III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Hydrogen sulfide, H_2S (formula weight 34.08), is a colorless, flammable gas which may be liquified under pressure and which occurs in a variety of natural and industrial settings. Some of its physical and chemical properties are listed in Table XIV-1 [1,2]. It is present in most volcanic gases, in "sulfur springs," and as a bacterial decomposition product of protein [2]. It occurs to some extent in most petroleum and natural gas deposits and in many mines, and it is therefore a potential health hazard in related drilling, mining, smelting, or processing operations. In other industries, hydrogen sulfide is usually an undesirable byproduct of some manufacturing process. It is formed whenever elemental sulfur or certain sulfur compounds are present with organic chemicals at high temperatures [2]. Industries in which hydrogen sulfide is a principal reagent or byproduct are listed in Table XIV-2 [3-6].

Hydrogen sulfide may be prepared directly from hydrogen gas and sulfur vapor, but this process is economical only if hydrogen is a waste product at the location [2]. Most hydrogen sulfide is obtained as a byproduct of other operations. Often its recovery is motivated more by the need to purify the source material than by the value of the recovered gas. Hydrogen sulfide in substantial quantities is recoverable from natural-gas and petroleum refining operations and is converted to sulfuric acid or high-quality sulfur or disposed of by burning in flares. Hydrogen sulfide is also used in the preparation of various sulfides and organic sulfur

compounds and is a common reagent in chemical laboratories [2].

NIOSH estimates that approximately 125,000 employees are potentially exposed to hydrogen sulfide in the United States; a partial list of their occupations is shown in Table XIV-2 [3-6]. Large or frequent exposures to hydrogen sulfide are peculiar to some occupations. Exposure to hydrogen sulfide in other occupations may be rare or at low concentrations.

Historical Reports

An 18th century treatise on occupational health, De Morbis Artificum Diatriba [7], was inspired by the observation of the physical condition of sewer cleaners. The author, an Italian physician named Ramazzini who is revered as the father of occupational medicine, described cases of eye irritation similar to those more recently being attributed to chronic exposures to hydrogen sulfide.

> I am inclined to think some volatile acid is given off by this carnerine of filth when workers disturb it...such effluvia ought, one would think, to impair the lungs. Nevertheless it is only against the eyes that these foul exhalations wage ruthless war, and they attack them so cruelly with their piercing stings that they rob them of life, that is to say of light [7].

In connection with an investigation of hydrogen sulfide poisoning, Mitchell and Davenport [8] reviewed the literature on the subject. The first description of the chemical properties of hydrogen sulfide, by Rouelle, dates back to 1773, although the composition of the gas was unknown at the time [8]. Scheele, in 1777, was the first to make a systematic study of the gas [8]. He observed the solubility of hydrogen sulfide in water and its oxidation to sulfur by air, nitric acid, or chlorine and noted its reactions with solutions of several metallic salts.

It was not until 1796 that Berthollet analyzed the gas and recognized it as hydrogen sulfide [8]. In 1785, a commission was appointed in Paris to investigate numerous accidental deaths which were apparently caused by gases emitted from the sewers [8]. Although hydrogen sulfide had not been identified at that time, two distinct types of poisoning, now recognized as being characteristic of exposure to low and high concentrations of hydrogen sulfide, were described. The first type, referred to as the "mitte," was an inflammation of the eyes and mucous membranes, and the second, referred to as the "plomb," was a form of asphyxia. Chemical analyses by Dupuytren, Thenard, and Barruel in the early 19th century confirmed the presence of hydrogen sulfides in the sewers, and these investigators attributed many of the sewer-related deaths to this gas [8].

Chaussier, in 1803, described an experiment on hydrogen sulfide toxicity in animals and indicated that skin absorption was a possible route of poisoning, as well as inhalation and injection into stomach or rectum [8]. In further experimentation, Nysten injected saturated hydrogen sulfide solutions into the veins of animals and found that three injections of 10 cc of a saturated hydrogen sulfide solution into a dog caused excitation followed by depression of respiratory and motor activity with complete recovery by the next day [8].

Christinson, in 1827, observed two types of hydrogen sulfide poisoning which he designated as acute and subacute [8]. In his 1829 analysis of air in Paris sewers, Gaultier de Claubry found up to 2.99%, with a mean of 2.29%, of hydrogen sulfide present [8]. In 1861, Holden and Letheby described the medical histories and post-mortem examination results of workers poisoned in London sewers [8]. Hoppe-Seyler, in 1863, observed

that a dark green substance termed "sulphmethemoglobin" resulted from the passage of hydrogen sulfide through blood, presumably from the action of hydrogen sulfide on the oxyhemoglobin. His work led to a number of chemical studies of hydrogen sulfide on the blood [8].

Experiments on animals were reported by Eulenberg in 1865 and by Biefel and Polek in 1880 [8]. Eulenberg found that cats, rabbits, and doves were killed within a short time by hydrogen sulfide at a concentration of 0.1% and that young animals were more sensitive to this substance than adult ones. Biefel and Polek observed that a rabbit died within 75 minutes when exposed to hydrogen sulfide at a concentration of 0.05%; they also observed crying, convulsions, trembling, respiratory disturbances, and increased salivation [8]. Total amounts of hydrogen sulfide used were not specified.

In the first case of hydrogen sulfide poisoning reported in the United States, Bell and Raphael described in 1851 an accident caused by the liberation of gas formed in an outhouse [8].

Most early industrial physicians in the United States were unfamiliar with hydrogen sulfide poisoning because hydrogen sulfide poisoning had become an important industrial hazard only in the last 60 years [9]. It was not until the 1920's that any practical information on hydrogen sulfide exposures became available in the United States. Since then, because of increased use and, therefore, an increased number of accidents caused by hydrogen sulfide, investigations have been undertaken by such groups as the Yale University Department of Applied Physiology, the Health Laboratory of the US Bureau of Mines, the American Petroleum Institute, the National Safety Council, and the Manufacturing Chemists Association [3].

Hand [10] reported in 1939 that more than 50,000 men and women were employed in about 20 viscose factories in 13 states. In one US viscose factory, where several hundred tons of hydrogen sulfide were produced over a period of 15 years, 174 poisonings, but no deaths, were recorded [3,11]. According to Legge [12], 78 workers in the spinning department and the acid cellars of an artificial silk factory in the Netherlands were surveyed in 1922. Complaints of burning and smarting of the eyes were recorded for 25 of the 78 workers, headache for 32, loss of appetite for 31, and loss of weight for 20. More than a quarter of the workers experienced dizziness. Hydrogen sulfide concentrations in the air of that factory were reported to vary from 20.4 to 35.4 mg/cu m [12].

Hydrogen sulfide had been cited as a potential hazard in 50 occupations in 1945 [13]. Its effects were recognized in the petroleum industry more than 40 years ago [13]. The discovery of large deposits of high-sulfur oil in the United States resulted in a substantial increase in occupational exposures to hydrogen sulfide, and hydrogen sulfide exposure in the petroleum industry was one of the major industrial hazards in this country in 1930 [9]. Men have been found dead on derrick floors, apparently overwhelmed by the rush of gas when they first drilled into a pocket [9]. Before the danger became known, exposures to large quantities of hydrogen sulfide gas occurred without respiratory protection, and as many as 31 workers became unconscious while "closing in" a single oil well [14]. In some oil-producing fields, gases were found to contain up to 10-12% of hydrogen sulfide by volume [9].

Several investigations have suggested that the toxicity of hydrogen sulfide is enhanced by humid air, such as that present in many mines [13].

In a 1942 mining incident [13], four men attempting to prevent water from entering a shaft were overcome by hydrogen sulfide. The hydrogen sulfide detector showed a concentration of 25 ppm hydrogen sulfide above the water 5 minutes after the fan that had been run to disperse the gas was stopped.

Historical reports of chronic hydrogen sulfide poisoning are relatively uncommon. Legge [12] described the case of a workman who had been exposed to hydrogen sulfide for 2 years in the early 1900's at a sulfur-black establishment. In April 1905, he experienced ataxia, pains, paresthesias, muscular atrophy, and a narrowing of the visual field. By December 1906, he was totally blind, with pain and persistent paresthesia; he died of bronchopneumonia in May 1910. Microscopic examination of sections of the spinal cord revealed no inflammation, but extensive degeneration. That this change can be attributed to the workman's exposure to hydrogen sulfide is uncertain.

Effects on Humans

Most of the reports discussed in this section describe effects of acute exposure to hydrogen sulfide. Persistent effects on humans after long-term exposure to hydrogen sulfide have not been conclusively demonstrated, but results of numerous studies [3,15-18] suggest that there are subacute effects.

In the high-sulfur oil fields of Wyoming and western Texas, 26 persons died from exposure to hydrogen sulfide at unspecified concentrations between October 1, 1974, and April 28, 1976 [19]. A young man was hospitalized with pneumonia that was attributed to exposure to hydrogen sulfide at unspecified concentration. He survived, but details of

his recovery were not reported [19].

A driver cleaning his chemical-waste tank-truck in 1971 was overcome by hydrogen sulfide and died [20]. Hydrogen sulfide was later measured inside the tank hatch at a concentration of 12,000 ppm. Small birds in the vicinity were also killed.

Breysse [21] reported that a worker was found dead after he had gone to plug a leaking exhaust line from a poultry feather cooker used to make fertilizer. Measurements were later made during the cooking cycle, and hydrogen sulfide was found to escape from the leaking pipe at concentrations of 2,000-4,000 ppm.

Prouza [22] reported in 1970 that 10 Czechoslovakian workers were poisoned, 1 fatally, when hydrogen sulfide seeped into an empty viscose spinning tank from another tank through a common overflow pipe. The hydrogen sulfide concentration inside the tank was measured at 2,800 ppm 4.5 hours after the accident. A maintenance worker who entered the tank to loosen and remove a heating element complained of the odor and of not feeling well, then collapsed. Two coworkers entered the tank without protective equipment and tried to lift the stricken man up to the foreman, who stood outside the tank, but the foreman felt weak as he bent over the tank and the two would-be rescuers within the tank were also becoming stuporous. The foreman let the first worker fall back into the tank and managed to help the other two out of it. A fifth worker went for protective equipment and returned to find that the total of poisoned would-be rescuers had risen to nine, six of them unconscious. The first victim and four of the rescuers were removed from the tank by workers wearing protective equipment and were taken to the factory first-aid station and

then to the hospital. The first man was pronounced dead.

The post-mortem examination showed a greenish discoloration of the gray matter of the brain. The four hospitalized rescuers complained of nausea, weakness, and pain in the chest. They were discharged after 7 days with normal eye, neurologic, and psychiatric examination results but slightly abnormal electrocardiograms (ECG's). Similar examinations showed no abnormalities in the remaining five, who declined hospitalization. One of these workers, who had had a history of heart trouble but normal ECG's for the preceding 13 years, had a nonfatal heart attack a month after the accident. Prouza [22] concluded that the first worker probably died in a few seconds and that his fellow workers had showed "solidarity and a loss of judgment" in rushing to the rescue without protective equipment and routine precautions.

In a similar incident in Michigan, hydrogen sulfide at a concentration of 1,000 ppm caused the death in a well of a worker and four would-be rescuers, including the fire chief, who entered wearing a supplied-air respirator but removed the face mask to attempt to shout instructions to men on the surface [23]. Hydrogen sulfide poisoning may be mistaken for drowning, as it was in this case [23], or heart attack [24], or electrocution [25], with grave hazard to rescuers.

McCormack [26] reported hydrogen sulfide poisoning of two sewer workers exposed at an unknown concentration. One descended into a small, confined space to unclog a drain and collapsed. A second worker attempted to rescue him and was also overcome. Paramedics were called and initiated resuscitation at the scene after the workers were removed from the sewer, but the first worker was dead on arrival at the hospital. The second was

hospitalized, cyanotic and unconscious, with rigid extremities, thrashing his legs in a bicycling fashion. He was breathing vigorously, and his pupils were dilated and reactive. He was incontinent of feces. Methane poisoning was suspected initially, but hydrogen sulfide was inculpated by blackened coins found in the patient's pocket. He was given amyl nitrite by inhalation and sodium nitrite intravenously to prevent poisoning of the cytochrome system and was given medication for agitation and pulmonary edema. The patient was discharged 5 days later without residual effects. This occurred in 1975; a similar incident was also reported by Breysse in 1970 [27].

St. Hill [28] reported the deaths, attributed to hydrogen sulfide, of two boys, 15 and 16 years of age, who worked in a tannery. A limepit had been filled with clean water and left unused for 2 years, in which time lime and acid solutions had drained off hides nearby and trickled into the pit. The pit, 7 feet deep and 6 feet square, was drained, and a man and the older boy stirred up the sludge at the bottom with water from a hose, then put on thigh boots and climbed in to move the sludge toward the open drain with their feet. After they had stirred and thinned the sludge for some time, the man collapsed and the boy clutched the ladder and fell backwards with it into the sludge. The foreman managed to prop the man against the wall and then collapsed himself. Two other workers, one of them the 15-year-old, also entered the pit and lost consciousness. Eventually, all were removed, but the two boys were dead. On autopsy, sludge saturated with hydrogen sulfide was found in the air passages and stomachs of the two boys, and their bodies smelled strongly of hydrogen sulfide. Followup data were not reported for the survivors. No air

concentrations were reported for hydrogen sulfide in the pit, but St. Hill [28] inferred that the gas was evolved in large quantities when the sludge was stirred. No one at ground level had noticed any unusual odors.

Freireich [29] reported the death of a 17-year-old boy exposed to an undetermined concentration of hydrogen sulfide while attempting to rescue his father in a cesspool-cleaning operation. The father had entered the cesspool to complete a cleanup undertaken the previous day by professional cesspool cleaners who had pumped the 10-foot-deep cesspool half empty and poured in several gallons of concentrated sulfuric acid. The father noticed smarting or burning of his eyes and left the cesspool, then returned and left twice more. On his fourth descent, he felt weak, called to his son, and lost consciousness. When he regained consciousness, he saw the boy lying on the floor of the cesspool. He tried to move the boy but was again overcome before both were rescued by neighbors. The father recovered quickly, but the son died despite artificial respiration.

At autopsy, the son's corpse had a greenish-blue cyanosis of the head and face, hands, and legs. A faint yellow-brown stain appeared on lead acetate paper applied to the pectoral muscles, and the paper turned dark brown when held near the cut end of a bronchus. Pulmonary edema and congestion and several large subpleural hemorrhages were present. Sandy material mixed with sewage obstructed bronchi of the third and fourth order. The spleen and kidney showed congestion. Spectroscopic examination of the blood failed to reveal the presence of sulfhemoglobin or methemoglobin. Whether the cause of death was hydrogen sulfide poisoning or mechanical asphyxia from aspirated material was not determined. Freireich [29] suggested that the increased respiration from the son's

attempts to rescue his father may have caused the son to inhale a greater quantity of hydrogen sulfide than the father.

Just as unconsciousness produced by hydrogen sulfide may cause death by drowning in as little as 6 inches of water [28-31], it may also cause death from falls. Spolyar [32] reported that a worker cleaning a 12-foot-deep gluten vat in a starch-manufacturing plant lost consciousness 25 minutes after entering the tank. The supervisor, on seeing the worker slump, entered the vat and placed the unconscious man on his shoulder. He started back up the ladder, but lost consciousness himself near the top and fell back to the bottom of the vat with the worker. Another worker went to summon a rescue squad with oxygen masks, but in the meantime a third worker also entered the vat and collapsed. The supervisor was dead on arrival at the hospital, and a fractured skull was confirmed at autopsy. The other two workers were hospitalized and remained unconscious for 2 days. They showed marked respiratory difficulty, but recovered completely in 7 days. The vat was aerated after the rescue operation, and analysis showed no more than 10 ppm of hydrogen sulfide the following morning. A 200-gram sample of sludge from the bottom of the vat was placed in a 5-liter jar, and within 4 hours hydrogen sulfide was detected in air from the jar at a concentration of 300 ppm; after 9 hours, the concentration was over 400 ppm. The vat had been idle for 10 days when the incident occurred, though normally it was emptied every 2-3 days. Spolyar [32] concluded that the men in the vat had been overcome by hydrogen sulfide liberated by the cleaning process. Several similar incidents of fatal falls caused by unconsciousness from hydrogen sulfide have been described [14,33].

Convulsions have been reported [15,31,33] with exposure to hydrogen sulfide, but the range of intensity of the convulsions seldom has been mentioned. Poda [3] mentioned twitching, but violent convulsions may occur. Milby [4] reported an acute exposure to hydrogen sulfide at an undetermined but high concentration when a cylinder containing the gas (liquified under a pressure of 250 psi) was punctured by a rifle shot. The liquid-and-gas cloud moved some 50 yards upwind and caused two men to collapse. One developed convulsions after 5 minutes of artificial respiration, and eight men were required to move him to the ambulance. Despite the severe convulsions, he survived.

Kaipainen [34] reported that a farm laborer was found unconscious in a cowshed where he had been shoveling manure. The duration and level of exposure were not known, but the exposure was reported to have lasted perhaps 2 hours and fit a pattern suggesting exposure to hydrogen sulfide. The worker was taken to the hospital, where he had epileptiform convulsions. The following day, he was restless and incoherent; patellar, Achilles tendon, and radial reflexes were absent, and the ECG showed negative T waves on leads II and III. Leg spasticity and the abnormal ECG persisted through the 3rd day but returned to normal by the 5th day. On the 3rd day, urinalysis showed 0.5% albumin and a sediment containing red and white blood cells and hyalin cylinders, indicating kidney damage. Two weeks later, blood cells and hyalin cylinders, but no albumin, were still present in the patient's urine. In the same 2-week period, nonprotein nitrogen in the urine decreased from 90 mg/100 ml of urine to 46 mg/100 ml of urine. The patient was discharged from the hospital after 3 weeks. At followup examination a month later, he reported that he had felt well

except for slight dizziness.

Accidental mixing of acid with sulfide solutions in a tannery [24,35], or in sewer lines [36,37], resulted in the release of enough hydrogen sulfide (concentrations unknown) to kill eight workers and sicken dozens of others, some of whom required hospitalization.

Kemper [38] reported a case of acute hydrogen sulfide poisoning that was unusual in several ways. The victim, a 31-year-old refinery worker, survived exposure to hydrogen sulfide at about 1,000 ppm, a concentration that generally is rapidly fatal. The concentration was measured soon after the accident. The worker was found unconscious and deeply cyanosed near a spill of diethanolamine contaminated with hydrogen sulfide. He was not breathing and was given artificial respiration by the back-pressure arm-lift method. He was admitted to the hospital within 25 minutes of the time he was last seen walking in the vicinity of the accident. Oxygen was administered en route. When he arrived at the hospital, red foam was coming from his mouth, his respirations were depressed, and his heart rate was 180/minute and regular. No blood pressure could be determined from either arm. Violent convulsive seizures occurred repeatedly, and the worker developed opisthotonos. Endotracheal intubation was performed to permit alternating suction and oxygen administration. The patient's condition improved within 5 minutes; his color became less dusky, his systolic blood pressure was 85 mmHg (diastolic unobtainable), and his pulse rate was 150 beats/minute and regular.

He was transferred from the emergency department to the respiratory unit of the hospital, and was rendered hypothermic to reduce his body's demand for oxygen. Convulsions were controlled with drugs, the excess

bronchial secretion stopped, and the patient's vital signs improved, although he was still comatose. He was given 500 ml of mannitol intravenously to promote urine flow, and he later showed gross hematuria. When respiratory distress occurred, the patient was ventilated by mechanical respirator. An hour after admission, the patient's color was normal, and 48 hours later he was awake and responsive. His kidney function was returning to normal, but he showed signs of lung consolidation and patchy bronchopneumonia. An ECG taken the following day showed "a left ventricular parietal block with posterolateral myocardial ischemic changes"; his heart rate was 132 beats/minute and regular. A chest radiograph was normal 12 days after the accident, and the patient was discharged from the hospital 3 days later. Serial ECG's taken during the latter part of his hospital stay and after his discharge showed a gradual return to normal over several weeks. There were sequelae; the worker suffered mild depression and lassitude for several months. He was absent from work for 134 days and a year later still had complete amnesia of the day of the accident. Kemper [38] believed that cerebral hypoxia probably accounted for the amnesia and the long period of depression and lassitude. The method of treatment departed from the usual supportive therapy by being much more active; the nearly complete recovery of the worker indicates that even severe poisoning by hydrogen sulfide may be overcome by sufficiently prompt, vigorous, and intensive treatment.

An air pollution incident in Poza Rica, Mexico, lasted only 20 minutes but resulted in the hospitalization of 320 persons and in the deaths of 22 [16]. About half the domestic animals, birds, and pets living in the area also died. The poisoning was attributed to hydrogen sulfide

released from a malfunctioning sulfur recovery unit of the local natural gas industry. No measurements of the gas concentrations were reported, but the investigators estimated the peak concentration to have been 1,000-2,000 ppm of hydrogen sulfide in the air [16]. Clinical findings for the exposed persons included loss of the sense of smell, burning eyes, cough, dyspnea, pulmonary edema, nausea, vomiting, unconsciousness, severe headaches, vertigo, partial paralysis, neuritis of the acoustic nerve, lingual difficulty, and aggravation of a preexistent case of epilepsy. Of the people who died, nine were dead on arrival at the hospital, four died within 2 hours, four within 6 hours, one 24 hours after arrival, and one each on the 2nd, 5th, 6th and 9th days after hospitalization. Lasting sequelae were reported for only four of the human survivors (two with acoustic-nerve neuritis, one with dysarthria, and one with aggravated epilepsy and new nervous manifestations). Most of the animals that died (canaries, chickens, ducks, geese, cattle, pigs, and dogs) did so in the acute phase of the air-pollution crisis, except for one pig that died 3 days later.

The release of hazardous quantities of hydrogen sulfide during the stirring of human sewage [39] and animal manure [34] has also been reported. Aufdermaur and Tonz [39] reported three cases of poisoning, one fatal, of children exposed to hydrogen sulfide evolved at unspecified concentrations in rustic latrines connected directly to cesspools equipped with stirrers. One child died, one recovered, and one had lasting sequelae in the form of aphasia, agraphia, and mental retardation.

Johnstone and Miller [31] reported the survival, but with massive brain damage, of a worker exposed to hydrogen sulfide at an unspecified

concentration. A few days after exposure, the worker's ECG recording gave indications of a right bundle branch block.

Sukhanova [40] reported observations of gastrointestinal changes in refinery workers and in animals exposed to hydrogen sulfide at unpsecified concentrations in air. Reduced gastric pepsin secretion (measured as uropepsin activity) was found in workers exposed to "cracking gas" (hydrocarbons, hydrogen, and hydrogen sulfide). These workers also had higher blood amylase activity levels and decreased trypsin activity. These results were generally confirmed in experiments with rats exposed for 5 months to cracking gas, but the concentrations of hydrogen sulfide were not specified, nor was the hydrogen sulfide exposure separate from exposures to hydrocarbons or other constituents of cracking gas.

In a few human subjects, the forearm was exposed to a solution containing 8.3% ammonium hydrogen sulfide or to pure hydrogen sulfide gas for 10-20 minutes; this produced a localized warm sensation, erythema, and pigmentation similar to a sunburn. Increased hydrogen sulfide absorption was reported in animals when the skin was damaged mechanically or by a chemical agent [41].

A case of chronic intoxication by carbonization gas (from the low-temperature distillation of lignite) appeared to resemble hydrogen sulfide intoxication in many ways [42]. The patient, who had worked in the gas plant for an unspecified time characterized as long by the author, complained of increasing torpor, coughing, and burning and a feeling of pressure in his eyes. Later, he developed stomach pains, headaches of increasing severity, and vertigo. There was bilateral conjunctivitis. The hydrogen sulfide content of carbonization gas averaged 2%. Methane and

carbon monoxide, about 10% each, and heavy hydrocarbons, almost 1%, were also present.

Howes [43] investigated tannery workers' complaints of painfully sore eyes, severe photophobia, and tears which "burned the cheeks." Sulfides were being used in an adjoining building, and rapid darkening of a piece of lead acetate paper exposed in the affected men's work area indicated the presence of hydrogen sulfide. Howes concluded that the eye inflammation was an early warning signal of hydrogen sulfide poisoning and that open-air ventilation of the work area had prevented more serious poisoning.

Brown [44] reported that a foreman in a rubber company developed "blue vision" after "heavy" but unspecified exposures to hydrogen sulfide. His vision was normal by the following day. Brown drew a parallel with the effect seen with amine accelerators, in which the superficial layer of corneal cells acted as a filter. The author [44] also described the sudden collapse of a worker during the splitting and handling of ebonite (hard rubber foam) boards in which hydrogen sulfide may be trapped. The hydrogen sulfide concentration was not measured, but the work area was poorly ventilated because large quantities of materials were stacked nearby, and smelled "overpoweringly" of hydrogen sulfide 2.5 hours after the accident. To determine the approximate exposure concentration, four boards were cut with the saw; a hydrogen sulfide concentration of 100 ppm was measured at face level. The worker who collapsed had handled 850 boards. He had not complained of the odor, but had said he had felt tired before his collapse. He recovered promptly, without complaints except of a severe frontal headache, and returned to work the following day.

Beasley [45] described three cases of delayed eye irritation in two maintenance fitters and a visiting engineer in a gas plant. Clogged pipes were being cleaned with steam, resulting in exposures to steam, ammonia, carbon dioxide, and hydrogen sulfide at unspecified concentrations. Beasley attributed the delayed eye effects to hydrogen sulfide. The exposed workers described a gritty sensation in the eyes, blurred or hazy vision (headlights merged into a dumbbell-shaped glare; a silk screen seemed to be interposed in the line of vision), rainbow rings seen around street lamps, spasm of the eyelids, and retro-orbital pain. Beasley [45] cited other papers describing similar eye effects produced by hydrogen sulfide in support of his conclusion that that gas was the principal irritant in the cases he reported.

Commenting on the same cases reported by Beasley [45], Carson [46] noted that, of five men who might have been exposed, it was the three oldest who had vision disturbances. None of the workers complained of heat, humidity, or odor at the time they were exposed, which lends support to Beasley's [45] conclusion that hydrogen sulfide, not steam or ammonia, was responsible for the eye irritation.

Michal [18] reported eye lesions caused by hydrogen sulfide in a sugar-beet washing operation. Hydrogen sulfide concentrations were not given. Water containing sulfites was drawn from a river and stored in a holding tank where microorganisms converted the sulfites to hydrogen sulfide. Workers (number unspecified) using this water to wash the beets first saw colored rings around lights and then developed ocular lesions, severe pain and burning in the eyes, lacrimation, spasms of the eyelids, and conspicuous redness of the eyes. After 2-4 days of rest, the condition

improved, so that the workers were able to return to work after 3-5 days.

Masure [47] reported studies of spinning-room conjunctivitis. Wide differences existed in individual susceptibility to the chemicals, including hydrogen sulfide and carbon disulfide, found in spinning rooms. Most workers appeared to become accustomed to the chemicals, but a few became sensitized. Related animal experiments led Masure to conclude that the conjunctivitis was caused by hydrogen sulfide, though concomitant exposure to carbon disulfide or sulfuric acid lowered the corneal threshold to hydrogen sulfide. The natural lack of blood supply to the central part of the cornea was thought to be a factor in the preferential development of lesions in that area.

Epidemiologic Studies

Nesswetha [48] studied etiologic factors in 6,500 cases of keratitis superficialis punctata (spinner's eye), attributed to occupational exposure to hydrogen sulfide in 1969. At a hydrogen sulfide concentration of 15 mg/cu m (about 10 ppm), eye irritation occurred after 6-7 hours of exposure. At a hydrogen sulfide concentration of 20 mg/cu m (about 14 ppm), symptoms developed after 4-5 hours. Spinner's eye appeared at hydrogen sulfide concentrations below the maximum allowable concentration (15 mg/cu m) when carbon disulfide was present. Other stressors, including noise, thioformaldehyde, and other irritating chemicals likewise caused increased susceptibility to eye irritation by hydrogen sulfide. Night-shift workers had a 41% higher incidence of spinner's eye than day-shift workers. The investigator [48] concluded that the mechanism of production of spinner's eye was neural and that the condition resulted from the joint

effects of several factors, of which hydrogen sulfide was the most important. The neural etiology is plausible because the conjunctivitis was reported to be usually accompanied by hyperemia of the ciliary body ("ciliarer Injektion") [48]. The concomitant presence of carbon disulfide in the air of spinning rooms should be considered in evaluating the correlation of effects on the eyes with the reported amount and duration of exposure to hydrogen sulfide.

According to Ahlborg [15], 70% of workers exposed to hydrogen sulfide in their daily work, often at 20 ppm or more, complained of fatigue, somnolence, lack of initiative, decreased libido, loss of appetite, headache, irritability, poor memory, anxiety, dizziness, itching, eye irritation, respiratory tract irritation, gastrointestinal disorders, insomnia, and backache. Acute exposures to hydrogen sulfide at higher, generally unspecified, concentrations were associated with signs of cerebral and extrapyramidal damage, facial paralysis, prolonged reaction time, absent or abnormal reflexes at both cranial and spinal nerve levels, poor memory for recent events, depression, either timidity or fierceness, and with an epileptic-like seizure. Sequelae of acute hydrogen sulfide exposure occurred even when the affected individual had not lost consciousness. In one person, gastritis persisted for 1 year after exposure at an unspecified concentration. Another worker developed problems of maintaining equilibrium 6 months after acute exposure to hydrogen sulfide at an unspecified concentration. The disturbance of equilibrium still persisted after 3 years [15].

Poda [3] observed 174 workers exposed to hydrogen sulfide at two heavy-water manufacturing plants. The hydrogen sulfide concentrations were

not reported, but the normal maximum working concentration limit voluntarily adopted at the heavy-water plants was 10 ppm of hydrogen sulfide for an 8-hour day, which was said to permit work with safety and to avoid the problems which had occurred before the adoption of this limit.

Examination of the records on 42 exposed workers who had become unconscious after exposure to hydrogen sulfide revealed that the majority described the odor of hydrogen sulfide as sickeningly sweet, rather than as that of rotten eggs. A survey of the signs and symptoms reported by 123 of the workers showed, in decreasing order of frequency: weakness, nausea, dizziness, headache, nervousness, burning or watery eyes, clinical shock, gastrointestinal upset, vomiting, elevated blood pressure, dyspnea, sweating, cyanosis, flushed face, abdominal cramps, flatulence, arm and leg pain, rigidity, irrational and combative behavior on returning to consciousness, twitching, and frothy sputum. The most significant sign is clinical shock. The combative individual had been drinking alcoholic beverages the previous evening; however, other papers have mentioned combative behavior, irritability [15], or excitability [49] without mentioning consumption of alcohol. The worker with frothy sputum had been drinking heavily the night before and had an upper respiratory infection [3]. In at least 27 workers, symptoms, including nervousness, headache, nausea, insomnia, weakness, cough, eye irritation, throat irritation, and soreness of the neck and shoulders, persisted for more than 4 hours. One mechanic, incontinent of urine and feces, was found unconscious and cyanotic with no apparent pulse or respiration. He was revived by artificial respiration. Upon hospitalization thereafter, he was discovered to have pulmonary edema, a productive cough, and a shock level of blood

pressure. His blood pressure failed to rise until the 3rd day, despite administration of caffeine, phenylephrine hydrochloride, digitalis, and carbogen (3-5% carbon dioxide in oxygen). When discharged from the hospital, the worker had only a dry cough. No sequelae were observed during the next 3 years. Poda [3] reported no increase or decrease in sensitivity to hydrogen sulfide with exposure, but did say that workers who had consumed alcohol in the 24 hours before exposure were affected at lower concentrations.

Bulatova et al [50] studied 2,465 high-sulfur petroleum refinery workers in two different cities who were exposed to hydrogen sulfide at unspecified concentrations, with 601 machine-tool workers and 706 railroad-station workers as controls. The incidence of cholecystitis (gall bladder disease), cholangitis (bile duct disease), and cholelithiasis (gallstones) and the number of workdays lost because of these were greater in the oil refinery than in the other groups. The morbidity of oil refinery workers with over 5 years service was greater than that of those with less time in service. With contrast cholecystography, it was determined that 56 of 74 cases of biliary dyskinesia in oil-refining workers were of a hypermotor type and 12 were of a hypertonic type, whereas hypomotor dyskinesia was more common in other patients with cholecystitis. An electrogastrogram showed unevenness, indicating an irritated stomach, in 20 of 68 subjects. Gastric secretion was normal in 49 persons; 56 showed reduced pepsin activity.

In May and June 1964, the city of Terre Haute, Indiana, had a succession of air pollution incidents in which citizens' complaints were recorded and the hydrogen sulfide concentration in the air was meas-

ured [17]. The highest concentrations of hydrogen sulfide reported in this study [17] were between 2 and 8 ppm at the fence line near a chemical-disposal lagoon. Some recorded data were lost. Hydrogen sulfide levels ranged between 0.022 and 0.125 ppm for 7 consecutive hours, and 26 odor complaints were registered. Citizens reported nausea, vomiting, diarrhea, abdominal cramps, shortness of breath, choking, coughing, sore throat, chest pain or heaviness, headache, burning eyes, fainting, awakening at night, loss of sleep, acute asthma attacks, anorexia, and weight loss. In general, they did not consult physicians or seek assistance at a hospital. There were, however, four deaths attributed to chest diseases (emphysema, asthma, bronchitis) in April and May 1964; no deaths from these causes were recorded in the preceding higher risk months of February and March. Conclusions of the study were that complaints were related to the concentrations of hydrogen sulfide in the air and that potential danger existed for susceptible individuals (notably infants, the aged, and the infirm). Worker populations are generally healthier than city populations and might prove less susceptible to the effects of hydrogen sulfide. Still, this study did suggest that hydrogen sulfide can irritate the eyes and respiratory system at concentrations below 1 ppm, and that it has adverse effects on sleep and appetite and poses a danger at low concentrations to individuals with heart or lung diseases.

Animal Toxicity

The effects of hydrogen sulfide on humans and animals are similar. The studies in this section have firmer data on environmental concentrations than do the human case studies and describe results that

could not ethically be obtained with human subjects.

Michal [18] exposed rats to hydrogen sulfide for 3 hours at 36 ppm or briefly at 860 ppm. Upon microscopic examination of the rats' corneas, he found nuclear pyknosis, edema, and separation of cells. Michal noted that these eye irritations were similar to those in workers in the viscose rayon industry, which he attributed, therefore, to the action of hydrogen sulfide.

Lund and Wieland [51] demonstrated the effects of exposure of three Rhesus monkeys in a chamber to hydrogen sulfide which reached a concentration of 500 ppm within 3 minutes. That concentration was maintained while the air was being recirculated to remove carbon dioxide and water vapor. The brain, liver, heart, kidneys, and adrenals were examined microscopically on autopsy. No control animals were mentioned. Typically, the animals lost consciousness abruptly in 15 minutes, without warning signals except repeated deep breaths as if gasping or yawning just before collapse, and fell from a standing position with stiff extremities, as if struck a violent blow. The first monkey had respiratory arrest and cardiac failure after 35 minutes of continuous exposure. No changes were observed on examination of the brain, heart, kidneys, or adrenals. The second animal was exposed to hydrogen sulfide at 500 ppm for 25 minutes on 1 day and for 17 minutes after a 3-day interval. The exposure was halted the first time because the monkey stopped breathing and required artificial respiration by compression of the thoracic wall. The second exposure was terminated when the monkey lost consciousness. The monkey was killed 5 days later and showed necrosis of the occipital cortex of the brain, necrosis, hyperemia, and gliosis of the basal ganglia, a decrease in the

number of Purkinje cells in the cerebellar cortex, moderate hyperemia of the liver, and normal heart, kidneys, and adrenals. The third monkey was exposed to hydrogen sulfide for 22 minutes at 500 ppm and was still breathing spontaneously upon termination of exposure. It regained consciousness 140 minutes later, but remained somnolent for days, had no appetite, and its few movements were uncoordinated. The monkey was killed 10 days later, its condition having become only slightly more normal by that time. Microscopic examination revealed extensive necrosis of the parietal and occipital cortex of the brain, a reduced number of Purkinje cells in the cerebellar folia, isolated accumulation of glial cells in otherwise normal basal ganglia, and normal heart, liver, kidneys, and adrenals. The results indicated that the brain, particularly the motor cells of the cerebellum, was the principal target of inhaled hydrogen sulfide. This finding is supported by the work of Evans [11], who noted that "the most conspicuous actions of sulphides are on the nerve centres, which are first stimulated, then paralysed." Evans suggested that artificial respiration may be an effective treatment for poisoning by hydrogen sulfide because the paralysis of the nerve centers, the "reduction of oxyhemoglobin," and the combination of sulfides with iron in cytochrome A3 are reversible processes.

Cralley [52] reported inhibition of tracheal ciliary activity of adult rabbit tissue in vitro by hydrogen sulfide at concentrations between 300 and 800 ppm in warm air pumped over the excised tissue at a rate and volume simulating respiration in a living rabbit. Exposure to hydrogen sulfide in air at 800 ppm resulted in cessation of ciliary activity in less than 2 minutes; at 700 ppm, in 2 minutes; at 600 ppm, in 2.5 minutes; at

500 ppm, in 3 minutes; at 400 ppm, in 4.5 minutes; and at 300 ppm, in 6.5 minutes. Exposure to hydrogen sulfide at 600 ppm for 5 minutes or at 400 ppm for 10 minutes caused cessation of ciliary activity without recovery in air but, after exposure at 800 ppm for 3, 5, or 10 minutes, recovery occurred in Ringer's solution. The ciliary response in rabbits was, according to Cralley [52], similar to that of human tracheal mucosa.

Kosmider et al [53] exposed rabbits, about 1 year old, to hydrogen sulfide at a concentration of 0.1 mg/liter (72 ppm). Ten animals were exposed once for 1.5 hours, and 17 were exposed for 30 minutes/day for 5 days. Ten rabbits were controls. ECG's were recorded under Evipan (hexobarbital) anesthesia. Baseline ECG's for all rabbits were obtained 10 days before exposure. Rabbits exposed for 1.5 hours lost consciousness and showed disorders of repolarization of the ventricles but no arrhythmias. Those exposed for several days had arrhythmias, including atrial fibrillation in two rabbits, ventricular extrasystoles, and one or more ectopic pacemakers, in addition to disorders of repolarization similar to those seen in the first group. Arrhythmias persisted for several days after exposure ended but could be controlled by intravenous injections of sodium citrate. The activity of the enzymes ATP phosphohydrolase and NADPH2 oxidoreductase in heart muscle and in the lining of blood vessels was reduced in exposed animals. The authors cited this in support of the contention that hydrogen sulfide inhibits intracellular respiration.

Kosmider and others [54] also investigated "subacute" hydrogen sulfide poisoning, using 70 adult rabbits of mixed breed and either sex. Twenty rabbits were used as controls; 10 were given "Vitaral" (a dietary supplement of vitamins and minerals) with their food but were not exposed

to hydrogen sulfide; 20 were exposed to hydrogen sulfide in air at a concentration of 0.1 mg/liter (72 ppm) for 1 hour/day for 14 days and received the dietary supplement with their food; and 20 were similarly exposed to hydrogen sulfide but were fed the regular food with no Vitaral supplement. Arterial blood samples were taken for chemical studies. The rabbits were killed after 14 days of exposure, and samples of blood, liver, kidney, cerebrum, and heart were taken for chemical tests or microscopic examination. Also, human blood serum was tested chemically in vitro, the tests being repeated 10 times. One part of the human serum served as control and four other parts were saturated for 20 minutes with hydrogen sulfide. Dilute solutions of magnesium chloride, cupric sulfate, or both, were added to three of the hydrogen-sulfide-saturated serum samples. Exposure to hydrogen sulfide resulted in a drop in the albumin level and a rise in serum globulins, especially beta globulin; although these changes were not statistically significant, more normal values were found after administration of Vitaral. The calcium ion concentration in the rabbit serum was unchanged after the animal was exposed to hydrogen sulfide, but there were lower serum concentrations of iron, copper, carbon dioxide, alkaline buffers, and magnesium, and a lower pH, the last two observations being statistically significant. Thymol turbidity and glutamic-oxaloacetic transaminase activity were singificantly increased in exposed rabbits, as were serum and heart alkaline phosphatase activity and ceruplasmin activity in serum, heart, and brain. All these changes were reversed by administration of Vitaral with the diet. Vitaral had little effect on the unexposed rabbits.

Microscopic examination of the rabbit tissues [54] for the enzymes succinyl dehydrogenase, acid phosphatase, alkaline phosphatase, and adenosine triphosphatase revealed a reduction in succinyl dehydrogenase activity in liver and kidney, reduction in alkaline phosphatase activity in the liver, and an increase in acid phosphatase activity in the liver after exposure to hydrogen sulfide. Vitaral increased the succinyl dehydrogenase activity and alkaline phosphatase activity in the liver.

The studies of human serum in vitro [54] showed a decrease or cessation of alkaline phosphatase and ceruloplasmin activity with exposure to hydrogen sulfide. These enzymes were reactivated by administration of "microelements of Vitaral." Magnesium chloride alone activated alkaline phosphatase after hydrogen sulfide inhibition; copper ions had a like effect on hydrogen-sulfide-inhibited ceruloplasmin. The authors concluded that hydrogen sulfide produces protein, mineral, and, consequently, acid-base disturbances. They also concluded that hydrogen sulfide poisoning disturbs brain, liver, and kidney metabolism and produces liver damage. One mechanism of action of hydrogen sulfide, they suggested, is based on its ability to bind alkali metals and thus decrease the activities of enzymes that require activation by these metals. "The protective mechanism of Vitaral is due to its ability to reactivate the disordered metal enzymatic activities [54]." The results of this study are consistent with the effects on cellular respiratory enzymes that have been attributed to hydrogen sulfide and with the observations of unconsciousness and other signs of adverse effects on the brain that have been produced by hydrogen sulfide.

Following injections by Sorokin and Olshanskaya [55] of 1-7.5 ml of water containing hydrogen sulfide at a concentration of 265 mg/liter into the ear veins of an unspecified number of rabbits, the heart rate slowed by lengthened diastole, and there were aberrations in the P and T waves of the ECG. The T wave increased at the start of injections, then decreased and, in some cases, disappeared. Usually, the T wave reappeared 30-40 seconds after an injection. The P wave disappeared at lower hydrogen sulfide concentrations and took longer to reappear. Rabbits that were given injections every 4-5 days for a month or longer showed adaptation, with less slowing of the heart and a quicker return to a normal rhythm in the ECG record. The authors noted that sensitivity (based on ECG) to hydrogen sulfide returned to original levels or higher, 10-15 days after cessation of repeated injections. It is not clear whether the authors attributed the adaptation to the heart itself or to some other organ or tissue, such as the blood or liver.

Duan [56] reported that 20 young male white rats weighing 60-90 g were exposed to hydrogen sulfide and tested for motor chronaxie. Ten other rats were used as controls and were tested similarly. All 30 were later autopsied. Twenty rats were exposed to hydrogen sulfide: 10 at a concentration of 0.02 mg/cu m (0.014 ppm) and 10 at 10 mg/cu m (7 ppm) for 12 hours each day for 3 months, except weekends. The chronaxie of extensors was longer than that of flexors in the control rats, as is normal. In the rats exposed to hydrogen sulfide, this relationship was reversed, beginning in the 8th week at the lower concentration and in the 3rd week at the higher concentration. By the 8th week, the group exposed at 10 mg/cu m (7 ppm) showed the normal relationship again but there was

greater than normal variability in both flexor and extensor chronaxies which continued into the postexposure recovery period. Microscopic examination showed swelling of dendrites on neurons in the cerebral cortices of the more heavily exposed rats, coupled with mild irritation of tracheal and bronchial mucosa. No microscopic evidence of damage was apparent either in the rats used as controls or in those exposed to the concentration of hydrogen sulfide reported to be 0.02 mg/cu m.

Hays [57] subjected mice, goats, and dairy cows to experimental exposures of hydrogen sulfide. Mice and goats were placed inside exposure chambers; cows were exposed in hoods that enclosed their heads and communicated with an established concentration of hydrogen sulfide in air. Each goat or cow served as its own control; groups of mice equal in number to the exposed groups served as controls. Body weight and food and water intake were recorded for all species, as were rectal temperatures for mice and goats. Carbonic anhydrase activity and pentobarbital sleeping time in mice, plasma cortisol concentration in goats, heart rate in goats and cows, and milk production in cows were measured. The goats were individually exposed; the data were then pooled in nominal experimental or control groups of 3-5 animals. Six Swiss-Webster mice were exposed to hydrogen sulfide at a concentration of 10 ppm and had a decrease in body temperature which was statistically significant within this experimental group but, because their mean body temperature was not significantly different from that of the control group, probably had no biologic importance. Eight mice exposed to hydrogen sulfide at a concentration of 20 ppm for 48 hours showed no significant difference from the control group in pentobarbital sleeping time. Hydrogen sulfide at 20 ppm depressed the food and water

intakes and body weight of mice. The LC50 for mice was 100 ppm for a 7.5-hour exposure, 50 ppm for 15 hours, and 30 ppm for 18.5 hours. Goats, like mice, showed decreases in food and water intake in the first few days of exposure to hydrogen sulfide, but the effects seemed only temporary. Hayes suggested different suppression mechanisms for exposure at 10 ppm versus 50 or 100 ppm. At these higher hydrogen sulfide concentrations, goats showed elevated plasma cortisol levels (about 50% mean increase). No statistically significant changes occurred in the cows, though milk production decreased both during and after exposure to hydrogen sulfide.

It is possible that toxic quantities of hydrogen sulfide can be absorbed through the skin, but the evidence is not conclusive. Walton and Witherspoon [58] reported the survival of two guinea pigs exposed for 1 hour to pure hydrogen sulfide gas on a 0.78-sq-in area of shaved abdominal skin and the deaths of two guinea pigs exposed, one for 38 minutes and one for 45 minutes, to pure hydrogen sulfide gas on half their bodies. A dog exposed for 1 hour to hydrogen sulfide gas on its shaved abdomen survived without adverse signs [58]. Petrun [59] observed changes in blood chemistry of rabbits whose backs were shaved and exposed to hydrogen sulfide at concentrations of 717 ppm and higher. Laug and Draize [41] found that, when rabbits' bodies were exposed to hydrogen sulfide for as little as 7 minutes, the air exhaled by the rabbits gave positive lead acetate tests for hydrogen sulfide. They also noted that two of the rabbits so exposed died in about 2 hours. The exposed skin showed a slate-gray discoloration with dark chocolate areas.

Wakatsuki [60] exposed four rabbits weighing about 2 kg each to hydrogen sulfide at a concentration of 100 ppm for 30 minutes/day for 4

months. Four rabbits were used as controls. The hydrogen sulfide was produced in a Kipp generator and passed through iodine to remove traces of arsine. Records were kept of the rabbits' body weight, erythrocyte and reticulocyte counts, leukocyte count, serum calcium concentration, serum proteins, and specific gravity of the blood. All results were normal, except for a leukopenia and lymphocytosis. These findings suggest that hydrogen sulfide may have an adverse effect on the reticuloendothelial system. Other effects might have developed if the exposures had been of longer duration.

Kuwai [61] conducted a similar study, using a somewhat more sophisticated gas-mixing apparatus, in which five rabbits were exposed to hydrogen sulfide at a concentration of 20-25 ppm for 4 hours/day for 150 days. He measured body weight, reticulocyte count, blood specific gravity, serum proteins, and serum cholesterol. Five rabbits were used as controls. Kuwai's rabbits, like Wakatsuki's, had results within normal limits in most of the variables measured. One rabbit exposed to hydrogen sulfide failed to gain weight, unlike the controls and the others exposed. The exposed rabbits also had higher amounts of serum gamma globulin than did the controls. It is difficult to conclude anything from studies using only four or five animals in the experimental and control groups. Kuwai's study does, however, tend to support the suggestion of reticuloendothelial system changes in Wakatsuki's results, and does match observations by other investigators of weight loss and loss of appetite in humans exposed to hydrogen sulfide.

Barilyak et al [62] studied the effects of a combination of carbon disulfide and hydrogen sulfide on reproduction in rats. Rats were exposed

to carbon disulfide and hydrogen sulfide at a combined concentration of 10 mg/cu m (the actual concentrations of carbon disulfide and hydrogen sulfide were not given); 26 rats were used as controls. In the first experimental group, 11 females and an unspecified number of males were exposed to the mixture continuously for 70-90 days and then mated; the pregnant females were then subjected to further exposure at the same experimental conditions until the 20th day of gestation. In the second group, 13 females were exposed for 70-90 days, mated with unexposed males, and kept under exposed conditions. In group 3, an unspecified number of males exposed for 70 days were mated with 11 unexposed females, with gestation under control conditions. The 12 females of group 4 were exposed during days 1-20 of gestation. In group 5, 11 females were exposed for 70-90 days, kept under control conditions for 70 days, and then mated to unexposed males. A control group of 26 females were mated to unexposed males. All pregnancies were terminated on day 20 of gestation. Fetuses were examined for terata, and portions of liver and kidneys were taken from both mothers and fetuses for microscopic examination. Numbers of corpora lutea, implantation sites, and live fetuses were determined for each group. These figures were used to calculate the numbers of embryonic deaths before and after implantation and the total number of intrauterine deaths.

The mean numbers of live fetuses were 5.4, 3.8, 6.4, 6.7, 6.5, and 9.0 for each female rat in groups 1-5 and controls, respectively. The corresponding percentages of deaths of concepti given by the authors were 50, 62, 39, 22, 35, and 9.3%; however, calculation from the authors' data gives a value of 35% rather than 22% for group 4. Carbon disulfide and hydrogen sulfide showed definite embryotoxicity; calculations from their

data show that differences between exposed and control rats were significant for all groups. The most pronounced effects were in group 2, although group 1 was also markedly affected. Even when exposed animals were not mated until 70 days after the end of exposure, preimplantation and postimplantation mortality rates were significantly higher than in controls ($P<0.005$ and $P<0.001$). In group 1, there were 2 cases of hydronephrosis in the 32 fetuses, and 1 fetus in 24 had a supernumerary 14th rib. Also, 5.4% of the embryos in group 1 showed "developmental anomalies," whereas there were none in the controls. In group 2, two fetuses had hydrocephaly and hydronephrosis. Microscopic examination showed changes in small blood vessels in the livers of the embryos of groups 1 and 2. Eight rats of group 1 and four of group 2 had retarded ossification. Rats of other groups did not show such substantial abnormalities. Barilyak et al [62] described their data as showing a "weak teratogenic effect" of exposure to carbon disulfide and hydrogen sulfide. However, data and many methodologic details of this study are inadequately reported. It is unclear whether the rats were exposed to 10 mg/cu m of carbon disulfide and 10 mg/cu m of hydrogen sulfide or to a total concentration of 10 mg/cu m. It is difficult to interpret the results quantitatively since individual litter data were not given. Proper statistical tests were not performed on the teratologic data; therefore, conclusions about the teratogenic effects of exposure to carbon disulfide and hydrogen sulfide cannot be made with confidence.

Sandage [63,64] conducted a series of experiments designed to simulate exposure during space flight to toxic chemicals found in feces. In the first study [63], 50 rats, 100 mice, and 10 monkeys were exposed

continuously for 90 days to a mixture of indole (10 ppm), skatole (3 ppm), hydrogen sulfide (20 ppm), and methyl mercaptan (50 ppm). Similar groups were exposed to fresh air and were used as controls. Hematology, blood chemistry (monkeys only), urinalysis, kidney function (monkeys and rats only), and swimming-stress tests were done on a sampling schedule. No clear pattern of results emerged, but all exposed species had sulfhemoglobin and an increased number of reticulocytes in the blood samples, and all exposed groups failed to gain as much weight as controls. Of the exposed monkeys, 80% died, but the cause of death was unknown.

The second study [64] was designed to sort out which compounds had caused which effects. There were four groups of animals composed of 10 monkeys, 50 rats, and 100 mice. Each group was exposed continuously for 90 days to one of the following: (1) a mixture similar to that used in the first experiment, methyl mercaptan (50 ppm), hydrogen sulfide (20 ppm), indole (10.5 ppm), and skatole (3.5 ppm); (2) hydrogen sulfide (20 ppm); (3) methyl mercaptan (50 ppm); and (4) indole (10.5 ppm). A fifth group was housed in the same room as the exposure chambers and served as controls. All animals were males. Again, studies were done on hematology, blood chemistry (monkeys only), urinalysis, and swimming stress. Liver function tests replaced kidney function tests and were done on monkeys only. The author stated that, "... in no single instance did all three species of the same group show the same physiological response to the toxic agent.... Only rats appeared to have pathology referable to H2S exposure, and this is in the lung [64]." Increased mortality over controls was seen in rats and mice, and all species showed a higher incidence of changes in the lungs than did controls, but these findings were not statistically

significant. It is unfortunate that the author did not report all the data said to have been collected. It is also unfortunate that the control animals were not sham-exposed in a chamber with the same air temperature, pressure, and humidity as the experimental groups' chambers, but the study does suggest that hydrogen sulfide, alone or in combination with exertion stress, may lead to pathologic changes of the lungs.

Correlation of Exposure and Effect

Clear and compelling evidence of chronic or cumulative effects of hydrogen sulfide exposure has not been found in the literature, though a few papers [50,54] suggested that there were such effects. A number of studies suggest that hydrogen sulfide produces subacute effects, particularly with indications of brain damage [3,15-18]. Among the signs and symptoms indicative of brain damage are rigidity [3] abnormal reflexes [15], dizziness [3,15,18], sleep disturbance [3,15,17], and loss of appetite [15,18]. Reports exist of a short-term effect (conjunctivitis) of hours-long, low-level exposure [43,48], and of residual effects (abnormal ECG, brain damage) of brief, massive exposure to hydrogen sulfide [15]. Zander [42] used the term "chronic," but the exposures that led to the "chronic" intoxication were to a mixture of gases and volatile substances. Legge [12] reported a case of spinal cord degeneration associated with a 2-year exposure to hydrogen sulfide, but the evidence for a cause-and-effect relationship is meager.

There have been many reports of adverse health effects produced by acute exposure to hydrogen sulfide at high concentrations (several hundred ppm or higher). There are few reports [17,65] showing untoward effects

from instances of prolonged exposure (several hours or longer) to hydrogen sulfide at low concentrations (below 50 ppm). There are few long-term studies (using animals) which reported exposure to hydrogen sulfide at low concentrations [57,64]. Hydrogen sulfide concentrations and related effects on humans and animals are summarized in Tables III-1 and III-2.

Measurements of the olfactory threshold for hydrogen sulfide have both dose-response and duration-response relationships. The lower limit for detection of hydrogen sulfide by odor is 0.02-.003 ppm [17]. At concentrations up to 30 ppm, the gas has an odor like that of rotten eggs. At a concentration of about 30 ppm, the odor of hydrogen sulfide may appear to be sweet or sickeningly sweet. Above 100 ppm, hydrogen sulfide rapidly abolishes the sense of smell, so that high concentrations may not be detected by odor at all. Similarly, olfactory fatigue may result from prolonged exposure to hydrogen sulfide at concentrations below 100 ppm. The sense of smell should not be relied on, therefore, to warn workers of the presence of hydrogen sulfide, particularly in dangerous quantities.

Hydrogen sulfide at low concentrations may cause headaches [17], but these headaches, unlike those caused by carbon monoxide poisoning, are not early warning signals of high hydrogen sulfide concentrations. Headaches were frequently associated with exposure to hydrogen sulfide [3,15-18,44].

Duan [56] described swelling of dendrites in the brains of two rats exposed to hydrogen sulfide in air at a concentration of 7 ppm. The change was small enough to be an artifact.

Cough, disturbed sleep, nausea, vomiting, and diarrhea have been reported after exposures to hydrogen sulfide at a wide range (0.022-2,000 ppm) of concentrations [3,16,17].

At high concentrations (several hundred ppm or more for 15 minutes or longer), hydrogen sulfide may cause respiratory difficulty, pulmonary edema with hemorrhage, respiratory depression, neural damage (central or peripheral), and abnormalities of the cardiovascular system [14,16,20,38]. Hydrogen sulfide at or above a concentration of 1,000 ppm usually produces unconsciousness immediately and causes death from respiratory arrest in minutes [21,23,38]. Hydrogen sulfide may also interfere with cellular respiration by poisoning the cytochrome system [26]. Sequelae of hydrogen sulfide exposure, including epilepsy [16], acoustic-nerve neuritis [16], abnormal ECG [31,38], and memory impairment or amnesia [15,25,38], may be the result of anoxia. Rarely, vegetative survival without a return to consciousness may follow survival of a major exposure to hydrogen sulfide [31].

At low concentrations (20 ppm or less), hydrogen sulfide may cause eye irritation after several hours of exposure, but this effect does not occur in all who are exposed [48,65]. Hydrogen sulfide causes painful conjunctivitis, sometimes with corneal erosion and spasm of the eyelids [18,43-46,48,66]. These effects may occur in less than 8 hours at concentrations of hydrogen sulfide at or below 15 ppm in air [48,65,67], and they develop more rapidly if carbon disulfide is also present in the air [48].

The reported eye effects in humans (conjunctivitis, keratitis, and corneal blistering, pitting, and opacity) from hydrogen sulfide exposure are generally acute effects, which have been confirmed in some instances by animal experiments. No reports of lasting eye damage were found, although recovery often requires absence from work for several days [15,18,48], and

secondary infection may lead to permanent blindness [68].

Although several papers have featured the adverse effects of hydrogen sulfide on the eyes [18,43-46,65-67], a summary of 26 signs and symptoms resulting from an acute exposure of 89 persons to hydrogen sulfide at unspecified concentrations which caused two deaths [37] placed conjunctivitis last in order of decreasing frequency. Also unusual in this frequency distribution [37] was the reported low frequency of pulmonary edema.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports associating hydrogen sulfide in air with carcinogenesis, mutagenesis, or teratogenesis were found in the literature.

Barilyak and his coworkers [62] reported what they concluded was a "weak teratogenic effect" in rats following low-level exposures to a combination of hydrogen sulfide and carbon disulfide. This study presents no strong evidence that supports teratogenic effects from exposure to hydrogen sulfide alone, so that without more specific corroborating evidence, the results of this investigation must be considered tentative.

TABLE III-1

EFFECTS OF HYDROGEN SULFIDE INHALATION ON HUMANS

No. of Subjects	Concentration (mg/cu m)	Duration of Exposure	Effects	Reference
1	17,000	-	Death	20
1	2,800-5,600	<20 min	"	21
10	1,400	<1 min	Death 1/10, unconsciousness, abnormal ECG	22
342	1,400-2,800	<20 min	Hospitalization of 320, death of 22 including 13 in hospital, residual nervous system damage in 4	16
5	1,400	Instant	Unconsciousness, death	23
1	1,400	<25 min	Unconsciousness, low blood pressure, pulmonary edema, convulsions, hematuria	38
4	400 - 760	-	Unconsciousness	69
1	320	20 min	Unconsciousness, arm cramps, low blood pressure	15
78	20 - 35	-	Burning eyes in 25, headache in 32, loss of appetite in 31, weight loss in 20, dizziness in more than 19	12
6,500	15 - 20	4-7 hr	Conjunctivitis	48
City of Terre-Haute	0.003-11	Intermittent air pollution episodes over a 2-mon period	Numerous complaints of nausea (13), headache, shortness of breath (4), sleep disturbance (5), throat and eye irritation (5)	17

TABLE III-2

EFFECTS OF EXPOSURE TO HYDROGEN SULFIDE ON ANIMALS

Route of Exposure	Species	Exposure Concentration*	Exposure Duration	Effects	Reference
Inhalation	Monkey	700	25 min; 17 min 3 d later	Extensive changes in gray matter, moderate liver hyperemia	51
"	"	700	35 min	Irritation of conjunctivae, sudden loss of consciousness, respiratory and cardiac arrest	51
"	"	700	22 min	Ataxia, anorexia, parenchymal necrosis in brain	51
"	"	28	90 d	Weight loss, increased blood amylase and alkaline phosphatase activities	64
"	Rat	28	"	Weight loss, abnormal changes in lungs, increased number of reticulocytes, increased mean corpuscular volume, death	64
"	"	10	12 hr/d 3 mon	Mild irritation of tracheal, bronchial mucosa; weight gain less than in controls; motor chronaxie abnormalities; abnormal cerebral cortex dendrites	56

TABLE III-2 (CONTINUED)

EFFECTS OF EXPOSURE TO HYDROGEN SULFIDE ON ANIMALS

Route of Exposure	Species	Exposure Concentration*	Exposure Duration	Effects	Reference
Inhalation	Rat	0.018	12 hr/d 3 mon	Motor chronaxie abnormalities	56
"	Mouse	140	7.5 hr	LC50; anorexia	57
"	"	70	15 hr	"	57
"	"	28	90 d	Weight loss, abnormal changes in lungs, increased number of reticulocytes, increased mean corpuscular volume	64
"	"	15	5 d	Anorexia	57
"	Rabbit	140	0.5 hr/d 4 mon	Leukopenia, lymphocytosis	60
"	"	100	1 hr/d 14 d	Disturbed metabolism in liver, brain, and kidneys; blood serum mineral, protein, and enzyme activity changes, depletion of buffers, lowered blood pH	53
"	"	100	0.5 hr/d 5 d	Cardiac irregularities, decreased myocardial enzyme activities	53
"	"	100	1.5 hr	Unconsciousness, cardiac irregularities, decreased myocardial enzyme activities	53

TABLE III-2 (CONTINUED)

EFFECTS OF EXPOSURE TO HYDROGEN SULFIDE ON ANIMALS

Route of Exposure	Species	Exposure Concentration*	Exposure Duration	Effects	Reference
Inhalation	Rabbit	28-35	4 hr/d 150 d	No weight gain, increased serum gamma globulin	61
Dermal	"	2 mg/l 1 mg/l	-	Decrease in carboanhydrase activity, anhydrase index, blood-hemoglobin content, erythrocyte respiration, and cholinesterase activity	59
"	Dog	100%	1 hr	No effects	58
Dermal, 0.78 sq in	Guinea pig	100%	"	Slight swelling and black discoloration of exposed skin	58
Dermal, half of body	"	100%	45 min	Leg-muscle relaxation, dyspnea, death	58

*Concentration in mg/cu m for inhalation exposures