III. BIOLOGIC EFFECTS OF EXPOSURE

Substances Presenting Exposure

The physical and chemical properties of hydrogen cyanide (HCN) are given in Table XIV-1. The boiling point of liquid HCN is sufficiently close to room temperature that it may be found in the workplace both as a liquid and as a gas.

The compounds herein denoted as cyanide salts are (1) inorganic, (2) appreciably dissociated or ionized in aqueous solution to produce cyanide ion or HCN, and (3) commercially important. The chemical and physical properties of various other cyanide containing compounds are listed in Table XIV-2. Those of major importance are described below.

Occurrence and Use

HCN is a colorless gas [1] or a colorless or bluish-white liquid [1,2] with a faint, characteristic odor of bitter almonds [2,3,4] perceptible to some people. [3,4] Kirk and Stenhouse [5] reported that 88% of 244 persons tested could smell hydrogen cyanide but that in a fourth of these, the determination was made only with difficulty.

The glucoside amygdalin which occurs in nature in some plants, notably almonds, [3] readily yields HCN upon hydrolysis. Recently, attention has been brought to the presence of HCN in automobile emissions. [6,7]

HCN is manufactured in the United States from coke-oven gas by reaction with sodium carbonate, from cyanide salts by reaction with acid, by the decomposition of formamide, from the reaction of ammonia, air, and

natural gas, or, most commonly, from the reaction of methane and ammonia under specific controlled conditions. [8]

The great bulk of the HCN synthesized is used directly in the same process system. [8] In 1973, the estimated consumption of HCN in the United States was approximately 310,000 short tons. [9] HCN is used primarily in the production of chemical intermediates for the manufacture of synthetic fibers, [8,10] plastics, [8] cyanide salts [8,10] and nitrites; in the fumigation of ships, [11,12,13,14,15] railroad cars, [14] buildings, [10,13,14,15,16,17,18] orchards, [10,19] tobacco, [20] and various foods [14]; it may be produced in electroplating, [21,22,23] metallurgy, [24,25,26] and photographic development. [27]

HCN is commonly sold as a technical grade liquid which assays between 96 and 99.5% HCN, as 5% and 10% solutions, as a 2% USP grade solution, or as a gas. [8] All grades usually contain a stabilizer (usually 0.05% phosphoric acid) to prevent explosive decomposition. When not pure or stabilized, it may polymerize spontaneously with explosive violence. [8] It is commonly sold or shipped in tanks, 75-lb cylinders, drums, or 5-lb bottles. [8]

Sodium cyanide, NaCN, is a white crystalline solid at normal temperature. [28] Currently, NaCN is manufactured chiefly from coke-oven gas, [8] by the reaction of HCN and NaOH, [29] or by the reaction of sodium carbonate, carbon, and ammonia. [28] Aqueous solutions of NaCN are slightly hydrolyzed (Kh = 2.5 x 10 exp(-5)) at ordinary temperatures to produce HCN according to the reversible reaction shown below. [28]

$$NaCN + H2O \rightleftharpoons NaOH + HCN$$

In the presence of any source of hydrogen ions in quantity, eg, strong mineral acid, the production of HCN from cyanide salts becomes both rapid and large. Above 50 degrees C, an irreversible decomposition to formate and ammonia, as shown below, becomes important. [28]

$$NaCN + 2\ H2O \longrightarrow NH3 + HCOONa$$

In the presence of NaCl, the hydrolysis of NaCN to HCN is increased at temperatures below 80 C, but decomposition to ammonia and formate is retarded. [28]

Sodium cyanide is marketed as a powder, granule, flake or block in pillow-shaped pieces weighing about 1 oz, and as a 30% aqueous solution. [28] Solid sodium cyanide is packed in steel or fiber drums, and the aqueous solution is shipped in tanks by truck or rail. [28,30] Potassium cyanide, KCN, is a white crystalline, deliquescent, solid. KCN is produced by methods similar to those for NaCN. [28,29]

The chemical reactivity of KCN is similar to that of NaCN. [28] Hydrolysis to HCN, as was the case with NaCN, is slight (Kh = 2.54 x 10 exp(-5)). [28] Potassium cyanide is sold in forms similar to those of NaCN but because KCN is more expensive, its world production for 1963 was only 5,000 tons. [28]

Calcium cyanide, Ca(CN)2, is also called "black cyanide" and is the only commercially important alkaline earth cyanide. [31] The hydrolysis of Ca(CN)2, which takes place in two steps, as shown below, is complete. [31] The resulting calcium hydroxide has dissociation constants of 3.74 x 10 exp (-3) and 4.0 x 10 exp (-2) but is much less soluble in water at 0 degrees C than sodium hydroxide [1,32] so that its aqueous solutions are

not as alkaline. For example, the pH of an aqueous solution of Ca(OH)2 saturated at 25 degrees (about 0.0203 M) is 12.4, while the pH of a 0.0125 M (0.05%) solution of NaOH is approximately 12. [33,34]

$$Ca(CN)2 + H2O \longrightarrow Ca(OH)CN + HCN$$

$$Ca(OH)CN + H2O \longrightarrow Ca(OH)2 + HCN$$

The basic cyanide is similar in general appearance and properties to Ca(CN)2. [31] HCN is released from Ca(CN)2 by water or even water vapor present in relatively humid air. Calcium cyanide does not melt but forms calcium cyanamide (CaCN2) on heating above 350 degrees C. [31]

Calcium cyanide, which is manufactured [31] in large tonnages, is made by heating crude calcium cyanamide, which contains elemental carbon, in an electric furnace above 1000 C in the presence of sodium chloride. [31] Rapid cooling apparently prevents the reversion to calcium cyanamide. [31] It is manufactured primarily in Canada, South Africa, and East Germany and sold as flakes or blocks. There is also some production elsewhere in Europe and Japan. [31]

Sodium cyanide is used in the extraction of gold and silver, [35,36, 37, 38] heat treating of metals, electroplating, hardening of metals, coppering, zincing, bronzing, manufacture of mirrors, soldering, manufacture of or as a pesticide, photography, fumigation, [39,40] and the preparation of derivative chemicals. [8] Potassium cyanide is used in the extraction of gold and silver, [35,36,37,38,41] in electroplating, gilding of precious metals, soldering, hardening of metals, coppering, zincing, bronzing, manufacture of mirrors, preparation of derivative chemicals, photography, fumigation, [39,40] and in laboratory testing. Calcium

cyanide is used as a fumigant, [39,42,43,44] stabilizer for cement, in the preparation of derivative chemicals, in the manufacture of steel, in gold extraction, and in case hardening. [31]

Extent of Exposure

Some occupations which entail possible exposure to dangerous concentrations of HCN and/or a cyanide salt are listed in Table XIV-3. The number of workers with potential exposure to HCN has been estimated by NIOSH to be approximately 1,000. The number of workers with potential exposure to NaCN has been estimated by NIOSH to be 20,000. The number potentially exposed to KCN, and Ca(CN)2 has not been estimated by NIOSH.

Historical Reports

The first experimental generation of HCN was reported by Scheele [45] in 1782-3. He reported that aqueous solutions of HCN had a peculiar, not unpleasant, smell and a slightly sweet taste. Scheele described many chemical properties of HCN and found that mixtures of air and HCN burned readily.

In 1884, De Tatham [46] reported a case of temporary hemianopsia after exposure to HCN. The woman affected had used a dilute HCN solution to clean some gold lace. The author [46] presumed that her only exposure was to HCN vapor. However, the possibility cannot be excluded that the intimate contact of the HCN solution with her skin resulted in skin absorption.

The first uses of the gas as a fumigant were in 1886 to control scale on citrus trees in California, [19] in 1898 to kill vermin in railway

cars, [11] in 1901 to kill bed bugs in prisons, [11] and, after 1910, for the fumigation of the holds of ships. [11]

Stock and Monier-Williams [11] observed several cases of occupational exposure to HCN used in fumigation in 1923. In one report, sailors were engaged in dropping cyanide eggs into vats of acid laid out in various locations on board ships and were overcome by HCN gas, presumably from other parts of the ship; five died. A second case was that of a would-be thief who entered the Krupp works in Essen, Germany, while it was being fumigated. Two other cases were due to pipe or duct connections to space adjoining that being fumigated. In other cases, workers entered spaces and were quickly overcome by "pocketed" HCN fumes in places that had been presumed to be safe.

In 1919, Fuhner [12] reported the death of a mate of a Swedish vessel, whose cabin had been fumigated with HCN. He returned to the ship the same day accompanied by a woman who remained in the cabin from 11:30 pm to 4:30 am. She said she was overcome, could scarcely stand upon reaching the open air, and had to sit down and rest before proceeding home. The mate was found dead at 7:30 the next morning, his body still warm. The author suggested that the bedding in the cabin had absorbed a good deal of gas and that the concentration of HCN in the air was too low to cause death in 5 hours, but sufficient to do so in 8.

Bernstein and Avital [20] reported an accidental mass poisoning in 1960 in Israel following fumigation of a tobacco warehouse with HCN. The warehouse was sealed for 3 days for effective fumigation. Windows were then opened and remained so for 48 hours, at which time they were closed so that a second fumigation with a 6.6% solution of an unspecified oil-soluble

fumigant could be performed. The building remained closed until the next morning. By 8:00 am that day, 46 of the 53 people who had entered the warehouse that morning had been affected. The symptoms of those poisoned included headache, dizziness, gastrointestinal upset, dyspnea, and heart palpitations.

The day after the incident, a test of the air in the warehouse was made using benzidine and copper acetate test papers. HCN was not found in the general room air but was detected in the vicinity of the tobacco bales in undetermined concentrations.

The problem of commercial fumigation of buildings as well as ships was discussed in a 1935 report by Cousineau and Legg [16] detailing their experiences in Montreal and Detroit, respectively. They noted that 1 death was reported as a result of every 2,000 fumigations in Detroit. They further noted that the addition to HCN of lacrymatory gases, such as CNCl and chloropicrin, was beneficial in the protection of public health. There apparently was controversy among others as to whether or not such additives were beneficial. [16]

There were several early cases of poisoning resulting from the inhalation of inorganic cyanide aerosol or contact with cyanide solutions. [47,48,49,50,51] In 1878, Souwers [50] reported the nonfatal poisoning of a photographer who had been working with both solid KCN and KCN solutions and complained of soreness of the scalp, heaviness of the head, sleeplessness, pain in the lumbar region, delirium, ringing in the ears, swelling of the upper eyelids, loss of appetite, nausea, constipation, and chills and cold sweats upon awakening from cat-naps. In addition, he complained of shortness of breath. Souwers removed him from KCN exposure and treated his symptoms. The patient made a full recovery in 3 days.

Skin absorption of inorganic cyanide was implicated in cyanide poisoning as early as 1905, when McKelway [51] reported a case of a woman hairdresser who moistened her fingers and rubbed them with solid KCN in an effort to remove a stain from a silver-based dye. She experienced vertigo and difficulty in breathing within 5-10 minutes and subsequently collapsed into an unconscious state. She was revived, treated with 2 oz whiskey, strychnine, atropine, and morphine, and recovered despite the therapy administered.

In 1913, Rambousek [49] noted that skin contact with cyanide solutions had been sufficient to cause symptoms of cyanide poisoning among electroplaters, especially among those with deep ulcerations and fissures from working with caustic soda. No further elaboration of systemic symptoms was offered.

Similarly, the International Labour Office [48] reported several cases of dermatitis which occurred prior to 1912 in the United States as a result of direct contact of the skin with cyanide solutions. In 1923, seven men were poisoned while emptying casks of KCN. [48] One died.

Industrial cases reported by the International Labour Office [47] in 1930 included a sudden death from inhalation of HCN escaping from a leaking pipe in a sodium cyanide factory, several severe cases of intoxication in a factory adjacent to a metal-treating plant, and several cases associated with factory or home fumigation operations. It is likely that many of these illnesses were the result of exposure separately or concomitantly to HCN.

The ingestion of KCN solutions has been a suicidal method since the nineteenth century. [51,52] Accidental ingestions in the workplace have

been rarely reported, but the International Labour Office [48] did report a case which occurred in 1920 in Germany where a female jewel worker died after drinking from a bottle which was previously washed with a solution of KCN.

Metabolism and Theoretical Considerations

It appears that HCN and cyanide salts have a common mechanism of action, ie, inhibition of cytochrome oxidase via reaction of its ferric iron with the cyanide ion in vivo.

Once absorbed into the body, cyanide can form complexes with heavy metal ions. [29,53,54] Formation of these complexes can rapidly cause disturbances in enzyme systems in which heavy metal ions, alone or as part of organic molecules, act as cofactors. [29,53,54]

Albaum et al [55] published in 1946 an in vitro study of the competition of methemoglobin and cytochrome oxidase for cyanide. Cytochrome c absorbs radiation at 550 nanometers (nm). In the presence of cytochrome oxidase, the optical density at 550 nm decreases at a rate directly proportional to the activity of cytochrome oxidase. This rate of change was determined in the presence of cyanide, demonstrating the ability of cyanide to inhibit cytochrome oxidase activity. Additions of methemoglobin, in which the iron had been oxidized electronically to the ferric state, to a solution containing cytochrome c, cytochrome oxidase, and cyanide were found to increase the activity of cytochrome oxidase, thus reversing the inhibitory effect of cyanide. The authors also found that the addition of cyanmethemoglobin to a solution of cytochrome c and cytochrome oxidase had no immediate effect on enzyme activity, but after a

few minutes the enzyme became increasingly inhibited. Thus, the authors demonstrated in vitro the abilities of cytochrome oxidase and methemoglobin to compete in a reversible fashion for the cyanide ion.

In a 1958 survey, Dixon and Webb [56] found that the concentration of cyanide necessary for inhibition of cytochrome oxidase was 2-6 orders of magnitude less than those required for inhibition of other enzymes. The interference of CN with many different enzyme systems other than those involved in respiration may thus contribute to its toxicity.

Schubert and Brill [57] in 1968 measured the inhibition and recovery of liver cytochrome oxidase in mice, rats, and gerbils after the intraperitoneal administration of KCN. Inhibition of the enzyme was found to reach a maximum 5 to 10 minutes after the cyanide injection. Depending on the dose, the enzyme activity returned to normal 5 to 20 minutes after maximal inhibition in mice but required up to 1 hour or more in the rat and gerbil. Interestingly, they found that the abilities of mice and rats to tolerate divided doses of cyanide depended on the total dose as well as on the time-dependent degree of enzyme inhibition. For example, they found that mice invariably survived a single sublethal dose of 6 mg/kg of KCN but not two doses of 3 mg/kg given 6 minutes apart or three doses of 2 mg/kg given at 6 minute intervals. They further showed that sodium thiosulfate and nitrite were able to reactivate liver cytochrome oxidase within minutes when administered to cyanide-treated rats and mice.

This mechanism of action was reported [58] in 1971 to be sufficiently well understood to be traceable from the initial lesion through the pathophysiologic responses to the clinical picture. The chain

of events is shown in Table XIV-4. Further, unless death intervenes, most of the HCN absorbed or formed in the tissues by biotransformation of cyanogenic substances is converted to the much less toxic thiocyanate which is then excreted, mainly in the urine. [58,59,60] The reaction for this conversion, which takes place in the presence of rhodanese, a sulfur transferase enzyme, is shown below. The reaction is reversible in the presence of thiocyanate oxidase, [61] so that if excretion of thiocyanate is not prompt there may be some regeneration of cyanide.

$$\text{thiosulfate} + \text{cyanide} \underset{\text{thiocyanate oxidase}}{\overset{\text{rhodanese}}{\rightleftharpoons}} \text{sulfite} + \text{thiocyanate}$$

The reaction has been verified in animals. [62] Inhibition of rhodanese, and thereby inhibition of the ability to convert cyanide to thiocyanate, or an inability to excrete thiocyanate [25] is perhaps responsible for the occasionally observed chronic toxicity of cyanide. [17,63,64] Thiocyanate itself has toxic effects, especially inhibition of uptake of inorganic iodide into the thyroid gland for incorporation into thyroxine. [65] Thus, failure to excrete thiocyanate or chronic exposure to elevated concentrations of this ion in the blood may have a deleterious action on the ability and inclination of an employee to perform his work. Other minor pathways for detoxication and excretion include direct excretion as HCN in breath or cyanide ion in secretions, oxidation to formic acid, metal coordination, and condensation with cystine to 2-iminothiazolidine-4-carboxylic acid and excretion. [66,67] The metabolism of cyanide as

summarized by Williams [66,67] is shown in Figure XIV-1. The detoxication rate for HCN injected intravenously in man has been estimated to be about 0.017 mg/kg/min. [68]

Cyanide is present in normal healthy human organs at concentrations ranging up to 0.5 mg/kg. [67] In 1954, Feldstein and Klendshoj [69] found concentrations of zero to 10.7 μg/100 ml (mean 4.8 μg/100 ml) in 10 blood plasma samples. These authors [69] also measured cyanide plasma levels in several cases of mild industrial exposure to cyanide fumes which did not terminate fatally. Their data suggested that the plasma levels returned to the normal range [67] within 4 to 8 hours from the time of exposure. [69] Their data also indicate that the half-life for the conversion of cyanide to thiocyanate from a non-lethal dose in man is between 20 minutes and 1 hour. Thus, as a rough approximation, one-half hour after exposure the plasma level of cyanide was 35 μg/100ml and after an additional half-hour, it was 18 μg/100ml. Normal concentrations of cyanide in tissues and fluids have been attributed to metabolism of foods [52,70,71] and cigarette smoking. [52,67,72,73,74,75,76] In 1973, Pettigrew and Fell [77] however, could not detect a significant difference between the amount of cyanide in the whole blood of smokers and non-smokers, but, as expected, the plasma thiocyanate levels of the smokers were significantly elevated. They suggested that the ratio of cyanide to thiocyanate in body fluids was about 1 to 1000 (1 to 50 in blood plasma [78]) and stated that a more reliable index of cyanide exposure may be measurement of plasma thiocyanate rather than determination of whole blood cyanide.

In 1950, Hardy et al [24] observed a group of 25 workers exposed to HCN who consistently excreted small amounts of thiocyanate, with average

spot urinary thiocyanate concentrations of 6-13 mg/liter. Three workers had no thiocyanate in their urine and three had concentrations of 21, 22, and 29 mg/liter. Those with the high concentrations may have been cigarette smokers. In a study of 10 spot urinary samples from 5 people not employed in industry, the thiocyanate concentration was 0-23 mg/liter; the highest was that from a man who smoked two packages of cigarettes a day.

Radojicic [79] in a 1973 study to be discussed below, found that smokers always eliminated more thiocyanate in the urine than nonsmokers. His values (n=10) were 4.40 ± 1.400 for smokers and 0.17 ± 0.136 mg/liter for nonsmokers. Maehly and Swensson [76] also found that non-smokers exposed to moderate cyanide concentrations in the air, as well as individuals exposed to high cyanide levels, show higher than average concentrations of cyanide and thiocyanate in their urine.

Effects on Humans

Illness and death due to exposure to cyanide have resulted from exposure to gaseous or liquid HCN itself, exposure to the cyanide salts, and exposure to HCN generated by the misuse of cyanide salts. In the last situation, the cyanide salt is converted to airborne HCN by treatment with acids, acid salts [8,29,30] or by water. [29,30] It has been noted [5,29,30] that cyanide salts have the odor of HCN. The rate of HCN release is much greater when acids contact cyanides than when they are treated with water. Considerable amounts of HCN are evolved when moisture acts on a dry alkaline cyanide, particularly $Ca(CN)2$. [42] The rate of such evolution from aqueous solution increases upon heating. [63,80]

Chronic HCN poisoning, at least in the serious or incapacitating form, is rare. Isolated reports [17,24,26,81] have described signs and symptoms of patients suspected of having chronic HCN poisoning. In 1899, Merzbach [81] reported a case of a printing shop worker exposed to cyanide aerosols generated when he placed copper plates in a cyanide bath and allowed an electric current to pass through the solution. His exposure probably also included skin contact with silver cyanide-potassium cyanide solutions. After 1 year of exposure, he experienced severe gastrointestinal symptoms and a generalized disturbance of the nervous system, including behavioral and mental disorders. He continued working for 12 years before he was completely disabled and died 2 years after cessation of exposure. A determination of the degree of his exposure is not possible from the data provided.

Hardy et al [24] in 1950 described two men who may have had chronic cyanide poisoning. Both men complained of headache and weakness or fatigability and were observed to have slight lid lag, enlarged thyroids, and excessive perspiration. One of the two also experienced dizziness and mental confusion, slurring of speech, coughing, sneezing, and occasional abdominal cramps, nausea, vomiting, and coarse tremor of the extremities followed by their temporary paralysis. Both men were exposed to cyanide aerosols generated by case hardening. Some exposure to HCN may have occurred.

Wuthrich [25] in 1954 described a 39-year-old German blacksmith who was exposed to cyanide in case hardening on a sporadic basis for 2 years and then more frequently for the next 4 years. The worker noticed some initial irritation, followed by a general worsening of health. He experienced loss of appetite, nervousness, vertigo, headaches, nausea, and

vomiting. During 2-3 week vacations, the symptoms disappeared but reappeared within a month after returning to work. His thyroid gland was slightly enlarged. After exposure to cyanide had ceased for about 14 days, the man was given a placebo of NaCl, iv, for three days during which time he reported an improvement in his condition. On the 4th day, 1.4 g of sodium thiocyanate was substituted for NaCl in the daily injections. The thiocyanate concentration in the blood serum increased rapidly following these injections and did not decay to normal between injections. From the day of the first NaSCN injection, the man began to complain of nausea, lack of appetite and nervousness. After three NaSCN injections, he reported nausea and vomiting and spontaneously stated that he felt the same symptoms as at his workplace.

If there are 5200 ml of blood in the average man, then a dose of NaSCN of 1.4g would give an immediate concentration in the blood of 27 mg %. The effect of these injections was a daily, stepwise increase in the concentration of thiocyanate in the plasma until the injections ceased. At this time, the serum thiocyanate concentration was approximately 20 mg %. The half-time of decay of the thiocyanate concentration in the serum was approximately 2 days. Urinary thiocyanate was also monitored, reaching a maximum of about 550 mg % 1 day after the maximum concentration of thiocyanate in the serum had been attained. The half-time of decay of the concentration of urinary thiocyanate also was approximately 2 days. When the daily NaSCN injections were replaced with ones of NaCl, the patient's symptoms disappeared completely after 2-3 days.

In 1932, Smith [26] reported three cases; first, a case hardener who experienced weakness, nausea, dizziness, and semiconsciousness following an

acute exposure to visible aerosols of potassium cyanide. The second was a gold plater of 20 years' tenure in a plant with poor ventilation. When plating and making up the cyanide solutions, he habitually heated them to the boiling point--an activity that may have evolved HCN gas. (The author pointed out that potassium or sodium cyanide solutions give off HCN when heated above 176 degrees F.) The health of the plater prior to 1931 was described as "good." He was first bothered by a rash on his arms, hands, and face, and occasional spells of nausea and vomiting. Prior to his vacation, he made up a large batch of KCN. On the 1st night after leaving, he experienced severe abdominal pains and convulsions. This attack lasted a week with persistent vomiting. After 10 days, he returned to work. His symptoms recurred on the 1st day back, and he was hospitalized. Incapacitated by weakness, headache, dizziness, muscular cramps, and recurring attacks of abdominal pain, he gave up work. Smith stressed that absorption of cyanide from the solution may have been a factor in this case. Each of the last two illnesses was caused apparently by a large, acute exposure to cyanide superimposed on a low-level, chronic exposure. Unfortunately no exposure data were made available.

The third case [26] concerned a 45-year-old case hardener who had worked for 15 years in a poorly ventilated shop plunging steel objects into a pot of molten potassium cyanide. He had spells of weakness and dizziness to the extent that he would fall down. He lost weight and became weakened. Three months later, he had to give up his job. Three years later he was entirely disabled, with paralysis and wasting of the muscles of his arms and legs. No exposure data were given, but the chronic effects may have been the result of acute and chronic exposure to inorganic cyanide and HCN.

In 1966, Jaroschka and Kropp [17] reported an illness following exposure for 2 years to KCN and HCN. The worker supervised operation of the galvanizing baths and made up cyanide solutions as a part of his principal job. He observed that his cigarettes had an unpleasant, metallic, sweet taste when he smoked in the cyanide area. He complained of weakness, debilitation, headache, dizziness, weight loss, coughing, and lack of appetite. He was depressed and suicidal. Upon examination, he was found to have toxic hepatosis and a moderate kidney insufficiency, but no thyroid enlargement. His condition improved after he began work without exposure to cyanide and was later found to have a normal liver and only a slight kidney insufficiency. Exposure data were not presented.

Chaumont [82] in 1960 described a case in which a foreman in a galvanizing shop who had been working near large ventilated cyanide and chromic acid tanks for 3 years and near small unventilated brass-plating tanks for 3 months experienced nausea, vertigo, tenesmus, and cold perspiration sporadically for about 49 days. He was then hospitalized for 11 days. Upon his return to work he was granted a transfer to another work site but was denied (French) compensation benefits because the "essential factors of sudden occurrence and violence" were missing. Chaumont [82] went on to describe the various symptoms which have been reported for chronic cyanide exposure and stated that it is clinically undeniable that cyanides can cause this type of occupational intoxication.

Colle [83] in a 1972 review paper also described the various symptoms reported for cyanide intoxication. He grouped them into systemic, digestive, pulmonary, cardiovascular, and nervous disturbances, as well as

hematic disorders and cutaneous and mucous lesions. He concluded that the symptomatology and pathoanatomic findings establish chronic cyanide poisoning as a true clinical entity. Colle also based his conclusion on the fact that this syndrome of chronic intoxication does not develop insidiously but that it improves or regresses when work is stopped for at least 2-4 weeks and that it recurs in 5-6 days when the individual returns to his old work. He pointed out that the experienced cyanide workers are aware that the subacute symptoms are transitory and that the breathing of fresh air or the stopping of work for awhile causes their disappearance.

Sato et al in 1955 [84] had occassion to open several 100-liter chambers containing 10 ppm of HCN. It was noted that persons who were working in the laboratory about 3 meters from the chambers at the time of opening complained of headache several hours later. The authors recommended that on the basis of headache development, human exposure should be kept down to about 2 ppm.

In 1947, Wexler et al [85] gave to 16 normal soldiers iv injections of NaCN sufficient to stimulate respiration and observed their electrocardiograms. The dose was 0.11-0.2 mg NaCN/kg, varying with the amount that was needed to elicit respiratory stimulation. The electrocardiograms of 15 of the 16 men revealed a sinus pause without evidence of auricular activity persisting for 0.88-4.2 seconds. This sinus pause immediately preceded or accompanied the respiratory stimulation. Immediately after the pause, there were marked sinus irregularity and a decreased heart rate which persisted for periods ranging from a few seconds to 2 minutes. Heart rates then accelerated to above preinjection rates. Heart rate and rhythm were generally restored within three minutes. The 16th subject failed to

show a sinus pause and exhibited only a slight acceleration in heart rate. One of the subjects experienced what the authors described as a momentary dim-out during the test. It should be noted that the doses of 0.11 to 0.20 mg/kg of NaCN are equivalent to approximately 0.06 to 0.11 mg/kg of HCN.

Wexler et al [85] also observed the execution of four men by HCN inhalation. These men exhibited striking electrocardiographic aberrations and had a marked decrease in heart rate which reached its nadir between the 1st and 3rd minutes. This slowing was accompanied by sinus irregularity and eventually by complete disappearance of P waves. A secondary increase in rate, but not to the rate prior to administration of HCN, was observed during the 3rd and 4th minutes along with the irregular reappearance of P waves, some of which were not conducted. All subjects showed A-V dissociation with a secondary decrease in rate during the 5th minute. During the 6th and 7th minutes, the heart rates again showed a slight increase and a return to normal sinus rhythm. Thereafter, the heart rates slowed progressively. Normal A-V conduction in one man and incomplete A-V block in another were maintained throughout the period of observation (approximately 13 minutes). A third subject developed Wenckebach's phenomenon, (2:1 block), and, finally, complete heart block. The fourth subject's heart had normal A-V conduction until the 14th minute, when it developed ventricular tachycardia and ventricular fibrillation. It must be remembered that the concentrations of HCN to which these men were exposed were huge, so that the details of the changes in their ECG recordings may not be entirely typical of those to be expected in occupational exposures. Wexler's observations do seem to demonstrate that cyanide has no specific action on the heart but rather exerts on the myocardium actions that are typical of hypoxia and anoxia.

There have been several reports of exposure to HCN which included both the airborne concentration of HCN and the human physiological response. However, in many cases no additional information relating to worker exposure was provided. These reports are summarized in Table XIV-5. In many cases it is difficult to attribute a specific concentration range directly to a group of investigators since many of the citations involve reference to the work of others with no additional supporting information. Therefore, the validities of concentrations presented only by secondary references may be questioned. In large part they appear to be based on the unreferenced work of Lehmann and Hess. However, the application of Lehmann's data to man has been questioned by McNamara [68] because Lehmann's work was apparently done entirely with rabbits, which McNamara considers to be more sensitive to a given dose (product of concentration and time) of HCN than man. He concluded that man has a susceptibility to HCN more like those of the comparatively resistant goat and monkey and on this assumption (and one that the LCt50 for man is four times that for the mouse) has estimated that 3,404 mg/cu m will cause 50% mortality in humans exposed to it for one minute. McNamara estimated that a concentration of HCN of 607 mg/cu m would kill 50% of men after a 10-minute exposure.

The various fatal doses of HCN seen in Table XIV-5 vary according to the species and method used for projection of data obtained with experimental animals to predictions of human responses. The wide variability in susceptibility between animal species and between individuals may be responsible for the discrepancies. Although the rapidly fatal dose has not been firmly established, it appears that concentrations above 90 ppm are incompatible with life and that concentrations from 5 to

45 ppm produce diverse symptoms (Table XIV-5). However, it is difficult to identify a threshold concentration for the appearance of these symptoms. A few of the studies included in Table XIV-5 provide additional information on workplace exposures and are described below.

In 1926, Parmenter [27] reported a mild cyanide poisoning of a photographic darkroom worker, who on three separate occasions had attacks of numbness, weakness, vertigo, nausea, rapid pulse, and a flushing of the face after working for only 1 hour. These attacks came each time at the end of the week and were followed the next day by headache and vague gastric distress with a rapid return to normal. During the course of his job, he routinely poured iron(II) sulfate solution from a washed plate into a sink, followed by an equal amount of a 30% KCN solution. It is likely that if the first solution had not drained, it would have reacted with the second, producing HCN. Even without supposing reaction with the ferrous sulfate, some HCN would be evolved from the KCN solution in the trap unless the latter was flushed away by a large volume of water. The author felt that the HCN produced could have accumulated in the unventilated room. No airborne concentrations of HCN were determined prior to the installation of ventilation equipment. After ventilation equipment was installed, the airborne concentration of HCN was 75 ppm at 6 in. above the sink under the hood and in the exhaust air. General room air contained 25-50 ppm HCN. It is likely that prior to the installation of the ventilation equipment, the worker was periodically exposed to concentrations of HCN greater than 50 ppm.

In a 1931 experiment [86] in which a 12-kg dog and a 70-kg man were exposed simultaneously in a chamber containing 500-625 ppm HCN, the dog

became unsteady in 50 sec, unconscious in 75 sec, convulsive in 90 sec, and developed respiratory arrest in 93 sec. At 91 sec, the man had developed no symptoms and left the chamber. Three and one-half minutes later, he had a momentary feeling of nausea; 8.5 minutes after leaving the chamber, he experienced difficulty in concentrating on conversation. The dog was presumed dead but recovered within about 12 hours without residual effects from the poisoning. Apparently there is considerable difference between the susceptibilities of man and the dog to acute poisoning by the cyanide ion. McNamara [68] has reported uncovering a statement in the literature to the effect that the exposed man suffered nausea and definite mental symptoms a few minutes after his exit from the chamber but that at least some of these symptoms persisted for about a year.

The signs and symptoms resulting from exposure to cyanide salts fall into two distinct classifications. The first class of inorganic cyanide symptoms is characterized by systemic effects which are the same symptoms as those described for HCN. [27,85] The second set of sequelae, distinct from those observed in response to HCN exposure, are upper respiratory irritation and dermatitis produced by inhalation and skin contact with cyanide salts. The salient details of some cases of human exposures involving each of these classifications are given below.

In 1970, Thomas and Brooks [87] reported a case in which a bag of KCN powder burst in the face of a 19-year-old photographic employee. He suffered from stomach cramps followed by abdominal pain and pallor, and then collapsed. He was revived with amyl nitrite inhalation followed by gastric lavage and injections of sodium nitrite and sodium thiosulfate. He later experienced tingling and numbness in his hands and abdominal cramps. He recovered in 48 hours following continued treatment.

Sandberg [88] reported in 1967 a case of a goldsmith's apprentice who experienced headache, general malaise, paresis of his left arm and left leg, grey skin, a dilated left pupil, left-sided hemianopsia, and an altered EEG showing diffuse frontal theta activity. During the previous 4 years, the man had cleaned goldenware with a 1.5% aqueous KCN solution but had just returned from a 13-month leave of absence 5 months prior to this episode. In use, the solution was heated to boiling whereupon 50 ml of hydrogen peroxide were added. The gold articles were cleaned in a manner causing splashing on the skin and the production of a visible aerosol. There may have been some exposure to HCN. No protective clothing was worn and ventilation was poor in the room in which the work was performed. The man's blood contained 10-12 μg/100 ml of CN and his urine contained 2 μg/100 ml of CN. He was treated with hydroxycobalamin. All symptoms subsided within 3-4 months and the cyanide concentration in his blood fell to 2-3 μg CN/100 ml.

Courville [89] in 1963 reported a case of a 22-year-old man found unconscious under a fumigation tent spread over an orange tree which had just been sprayed with a cyanide solution. He was probably exposed to Ca(CN)2 and HCN. Post-mortem examination revealed microscopic changes in the brain. Cortical nerve cells showed either mild swelling or pyknosis, total loss of tigroid material, and shrinkage of nuclei. Occasional neuronophagia was also seen. Sections from the hippocampus showed areas of focal necrosis. Sections from the cerebellar cortex showed early softening of the molecular layer with loss of structural detail and loss of tigroid staining of the Purkinje cells.

Johnstone [42] in 1948 reported an incident in which three men were dusting grapevines with Ca(CN)2 powder thrown 24 feet on each side of the truck at a height of 6 feet. The calcium cyanide decomposes upon coming into contact with water vapor, liberating HCN. The men usually worked at night when it was not windy and were instructed to work upwind from the section already dusted. At midnight, one man was found dead and the other two unconscious. The two were given first aid and were hospitalized. They developed pneumonia but recovered without disability.

Barsky [90] in 1937 reported a study of nasal lesions in 17 people in a plating department. One of these was a departmental foreman. In addition, two other employees, a forelady and an electrician, spent a good deal of time in the plating area. Plant conditions and operating procedures were very poor and housekeeping was nearly nonexistent. The facility contained five bronze-plating tanks, four nickel-plating tanks, one large acid copper-plating tank and four soft copper-plating tanks, tumbling barrels, storage crocks containing copper, bronze, and nickel solutions, crocks of potash and soda solutions, acids, etc. A 10 x 15 foot corner section of the plating department, which served as the acid room, had been partitioned off by 3/4 inch boards. All plating tanks had 300-gallon capacity except for the larger acid copper tank. The aqueous solution in the copper tanks contained 8 oz Cu(CN)2 and 8 oz NaCN per gallon. The aqueous solution in the bronze tank contained 6 oz Cu(CN)2, 6 oz NaCN, and 1/2 oz Zn(CN)2 per gallon. No chrome plating was done at this plant. The only forced ventilation was local exhaust over the acid tank. General ventilation was provided only by opened windows, which were routinely closed in cold weather.

Of the 17 employees, 9 had been engaged in this particular work for 1-8 weeks. The other eight, as well as the electrician and the forelady, had had one to several years of experience. All 19 persons had nasal lesions of varying severity, characterized by congestion of the nasal mucosa and superficial sloughs of varying size on the anterior portion of the septal wall and middle and inferior turbinates. Ulcerations of considerable size and depth were present at these sites. Two of the employees developed perforations during the course of observation and treatment. In all cases, pharyngeal congestion was pronounced. Particular note was made of the departmental foreman's case, which progressed from alternate running and dryness of the nose, nasal bleeding, obstruction, headache, and sore teeth to weight loss, increased body temperature, and a crusty nasal lesion which spread eventually to the right eyelid. Finally, he developed pneumonia of the left lower lobe and signs of meningeal irritation. He died 5 days later. Autopsy findings were ulcerated nasal septum and middle and inferior turbinates, carbunculosis of the tip of the nose, cavernous sinus thrombosis, basilar meningitis, septic pleurisy, septic pneumonia, and septic infarct of the right lung.

A study of plant records revealed another plater who developed typical signs and symptoms in 1 month. The man had been treated for 7 weeks, was removed from exposure, and recovered. An investigation of the plant was made and these 19 illnesses were attributed to aerosols emitted by the improperly operated plating tanks. After engineering controls and housekeeping procedures had been instituted, there were no recurrences of these illnesses. No airborne concentrations of contaminants were reported.

Elkins [91] in 1963 reported that in a plant where there was considerable brass plating the ambient air contained a mist. The mist was reported to have contained NaCN in a concentration not greatly exceeding 5 ppm, expressed as HCN. Severe irritation was a widespread complaint and there were some incidents of ulceration of the nasal septum. The author noted that other alkalies of undetermined concentration in the air may have contributed to the irritating action of the mist.

Cohen et al [92] studied nasal and skin irritation in two groups of electroplaters in 1974. One group only was exposed to chromic acid and the other one had been exposed to cyanide in the course of copper and zinc plating. Airborne cyanide concentrations were determined in seven locations by collection into 10 ml 0.1 M NaOH in a midget impinger and analysis by specific ion electrode. Air levels ranged from not detectable to 0.09 mg/cu m of CN with an average of 0.006 mg/cu m of CN. No cutaneous or nasal injury was found in the 15 workers in the cyanide-exposed group with the exception of one with a perforated septum who gave a history suggestive of previous exposure to chromates. The cyanides were not described but they were likely a mixture of NaCN, KCN, and some alkaline complex of CuCN in the copper plating tanks, and alkaline NaCN in the zinc bath. [93]

In 1905, McKelway [51] reported a case of a 38-year-old female hairdresser, who used a hickory-nut-sized piece of KCN to remove stains from a silver-containing dye from her fingers. She moistened her fingers and hands and rubbed them vigorously with the lump of KCN for 5-10 minutes, thus removing the stain. Before washing her hands, she experienced vertigo, then screamed and fainted. Her husband revived her in fresh air. Later that evening she vomited, and a physician was called. He found her

in a state of shock and that her lips, fingers, and hands were deeply cyanosed. She was treated for shock and recovered in 3 days.

In 1908, Nolan [94] reported a case of dermatitis in a worker engaged in scrubbing zinc shavings in the KCN "clean up" in the cyaniding process of gold reduction. In this process, the auriferous ore is crushed into a fine aggregate through which a 0.5% KCN solution is passed. This solution then passes into boxes filled with zinc shavings onto which the gold is precipitated from the auro-potassic cyanide in solution. The man's hands and arms were in close contact with this solution. He experienced an itching sensation immediately upon immersion of his hands. Scarlet specks soon appeared on the skin in contact areas and grew larger with time. They coalesced to form a large scarlet area with darker scarlet papules where the original lesions had been. They itched and burned for about 2 hours and the redness began to disappear after 12 hours. Slight giddiness and headache were the only systemic symptoms noted.

Collins and Martland [95] in 1908 reported that cyanide was absorbed through the skin of a 38-year-old hotel worker who polished silver for 2 years by placing it by hand in a KCN solution and then drying it. His hands and arms became brownish-red, his fingernails were black, and he had distressing itching, diarrhea, headache, pain and stiffness in the back and neck, weakness in the arms and legs, and retention of urine. He eventually developed clinical manifestations resembling those of acute anterior poliomyelitis. He remained incapacitated during 6 months of treatment and then gradually responded to electrical treatment to the point where he could walk with braces and crutches. Whether this paralysis should be attributed to cyanide is not clear.

The International Labour Office [48] in 1930 summarized a report first presented by Bridge in 1923 of a fatal case of skin contact with an unspecified inorganic cyanide. The skin of the victim had been removed in patches as if it had been burned.

Smith [26] in 1932 reported a case of a gold plater who had worked at his trade for 20 years, 10 in a small shop plating rings and pins in small pans containing KCN solution, which he made up. When plating, he heated the solution to boiling, which probably resulted in splattering and caused HCN evolution. He had a rash on his hands, arms, and face which he attributed to the cyanide solution. He also had abdominal pain, convulsions, weight loss, weakness, dizziness, muscular cramps, and vomiting. Some of these signs and symptoms could be attributed to skin absorption and some to inhalation of HCN and aerosolized cyanide salts.

In 1955, Tovo [96] described a fish poacher who died from absorption of KCN through the skin. The poacher added KCN to a river upstream and others netted the trout downstream. He was found 3 hours later curled up on the side of the road and without his boots and stockings, which were found on the river bank. He died later that day without recovering consciousness. Necropsy revealed brownish-red blotches from knee to instep that smelled of bitter almonds, as did the blood. The body had a violet hypostatic coloration. The mother of the man pointed out that the legs of his trousers had been rolled up above his knees and were dry but that those of his long cotton underwear were wet at the bottom. Chemical examination showed the presence of cyanide in the blood, urine, and several of the vital organs, but concentrations were not reported. Tovo suggested that

the man had placed his stock of KCN temporarily in his boots to wade into the water and that, either by accident or by misjudging the depth of the water, he stepped into water deep enough to flow over the tops of his boots. Although he escaped from the river as quickly as possible and removed his boots and stockings, he did not have the caution to remove his long underwear soaked with a solution of KCN. Consequently the poison was able to continue to penetrate through the man's skin, more readily because of its corrosive activity, and eventually to cause his death.

In 1926, Raestrup [97] described an accident in which a man was killed when the fused KCN that he was carrying spilled into a puddle of water. The boiling water-cyanide solution splashed in his face. He lost consciousness and died 3 hours later. A similar case was reported by Muller-Hess [98] in which a worker was struck in the head and shoulders with a splash of 80% NaCN and died in less than 1 hour. Several other similar cases reported by various authors were summarized by Tovo [96] but most of these did not involve occupational poisonings.

Specific antidotes for cyanide intoxication have been shown to be effective in 49 cases. [87,99-106] Forty-nine of these involved the use of nitrites to form methemoglobin. Of these, 20 received artificial respiration or oxygen, 41 received amyl nitrite inhalations, 40 received $NaNO_2$ injections, and 39 received sodium thiosulfate. Specific procedures used upon humans have been reviewed by Chen et al [101], Wolfsie and Shaffer, [107] and Wolfsie [100], who all agree that such treatments are effective because they produce methemoglobin and become more effective if sodium thiosulfate is provided to assist in the detoxication of cyanide to thiocyanate. A recent review on the use of oxygen in the treatment of poisoning by cyanide is also available. [108]

Epidemiologic Studies

In 1970, Saia et al [22] reported examining 62 workers; 21 worked near cyanide vats in the galvanizing department, 19 were either wire handlers or zinc platers in the same department and a 22-member control group washed wire in caustic soda. A questionnaire was also given to the 62. Venous blood was analyzed for cyanmethemoglobin. The incidences of insomnia, agitated sleep, tremor, eczematous dermatitis, and nosebleed among the workers exposed to cyanide were more than twice those of the control group. The incidence of vertigo was nearly twice. It is significant that comparatively high incidences of frequent and prolonged headache, vertigo, rapid pulse, buzzing in the ears, eye irritation, frequent cold sweat, sluggish digestion, abdominal pain, weakness in the legs, and dyspnea were found in the control group of men who washed wire with caustic soda at elevated temperatures and had no cyanide exposure. Further, it should be noted that the high incidence of dermatitis was likely caused by poor work practices. Five of the 21 cyanide workers' blood had changes in hemoglobin indicative of cyanide absorption. In one of these five men, the condition persisted for weeks after he quit working. No workplace environmental data were given. [22]

In 1955, Carmelo [109] observed about 600 HCN fumigators and noted a sense of suffocation, tachycardia with palpitation, vertigo, buzzing in the ears, headache, epigastric burning, vomiting, general weakness, tremor, sensory obtusion, dyspnea, precordial pain, and loss of consciousness in workers who, in the opinion of the authors, received small acute intoxications from HCN.

Carmelo [109] examined in detail 17 fumigators using HCN, 13 of whom had suffered acute episodes with loss of consciousness. He recorded ages, qualifications, places of origin, duration of service in fumigation work, frequency of accidental inhalations, medical histories and subjective complaints at the time of examination, as well as objective results of various general examinations and diagnostic tests. These men had worked for from 1 to 27 years; the four without histories of acute episodes of intoxication by HCN had worked for 7, 8, 25, and 27 years. A high incidence of nervous disorders, including equilibrium disturbances, vertigo, nystagmus, and Moebius sign, were found. Nine of the 13 experienced precordial pain after exposure to HCN; eleven of the 13 had electrocardiographic alterations. Eleven of the 13 had radiographic evidence of hypertrophic gastritis. None of the four unexposed men had evidence of disease of the stomach or duodenum. The author reported that three of the exposed and two of the unexposed men had erythrocyte counts above 5,000,000 but below 6,100,000/cu mm and that seven of the exposed and none of the unexposed men had a percentage of lymphocytes above 40 but below 49%. He attributed the latter change to stress resulting from repeated exposure to small doses of HCN. He concluded that his results demonstrated that not all the effects of repeated acute or subacute exposures to HCN are entirely reversible.

In 1972, Dinca et al [23] published a study of leukocytic oxidative enzyme changes in 31 men and 12 women in Romania engaged in galvanizing metal who were chronically exposed to low airborne concentrations of HCN. Their ages were 18-49 (mean 36); their years on the job were 0.25-16 (mean 5.4); their average exposure for the past 5 years to HCN at a concentration of 0.26 mg/cu m (0.23 ppm). No exposure to cyanide salts was mentioned and

no details of cutaneous exposure or general health were given. Samples of blood were analyzed for serum catalase. Blood smears were also stained with various dyes to enhance particular granules of the neutrophilic leukocytes. The authors compared the number and intensity of "cytochrome oxidasic", "peroxidasic", and "succinodehydrogenasic" granules with similar findings in a control group. No details of the size or nature of the control group were presented. Based upon the percentage of subjects whose rating was "0", "+", "++" or "+++", the authors concluded that there was a significant decrease in the cytochrome oxidase activity of the leukocytes of workers exposed to HCN at 0.23 ppm. Further, they felt that the peroxidase and succinodehydrogenase activities of the exposed group were considerably reduced, while serum catalase was lowered less markedly. It should be noted, however, that the staining techniques used by the authors were quite crude and were not confirmed by quantitative analysis of the activities of any of the enzymes. Therefore, these data must be regarded as questionable until substantiation of the conclusions of Dinca et al is obtained. Therefore, a "?" has been inserted after the response noted in the last entry in Table XIV-5.

In 1973, Radojicic [79] reported a study of 43 workers in the electroplating division of an electronics firm in Nis, Yugoslavia. Among them, 28 worked in the electroplating shop and 15 in the annealing department. A control group of 20 non-exposed workers was used for comparison. The cyanide concentration was measured at four work places in the electroplating shop and ranged from 7 to 11 mg/cu m.

At three sites in the annealing shop the cyanide ranged from 6- mg/cu m. It was found that the majority of the exposed workers complaine

of fatigue, headache, asthenia, tremor of the hands and feet, and pain and nausea. The urinary thiocyanate concentrations of both of the exposed groups were higher at the end of the work shift than before work. Workers who had been on the job longer usually eliminated more thiocyanate than those with fewer years of exposure. In both groups, the exposed workers who smoked eliminated more thiocyanate (both before and after work) than smoking controls. Likewise, the nonsmokers in both departments who had cyanide exposure eliminated more thiocyanate than nonsmoking controls. These values were reported to be significantly different. The smokers eliminated more thiocyanate than the nonsmokers in each case. It appears that the workers in the group with higher exposure (electroplating) also eliminated more thiocyanate than the workers with less exposure (annealing), regardless of smoking habit.

Most recently, El Ghawabi et al [110] studied the effect of chronic cyanide exposure in the electroplating sections of three Egyptian factories. A total of 36 male employees were interviewed, medical histories were taken and medical examinations, which included radioisotope assay of iodine uptake and hematological evaluation, were performed. The ages of the employees ranged from thirty years into at least the fifties and their durations of exposure up to at least 15 years. The results were compared with those from a control group of 20 normal male non-smokers, as the exposed employees all disliked the smell of cigarettes. The breathing zone cyanide concentrations at the three plants averaged 8.1, 6.4, and 10.4 ppm, respectively. Two employees were encountered who exhibited psychotic episodes. None of the exposed employees exhibited clinical signs of hypo- or hyperthyroidism. However, 20 had mild to moderate thyroid enlargements.

Sixteen of these enlarged glands were soft and smooth while the remaining four were firm and slightly nodular. The radioactive iodine uptakes of the thyroid glands of the exposed workers 4 and 24 hours after administration of 131I were significantly higher than those of the controls. (38.7 versus 22.4%, P=0.001; and 49.3 versus 39.9%, P=0.001, respectively). At 72 hours, the PB131I was within normal limits and no significant difference was found between the two groups. As thiocyanate blocks the uptake of iodine by the thyroid [111] and as there was no cyanide exposure for two days preceding the study, the authors expected this rapid accumulation of iodine by the thyroids of the exposed group. Another possibility put forward by the authors was that the competition between thiocyanate and iodide had resulted in a hypertrophied thyroid and thus to a sufficient concentration of organic iodine through an expanded volume of tissue, which would not be saturated with iodine, however. The authors also found slightly increased hemoglobin and lymphocyte percentages in the blood, as well as cyanmethemoglobin, in the exposed group. The urinary thiocyanate levels were found to increase at the beginning of a work week and to remain almost stationary during the latter half. These stationary values were said to be related to the airborne cyanide concentrations but no correlation coefficient was reported.

Animal Toxicity

In 1900, Heymans and Masoin [112] found that the lethal dose of KCN (calculated as HCN) was 2-3 mg/kg for the rabbit. When this dose was divided into 12 equal parts and administered during an hour at 5 minute

intervals, it still proved fatal. Using this method they were able to show that the detoxication potential of the rabbit for KCN was about 0.5 mg/kg per hour (as HCN) for at least 10 hours and that the dose-time of survival relationship was hyperbolic. The authors concluded that at low concentrations, normal metabolism was able to detoxify the cyanide but that upon prolonged exposure this metabolic potential became exhausted and with high exposure levels this metabolic mechanism became saturated.

Lehmann [113] reported in 1903 that inhalation of 30-40 mg/cu m of HCN (27-36 ppm) did not affect cats after exposures of 4-5 hours. However, cats exposed to airborne HCN concentrations of 50 mg/cu m (45 ppm HCN) for 1.5 hours exhibited respiratory distress, increased salivary flow, vomiting, dilatation of pupils, and convulsions. Most cats died after 2.5-5 hours of exposure to HCN at 50-60 mg/cu m (45-54 ppm).

In 1906, Kobert [52] reported that the dog was the species most sensitive to HCN, but that it was less sensitive to the cyanogenic glycoside, amygdalin, than the rabbit. He also explained the complex effects of HCN on man and higher animals by differentiating four basic effects: those on the nervous system, on metabolism, on blood, and on the heart. Effects on the nervous system were primarily motor disturbances, including paralysis, but could also include some of the symptoms of peripheral nervous disorders, more commonly associated with exposure to cyanogen gas at that time. Experiments with "surviving hearts" showed that they are paralyzed by small doses of HCN, but that the nervous system could be paralyzed with even less. Blood was shown to be affected by "losing its ability to split up H2O2" (presumably an inactivation of catalase) and by the formation of what Kobert discovered and called cyanmethemoglobin.

In 1915, Creel et al [114] exposed groups of 1-6 rats to various concentrations of HCN generated from potassium cyanide and sulfuric acid. Rats generally died within 15 minutes when exposed to HCN concentrations above 500 ppm HCN.

In 1917, Grubbs [115] exposed guinea pigs, rats, mice, cats, sparrows, and pigeons to various concentrations of HCN in an airtight room of 500 cu ft in order to find an animal that could be used as an index of safety on fumigated ships. Airborne concentrations calculated from the data were about 130-540 mg/cu m. The effects which were observed are included in Table XIV-6. Sparrows and small birds were said to be the most susceptible to HCN and guinea pigs the least susceptible.

Walton and Witherspoon [116] investigated the degree to which HCN penetrates the skin in 1926. In one series of experiments, they shaved the abdomens of eight guinea pigs and 24 hours later fastened them, belly down, to a board with a large hole in it. A circular area of 1 in in diameter was exposed to the vapor from a preparation of HCN that contained 97% HCN and 3% water. First signs, appearing in a few minutes, were rapid respiration followed by general twitching of muscles, convulsions, and finally death. In a second series of experiments, the authors [116] exposed the abdomens of nine dogs shaved or depilated 24 hours earlier and of two additional unshaven dogs to various concentrations of airborne HCN. The dogs were lightly morphinized before being placed in a chamber in which their bodies, except for the head and a portion of the neck, were exposed to airborne HCN. These experiments were designed to minimize HCN entry by any route other than absorption through the skin. This experiment showed that HCN penetrated the intact skin of the dogs. For example, a fatal

result was obtained with exposure to 15,200 ppm of HCN after 47 minutes whereas no symptoms were observed with exposure to 5,000 ppm HCN for 180 minutes.

Fairley et al [117] in 1934 exposed 1.23 sq in of the closely clipped bellies of five guinea pigs (approximately 2% of the surface area of their bodies) to HCN at a theoretical concentration in the range of 312,500-455,000 ppm. Coma, convulsions, or death resulted in four of the guinea pigs in 45-65 minutes; the fifth was removed from exposure when it collapsed at 15 minutes. It appeared to have recovered 45 minutes later.

In 1931, Flury and Zernik [118] recorded the results of extensive exposures of mice, rats, guinea pigs, rabbits, cats, dogs, pigeons, and a monkey to airborne HCN concentrations of 50-1450 mg/cu m (45-1305 ppm). The salient results presented in this paper are summarized in Table XIV-6. These authors also noted that differences in individual animal responses were pronounced at HCN concentrations of 40-70 mg/cu m (36-63 ppm). Reactions proceeded more slowly at these levels and vomiting, convulsions, unconsciousness, and difficult breathing were the chief signs. They noted further that concentrations under 35 mg/cu m (31.5 ppm) were generally completely and lastingly safe except for certain individual animals which were especially sensitive. They further noted that, at concentrations of 100-140 mg/cu m of HCN (90-126 ppm), monkeys were slightly, but not significantly, less sensitive than cats and dogs.

Prior to 1933, methylene blue was recommended as a treatment for HCN poisoning. In 1933, Trautman [119] demonstrated that injections of methylene blue were of no value in the treatment of overexposure to HCN gas. He placed the animals in large glass jars, added small amounts of liquid HCN

and noted the results. Rabbits were exposed to HCN at approximately 450 ppm, while white rats and guinea pigs were exposed to HCN at approximately 900 ppm. (The exposure concentration for the rats was variously stated as 450 or 900 ppm.) Animals were exposed until they breathed a lethal or near lethal amount of gas, the times of exposure were noted, and then the animals were removed and given injections of a 1% solution of methylene blue. Fifty-four guinea pigs were exposed to HCN and 29 were injected ip with a 1 cc/100 g dose of methylene blue solution. Seventeen (59%) recovered and 12 (41%) died. Of the 25 control guinea pigs, 15 (60%) recovered and 10 (40%) died. Of the 35 rabbits exposed to HCN, 18 were injected iv with 1 cc/kg of methylene blue and 17 received no treatment. Three (17%) of the 18 treated animals died as did 2 (12%) of the 17 untreated animals. Results were again similar when 98 white rats were exposed to HCN. Twelve (38%) of the 32 receiving 1 cc/kg of methylene blue ip died, as did 11 (32%) of the 34 given 0.5 cc/kg of 1% methylene blue solution ip and 10 (31%) of the 32 controls.

Gettler and Baine [120] in 1938 gave doses of 16.0 and 10.1 mg of HCN, respectively, to two dogs by inhalation. The former died in 12-15 minutes and the latter in 8-10 minutes. They also injected 20, 50, and 100 mg of KCN (expressed as HCN) into the stomachs of three other dogs, and they died in 155, 21, and 8 minutes, respectively. It was determined by analysis of stomach contents that the three dogs had absorbed 14.4, 12.0, and 16.6 mg of KCN (expressed as HCN), respectively. The authors calculated the lethal oral absorbed dose for dogs to be 1.06-1.40 mg/kg of HCN.

In 1939, Etteldorf [121] exposed dogs in a dynamic system to various airborne concentrations of HCN, which were determined by sampling and analysis. The author noted that convulsions were always preceded by definite prodromal signs, namely salivation, lacrimation, defecation, urination, and increasing restlessness. Three dogs exposed to 0.05 mg HCN per liter of air developed convulsions, while three others pretreated with sodium thiosulfate and sodium nitrite did not develop convulsions until the HCN concentrations were 0.175, 0.29, and 0.30 mg/liter.

In 1946, Jandorf and Bodansky [122] reported testing the therapeutic and prophylactic effects of methemoglobinemia in HCN poisoning by exposing dogs to HCN. The concentration of HCN in the chamber was sampled with a sodium carbonate solution and analyzed by silver nitrate titration. Amyl nitrite was administered 30-45 seconds after removing the animals from the chamber by exposing their noses to 0.3 ml of the liquid in a muzzle. Manual artificial respiration was used to facilitate the inhalation of the amyl nitrite and was continued until respiration resumed or death occurred. Eighteen dogs were exposed in pairs to HCN at 170-1400 mg/cu m for 1-10 minutes. Nine dogs were given artificial respiration and treated with amyl nitrite. The other nine served as controls and received only artificial respiration. Five of nine (56%) treated dogs were revived, while only three of nine (33%) untreated dogs were revived. The authors felt that this difference was not significant.

In a second phase of the study, [122] dogs were exposed to HCN at 530-2200 mg/cu m after treatment with oral doses or injections of p-aminopropiophenone to induce methemoglobinemia. Dogs protected with 4-10% methemoglobin were able to withstand 2-8 times more HCN than the unprotected dogs.

unprotected dogs.

Gordh and Norberg [123] published a study of oxygen treatment of HCN poisoning in 1947. They exposed 2-3 kg rabbits to HCN at 284-1290 mg/cu m (256-1,161 ppm) for 37-47 minutes. Exposure was continued until the animals became apneic, their heart beats became irregular and weak, and distinct cyanosis was apparent. Administration of oxygen through a plaster of Paris mask, modelled to fit the rabbit's muzzle, by hand pressure applied to a rubber bag connected to the mask succeeded in reviving 18 of the 36 rabbits. The authors stated that the hearts of the other 18 rabbits had become too weak when oxygen administration was started to be able to perform the necessary movement of oxygenated blood to the important organs.

In 1951, Moss et al [124] exposed 16 rats to HCN at 24-465 ppm for up at 22 minutes. The rats exposed at 25-50 ppm survived, except for one exposed at 50 ppm. This rat was violently agitated after 1 minute 49 seconds, paralyzed after 2 minutes 30 seconds, unconscious after 3 minutes, and dead after 8 minutes.

In experiments reported in 1952 by Haymaker et al, [125] six dogs were exposed at concentrations of 620, 590, 700, 700, 165, and 690 mg/cu m, for periods of 2.0, 2.0, 1.75, 1.75, 10.0, and 2.0 minutes, respectively. The first three dogs died in 20 hours or less and the others were killed 24, 26, and 28 hours after exposure. Four of the six dogs had convulsive seizures. The dog exposed at 620 mg/cu m had marked proliferation of histiocytes in the leptomeninges and in the perivascular spaces of the molecular layer of the cerebellum. Only shadows of the Purkinje cells remained. Some of these dogs suffered necrosis of gray matter. Definite alterations of structure were not seen in dogs that died within 21 minutes

after being exposed to HCN; they were found in dogs that died 2.5 or more hours after exposure. At these comparatively early times, there was subpial edema of the cerebrum and the cerebellum. Dogs that survived for as long as 16 hours had cellular damage, particularly in the cerebral cortex. The frontal and parietal lobes were more likely to be affected than the temporal or occipital. Cortical damage was concentrated frequently in the trough of a sulcus in the form of massive coagulation necrosis.

Valade [126] in 1952 exposed four dogs to HCN at 50 mg/cu m for 12 30-minute periods, conducted at 8-day intervals. Of these dogs, two survived, one died after 38 days, and one died of an intercurrent disease. In a second experiment, four dogs were subjected to 19 30-minute inhalation periods at 2-day intervals and at the same HCN concentration. One died after 73 days, the other after 77 days. Another group of five dogs went through seven 30-minute inhalations at 2-day intervals, but this experiment was interrupted when pulmonary inflammation occurred, causing the death of three dogs. Still another group of four dogs were subjected to fourteen 30-minute inhalation periods at 2-day intervals; one of these died after 34 days. The first signs were dyspnea, nausea, exaggerated intestinal peristalsis, and diarrhea. Later, the dogs developed tremors followed by loss of equilibrium and convulsions. These observations tend to support the hypothesis of a cumulative effect from exposure to HCN.

Valade [126] autopsied the dogs immediately after they died or were killed and observed similar central nervous system lesions in each of them. Vascular changes were vasodilatation and hemorrhages which were most pronounced in the central gray nuclei, brain stem, bulb, and medulla

cervicalis. Cellular lesions manifested themselves by glial reactions throughout the central nervous system and by cytologic changes in the Purkinje cells of the cerebellum and in the bulbar gray nuclei. These histopathologic examinations led the author to conclude that the lesions resulted from anoxia caused by inhibition of cytochrome oxidase or from a selective effect of the poison. To support the contention that the latter cause was the more significant, the author noted that the dogs were very quickly affected by respiratory disorders before the onset of other signs. He thought there was reason to believe that the suddenness with which these disorders appeared was linked to a particular sensitivity of these animals' bulbar cells to cyanide, rather than to an inhibition of cytochrome oxidase.

Sato et al in 1955 [84] placed groups of 10 mice in a series of 100 liter air tight chambers containing HCN gas in various concentrations, which were verified during the experiments by occasional analysis. The amount of HCN was kept constant throughout the experiments. At 20 ppm, about 20% of the mice died after 4.5 hours. Some mice also died after 4 hours at 15 ppm. Mobility became hindered and respiration rough when exposed at 10 ppm for 2 hours. At 5 ppm, there was a marked decrease in food intake compared to that of controls. The authors concluded that chronic HCN intoxication at low concentrations would eventually exhaust the detoxication ability of the mice and eventually cause adverse effects.

In 1955, Howard and Hanzal [127] reported a feeding study with HCN-fumigated food. Thirty male and 30 female weanling albino rats were divided into 3 groups of 10 males and 10 females each. Two of the groups were given dog meal containing 300 ppm and 100 ppm of HCN, respectively. A

third, similar group was fed unfumigated food as a control. At the end of a 2-year feeding period, no gross signs of cyanide toxicity were observed. Autopsies revealed the same general abnormalities and signs of senility in control and experimental rats. Microscopic examination of heart, lungs, liver, spleen, stomach, small and large intestines, kidneys, adrenal, thyroid, testes or uterus and ovary, and the cerebrum and cerebellum revealed no evidence of pathology due to HCN feeding. All findings were compatible with those usually seen in aging animals, and the same general changes were found in both the control and the experimental animals. Thiocyanate concentrations in plasmas, RBC's, and kidneys, but not in the livers, of rats given food containing 300 or 100 ppm HCN were about twice as high as those in controls.

In 1959, Levine and Stypulkowski [128] reported lesions in several areas of the brains of rats which survived exposure for 20-45 minutes at an unknown concentration of airborne HCN. The concentration of the airborne cyanide aerosol, which the authors presumed to be HCN, was not determined but was sufficient to debilitate the rats in 10 minutes. Earlier, Flury and Zernik [118] found that persisting prostration occurred in 9.5 minutes at 127 ppm and, thus, it may be estimated that the rats in this experiment had exposures to HCN at approximately 127 ppm. Below this concentration (127 ppm), exposure to HCN for 2 hours did not produce brain lesions. Above this concentration at which persisting prostration occurred, brain lesions were produced readily in 20-30 minutes. These lesions involved a multiplicity of sites in the brain although they were not universal in distribution. For example, the cord, most of the stem, cerebellum, diencephalon, and portions of the cerebrum were spared. A predominance of

isolated lesions appeared in the callosum and striatum. Later that same year, Levine and Weinstein, [129] using the same technique described above, reported that high concentrations of HCN generally caused the death of rats without causing brain damage. Low concentrations did not produce either, but moderate concentrations (perhaps 100-150 ppm) caused brain lesions while consciousness was maintained for an hour or so, followed by sudden unconsciousness and death. Unfortunately, in neither of these studies was the airborne concentration reported.

Necrotic lesions and demyelination were also observed in the rat brain by Ibrahim et al [130] in 1963 with chronic subcutaneous injections of NaCN. The initial dose was 8 mg/kg with increments of 0.5 to 1.0 mg up to a maximum of 6 mg per animal per day. This schedule was maintained 5 days per week for 3 weeks. The brains of injected animals were examined by cytological and histochemical methods and compared with those of controls.

In 1963, Smith et al [131] noticed cellular changes and neuronal degeneration in the cortex, hippocampus, and cerebellum of three adult Wistar albino rats receiving 0.5 mg of KCN subcutaneously once weekly for 22 weeks. They reported some pallid myelin but found it difficult to estimate whether or not there was demyelination. The animals appeared to be without other ill-effects from these small doses. The authors suggested that these lesions were due to excessive utilization of hydroxocobalamin to form cyanocobalamin. Whether these effects on nervous tissue are due to a specific action of the cyanide ion or of the thiocyanate ion, or to general histotoxic anoxia, is not clear.

Moss et al [124] in 1951 subjected from one to three rats to mixtures of CO and HCN. Atmospheres containing either HCN or CO alone were

generally lethal to rats at concentrations of 50 or 5000 ppm, respectively. A mixture of 10-20 ppm of HCN and 2000 ppm of CO was lethal to some. Mixtures of 30 ppm of HCN and 1000 ppm of CO and of 5 ppm of HCN and 2000 ppm of CO were not lethal.

Hirner [132] in 1969 subjected male rats weighing about 250 g to subcutaneous injections of 0.2% KCN. The daily dose, which averaged between 3 and 5 mg/rat, was divided into parts, which were injected within the span of 1 hour. Five rats received single daily doses and were killed 2 or 3 days later. Six rats received 4 to 12 daily doses, two received 14, and four received 20. All the multiply dosed rats were killed at the end of 9 weeks from the first daily dose. These rats were perfused through the left ventricle with a sodium cacodylate-glutaraldehyde solution; appropriate samples of nervous tissue were ultrasectioned and examined electronmicroscopically as well as by conventional optical microscopy. The principal lesion found in this study was necrosis in the caudal part of the corpus callosum, with spongy alteration at the margin of the necrotic area. Phagocytes invaded the necrotic area 2 days after the last dose of KCN; astrocytic gliosis followed. In the area of spongy change, there was vacuolization of axons and swelling of the astrocytes and oligodendroglia. Demyelination was visible in the later stages of the study. Hirner considered that the effects on glial cells were primary effects of cyanide, but that disintegration of myelin and axonal degeneration were secondary effects, the axon remaining intact when swelling of the glia had occurred. He stated the belief that the oligodendroglia are particularly susceptible to injury by cyanide.

In 1972, Higgins et al [133] exposed 6 groups of 10 rats each to HCN

for 5 minutes at 283,357,368,497,583, and 690 ppm, respectively. Deaths occurred within 20 minutes for 0,1,2,2,8, and 10 rats, respectively. In another experiment 6 groups of 15 mice each were exposed to HCN for 5 minutes at 200, 283, 357,368,414, and 427 ppm, respectively. Deaths occurred within 20 minutes for 0,4,12,10,12, and 15 mice, respectively. The LC50 was 503 ppm for rats and 323 ppm for mice. In later experiments, the authors found that the presence of CO at 2,100 ppm for rats and 1,500 ppm for mice changed the LC50's for HCN to 467 ppm and 289 ppm, respectively, so that there seems to be some slight additive action between CO and CN.

Studies of the systemic toxicity of cyanide salts usually involved the injection, infusion, or oral administration of cyanide solutions into experimental animals. The studies designed to elicit dose-response relationships are summarized by animal, compound given, route of entry, dose, and response in Table XIV-7. These studies have been extremely useful in describing the metabolism and toxicities of cyanide salts.

Three recent reports by Ballantyne et al [134,135,136] addressed themselves to the question of whether or not there is a difference between the acute toxicities of KCN and HCN. They administered intramuscular injections to male and female rabbits. In essence, they found only a slight difference in the observed LD50's in that the LD50 for HCN (as CN) in female rabbits was about 69.5% of that for KCN (as CN) in female rabbits, whereas for male rabbits the corresponding figure was 117.9%. [134] The times to death with HCN for male and female rabbits were 44.1% and 90.6% of those with KCN, respectively. The authors [134,135,136] also analyzed for cyanide in skeletal muscle, kidney, liver, spinal cord, brain,

whole blood, and serum from rabbits killed with HCN or KCN at a dosage of 8 mg CN/kg before and after perfusion with saline. Results showed that observed increases in various tissues generally were due to the cyanide in the blood. However, brain and spinal cord samples from both the HCN- and KCN-injected rabbits remained elevated after saline perfusion and were thus shown to be cyanide depots.

There have been only two animal studies reported of inorganic cyanide aerosol inhalation. [128,137] Both sought to generate HCN by passing air at various flow rates into a 5% aqueous solution of KCN. In both cases the apparatus undoubtedly created a mixture of HCN generated from the hydrolysis of the KCN and of a fine aerosol of KCN. Unfortunately, neither report sought to quantify the dose of either HCN or KCN.

In the first study, Levine and Stypulkowski [128] in 1959 controlled both the depth and duration of intoxication and classified their findings by the observed reactions in exposed rats. Their Stage 1 response was characterized by restlessness, increasing activity, and violent attempts to leave the chamber. Stage 2 involved a decrease in voluntary muscular activity followed by collapse to the floor of the exposure chamber and convulsive movements of the extremities and tail with respiration varying from very deep, slow, and regular to irregular respiration with short periods of apnea. Stage 3 was evidenced by a more complete loss of motor activity with only slight twitching of extremities and respiratory frequencies varying between 40 and 80 per minute. In Stage 4, there was no movement at all other than respiration, which diminished in both amplitude

and frequency until death.

In the second study, Levi and Amaducci [137] in 1968 brought their animals through the first two stages, after which they were allowed to partially recover, and were then killed by decapitation. The meninges appeared congested. Some rats had hemorrhagic pulmonary infarctions. In some animals trypan blue was injected iv to test the integrity of the blood-brain barrier. Subsequent examination of the brains did not show any abnormal passage of the trypan blue into the nervous tissue. Brain slices of other rats were used to study the active transport of amino acids. Initial and steady state accumulation of amino acids and rates of amino acid exit were identical in brain slices from control and treated animals when a glucose-containing incubation medium was used. Tissue respiration rates were also measured in vitro and found to be identical in both control and treated animals.

In 1935, Perry [138] found that prolonged inhalation of cyanide arrested body growth in young rats and retarded the growth of Jensen sarcoma implants. However, she concluded that the effective dose was too close to the lethal dose to be practical. No conclusions can be drawn from this study as to any possible carcinogenicity of cyanide or thiocyanate.

In 1973, Hrizu et al [139] found slightly increased 21-day survival rates in mice inoculated with Ehrlich ascites tumor cells and given two or three injections of 0.2 ml of a 22% potassium thiocyanate solution. However in non-inoculated mice, the thiocyanate injections decreased the survival rate below that of controls (60 versus 74%). Assuming the average weight of the mice to be 15 g, these doses were approximately 3 g/kg of KSCN. They [139] also reported cytostatic effects on cultures of rabbit

spleen and human KB cells with KSCN in concentrations of 110 to 2200 μg/ml of buffered solution. These constitute high doses or high concentrations and any extrapolation to the human experience in the working environment appears meaningless.

In 1946, Nowinski and Pandra [140] injected unincubated chick eggs with 0.3-0.7 ml of sodium thiocyanate solutions of varying concentrations (0.1, 0.5, 1.0 M). Upon incubation for 42-47 hours, the embryos developed anomalies in the rates of development of different organs. For example, in comparison with the rest of the body, the heart was found to show a slower growth rate than other organs. NaSCN was found to have its greatest effect on the brain; however, no definite changes other than inhibitory effects on mesodermal and endodermal development were evident. For an egg with a weight of 50 g, 0.7 ml of 1.0 M solution of NaSCN would correspond to approximately 1,000 ppm on a w/w basis. The possibility of conversion of thiocyanate to cyanide and cellular inhibition by enzymatic blockade should be noted. [65] In light of the high concentration of thiocyanate used and the closed system of the egg, extrapolation of the results of this study to exposure of humans to cyanide does not appear to be warranted.

In 1969, Ortolani [141] exposed unfertilized ascidian eggs to 0.8% NaSCN in sea water (approximately 8,000 ppm) for 12 hours. They were then washed, fertilized, and allowed to develop in sea water. The larvae were found to have abnormalities in the development of the nervous system, sense organs, palps, tails and in the overall size of the organism. Similar results were obtained with treatment of fertilized eggs (2-8 blastomeres) for two hours. Ascidian larvae have the same fundamental structure as vertebrates; however, since their eggs were directly exposed at 8,000 ppm,

the significance of this study to the occupational environment is not clear.

Correlation of Exposure and Effect

HCN is primarily a rapid acting acute poison which can be dangerous to life for humans at concentrations of 90 ppm (about 100 mg/cu m) or more. [118,142,143] However, it is apparent from the data in Table XIV-5, which lists the observed human responses as a function of airborne HCN concentration and time, that this acute human toxicity is truly a function of dose, ie, a function of concentration and time of exposure, rather than just a function of concentration, since exposures at concentrations of between 90 to 135 ppm may be fatal if continued for 30-60 minutes; while exposure above 300 ppm may be fatal within a few minutes. This fact is reinforced by the animal responses to given concentrations of HCN for given periods of time. These data, which confirm that animal responses are also a function of dose, are listed in Table XIV-6 by species. However, as discussed above, these values of 90, 135, and 300 ppm appear to come from research performed by Lehmann and by Hess and known to us only through quotations by other authors (see Table XIV-5). Lehmann's values were apparently derived from studies with rabbits, [68] whereas those of Hess seem to come from exposures of human subjects to low concentrations of HCN vapor. [118]

Inorganic cyanides are also rapid-acting acute poisons to humans. [51,120,144] They also appear to exhibit a dose-response relationship. The primary routes of entry of significance in the workplace are inhalation [26,27,63,81, 88,90,95,145] and absorption through the skin. [26,88,95,

96,145,146] Ingestion as a route of entry for occupational exposure could be significant but is probably secondary. Further, NaCN, KCN, and $Ca(CN)_2$ will liberate HCN gas upon hydrolysis [28,31] or in the presence of acids. [39,40,115]

HCN may also be fatal to humans when absorbed through the intact or damaged skin. [39,118,147,148] Drinker [147] described three men who entered a 2% HCN atmosphere wearing working gas masks and no additional protective clothing. Presumably inhalation was not a factor. They were overcome in 8 - 10 minutes but escaped before they collapsed. The men were incapacitated for 2 or 3 days but apparently recovered completely. This could easily have resulted in three fatalities in view of animal responses to cutaneous exposures to HCN at concentrations near or below 20,000 ppm. [116, 117] The incapacitation of these men suggests that, although the dose required is higher, the same general symptoms occur following exposure to adequate concentrations of HCN via either inhalation or percutaneous absorption.

Although acute poisoning is the chief hazard from HCN, there have been reports of isolated cases of chronic poisoning. [17,24-26,81] In one of these reports, it was pointed out that there was normally an increased urinary thiocyanate level in case hardeners and that, if a person did not excrete thiocyanate well, he could be susceptible to chronic poisoning. Credence is given to this argument by noting that the symptoms observed in this [24] and other cases [17,25,26,81,99] are similar to those noted when thiocyanate is administered. [25] Many of the symptoms reported for chronic poisoning have also been reported after short term exposure. [27,118] These include weakness, vertigo, nausea, rapid pulse, headache,

flushing of the face, and gastric distress. Therefore, the chronic effects appear to result from summation of repeated small exposures, discounted by the extent of detoxication of cyanide within the period elapsed between the exposures. The truth of this supposition has not been demonstrated unequivocally, however.

Regardless of whether it is defined as acute or chronic, exposure to HCN in concentrations of 20 ppm or more has produced adverse effects in humans in a matter of hours. [20,118,142,143] At lower levels of human exposure the effects are not as dramatic, do not occur as rapidly after exposure, and are not as well documented.

Hess (see Flury and Zernik [118]) reported 18-36 ppm to be effective after several hours of exposure. This statement has been interpreted to mean minimal symptoms after several hours of exposure. [29,149] Meanwhile, Lehmann (see Flury and Zernik [118]) reported that humans survived 6 hours without symptoms at these same concentrations.

Hardy et al [24] did observe increased urinary excretion of thiocyanate in a group of case hardeners who were exposed to HCN and possibly to cyanide salts. Breathing zone concentrations of HCN among those workers in controlled operations were measured and found to be 4-6 ppm HCN or less, but neither the HCN levels among those in uncontrolled operations nor any of the inorganic cyanide exposures were quantified. No symptoms were noted in those exposed to 4-6 ppm; however these men may have been included in a group of 25 workers with increased thiocyanate excretions.

Lazareff, in review papers [142,143], described some headache and vertigo in a group of workers exposed to HCN concentrations between 5 and 18 ppm while no ill-effects were noted on exposure at 0.1-0.9 ppm. Details

were not given, however. Similarly, Grabois [150] did not note any symptoms in a group of workers exposed to HCN at concentrations of less than 1 to 17 ppm; however, medical history questionnaires were not given.

Dinca et al [23] reported slight decreases in the activity of cytochrome oxidase, peroxidase, and succinyldehydrogenase in the leukocytes of a group of 12 men and 31 women working in the Romanian galvanizing trade. The group had worked at this trade for an average of 5.4 years. The average concentration for the 5 years preceding the study was 0.26 mg/cu m of HCN (about 0.23 ppm), or just below the Soviet limit of 0.3 mg/cu m of HCN. The tests used to determine enzyme activities involved selective staining of the neutrophilic granules. Such a test is an estimation at best. In addition, it is difficult to detect a significant difference of response in control versus exposed subjects from the data presented. Further, leukocytes are not the normal choice for sampling to determine the activity of oxidative enzymes, particularly cytochrome oxidase. No information was given regarding cutaneous exposure or exposure to any other form of cyanide. Since the staining techniques used were unsupported by quantitative biochemical studies, one can not put much weight on the authors' conclusions. Therefore, one doubts that workers would be adversely affected by prolonged exposure at 0.26 mg/cu m (0.23 ppm).

It appears that there are no documented pathological conditions or major adverse effects from human exposure to airborne HCN at concentrations below a value somewhere between 5 and 18 ppm. However, chronic exposure at levels of 5.4 to 12.7 ppm was reported by Radojicic [79] to give rise to subjective complaints and disturbances in the normal well being of 43

cyanide workers. These complaints included headache, weakness, nausea, and what was described as effort dyspnea. These symptoms were also reported in 40 cyanide workers by Saia et al [22], although the airborne cyanide concentrations were not determined. Similarly, El Ghawabi et al [110] found these same complaints in 36 cyanide workers at airborne cyanide concentrations of 4.2 to 12.4 ppm.

Colle [83] advanced the belief that these symptoms of headache, dyspnea, epigastric burning, vertigo, tinnitus, nausea, vomiting, tremor, and precordial pain represent a true clinical entity and that they are sufficiently documented and characteristic of chronic cyanide exposure to be grouped into a true syndrome. He suggested that these symptoms are due to subacute exposure and are transitory in that rest and the breathing of fresh air cause their reversal, but that these subacute exposures, when repeated regularly over a long period, lead to vascular and cellular lesions which eventually result in this classic syndrome.

Chaumont [82] also stated that there is no clinical evidence to deny that cyanides can cause this type of occupational intoxication. He apparently found the debate on whether this intoxication is truly chronic or whether it involves repeated subacute symptoms to be semantic in nature and opted for the admission that chronic intoxication caused by HCN and the cyanide salts is a true occupational disease.

Heymans and Masoin [112] showed in 1900 that fractions of a lethal dose were cumulative if administered in adequately shortened intervals, and noncumulative when given at widely spaced intervals. The authors suggested that these small fractional doses caused a general weakening of the organism. The authors went on to attribute this general weakening of the

organism's cyanide detoxicating potential to the removal of sulphur by each successive dose, thus reducing the organism's natural defenses and increasing its sensitivity to the poison. Thus one might describe chronic cyanide poisoning as a slow deterioration of resistance, and, therefore, an intensified sensitivity, due to inadequate time between exposures for replacement of damaged tissues, enzyme systems and metabolic stores, the elimination of detoxication products, and the regeneration of homeostatic mechanisms.

Unfortunately, there are only a few studies involving humans which quantified the inhaled or administered dose of cyanide salts. [23,27,85,91,92] Wexler et al [85] gave iv injections of NaCN to 16 soldiers. They noted altered electrocardiograms with doses of 0.06, 0.08, and 0.11 mg/kg of CN. One case of a momentary dim-out was encountered at 0.11 mg/kg. If these soldiers weighed approximately 70 kg, then these doses would correspond to the injection of approximately 4.2, 5.6, and 7.7 mg of CN, respectively. Further approximations extending these injected amounts to air concentrations, given an assumed absorption efficiency, are fraught with peril. However, estimates of the air concentrations of HCN which would produce 50% mortality in humans exposed for different lengths of time have been made assuming an iv LD50 of 1.1 mg/kg and a pulmonary absorption of 70%. [68] Landahl and Herrmann [151] found that the percentage of HCN retained in the human lung with a normal breathing pattern approximated 60% at air concentrations of 0.5 to 18 ppm when breathing through the mouth. Higher absorption might be expected when breathing through the nose. The report by Parmenter [27] mentioned earlier detailed some after-the-fact measurements of HCN taken in such a manner as

to have included any other cyanide aerosol present. Similarly, Dinca et al [23] reported HCN air concentration in a galvanizing shop but did not mention cyanide salts.

However, the reports which give both airborne HCN levels and the human response are essential in evaluating the hazard potential associated with HCN released during the use of cyanide salts in the workplace. There have been several such reports, which are summarized in Table XIV-5.

The only human dose-response information for the cyanide salts is represented by estimations of a lethal dose [29,44,152,153] and the study by Wexler et al. [85]

Sollmann [152] estimated the lethal dose of KCN in man to be 0.2-0.3 g, although it has been reported [153] that ingestion of an estimated 3-5 g was survived without specific treatment. Fassett [29] estimated the lethal dose of NaCN to be 1-2 mg/kg.

Two cases of upper respiratory irritation have been reported. [90,91] The study by Barsky [90], described previously, failed to measure any air cyanide concentrations. However, the incidence of the lesions in a plant with poor housekeeping was given. Conditions were such that one fatality resulted as a consequence of secondary infection.

Elkins [91] noted nasal irritation in an electroplating room where brass plating was being done. He stated that irritation was a commom complaint and in some cases ulceration of the nasal passages resulted. The concentration, expressed as HCN, did not greatly exceed 5 ppm. He did not state whether this concentration was found in the area just above the plating tanks or the general workroom air.

Recently, Cohen et al [92] reported a study in which 15 people exposed to CN at an average concentration of 0.006 mg/cu m showed no ill effects whatsoever.

Skin contact with concentrated cyanide solutions has been responsible for deaths [48,96] and permanent disability. [95] Contact with inorganic cyanide solutions as dilute as 0.5% KCN have caused headache and dizziness. [94]

Although no further systemic toxicity studies in humans have measured the inorganic cyanide exposure levels, the work of Ballantyne et al [134, 135,136] has clearly demonstrated in animals that the systemic toxicities of HCN and KCN are roughly equivalent on the basis of the cyanide contents of the two materials (mean toxicity of CN administered im to rabbits as HCN was 106.7% of that administered as KCN). This study is reinforced by the numerous previously described cases of inorganic cyanide exposure which gave the same symptoms as HCN poisoning. Treatment as outlined in Appendix V has been shown to be equally effective for cases of acute poisoning resulting from HCN and cyanide salts.

Cyanide solutions or cyanide aerosols generated in humid atmospheres have also been reported to cause irritation to the skin [26,48,94,96,145,154] and to the upper respiratory tract [90,91] and to cause allergic contact dermatitis. [155] Human skin has been irritated by solutions as dilute as 0.5% KCN (0.2% CN). [94] The typical lesion is manifested in eczematoid dermatitis or skin discoloration or a rash of a nonuniform nature which may itch or burn. [26,48,94-96, 146] Long periods of close contact with solutions of the cyanide salts have been sufficient to cause caustic burns. [48,96] These cases were generally fatal. [48,96]

The cases reported as allergic contact dermatitis by Somov and Khaimovsky [155] in the USSR involved 37 workers in galvanic gilding shops. The condition involved the hands and was caused by prolonged contact with solutions of a gold cyanide. Applications of 1% solution of gold cyanide gave positive results in 28 of 35 patients so tested. Plant conditions were improved and barrier creams were employed. The conditions of 31 of the 37 workers improved and they resumed work. The other six were given work where they would not come in contact with gold cyanide.

Carcinogenicity, Mutagenicity, and Teratogenicity

Data on other possible effects of hydrogen cyanide, sodium cyanide, potassium cyanide, and calcium cyanide, such as carcinogenicity, mutagenicity, and teratogenicity, have not been reported and there is no analogy on which to postulate such effects on long-term, low-level exposure. It seems probable that cyanide as a general cell poison and histotoxic agent would depress the activity of all cells, both normal and transformed. Indeed, Perry [138] found a low therapeutic index for cyanide in the treatment of rat sarcomas.

Thiocyanate, the main metabolic product of cyanide detoxification, has been shown to cause abnormalities in the development of chick [140] and ascidian [141] eggs at high concentrations. However, these studies do not allow extrapolation to the human experience of industrial exposure to cyanide. Hrizu et al [139] found that thiocyanate exhibited a cytostatic effect on human KB cells in vitro and an increased survival rate in mice inoculated with Ehrlich ascites tumor cells. However, the amounts used

preclude any meaningful extrapolation to the in vivo response of humans. Thus, NIOSH has no evidence that chronic exposures to HCN and cyanide salts should be considered as possible causes of carcinogenicity, mutagenicity, or teratogenicity.