked potentials testing revealed central axonal auditory and somatosensory propagation damage. MRI revealed acute and subacute damage to the caudate nucleus and globus pallidus bilaterally and discrete cortical damage localized to sensory motor cortex consistent with pseudolaminar necrosis, and functional imaging with  $\beta$ -CIT SPECT showed loss of nigrostriatal dopaminergic neurons.

As contrasted with acute, high-dose survivors, thousands of people survive with lesser overdoses from excessive consumption of cyanogenic foods on a chronic basis, particularly in the setting of overall nutritional inadequacy. Such chronic overexposure to cyanide and its metabolite thiocyanate is thought to account for prevalent peripheral nervous system disorders and perhaps also for excess goiters found within subpopulations of sub-Saharan Africa and Asia.<sup>125,174</sup>

In summary, most severely poisoned cyanide casualties die in the absence of early intervention. Based on limited case reports, long-term survivors may develop significant neurological morbidity arising from apoptotic demise of neurons of the basal ganglia and sensory-motor cortex. Case series from occupational settings where potentially lethal intoxications are typically identified and definitive treatment begun within minutes of exposure report early return to full duty.<sup>175</sup> In addition, it is likely that developing knowledge in

the fields of neuroprotection and resuscitation will afford even gravely ill cyanide casualties better opportunity for excellent recovery.

Cyanide is associated with neuropathies worldwide (but not endemic to Westernized nations) that appear to result from excessive daily dietary cyanide, perhaps in combination with insufficiently varied diets with low-quality protein content. Bitter cassava root in particular is noted for this association. Cassava is a dietary staple, but it requires extensive processing to remove cyanogens prior to consumption. During food shortages or civil unrest, preparation is shortened while dependence on the staple crop increases. The upper motor neuron disorder konzo notoriously occurs in individuals—especially children—at these times.<sup>176-178</sup> Konzo is a persistent but nonprogressive spastic paraparesis (muscle weakness) that has been studied extensively by Rosling and colleagues.<sup>179,180</sup> Konzo sufferers display lower-limb dysfunction, limited mobility, and impaired fine motor function.<sup>181</sup> Populations recently affected by konzo have been found to have elevated urinary thiocyanate outputs and decreased inorganic sulfate excretion, consistent with high cyanide intake and low sulfur-containing amino acids intake.

### Pediatric Considerations

Pediatric considerations for any toxicant must be discussed with awareness of normal development and how that toxicant interacts with specific stages of development.<sup>182</sup> Very little knowledge of cyanide impact on fetal development exists. Because fetal well-being is most dependent on maternal well-being, the primary therapeutic consideration for severe acute cyanide toxicity in a pregnant woman must be urgent restoration of maternal circulatory, respiratory, and neurologic status. Chronic excess of thiocyanate is thought to be thyrotoxic to both the mother and the fetus<sup>125</sup>; this situation is endemic in certain parts of the world where maternal-fetal wellness is already threatened by serious nutritional and socioeconomic problems. Treatment of cyanide intoxication with methemoglobin formers does induce fetal methemoglobinemia. The amount of fetal methemoglobin formed, however, is not likely to be clinically important as weighed against the necessity to treat the mother.<sup>126</sup>

Relatively few case reports and no epidemiological reports of survival of acute cyanide intoxication in young children are available. The few published cases resulted from consumption of cassava or apricot kernels. Children do seem to be more vulnerable to intoxication through food sources, presumably because of lower body weight.<sup>126</sup> In one report, two young Thai children (ages 4 and 1.5 years) became comatose

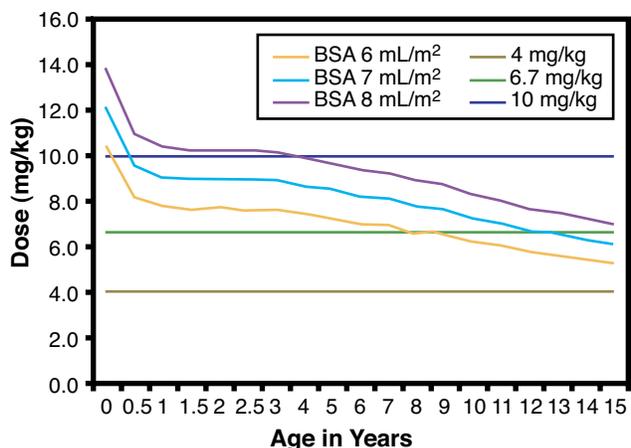
9 hours after ingesting boiled cassava. They were intubated and put on ventilatory support, but antidotes (nitrite and thiosulfate) were given several hours later upon the children's arrival at a regional intensive care unit. Both received appropriate general support for circulation and ventilation, including fluid loading and dobutamine for hypotension. The older child received nitrite and thiosulfate at 19 hours after ingestion plus gastric decontamination and recovered fully. The other child received only general supportive care because he was not sufficiently stable for transport to the regional hospital until 23 hours after ingestion; by that time he was alert and without cyanosis or serious acidosis.<sup>183</sup> In a second report, eight Venezuelan boys between 8 and 11 years of age consumed cyanogenic bitter cassava. Pigs that ate the remaining cassava died. On arrival at the emergency room, all were critically ill with respiratory failure, bradycardia, and hypotension. Two also displayed generalized seizures. All the children received 100% oxygen and general supportive care. The four least ill children received in addition intramuscular hydroxocobalamin (500 mg). The four sicker children received nitrite and thiosulfate on a milligram per kilogram basis. Their blood was noted to be bright cherry red with identical arteriovenous  $PO_2$  values. All the children improved within a few minutes and were discharged in good condition in 1 day.<sup>184</sup> A third case suggests that methemoglobin formers should be used with particular care in children. Children have higher oxygen demands than adults, and infants in particular are unable to reduce methemoglobin efficiently because of immature methemoglobin reductase systems.<sup>185</sup> This case reports that a 17-month-old child died after receiving a double dose of sodium nitrite for sublethal cyanide ingestion. Antidotes were given in the absence of serious illness and were repeated without first assessing levels of methemoglobin. Furthermore, antidote dosing was not adjusted for body weight and hemoglobin. Toxicological estimates place the child's induced methemoglobin at 92%.<sup>186</sup>

These three case reports and principles of toxicology and pediatrics demonstrate that young children who are critically ill with cyanide overdose can be successfully resuscitated with expectation of full recovery. As with adults, resuscitation of the poisoned child involves life support and stabilization measures, followed by identification of the toxin and detoxification as appropriate. General measures include 100% oxygen and general life support, including gut decontamination with lavage and adsorbents. Antidotes should be administered in accordance with local availability and dose adjusted for weight. General dosing guidelines per package insert should be followed. In general, sodium nitrite should be dosed in the range of 4 mg/

kg to 6.6 mg/kg. The former is equivalent to the standard adult dose, and the latter is recommended in the manufacturer's package insert. These doses are considerably less than the often published 10 mg/kg dose. Figure 11-5 demonstrates how the 10-mg/kg dose is unacceptably high for young children in particular. Children over approximately 40 kg body weight can receive an adult dose of sodium nitrite assuming absence of anemia. Hemoglobin levels under 12 g/100 mL dictate dose reductions.<sup>186</sup> It is appropriate to administer the nitrite slowly and consider partial doses so that methemoglobin levels can be carefully monitored. Methemoglobin levels must be monitored before retreatment; successful therapeutic levels appear to be well under 20%, often under 10%. If a treated child becomes cyanotic despite adequate oxygenation during nitrite therapy, methylene blue should be considered even if the methemoglobin level is less than 30%.<sup>187</sup> Although repeat dosing with half the original dose of antidote may be required, it should not be given until caregivers are confident that lethal exposure has occurred, that acidosis persists, that the condition remains unstable, and that adequate oxygen transport capability remains. If poor clinical state persists despite adequate methemoglobin levels, other diagnoses must be considered.

### Polyintoxications

The most likely cointoxications with cyanide are alcohol and carbon monoxide. Although alcohol is frequently used before a cyanide suicide attempt and clearly complicates the clinical management of the cyanide-overdosed patient, it is not understood to directly influence outcomes of cyanide intoxication and will not be further discussed here. Of greater concern is the extent to which HCN contributes to mortality and morbidity in fire victims. The pathophysiology of smoke inhalation is complex. Thermal conditions, as well as the constituents of smoke vary not only from fire to fire, but also from one location to another within the same fire. Morbidity and mortality result from a number of interacting processes including thermal injury, carbon monoxide poisoning, trauma, reduced oxygen tension in the heated atmosphere, and other toxicants present. Cyanide is one of those toxicants that might be present in significant amounts because of incomplete combustion in hypoxic conditions.<sup>128,188,189</sup> Although no single factor or group of factors reliably predicts the extent to which HCN intoxication contributes to the clinical picture of any single smoke inhalation casualty, severity of carbon monoxide illness and lactic acidemia greater than 10 mmol/L are most closely associated with severe cyanide cotoxicity.<sup>126,138,145,190-192</sup>



**Fig. 11-5.** Body surface area versus weight dosing. This figure describes the relative dose in mg/kg when charted against median weight and height for age. These data illustrate why the authors propose that dosing children with sodium nitrite at greater than the package insert recommended 6.6 mg/kg is excessive and potentially harmful. Curves were drawn after converting to dose per body surface area using 50th percentile for weights and length/stature, based on the Centers for Disease Control and Prevention 2001 weight-for-age percentiles, ages birth to 36 months and ages 2 to 20 years. For conversion purposes, 4 mg/kg is equivalent to 0.13 mL/kg of 3% solution, 6.6 mg/kg is 0.2 mg/kg of 3% solution, and 10 mg/kg is 0.33 mL/kg of 3% sodium nitrite solution. Body surface area calculated using the DuBois and DuBois formula.

BSA: body surface area

Chart: Courtesy of MAJ Thomas B Talbot, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

The awareness that carbon monoxide has the dominant effect on time of survival, but that both carbon monoxide and HCN, when present, appear to synergistically affect hypoxic fatality, guides some general recommendations. Oxygen, general supportive measures, and burn and trauma management are

generally indicated, with high benefit-to-risk ratios. Analysis for carboxyhemoglobin, lactic acidosis, oxygenation, and HCN levels should be accomplished at the earliest opportunity. HCN-specific treatment may be a reasonable option for severely affected smoke inhalation victims who have been properly stabilized otherwise. Thiosulfate is reasonable, effective, and safe, and appropriate for mass casualty situations. It does not diminish oxygen carrying capacity and is widely available; however, it does require a parenteral line be established. Hydroxocobalamin is also reasonable, effective, and safe. It is typically used with thiosulfate, and it does not diminish oxygen carrying capacity. It does require a parenteral line. Amyl nitrite is reasonable and effective; it does not require parenteral access and can be given to persons on supported ventilation. It does reduce oxygen carrying capacity modestly. Because treatment requires close monitoring for hypotension, amyl nitrite is not the first choice in a mass casualty situation. Similarly, sodium nitrite is effective and likely reasonably safe if a high level of oversight is available.<sup>190</sup> The other antidotes described in this chapter have demonstrated general effectiveness against cyanide poisoning but not necessarily against fire exposures. They also require parenteral lines and substantially more monitoring because of their side effect profiles.

In summary, clinical management of cyanide intoxications, regardless of the victim's age or source of intoxication, is based on early recognition, aggressive general support measures, and early antidotal enhancement for severely ill persons otherwise at risk for hypoxic injury. In the absence of history of cyanide exposure, clinicians have to proceed without a confirmed diagnosis, maintaining high levels of awareness for adverse effects of therapy and changes in clinical course. Successful acute intervention must be followed with sustained care directed at underlying causes of intoxication and detection of delayed sequelae.

## CYANIDE-CAUSED CARDIAC TOXICITY

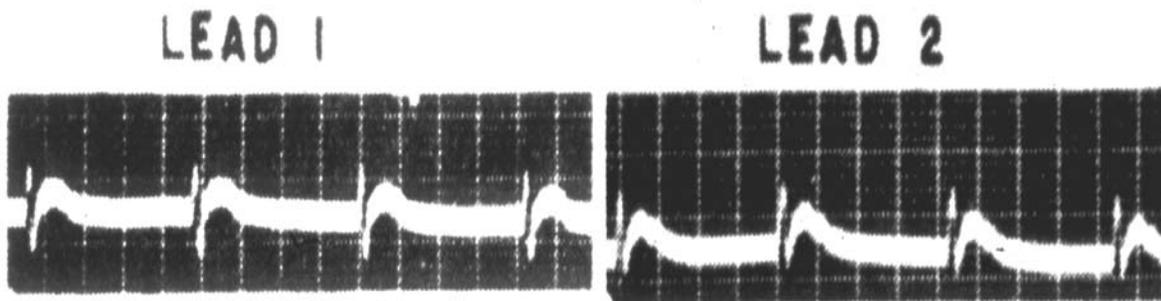
### Histopathologic Changes

Cyanide is deposited heterogeneously in cardiac tissue, with the ventricles heavily affected. The resulting histological changes include cell swelling and hemorrhaging.<sup>193</sup> Cell swelling activates chloride membrane currents, as part of the ionic derangement, changing the homeostasis of the tissue. Substrate changes include formation of lactic acid and secretion of catecholamines.

One of the first manifestations of the changed elec-

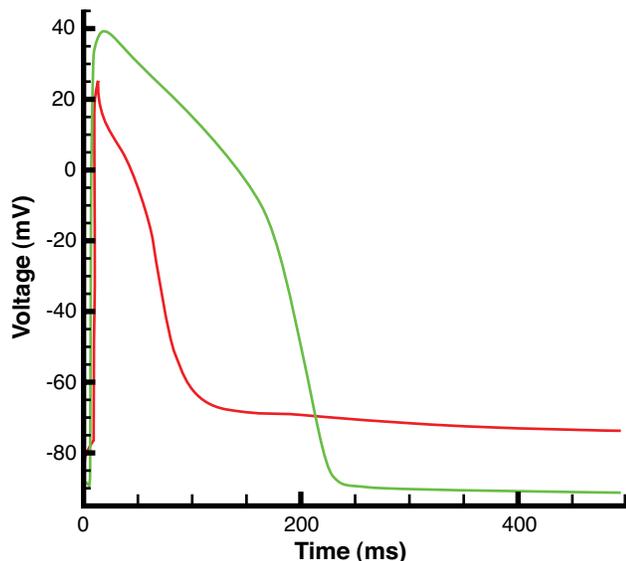
trophysiology is bradycardia, which may soon change to torsade de pointes and possibly culminate in ventricular fibrillation (Figure 11-6). Katzman and Penney and Wexler et al provide additional details.<sup>194,195</sup>

On the cellular level, changes in the ion concentrations become important, especially calcium overload of the cell and increase in the extracellular potassium concentration,  $[K^+]_o$ . The cell's energy homeostasis<sup>196</sup> is profoundly disturbed, and several compensatory membrane currents are activated and others diminished. Three of the most important ones are the ATP-



**Fig. 11-6.** Electrocardiogram from a cyanide-intoxicated individual. The P-wave (the atrial depolarization) is eliminated, and ST-segment deviation, usually a rise in the slope, becomes noticeable, followed by modulation of the T-wave. The changed morphology is expressed in steepening and coalescing of the QRS and the T-waves. A J-wave becomes noticeable. Reprinted with permission from: Wexler J, Whittenberger JL, Dumke PR. The effect of cyanide on the electrocardiogram of man. *Am Heart J.* 1947; 34:170.

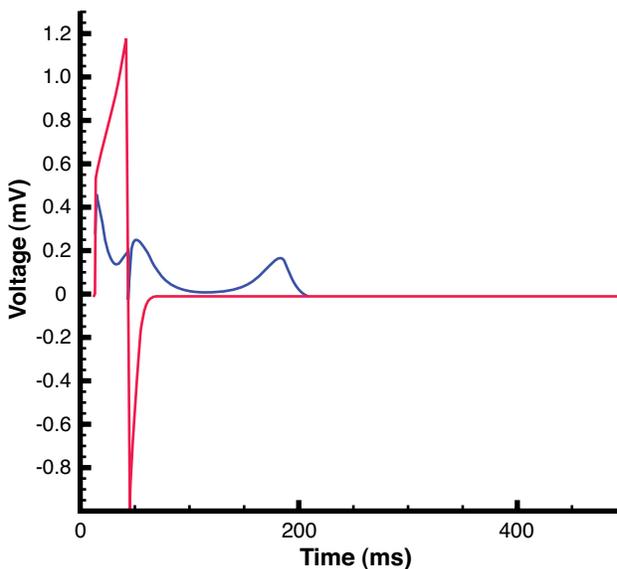
dependent  $I_{KATP}$ <sup>197</sup> the osmotic swelling-activated  $I_{Cl,swell}$  and the calcium-dependent  $I_{Ca-L}$ . The disequilibrium in the membrane currents caused by cyanide has grave implications for the cell's electrophysiology. Cyanide-caused cardiac toxicity shares some commonality with ischemia but is different in the level of acidity of the tissue and the nature of some of the activated currents. A number of ancillary effects, including enhanced catecholamine secretion where CA binds to  $\alpha$  and  $\beta$  receptors that affect membrane currents, increase in free  $Mg^{2+}$ , and pH changes also occur.<sup>54,198-200</sup>



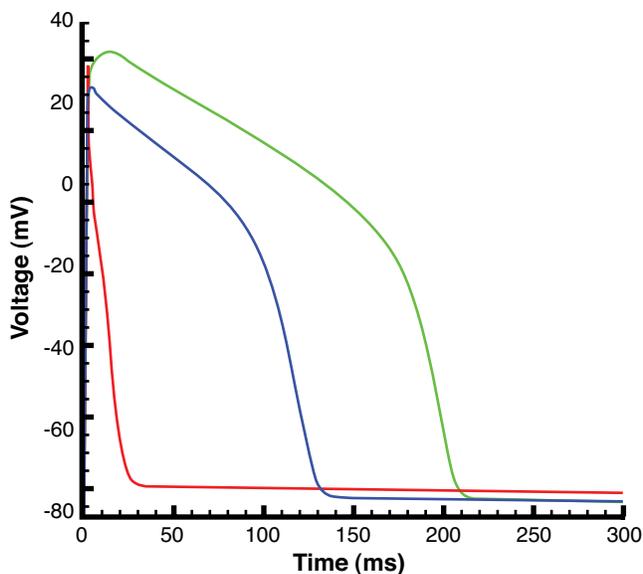
**Fig. 11-7.** The effect of cyanide on a ventricular cell. The red curve shows the change in the resting voltage and the drastically shortened cycle length. The green curve is the unaffected condition; the red curve shows the affected cell voltage.

### Computational Models

ECGs and action potential morphologies are markers of the electrophysiological state of cardiac tissue. High-performance computer simulations of the electrophysiology of the three types of cardiac cells—endocardial, midmyocardial, and epicardial—model the impact of specific changes to identified ionic currents on cardiac electrophysiology.<sup>201-204</sup> Usually dormant currents appear to be critical to understand-



**Fig. 11-8.** The change in the electrocardiogram (ECG) caused by the presence of cyanide in the tissue. The red curve shows the normal ECG, with T-wave present. The blue curve shows the effect of cyanide on the ECG. The cyanide-affected tissue shows considerable morphological changes and elimination of the repolarization.



**Fig. 11-9.** Blocking the anionic, cell swelling-activated chloride current can restore the morphology of the cyanide affected action potential, the curve at the left (red curve), to the unaffected state. A partial block moves the curve toward the right (blue curve) and also restores the resting potential. A total block (green curve) achieves complete restoration to the normal.

ing cyanide-induced electropathophysiology. Two of the more important activated currents are the  $I_{K_{ATP}}$  because of the decline in the ATP stores, and  $I_{Cl,swell}$  when the cell volume is modulated. Change in cellular ion concentrations, also an important aspect of cyanide toxicity, includes calcium overload, which causes the

## NEUROLOGICAL/PSYCHOLOGICAL RESPONSES TO CYANIDE AND ITS COUNTERMEASURES

Explicit understanding of the specific effects of cyanide exposure on the neuropsychology of humans or animals is limited. Impact would be expected, however, based on understood pathophysiology. Using various animal models, alterations have been observed in learning, sensory responses, and neurologic reflexes after exposure to sublethal doses of cyanide. These data have been reviewed elsewhere<sup>176</sup> and will not be further discussed in this clinically oriented review.

Unfortunately, EEG recordings in humans have only occasionally been reported in cases of known or suspected chronic cyanide toxicity. Sandberg described a case study of suspected chronic cyanide exposure in a goldsmith apprentice who used KCN for cleaning gold articles.<sup>211</sup> The patient presented with headache, general malaise, and paresis in the left arm and leg. Blood cyanide was mildly elevated at 10 to 12  $\mu\text{g}$  per 100 mL of blood, and the EEG was described as ex-

hibiting “diffuse frontal theta activity,” a nonspecific finding. Treatment consisted of physical therapy and hydroxocobalamin therapy. After several months, blood cyanide levels dropped to 2 to 3  $\mu\text{g}$  per 100 mL of blood, the EEG normalized, and paresis diminished, suggesting a diagnosis of chronic cyanide exposure. Diffuse frontal theta activity in the EEG is not specific to cyanide exposure, however; it has also been reported in a group of 13 people who worked with various toxic substances.<sup>212</sup> Zaknun et al also report EEG findings of diffuse, abnormal beta activity more pronounced in frontal and front-temporal regions but no focal epileptic activity in the case summarized previously.<sup>163</sup> Animal cyanide exposures provide evidence of transient EEG changes in the dog,<sup>213</sup> but in other studies, single or repeated IV infusions resulted in progressive deterioration in the EEGs.

Disturbances of the energy homeostasis and ion concentrations in cardiac tissue from cyanide result in reversal of the normal directions and magnitude changes in cellular membrane currents. These effects in turn change the morphology of the action potential and ECG. These disturbances eventually lead to ventricular fibrillation, the usual endpoint in the effect of cyanide on the heart. The negative trending T-wave in the ECG indicates pathological behavior, the abnormal repolarization of the ventricle.

The computer simulation demonstrates that pharmacologic intervention has the potential to reverse or minimize the impact of cyanide on cardiac electrophysiology. Further research is needed to validate the conclusions of simulation. Simulation can focus research and also provide leads for successful interventions. However, no drugs have yet been assessed for their specific utility to reverse cyanide-induced perturbations in cardiac physiology. Oxygen clearly enhances antidotal efficacy, and it is possible that drugs to enhance delivery of oxygen into the mitochondria will soon improve cardiac recovery.

The general psychological impact of terrorism and

actual or suspected chemical agent exposure on the behaviors of human populations has received much attention, particularly after September 11, 2001.<sup>214-217</sup> Clearly, individual psychological reactivity is a critical determinant of situational outcome. In addition, cyanide's well-earned reputation as a fear-inducing substance will likely enhance fear responses to a threatened or actual cyanide deployment. Rapid chemical detection or other means of confirming or dismissing suspicion of chemical exposure will advance application of appropriate medical and logistical procedures. Some individuals suffering from acute panic disorder have presented with symptoms similar to respiratory-distress responses, such as those seen following cyanide exposure (eg, respiratory gasp and dizziness).<sup>65,218-220</sup> Responders should expect some initial difficulty in distinguishing lesser cyanide intoxications from situational stress reactions.

Relatively little is known about the psychobehavioral effects of specific cyanide antidotes beyond the prevalent hypotensive response to the nitrite methemoglobin

formers. In humans, the behavioral effects of p-aminopropiophenone (PAPP), a methemoglobin-forming aminophenone, have been reported. Paulet et al report no untoward effects on intellectual functioning, subjective feeling of personal comfort, or physical condition in individuals with up to 48% methemoglobin following oral administration of PAPP.<sup>221</sup> A small percentage of individuals were insensitive to PAPP, however, and did not develop methemoglobinemia. Bodansky and Hendley reported that up to 30% methemoglobin did not adversely affect visual detection threshold in PAPP-treated subjects, although immediately after exercise, an average of 15% methemoglobin was associated with a significant decrease in visual threshold.<sup>222</sup> Tepperman et al reported an interaction between exercise load and muscle oxygenation changes following PAPP administration in human volunteers.<sup>223</sup> Although impaired oxygenation of muscle was observed during moderate exercise in subjects with 10% to 20% with light exercise, no effect on muscle oxygenation was observed with 7% to 17% during light exercise.

## SPECIFIC ANTIDOTES

The clinical use of most antidotes is based on animal experiments<sup>224</sup> and on extrapolations made from reported clinical cases. Antidotes are usually unnecessary, if the casualty is conscious. 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. General advantages and disadvantages of each antidote are listed in Table 11-5; however, objective comparison of antidote efficacy is hampered by the following factors<sup>126,225</sup>:

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

### Methemoglobin Formers

#### *Sodium Nitrite and Amyl Nitrite*

Sodium nitrite ( $\text{NaNO}_2$ ) has been used successfully as a cyanide countermeasure in humans for many years,<sup>226</sup> usually in combination with other antidotes such as amyl nitrite, thiosulfate, and oxygen. Particular side effects include hypotension and excessive meth-

emoglobin formation.<sup>227-229</sup> Kiese and Weger described serious side effects of sodium nitrite in humans. They noted that the recommended dosage for the treatment of cyanide poisoning (4.0 mg/kg) resulted in an average of 7% methemoglobin in adults. One subject who received 12.0 mg/kg developed methemoglobin levels reaching ~30% and experienced undesirable cardiovascular effects. Children must be dosed on a milligram per kilogram basis with adjustment for anemia if present. The recommended dose for children is 6.6 mg/kg (0.2 mL/kg of 3% solution) although the lesser dose of 4 mg/kg (0.13 mL/kg of 3% solution) can be used. Patients can be redosed with half the original dose, but redosing should not be done until methemoglobin levels are ascertained to be under 25%. Ideally, non-invasive monitoring for methemoglobinemia should be used if available.

Sodium nitrite for injection is made by dissolving solid sodium nitrite with water to make a final solution of 3%. Sodium nitrite is stable in light. It is incompatible with acetanilide, antipyrine, caffeine, citrate, chlorates, hypophosphites, iodides, mercury salts, morphine, oxidizing agents, permanganate, phenazone, sulfites, tannic acid, and vegetable astringent decoctions, infusions, or tinctures. The shelf life of sodium nitrite solution for injection is 5 years. The manufacturer recommends it be stored at temperatures between 15°C and 30°C; testing for stability in elevated temperatures has not been done. Sodium nitrite blood levels have not been measured during antidote therapy, and most pharmacokinetic parameters have not

**TABLE 11-5**  
**ANTIDOTES USEFUL IN ACUTE CYANIDE POISONING**

Antidote	Advantages	Problems
Methemoglobin-forming agents	Potent, effective	Risk of impairment of oxygen delivery to the tissue, hypotension
Sodium thiosulfate	Efficient, safe	Delayed action
Cobalt EDTA	Very potent, effective if late	Numerous side effects
Hydroxycobalamin	Safe, no methemoglobinemia	Expensive therapy, red discoloration of urine, less potent

EDTA: ethylenediaminetetraacetate

Data sources: (1) Meredith TH, 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. (2) Mégarbane B, Delabaye A, Goldgran-Tolédano D, Baud FJ. Antidotal treatment of cyanide poisoning. *J Chinese Med Assoc*. 2003;66:193–203.

been determined.

At least two studies suggest that sodium nitrite's efficacy is accounted for by other mechanisms in addition to methemoglobin formation. Vasodilation with improved capillary blood flow may contribute to its efficacy. Treatment of acquired methemoglobinemia from sodium nitrite poisoning in circumstances similar to those described above may involve only supplemental oxygenation and observation if the patient is asymptomatic and the methemoglobin level is 20% to 30% or less. With higher methemoglobin levels or in symptomatic patients, intravenous infusion of methylene blue at the usual dose of 0.1 to 0.2 mL/kg of a 1% solution may be necessary. Toluidine blue can also be used. Exchange transfusion may be required if severely poisoned patients are not responsive to the above measures.

Amyl nitrite is applied via inhalation and is the only simple first-aid measure for serious cyanide intoxication. Neither it nor sodium nitrite should be given to casualties who are awake and ambulant.<sup>19</sup> Most protocols call for 30 seconds of inhalation of an ampule per minute (30–60 seconds between ampules) by forced inhalation with attention paid to blood pressure drop or elevated heart rate. It can be delivered into the respiratory system by breaking an ampule into an Ambu Bag (Ambu, Copenhagen, Denmark) or other ventilation support system. Amyl nitrite is a less powerful producer of methemoglobin than is sodium nitrite. Its duration of action is approximately 1 hour. Amyl nitrite is usually followed by sodium nitrite infusion. Amyl nitrite is also a vasodilator, and hypotension should be treated with volume expansion. Ampules last for only 24 months. They must be protected from light and should be stored at cool (below 15°C/59 °F) conditions. Amyl nitrite capsules were shown to be stable for brief (1 day) periods of freezing.<sup>230</sup> Storage

at high temperatures risks rupture of ampules and chemical decomposition of the drug. Amyl nitrite is highly flammable and must be stored accordingly.

#### *Other Methemoglobin-Forming Drugs*

A German-developed compound, 4-dimethylaminophenol (4-DMAP), is a methemoglobin-forming aminophenol that rapidly stimulates methemoglobin formation. It 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 and 30% in 10 minutes. 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>231</sup>

The disadvantages of 4-DMAP are necrosis in the area of injection after intramuscular administration, phlebitis at intravenous infusion sites, and possible nephrotoxicity.<sup>232</sup> Overdoses of 4-DMAP have resulted in excessive methemoglobinemia and occasional hemolysis. Even the usual 4-DMAP dosing of 3.25 mg/kg of body weight has resulted in a methemoglobinemia of 70%. The compound must be stored in opaque containers, with a maximum storage time of 3 years.

Kiese and Weger demonstrated that 4-DMAP increased methemoglobin levels in a variety of animal species, including dog, cat, mouse, and rabbit.<sup>228</sup> Methemoglobinemia was also demonstrated by these authors in humans, whereby 4-DMAP (3.25 mg/kg, IV) yielded a maximum methemoglobin level of 30%, approximately 20 minutes after injection. The compound produces methemoglobinemia more rapidly than the nitrites and the aminophenones,<sup>228</sup> and is currently the primary specific antidote for cyanide toxicity in Germany. Although a potent and rapid methemoglobin former, 4-DMAP has been shown to produce tissue ne-

crisis at the site of injection<sup>57,233</sup> and may be associated with nephrotoxicity.<sup>234</sup> In a recent report from Germany, 4-DMAP was administered to a subject exposed to methyl isocyanate. Excessive methemoglobinemia ensued (86.7%), followed by major organ failure.<sup>235</sup> The authors recommended against continued use of 4-DMAP as a treatment for cyanide toxicity.<sup>235</sup>

Vandenbelt et al studied a group of aliphatic phenones in dogs and identified PAPP as a potent, short-acting methemoglobin former.<sup>236</sup> In subsequent reports, PAPP was shown to be efficacious against cyanide toxicity in both dogs and rodents.<sup>223,237-239</sup> It was also demonstrated that PAPP formed methemoglobin in humans.<sup>221,222,240</sup> Paulet et al noted the lack of deleterious effects of PAPP on psychological and physiological parameters, although several volunteers failed to respond to PAPP and did not exhibit elevated methemoglobin levels.<sup>221</sup> PAPP has been described as safe and benign, with little effect on the body other than methemoglobinemia.<sup>182</sup> Although methemoglobin formers such as sodium nitrite are generally administered as a treatment for cyanide exposure, the toxicokinetics of the amiphenones may support preexposure prophylaxis.<sup>241</sup> P-aminoheptanoylphenone appears to be the safest of the amiphenones. Baskin and Fricke provide an in-depth discussion on PAPP pharmacology.<sup>227</sup>

### Thiosulfate and Other Sulfur Donors

Thiosulfate is used for multiple conditions, including poisoning with sulfur mustard, nitrogen mustard, bromate, chlorate, bromine, iodine, and cisplatin. In combination with sodium nitrite in a fixed antidotal regimen, thiosulfate has been used for cyanide poisoning. Thiosulfate is also used in combination with hydroxocobalamin. The standard dose of sodium thiosulfate, which is supplied in the standard US 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>186</sup> The pediatric dose equals the adult dose at about 21 kg of body weight. Thiosulfate functions as a sulfane donor to rhodanese and other sulfur transferases. However, rhodanese is located within mitochondria, and thiosulfate has poor ability to penetrate cell and mitochondrial membranes (although one rat study demonstrated that thiosulfate can utilize the dicarboxylate carrier to enter the mitochondria). Whereas rhodanese is available in excess in the body, relative deficiency of a sulfur donor capable of entering the mitochondria is the rate-limiting factor for this route of detoxification in cyanide poisoning. When a cyanide formulation is infused simultaneously with thiosulfate in dogs, a cyanide-sensitive species, the cyanide is detoxified

“real time” (the actual time for the physical process of cyanide detoxification to take place in the body). The mechanism of thiosulfate protection appears to be the exceptionally rapid formation of thiocyanate in the central compartment, which limits the amount of cyanide distributed to sites of toxicity. The mechanism of action of thiosulfate, when given after cyanide exposure, is uncertain. Nevertheless, thiosulfate substantially enhances survival from cyanide. There are no specific contradictions to the use of sodium thiosulfate; its toxicity is low and adverse effects are mild. Side effects include nausea and vomiting with rapid infusion, headache, and disorientation. Rapid conversion to thiocyanate has resulted in reported hypotension. Excess thiosulfate is cleared renally. Premixed sodium thiosulfate can be stored for a maximum of 3 years. Solid thiosulfate may be stored in an airtight container for 5 years without change.

### Hydroxocobalamin

Limitations associated with sodium nitrite (eg, hypotension and excessive methemoglobinemia) treatment and a desire for safer approaches to potentially cyanide-intoxicated fire casualties have increased domestic interest in identifying alternative or complementary approaches to treat cyanide poisoning.<sup>228,242-246</sup> Hydroxocobalamin is a major option.<sup>145,247,248</sup> Hydroxocobalamin is a registered antidote for cyanide poisoning in several European and Asian countries, and was approved by the Food and Drug Administration in 2006 under the animal efficacy rule. The efficacy of hydroxocobalamin versus the known effectiveness of the nitrite and thiosulfate combination in severe intoxications is still under study at the US Army Medical Research Institute of Chemical Defense. Current doctrine in France is to initially administer hydroxocobalamin (5 g in 200 mL saline, IV) over 15 to 45 minutes. Baud<sup>249</sup> has indicated that recovery often begins to occur before the full complement of hydroxocobalamin has been administered. Up to 15 g of hydroxocobalamin has been used in some clinical cases.<sup>249</sup>

The most common side effect is an orange-red discoloration of the skin, mucous membranes, and urine that lasts until the hydroxocobalamin is cleared from the body over several hours to a couple of days.<sup>250</sup> In rare instances, urticaria can result from hydroxocobalamin administration. Hydroxocobalamin is volumetrically inefficient, and infusion volumes are very large. The available packaging requires infusion of two full reconstituted bottles for the initial dose of 5 grams. Hydroxocobalamin must be protected from light and maintained at temperatures below 25°C. Its shelf life is 3 years. It is incompatible with reducing or basic substances such as ascorbic acid, saccharose, sor-

bitol, and other B vitamins. Its presence in serum can interfere with some laboratory measurements. Large volumes of hydroxocobalamin may cause significant amounts of cobalt to be released later, similar to the effect of cobalt EDTA.

### Cobalt Salts

A commercial preparation of the cobalt salt of EDTA, Kelocyanor, is available in Europe but not in the United States. Cobalt salts, which are chelating agents, directly bind cyanide in the periphery but likely also cross the blood-brain barrier. Cobalt EDTA is administered intravenously.<sup>251</sup> In comparison studies against nitrite and hyposulfite, cobalt EDTA was thought to be superior<sup>64</sup>; however, in other studies the nitrite-thiosulfate combination was found to be

superior.<sup>252</sup> No human volunteer studies or clinical trials of cobalt EDTA have been done. Following administration of cobalt EDTA, cyanide is excreted with cobalt in the urine; no follow-on treatment with thiosulfate is required.

The drawback of cobalt compounds is their severe toxicity, particularly when administered in the absence of confirmed cyanide intoxication. Massive urticaria with swelling of the face, lips and neck; convulsions; chest pains; dyspnea; and hypotension have been reported. Severe toxicity from cobalt can be seen even after initial recovery from acute cyanide poisoning. The usual dose of cobalt EDTA is one ampule followed by 50 mL of dextrose solution (500 g/L). Cobalt EDTA has a shelf life of 3 years at temperatures under 25 °C. It should be stored in the dark; if stored in the light, its color lightens, but it is otherwise unchanged.

### SUMMARY

Cyanide 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. During World War II it was deployed effectively by the Nazi regime against internal enemies. It may have been used by Iraq against the Kurds in the Iran-Iraq War during the late 1980s, although no objective evidence supports this premise. Cyanide's widespread industrial use and ready availability provide the major opportunity for human injury today, particularly for exposure to large populations. Muslim extremists worldwide have been intercepted multiple times with cyanide and specific plans for its deployment.

Cyanide causes intracellular hypoxia by inhibiting the intracellular electron transport mechanism via binding to cytochrome-*c*-oxidase. This action stops aerobic metabolism and forces a shift to anaerobic metabolism. The nervous system and the heart are particularly intolerant of ATP deficiency. The liver is particularly tolerant of cyanide exposure, probably because of its generous supply of rhodanese. Cyanide additionally binds multiple other enzymes and nonen-

zymatic proteins, although the clinical consequences of these actions are less well understood. The dose toxicity curve for cyanide is steep, with very large exposures, particularly respiratory, causing rapid onset of central nervous system toxicity with the potential for death within several minutes.

Rapid removal from further exposure, administration of general support measures including 100% oxygen, and administration of specific antidotes in critically impaired casualties effectively reverse the effects of exposure. Multiple antidotes are available worldwide. The most widely used are nitrites with thiosulfate. This combination has demonstrated efficacy. Hydroxocobalamin, used in France and a few other countries, has now been introduced into the US formulary. Cobalt EDTA is falling out of favor because of its high side-effect profile. The only antidote formulated for use by nonphysician emergency responders is amyl nitrite. No antidotes are currently carried by US military medics or corpsmen. Current research efforts are focused on improving the understanding of cyanide's mechanisms of toxicity and developing improved antidotes, with better safety profiles and utility in spartan environments.

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