therefore is manufactured in 10-mg injectors for IM use and given to U.S. forces for this purpose (Fig. 262e-5*B*). Civilian agencies are stockpiling this field product (convulsive antidote for nerve agent, CANA), which generally has not been used in hospital practice. Extrapolation from animal studies indicates that adults will probably require 30–40 mg of diazepam given IM to stop nerve agent–induced status epilepticus. In the hospital or in a small child unable to receive the autoinjector, IV diazepam may be used at similar doses. The clinician may confuse seizures with the neuromuscular signs of nerve agent poisoning. In the hospital, early electroencephalography is advised to distinguish among nonconvulsive status epilepticus, actual seizures, and postictal paralysis. Animal studies have shown that the most effective benzodiazepine in this situation is midazolam, which is not FDA-approved for seizures. At the time of this writing, a new drug application for use of midazolam against seizures has been submitted to the FDA. The superiority of IM midazolam to IV lorazepam in a large community trial of status epilepticus suggests that emergency personnel will soon incorporate autoinjectors into routine clinical practice and that these field products will thus become integrated into clinical medicine.

Peripheral neuropathy and the so-called intermediate syndrome, which are prominent long-term effects of insecticide poisoning, are not described in nerve agent survivors.

Recent research has explored approaches leading to transient "immunity" and eventually to biologic products that will be protective against lethal nerve agents yet be devoid of side effects. A novel approach is to use enzymes to scavenge these highly toxic nerve agents before they attack their intended targets. The accumulated work has shown that if a scavenger is present at the time of nerve agent exposure, toxicant levels are rapidly reduced. This reduction is so rapid and profound that the need to administer a host of pharmacologically active drugs as antidotes is, according to laboratory studies, eliminated.

CYANIDE

Cyanide (CN^-) has become an agent of particular interest in terrorist scenarios because of its applicability to indoor targets. In recent years, for example, attacks with this agent have targeted the water supply of the U.S. Embassy in Italy. The 1993 World Trade Center bombing in New York may have been intended as a cyanide release as well.

Hydrogen cyanide and cyanogen chloride, the major forms of cyanide, are either true gases or liquids very close to their boiling points at standard room temperature. Hydrogen cyanide gas is lighter than air and does not remain concentrated outdoors for long; thus it is a poor military weapon but an effective weapon in an indoor space such as a train station or a sports arena. Cyanide is also water-soluble and poses a threat to the food and water supply from either accidents or malign intent. It is well absorbed from the gastrointestinal tract, through the skin, or via inhalation—the preferred terrorist route. Cyanide smells like bitter almonds, but 50% of persons lack the ability to smell it.

Unique among CWAs, cyanide is a normal constituent of the environment and actually is a required cofactor in many compounds important in metabolism, including vitamin B_{12}. Cyanide is present in many plants, including tobacco; therefore, smokers, for instance, chronically carry cyanide at three times the usual level. Humans have evolved a detoxification mechanism for cyanide. Cyanide poisoning results if a large challenge of CN^- overwhelms this mechanism, while treatment of cyanide poisoning exploits it.

Mechanism Cyanide directly poisons the last step in the mitochondrial electron transport chain, cytochrome a3, which results in a shutdown of cellular energy production. Tissues are poisoned in direct proportion to their metabolic rate, with the carotid baroreceptors and the brain—the most metabolically active tissues in the body—affected fastest and most severely. This poisoning results from cyanide's high affinity for certain metals, notably Co and Fe^{+++}. Cytochrome a3 contains Fe^{+++}, to which CN^- binds. Cyanide-poisoned tissues cannot extract oxygen from the blood; even though pulmonary oxygen exchange and cardiac function are preserved, cells die of hypoxia—i.e., of histotoxic rather than cardiopulmonary cause.

Clinical Features Hyperpnea occurs ~15 s after inhalation of a high concentration of cyanide and is followed within 15–30 s by the onset of convulsions and electrical status epilepticus. Respiratory activity stops 2–3 min later, and cardiac activity ceases several minutes after that. Exposure, especially via inhalation, to a large challenge of CN^- can cause death in as little as 8 min. Smaller challenges will cause symptom spread over a longer period; very low doses may produce no effects at all because of the body's ability to detoxify small amounts. Cyanogen chloride additionally produces mucous membrane irritation. Many but not all patients have a cherry-red appearance because their venous blood remains oxygenated.

Differential Diagnosis In a mass casualty incident caused by a chemical agent, the primary differential diagnosis of cyanide poisoning will be nerve agent poisoning. Cyanide-poisoned patients lack the prominent cholinergic signs seen in nerve agent poisoning, such as miosis and increased secretions. The cherry-red appearance often seen in cyanide poisoning is never seen in nerve agent poisoning. Cyanosis, confusingly, is *not* a prominent early sign in cyanide poisoning.

TREATMENT CYANIDE

Treatment of cyanide poisoning may require simply evacuation of the patient from the source of contamination. Decontamination of a true gas, other than clothing removal to avoid gas trapped in clothing air cells, is probably not a major concern.

Oxygen, supplied via mask, nasal cannula, or endotracheal tube, has been shown to benefit patients, although the benefit is not explained by the known mechanism of action of CN^-.

Cyanide antidotes exploit the body's innate detoxification mechanism, the hepatic enzyme rhodanese. They also exploit cyanide's affinity for certain metal ions. Antidote recommendations are summarized in **Table 262e-4**.

The classic two-step cyanide antidote kit includes two IV solutions: sodium nitrite and sodium thiosulfate. It may also include amyl nitrite perles for inhalation. Nitrites are methemoglobin formers; when administered to a patient, nitrite converts a fraction of the body's hemoglobin into methemoglobin by converting heme iron from Fe^{++} to Fe^{+++}. CN^- has a greater affinity for methemoglobin Fe^{+++} than for cytochrome a3. As a result, administration of nitrite creates a "sink" of cyanmethemoglobin; formation of methemoglobin pulls CN^- off mitochondrial cytochrome a3, allowing cellular respiration to resume. Recent work suggests that nitrites may also work via a second mechanism involving the neurotransmitter nitrous oxide; if so, this mechanism may explain why cyanide-poisoned patients improve after nitrite administration faster than is explained by the known rate of methemoglobin formation.

Nitrite administration may save the patient acutely but creates an unstable pool of cyanmethemoglobin, the elimination of which requires a sulfur donor: sodium thiosulfate. Sodium thiosulfate donates sulfur to the reaction catalyzed by rhodanese; cyanide is converted to thiocyanate, a compound the body eliminates harmlessly in urine. Sodium thiosulfate alone may be administered to fire victims, whose oxygen-carrying capacity is already reduced and in whom the administration of nitrite may form so much methemoglobin as to render the blood unable to carry oxygen at all.

Hydroxocobalamin, or vitamin B_{12a}, has recently been approved for use as an alternative cyanide antidote. Unlike sodium nitrite and sodium thiosulfate, it must be reconstituted at the scene. Hydroxocobalamin lacks the propensity of nitrites for hypotension, but many cases in which it has been beneficial have also required the use of sodium thiosulfate. Hydroxocobalamin causes an orange discoloration of the skin that is of no functional significance.

All of these antidotes require the placement of an IV line. Amyl nitrite is currently the only non-intravenous cyanide antidote available and has never been formally approved by the FDA. Amyl nitrite