III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

At workplace temperatures and pressures, chlorine is a yellowish green gas with a distinctive, irritating odor. Chemical and physical properties of chlorine are presented in Table XIII-1. Because of its reactivity, it is not found in the uncombined state in nature, but commonly occurs in salt (NaCl), sylvite (KCl), and carnallite (KMgCl3.6H2O). [1] Chlorine is produced commercially by electrolysis of brine, electrolysis of fused sodium chloride, or by oxidation of chlorides using chemical methods. [1] By far the most important production method is the electrolysis of brine using diaphragm cells or mercury cells. [1] In 1973, [2] chlorine was produced by 33 companies in 65 operating plants, including 6 pulp mill plants producing their own chlorine. Of these 65 plants, 29 were diaphragm cell plants, 23 were mercury cell plants, 5 were combined mercury cell and diaphragm cell plants, 4 were fused salt plants, 1 was a diaphragm and fused salt cell plant, 1 a hydrogen chloride electrolysis plant, 1 a nonelectrolytic plant, and 1 a diaphragm and magnesium cell plant.

US chlorine production increased from 24,754 short tons in 1909 to 10,753,109 short tons in 1974. [2] The production of chlorine increased at a compound annual rate of 8.1% between 1948 and 1968. [1] Preliminary estimates place the 1976 production at 11,000,000 short tons. [3]

In 1968, the pulp and paper industry used chlorine primarily in the elemental form for bleaching pulp and paper. [1] Chlorine is used in the production of plastic and resins which are ultimately used in the

manufacture of upholstery fabrics, floor coverings, food packaging, films, bottles, utensils, hose and tubing, and electrical insulation. Chlorinated solvents are used as drycleaning agents, paint thinners, metal degreasing agents, and machinery cleaners. The production of automotive fluids, such as ethylene glycol antifreeze and ethylene chloride (used in antiknock additives), uses chlorine as an intermediate. Chlorine is also used in textile and household bleaches, refrigerants, pharmaceuticals, cosmetics, in the beneficiating of ores, and in metal extraction. [1] Exposure to chlorine can occur in any of these operations.

In addition, exposure to chlorine can occur when hypochlorites are mixed with materials such as toilet bowl cleaners [4] or vinegar [5], and when chlorinated hydrocarbons are decomposed thermally [6] or by actinic rays from welding operations. [7,8]

Some occupations with potential exposure to chlorine are listed in Table XIII-2. In 1968, it was estimated that 26,000 persons were employed in the chlor-alkali manufacturing industry. [1] NIOSH estimated in 1973 that 15,000 workers had potential occupational exposure to chlorine.

Historical Reports

Interest was focused on the toxic effects of chlorine by its use during World War I as a war gas. Four reports [9-12] centered on the health effects of acute exposure to chlorine as a war gas and the possibility of residual effects from acute chlorine overexposure. Meakins [9] in 1919 reviewed the after-effects of chlorine war-gas poisoning by following 700 consecutive cases in the admission and discharge books of the

Canadian field ambulances serving at Ypres, France, for several weeks in the spring of 1915. Of these, 222 (31.7%) had no further details of clinical conditions ascribed to gas poisoning in their records; 478 were evacuated to the base. At the base, 146 (20.8%) were treated at the hospital: 6 patients died and the rest returned to duty. The remainder, 332 (47.4%), were evacuated to the United Kingdom for further treatment. Later, 80 returned to France and resumed duty. Forty had had irritable heart (cardiac neurasthenia), 10 bronchitis, and 4 gastric symptoms while in the hospital. [9] Of 204 invalided to Canada, 118 had symptoms of irritable heart, 30 symptoms of bronchitis and pneumonia, 4 symptoms of hemoptysis, 22 symptoms of asthma, and 20 symptoms of neuroses. The remaining 30 cases were grouped in an "indefinite symptoms" category. The average duration of hospitalization before personnel were invalided to Canada was 17 weeks. Four years after exposure to chlorine, 188 of the men invalided to Canada were studied. Seventy-eight of the men had irritable heart, 18 had neuroses, 8 had asthma, 18 had "bronchitis, etc," 14 could not be traced, and 54 were reported to have no appreciable disease.

In 1919, Berghoff [10] observed a total of 520 soldiers who, 3 - 4 months earlier, had been exposed to chlorine during warfare. Clinical examinations revealed instances of bronchitis and emphysema, but the author did not distinguish between physical findings unique to those soldiers exposed to chlorine and those findings resulting from exposures to other war gases.

As reported by Gilchrist and Matz [11] in 1933, US War Department statistics showed that 1,843 casualties out of a total of 70,742 casualties

caused by gas poisoning were the result of exposure to chlorine. A study was made of 838 of these 1,843 casualties for the purpose of ascertaining the sequelae; of the 838, 28 had died. Four of the deaths were attributed to "later effects" of chlorine gassing: bronchopneumonia, lobar pneumonia, purulent pleurisy, and tubercular meningitis. Nine of the 838 were discharged because of disabilities attributable to gassing. These disabilities included pulmonary tuberculosis, bronchitis, pleurisy, neurocirculatory asthenia, tachycardia, dyspnea, and nephritis. Of the 838, 39 were disabled at the time of discharge from conditions attributed to chlorine gassing: bronchitis, pleurisy, laryngitis, valvular heart disease, keratitis, and conjunctivitis. Of the 838, 96 were reexamined clinically and by X-ray at the time of the study. The authors concluded that 9 of the 96 men showed definite asymptomatic or symptomatic residual effects which could be attributed to chlorine gassing. The relationship of disabilities to chlorine gassing was questionable in seven instances. In 80 patients, the disabilities found at the time of the study were concluded to be in no way related to chlorine gassing incurred during the service. Of the nine men showing definite residual effects [11], five had pulmonary tuberculosis, with a coexisting emphysema in three. Three of the nine men showed evidence of chronic bronchitis; of these, one had a coexisting emphysema, one had chronic conjunctivitis, and one was free of coexisting conditions. One of the nine men had chronic adhesive pleurisy. In analyzing the five cases of pulmonary tuberculosis, the authors concluded that it was probable that gassing led to reactivation of previously quiescent tuberculous foci.

Seven men who showed disabilities that were questionably related to chlorine gassing had a history of intercurrent respiratory disease or a history of respiratory disease for which the claimants were treated just prior to, or immediately after, the gassing. In these cases, it was not possible to determine the role played by chlorine in the causation of the disabilities which appeared subsequently.

Pearce [12] in 1919 studied one person who was gassed with chlorine during the war. The man, who first received treatment some 12 months after he was gassed, failed to exhibit on medical examination any impairment of his heart and lungs, except for bronchitis. The respiratory quotient, minute volume of air, depth and rate of respiration, and tension of carbon dioxide in the alveolar air were determined at rest, while walking, and while running at a "dog trot" for a short distance, and were compared with those of the author. At rest, practically "normal" values were obtained. At exercise, the patient's minute volume of air was greater than expected from the work done, as measured by the oxygen consumption. His breathing was labored and rapid, and he felt faint. The disability in this case was interpreted as being due to a discrepancy between the ability of the blood to obtain oxygen and to rid itself of carbon dioxide. The patient was considered to be able to excrete his carbon dioxide without difficulty but to be unable to get enough oxygen. This condition was thought to be caused by the presence in many of the alveoli of bubbles of foam which prevented a free exchange of air. No definite improvement was found when the man worked while breathing oxygen at high pressures, however. He was kept under observation for about a year. He gradually developed a more severe

bronchitis, together with asthma and emphysema. No information on his smoking habits or any other significant exposure was given.

Effects on Humans

(a) Odor Perception

The effect of chlorine on the sense of smell was studied in 1957 by Styazhkin [13] who conducted 144 tests on 12 persons ranging in age from 17 to 28 years. They were exposed to chlorine at low concentrations and asked if they detected the gas. Subjects inhaled through the nose from two tanks, one with clean air and one with chlorine, and were asked to designate the one containing chlorine. The threshold of chlorine odor perception occurred at 0.7 mg/cu m (about 0.2 ppm). Leonardos et al [14] determined odor threshold under controlled laboratory conditions. The odorants were presented to a trained odor panel in a static air system using a low odor background air as the diluting medium. The odor threshold was defined as the first concentration at which all four panel members could detect the odor. The odor threshold for chlorine was reported as 0.314 ppm. Ryazanov [15] reported that the odor threshold of a group of volunteers ranged from 0.80 to 1.30 mg/cu m (0.3-0.4 ppm).

Rupp and Henschler [16] determined the olfactory thresholds for chlorine in 20 healthy subjects; they were exposed for 30 minutes to chlorine. Odor was first perceived at concentrations of 0.012-0.92 ppm. Seven of 14 persons detected the smell of chlorine at concentrations which averaged 0.02 ppm. All 20 test subjects detected the odor of chlorine at a

concentration averaging 0.452 ppm, and at concentrations averaging 0.72 ppm, all subjects correctly identified it as chlorine.

The authors qualified the results of these tests by stating that the concentration of irritant gas in the test room before the test subjects entered dropped considerably after they entered. The drop amounted to 26-57% when four test subjects were exposed, and it varied from 17 to 40% for two persons. The higher the concentration set beforehand, the less the drop. In another series of experiments, chlorine was slowly introduced so that the concentration increased from 0 to 1.3 ppm during a 50-minute period. The odor of chlorine was first detected at 0.06 ppm, and by 0.2 ppm all persons exposed (number unspecified) could smell the gas.

Odor perception also was studied by Rupp and Henschler. [16] They found that the ability to perceive chlorine did not remain constant. There was a positive correlation between the length of time the odor impression remained and the chlorine concentration. At concentrations averaging 0.022 ppm, the impression disappeared for most observers within the first 5 minutes after exposure. At concentrations averaging 0.027 ppm, the impression disappeared between 5 and 15 minutes. At concentrations averaging 0.058 ppm, only a few persons still perceived the odor after 20 minutes. Starting with concentrations averaging 0.12 ppm, the test subjects in increasing numbers still had an impression of odor until the end of exposure (30 minutes), and concentrations averaging 0.72 ppm were clearly perceived by all until the end of exposure. There was no comment on the mechanism of this tolerance.

Beck [17] exposed four subjects to chlorine at concentrations increasing from 0 to 1.8 ppm. The first perception of chlorine appeared for the individuals after 31 minutes at 0.3 ppm, 35 minutes at 0.32 ppm, 44 minutes at 0.4 ppm, and 48 minutes at 0.46 ppm. When Beck exposed 10 subjects to chlorine at 0.044 ppm, 4 perceived an odor which "became increasingly weak and after 1-24 minutes could no longer be objectified." When the concentration was raised to 0.09 ppm, 7 of the 10 noticed an odor and recognized the gas, but for 6 of the 7 the odor disappeared after 1-25 minutes (average: 9 minutes). At 0.2 ppm, 13 subjects all noticed an odor, and the duration of the perception was longer by an average of 13 minutes than that for lower concentrations.

Laciak and Sipa [18] studied olfaction in 173 randomly selected workers; 17 came in contact with chlorine. The 173 workers were asked to identify eugenol, coumarin, iodoform, dinitrobenzene, and methyl salicylate in increasing olfactory dilutions of 1,5,10,20,50,100, and 200. The results were measured in "olfacties," not further described, such that a slight olfactory deficiency meant an average loss of 20 olfacties; a moderate one, 20-100; and a severe deficiency, 100 olfacties to complete anosmia. Four workers had been exposed to chlorine for 1 year or less; of these four, olfactory deficiency was slight in two, moderate in one, and severe in one. Of the 13 workers exposed to chlorine for 2-5 years, 1 suffered slight deficiency, 1 moderate, and 11 severe. The significance of the relationship between chlorine exposure and olfactory deficiency was not discussed.

According to CB Kramer (written communication, June 1974), Dow Chemical Company collected information on odor thresholds for chlorine. In 65 tests, individuals who were industrial hygienists with the company perceived no odor when exposed to chlorine at concentrations ranging from 0.08 to 2.9 ppm; in 16 tests, the odor was described as minimal at an exposure concentration of 1.1-2.7 ppm. Data illustrated individual variation. Furthermore, it was noted that odor perceptions by the same individual made late in the day, after previous exposure, were frequently less discerning than those made earlier the same day.

(b) Case Reports

(1) Severe Exposures

The dramatic response to substantial exposure is well documented in a number of accidents involving chlorine. Romcke and Evensen [19] in 1940 reported an accident in Norway that released 7-8 tons of chlorine. The number of those exposed was not given, but 85 were hospitalized and 3 died. The authors commented that some victims had latent periods as long as several hours before they developed symptoms of pulmonary congestion disturbing enough for them to seek medical attention. The authors also commented that the most severe symptoms of pulmonary edema developed most rapidly in those subjected to physical exertions. In the milder cases, the pulmonary symptoms disappeared in 2-3 days; 54 of the hospitalized patients were discharged in 3 days. In other hospitalized patients, the bronchitic sounds lasted for 8-10 days. Signs of pulmonary edema occurred in 6 patients. Autopsies of two victims revealed intense tracheobronchitis, hyperemia of the brain, and intensely edematous lungs

weighing 2,300 and 2,500 g that almost completely covered the heart.

Stout [20] recounted the occurrence of oral burns from an unusual exposure to chlorine. As a prank, a laboratory student who had filled a bottle with chlorine gas poked it under the nose of a second student. The second student recoiled and gasped for air through his mouth, but inhaled some chlorine instead. The pain in his throat increased during the first day, and he became unable to swallow. Although the inflammation gradually subsided, an unproductive cough continued for several months after the incident.

Monto and Woodall [21] reported the case of a 20-year-old man exposed to chlorine gas at approximately 0.05 ppm for several minutes because of a poorly fitting gas mask. At the time of the exposure, there was no unusual burning of the eyes, throat, or nasal passages, or any difficulty in breathing. Several hours later, he was admitted to a hospital and treated for mediastinal emphysema. His convalescence was uneventful, and all signs of disorder had disappeared by the sixth hospital day. He had had a questionable asthmatic attack 5 years before. At that time, the patient had been told that he was sensitive to dust, but diagnostic tests were not made. Since then, he had been free of asthma. In this case, chlorine gas probably produced irritation in the terminal bronchioles, causing their occlusion and resultant trapping of the contained air. It then found its way into the interstitial tissue of the lungs, probably as a result of coughing and previous chemical injury to the cells lining the alveoli.

Chasis et al [22] reported a chlorine accident which occurred in 1944 in Brooklyn, New York, and involved at least 418 persons. During

transport, one of several cylinders containing approximately 100 pounds of chlorine leaked liquid chlorine through a 1/8-inch hole for about 17 minutes. Most of the chlorine contaminated the air in a nearby subway; the chlorine created a visible cloud. No other estimates of the actual concentration or duration of exposure were made.

Of 418 persons exposed and examined, [22] 208 were hospitalized; 133 were in one hospital under the care of the authors. Of these, 33 exhibited evidence of moderate-to-severe chlorine intoxication and remained in the hospital 1-2 weeks; 35 others had milder symptoms, and the rest left to seek care elsewhere. The records of the 140 admitted to other hospitals (75 directly and 65 by transfer from the first hospital) were reviewed and, where possible, the attending physicians were interviewed. When first exposed, most persons were overcome by choking, nausea, vomiting, anxiety, and syncope.

The 33 who remained in the first hospital [22] appeared acutely ill on admission and were in moderate-to-marked respiratory distress. Twenty-eight of the 33 had a slight fever. Approximately half were cyanotic. Adventitious pulmonary sounds were present in all: 28 had dry rales on admission, whereas the rest of the patients, with one exception, developed them shortly thereafter. Subsequent moist rales developed in all but two patients. Pulmonary edema was seen in 23 of 30 patients; the others were not observed in the early postexposure period. Respiratory distress subsided, for the great majority, within 72 hours. [22] However, in five patients, it ceased within 6 days; only one patient had prolonged dyspnea, a symptom to which preexisting heart disease was presumed to have

contributed. Substernal pain generally subsided in the first 3 days, leaving a soreness attributed to tracheobronchitis. A dry cough was present initially in every patient, but promptly became quiescent with administration of oxygen and codeine, only to return in most patients after 2-5 days with the production of tenacious mucopurulent sputum, blood-tinged when first produced. Dry rales cleared by the 10th day; moist rales were still present in 20 patients during the second week. The febrile period lasted 2-13 days.

The following summarizes the clinical test data: chest X-rays showed mottling, patches of irregular densities, and differences in the degree of aeration in both lung fields. X-ray changes in most patients were not remarkable, and it was felt that readings of single roentgenograms could easily have been judged to be normal. In 3, a transient unequal aeration was noted, consistent with obstructive emphysema. In 14, serial changes permitted the diagnosis of pneumonia, basilar in 13. At the time of discharge, all chlorine-related abnormalities visible on chest X-rays were clearing or had cleared. Arterial oxygen saturation was measured 7-8 hours after exposure in eight patients selected for examination because of cyanosis and extensive pulmonary involvement. The values, ranging from 88.1 to 91.2%, were lower than normal (reported as approximately 96%) in six. Serial ECG tracings on 12 patients showed either no abnormality or a preexisting heart disease. For eight patients, vital capacity determined 48 hours after exposure gave values ranging from 16 to 57% of the predicted normal.

A special follow-up clinic [22] was established and attended by 29 of these 33 patients, usually for 16 months after exposure. Eleven had no abnormal symptoms or signs. One patient had cough and sputum for 6 months, with medium moist rales at the base of the left lung for 3 months. Upon death 10 months after exposure, a post-mortem examination showed a pulmonary embolus, but otherwise normal lungs and bronchi. A second patient, who had marked congenital kyphoscoliosis with pulmonary fibrosis (there was no comment as to its etiology), had periodic episodes of cough and dyspnea, each lasting a few days to a few weeks. Sixteen patients had what were considered anxiety reactions with phobias, hysterical phenomena, and psychosomatic dysfunctions for 1-16 months: anorexia, nausea, vomiting, weakness, nervousness, dizziness, palpitation, a sense of suffocation, and the odor and taste of chlorine. Two intrauterine pregnancies were reported to be unaffected by the exposure, but no details were given. There was no correlation between severity of symptoms during the hospital stay and the continuance of symptoms thereafter. No pulmonary function studies were reported from the special follow-up.

Baader [23] described a freak nighttime industrial accident in which there was a release of "enormous" amounts of "chlorine anhydride". Fortunately, only 190 of the 900 workers of the mill were at work, but the wind carried the cloud of gas to the town. Reportedly, some 240 people were taken to clinics, 4 workers died, and another 42 persons were in very serious condition. The signs and symptoms present in 46 patients examined by the author were as follows, in order of decreasing frequency: fever, moist rales in some pulmonary fields, dyspnea, blood in sputum,

tachycardia, vomiting or nausea, reduced arterial pressure, cyanosis, blood in urine, coated tongue, headache, severe diarrhea, "sticky sweat", fainting, infrasternal pains, constipation, pains below the costal ridge, heart pains, bradycardia, and arrhythmia. One patient who fainted from the exposure developed glucosuria. Three autopsies were performed; aside from pulmonary edema, emphysema, and the presence of bronchopneumonic condensation foci in the lungs, the most striking findings were small hemorrhages in the white matter of the cortex, corpus callosum, internal capsule, and cerebellum.

Hoveid [24] described a railcar accident in Norway which released 14 tons of chlorine. The exposure resulted in the hospitalization of 85 people. No information was presented about any others exposed. Three of the 85 died and the others were discharged following treatment as in-patients. Information on 75 was secured by mail questionnaires; 4 had died since discharge, and 3 could not be located. The questionnaire asked about "difficulties of any type...caused by this gas exposure," the use of physician services in this regard, and the incidence of recurrences. How long after the incident the questionnaires were mailed was not given, but the spill occurred in 1940 and the article was published in 1956. No difficulties were ascertained in 48 of those who responded, 16 reported difficulties "believed to be a reasonable consequence of the accident," while 11 had a "possible, but somewhat doubtful consequence." The "reasonable consequences" included dyspnea (1 person with dyspnea had pulmonary tuberculosis), bronchitis, "tightness under the chest," and "lacing under the chest." "Possible consequences" included coughing,

spontaneous pneumothorax, asthma, emphysema (6 years after exposure), bronchitis (beginning 4 years after exposure), loss of memory, "bad throat," "legs and the strength failing," "poor heart, high blood pressure," and claustrophobia. Half of those with dyspnea did not consult a physician. Eight of 16 with "reasonable consequences" had received oxygen, while 5 of 11 with "possible consequences" and 11 of 48 without difficulties received this therapy; the differences were not statistically significant.

In 1962, Joyner and Durel [25] reported a spill of about 36 tons of liquid chlorine in Louisiana. Three hours later, chlorine at an airborne concentration of 10 ppm was found in the fringes of the contaminated area; 7 hours after the spill, levels of 400 ppm were recorded 75 yards from the spill, and this was felt not to represent maximal values even at that time. Approximately 100 persons were treated for exposure to chlorine of various degrees. Of the 65 casualties handled in one hospital, 15 were admitted. Three children and one adult were unconscious on admission; an 11-month-old infant died. Ten of the hospitalized patients developed frank and unmistakable pulmonary edema. All heavily exposed victims experienced severe dyspnea, coughing, vomiting, and retching. Most of these patients complained of burning of the eyes and had acute conjunctival injection with profuse tearing and photophobia. Some victims had minor first-degree skin burns, principally of the face. The authors stated that these burns resulted from gas exposure rather than from splashes. Examination of the chest in all heavily exposed patients revealed diffuse, moist, crackling rales throughout both lung fields which were loud both on inspiration and

expiration. Harsh, sibilant rales were also audible in one patient. Sputum in bedside containers was copious, thin, and very frothy; in one patient, sputum was faintly tinged with blood on the second day after exposure. Chest X-rays made on hospitalized patients on the third and fourth days after exposure revealed striking changes: fine miliary mottling was distributed bilaterally and symmetrically throughout both lung fields. With therapy, these clinical findings slowly cleared and all hospitalized patients were discharged by the sixteenth day.

In 1969, Weill et al [26] reviewed the case histories of 12 of those who had been exposed in the spill reported above by Joyner and Durel. [25] In general, these 12 patients were the ones most severely affected in the community. Three of the 12 were studied 3 years after exposure; all 12 were studied again 7 years after exposure. The 12 study subjects included 11 of the 16 surviving hospitalized patients and the spouse of one subject, an individual who had had prominent symptoms after exposure. Observed values for total lung capacity (TLC), vital capacity (VC), residual volume (RV), and forced expiratory volume at 1 second (FEV 1) were all within two standard deviations of predicted values. [26] (A complete listing of pulmonary function abbreviations used here and subsequently is given in Appendix V.) The subjects were essentially asymptomatic from a respiratory standpoint. Chest X-rays were normal in all cases. Minor abnormalities in lung volumes were accounted for by factors other than chlorine exposure. No definite change in respiratory function was found in the three subjects who were studied both 3 and 7 years after exposure.

Gervais et al [27] studied a worker accidentally exposed to chlorine in 1965. There was no estimate of the degree of exposure except that the worker was unable to leave the area by his own efforts. The patient had rales in both lung fields but the chest X-ray was normal. The ECG showed a transient right heart block. The authors did not clearly indicate that they considered the transient heart block to be of any clinical significance or associated specifically with the exposure. The patient recovered uneventfully.

In 1967, Kowitz et al [28] presented details of an accidental chlorine exposure of at least 156 workmen during cargo unloading. No estimates of chlorine concentrations or durations of exposure were reported. Most men experienced acute symptoms. All were taken rapidly to 3 local hospitals, and 37 of the 156 were admitted. Several men returned to the hospital within 48 hours and were admitted at that time. There were no recorded deaths. Of the 17 subjects admitted to the first hospital, 11 were studied serially. All 11 had shown respiratory distress on admission; it was judged to be severe in 7. One developed bacterial pneumonia. Other clinical findings included hemoptysis, rales, wheezes or rhonchi, or both, and edema of the lungs. Within 1-3 weeks, all findings had disappeared except for symptoms of exertional dyspnea, easy fatigability, and cough. Two months after exposure, all 11 appeared clinically recovered, despite the findings of reduced lung volumes, reduced arterial oxygen partial pressures at rest which were significantly lowered upon mild exercise, and hyperventilation at rest and upon exercise. This symptomatology is consistent with acute alveolo-capillary injury (Table III-1).

Six months later, mean total lung capacity was still reduced, mean vital capacity was further reduced, and mean airway resistance had significantly increased. There was arterial hypoxemia at rest and after exercise, and a decrease in the degree of hyperventilation. At the time of the last two studies lung volumes were returning to normal, although they were still low for up to 3 years after the incident, while airway resistance remained

TABLE III-1

ARITHMETIC MEANS AND STANDARD DEVIATIONS OF THE MEANS OF SELECTED RESPIRATORY FUNCTION TESTS IN MAN OBTAINED SERIALLY FOLLOWING CHLORINE EXPOSURE

Test***	Before Cl Exposure	Time of Testing After Exposure, in Months			
		2	6	14	19-35
TLC (liters)	6.31 (±0.76)	5.56 (±1.06)	5.23* (±1.00)	5.44 (±0.88)	5.74 (±0.89)
RV (liters)	1.94 (±0.4)	1.62 (±0.61)	1.91 (±0.49)	1.80 (±0.55)	1.69 (±0.57)
FRC (liters)	3.40 (±0.50)	2.51** (±0.61)	2.78* (±0.58)	2.79** (±0.55)	2.91 (±0.62)
VC (liters)	4.37 (±0.47)	3.94 (±0.78)	3.33** (±0.83)	3.64** (±0.68)	4.05 (±0.67)
Raw $\frac{(cm\ H2O)}{liter/sec}$	1.50 (±0.20)	1.36 (±0.78)	1.95 (±0.69)	2.11 (±0.81)	2.13 (±1.08)
Glaw $\frac{(liters/sec/cm\ H2O)}{liter}$	0.900	-----	0.966 (±0.361)	0.966 (±0.386)	0.883 (±0.581)

TABLE III-1 (Continued)

ARITHMETIC MEANS AND STANDARD DEVIATIONS OF THE MEANS OF SELECTED RESPIRATORY FUNCTION TESTS IN MAN OBTAINED SERIALLY FOLLOWING CHLORINE EXPOSURE

Test***	Before Cl Exposure	Time of Testing After Exposure, in Months			
		2	6	14	19-35
PaO2 rest	>90.0 (mmHg)	71.3 (±24.0)	68.0* (±15.2)	75.5* (±12.3)	81.8 (±12.1)
PaO2 exercise	>90.0 (mmHg)	63.7* (±18.5)	70.8* (±8.9)	80.3 (±17.2)	87.3 (±10.7)
Blood pH rest	7.38-7.42	7.481 (±0.066)	7.443 (±0.042)	7.419 (±0.042)	7.427 (±0.029)
Blood pH exercise	7.38-7.42	7.476 (±0.060)	7.424 (±0.021)	7.423 (±0.037)	7.421 (±0.043)

* Comparison of test results with predicted values when $p < 0.05$
** Comparison of test results with predicted values when $p < 0.01$
***Refer to Appendix V for explanation of test abbreviations

From reference 28

elevated. Carbon dioxide partial pressure and blood pH returned to normal levels, although hyperventilation was still apparent 14 months after the study. Arterial oxygen partial pressure at rest improved and, by the fourth study, definitely increased upon exercise. The authors concluded that these serial studies suggested the presence of permanent lung damage with prior attempts at repair.

All of the men involved in the foregoing accident [28] were asked to participate in a respiratory disease study approximately 18-20 months after

the accident; 73 of the 156 were evaluated. The authors commented that it was likely that the majority of those who refused to participate considered themselves well so that those studied were not a representative sample of all exposed. Of the 73, 12 were excluded because of conditions other than chlorine exposure that might have altered pulmonary function, and studies of 2 were incomplete, leaving 59 for analysis. These 59 included the original 17 admitted to the first hospital. All but 2 of the 59 subjects [28] were black, with an average age of 51.3 years. At the time of follow-up examination, the authors judged 16 of the 59 to have moderate-to-severe dyspnea on the basis of subjective complaints. Other signs and symptoms described at the time of follow-up, in order of decreasing frequency, were: cough, nonspecific chest pain, oropharyngeal membrane irritation, decreased stamina, and muscular weakness. Gross abnormalities on follow-up physical examination of the chest were the exception. Abnormal findings consisted of diminution of chest expansion, decreased breath sounds, and prolongation of the expiratory phase. Wheezing or rhonchi appeared infrequently.

An attempt was made by the authors to quantify the degree of association between the results of pulmonary function tests performed on the 59 patients and (a) antecedent history not related to chlorine exposure (cardiovascular disease, smoking, abnormalities of the chest) and (b) amount of chlorine exposure (patient's account of exposure, hospitalization, dyspnea, and reduced exercise tolerance). The profiles developed did not make a strong case for an effect resulting from chlorine exposure; however when the categories were considered individually, those with a history of more severe exposure, hospitalization, or persisting

decreased exercise tolerance had a lower diffusion capacity ($p < 0.05$).

Dixon and Drew [29] reported a fatal case of chlorine poisoning. A chlorine cloud resulted when a valve was incompletely closed. For reasons which were not clear, a boiler plant operator, age 49, remained in the cloud for about 30 minutes without immediately putting on the canister mask which was available; it is not certain that he used the mask. When he reported for medical assistance, he began vomiting and complained of severe pains in the stomach and chest. There were signs of bronchial irritation and congestion, which were not further described. After an hour's observation, he was sent home; on the way, he became increasingly ill and died. The interval between initial exposure and death was 3-3.5 hours. Post-mortem examination revealed pulmonary edema as the cause of death, with coronary insufficiency due to atheroma also reported.

Beach et al [30] published the case history of a 44-year-old process worker exposed to chlorine gas at an unstated "high" concentration because of a leaking valve. He soon began to choke and then developed severe dyspnea, a persistent cough, and chest pain. His eyes "smarted" and his conjunctivae were markedly injected. Ten hours later, he was cyanotic and had rapid and shallow breathing; he coughed up pink frothy sputum. Numerous coarse crepitations were heard. He was given "continuous oxygen" for 9 days and prednisolone for 12 days. He remained critically ill for 48 hours and then gradually improved. His dyspnea at rest slowly abated and disappeared by the 10th day. The patient was discharged from the hospital after 13 days. Exercise dyspnea persisted for 5 weeks. Further followup data were not reported.

Uragoda [31] reported on a water purification plant worker who was exposed to leaking chlorine gas for a period of 20 minutes before he finally succeeded in controlling the leak. There was no further description of the exposure. He had immediate tightness of the chest, bouts of nonproductive coughing, and a severe headache. He sought medical treatment 4 days later because the cough persisted. Upon auscultation, there were scattered post-tussic rhonchi. His initial ECG showed ventricular extrasystoles every 3 beats with a pulse of 56; 27 days later, the ventricular extrasystoles occurred only occasionally. A slight cough was still present at that time. No further followup data were reported.

In 1970, Faure et al [32] analyzed 87 cases of chlorine exposure over approximately 10 years in 2 French industrial towns. Reported signs and symptoms included smarting of the eyes in 20%, burning of the nose, pharynx, and respiratory tract in 35%, a feeling of suffocation with a sensation of chest tightness in 45%, dyspnea in 45%, and cyanosis in 15%. Objective medical examination revealed signs of bronchitis with rhonchi and wheezing in 35%, indications of parenchymal disorders with crepitating rales in 20%, hemoptysis in < 3%, and lung edema in 7%. No data regarding chlorine exposure concentrations were provided. Neither the total number of workers nor the number of exposure-years in this group was given. One woman, age 40, had her first attack of asthma 6 months after excessive chlorine exposure. The authors made a strong point of the need for workers to have hazard information. Of 99 workers, 80% were ignorant of the dangers of chlorine. In a group of 55 workers supposedly better informed about hazards, with a total of 306 years of work, only 8 had exposure of "a

certain gravity." The authors felt that this paucity of serious exposures reflected the workers' better information about chlorine, presumably derived from their work experience.

Sessa et al [33] studied 12 workers who had been poisoned by chlorine. The authors made clinical observations at an unspecified time following exposures. The average age of the workers was 54 years, and the average period of employment was 28 years. Vital capacity was normal in 4, reduced in 2, and severely reduced in 6. The diffusing capacities of the lungs of chlorine workers, when averaged, were less than the normal value, but no value for range or variance was given. The timing of pulmonary function studies in relation to exposure, the criteria for these classifications, and the actual chlorine exposure concentrations were, unfortunately, not given.

Leube and Kreiter [34] examined 90 persons acutely poisoned when chlorine gas was blown by the wind across a factory site. These people were treated at a local hospital, 72 as inpatients and 18 as outpatients. There was no estimate of the degree of exposure. The following signs and symptoms were reported in 88 of the 90: coughing in 97%, dyspnea in 75%, headaches in 66%, retrosternal pain in 47%, nausea in 44%, vertigo in 33%, and vomiting in 11%. All inpatients had chest X-ray examinations between 5 and 8 hours after exposure; 10 showed early pulmonary edema. In the 48 who had ECG examinations, there were several instances of significant sinus tachycardia, isolated ventricular extrasytoles, and a repolarization disturbance of the left ventricle. Blood sedimentation rates were normal in the 30 patients who were checked. Two hours after exposure,

leukocytosis was marked -- in 60 of 68 inpatients so tested the number of white cells was above 10,000 /cu mm. Within 7 hours, 36 patients still had values over 10,000. On the following day, only six persons still showed white cell values over 10,000/cu mm; the average was once again within the norm. The activity of serum glutamic oxalic transaminase (SGOT) was abnormal in 15%, and serum glutamic pyruvate transaminase (SGPT) was abnormal in 40% of the inpatients (normal range: 12- >48 mU/ml). Sixty-six determinations of LDH (lactate-dehydrogenase) activity in serum yielded normal values. Liver biopsies were taken for two patients with exceptionally high SGPT values. In one case, some individual swollen liver epithelia, besides a nuclear perturbation was seen. No complications developed, even for the patients with heavy intoxication who were released from the hospital after 3-5 days. No further follow-up was reported.

Kaufman and Burkons [35] studied persons exposed to chlorine as a result of a leak in a liquid chlorine storage tank. Within 30 minutes of exposure, 27 exposed persons were examined in an emergency room: 5 were infants and children under 7 years of age who required hospitalization but who were not included in the study; 2 adults died of severe hemorrhagic pulmonary edema. Of the 20 survivors, 9 men and 9 women, ranging in age from 21 to 68 years, agreed to participate in the study. Thirteen of the participants were nearby-residents or passers-by at the time of the leak, while the other 5 were workers heavily exposed in the storage room. Eleven were studied within 48 hours of exposure and the rest within 48 hours to 7 days. Repeat studies of all were done at 1, 2, and 4 months following exposure. Only 12 subjects returned for examination 12-14 months after

exposure, but this number included those most heavily exposed.

Each member of the group received an exposure rating of from 1 to 4, based on the subject's description of the color and density of the chlorine gas and on the length of exposure time. A rating of 4 represented the most extensive exposure. This subjective estimate of exposure was then related to the signs and symptoms each subject displayed (Table III-2). All subjects were questioned in regard to their cardiopulmonary disease history. Pulmonary function tests measuring forced expiratory volume (FEV), FEV 1, maximum midexpiratory flowrate (MMF), RV, DLCO, VC, maximum voluntary ventilation (MVV), and partial pressure of oxygen (PO2) were performed.

Clinical results [35] revealed that exposure ratings above 2 were often associated with manifestations of pulmonary edema, although this condition was diagnosed in only one heavily exposed chlorine worker. In addition, rales, dyspnea, and cyanosis were seen in those most heavily exposed and cough was present in nearly all patients. At the time of the 30-day follow-up and subsequently, roentgenologic findings were all normal, and abnormal signs and symptoms were no longer present. Subnormal VC was observed in three patients initially, while reduction in FEV 1 was noted in four patients, three of whom were chlorine workers. Residual volume was above the predicted level in those persons most heavily exposed. Within 30-90 days, these abnormalities were less evident. Subnormal levels of MMF's were evident in six patients, all heavily exposed, but within 30 days after exposure, MMF values were normal except in one nonworker and in three chlorine workers; these three still showed low MMF's a year later. Low MVV

values returned to normal in two heavily exposed and in two mildly exposed nonworkers within 30 days. Persistently low MVV was seen in two chlorine workers up to a year after exposure. The DLCO remained persistently low

TABLE III-2

ASSOCIATION OF CHLORINE EXPOSURE RATING
WITH SIGNS AND SYMPTOMS

Patient	Sex	Age	Exposure Rating	X-Ray Abnormalities	Rales	Dyspnea	Cough	Cyanosis
Nonworkers								
1	F	28	4	+	+	+	+	+
2	F	30	4	+	+	+	+	+
3	F	29	3	+	0	+	+	0
4	M	21	3	+	+	+	0	0
5	M	25	3	0	+	+	+	0
6	M	33	3	0	0	0	+	0
7	F	68	3	0	0	0	+	0
8	F	30	3	0	0	0	+	0
9	F	47	3	0	0	0	+	0
10	F	65	2	0	0	0	0	0
11	F	53	2	0	0	+	+	0
12	F	48	1	0	0	0	+	0
13	M	46	1	0	0	0	+	0

TABLE III-2 (Continued)

ASSOCIATION OF CHLORINE EXPOSURE RATING
WITH SIGNS AND SYMPTOMS

Patient	Sex	Age	Exposure Rating	X-Ray Abnormalities	Rales	Dyspnea	Cough	Cyanosis
Workers								
14	M	55	4	+	+	+	+	0
15	M	56	4	0	+	+	+	+
16	M	49	4	0	+	0	0	0
17	M	32	4	0	+	0	0	0
18	M	22	4	0	0	0	+	0

Note: + indicates the presence of the sign or symptom
0 indicates the absence of the sign or symptom

From reference 35

throughout the study only in one mildly exposed nonworker. The PO2 was subnormal initially in four patients, and 3 months later in two nonworkers who were over 65 and had no previous history of cardiopulmonary disease, and in three chlorine workers.

In summary, [35] the most heavily exposed residents and neighbors showed a pattern of airway obstruction and uneven ventilation which, for the most part, was transitory. Those moderately or lightly exposed had no physiologic disturbance except for that considered commensurate with age. Four of the five chlorine workers, with occupational exposure in a chlorine

environment for 5-30 years, showed persistent airway obstruction and mild hypoxemia. There was no comment as to their degree of exposure preceding or during the accident. Only one patient, not a worker, had continuously reduced DLCO, arterial hypoxia, and excessive ventilation, despite a mild chlorine exposure and lack of symptoms.

(2) Less Severe Exposures

Instead of having been exposed to massive amounts of chlorine because of accidents, many workers have been exposed for relatively long periods to chlorine at low airborne concentrations. Some reports [36,37] suggest a possible chronic effect from such exposures. McCord [36] reported on one worker who was employed in 1920 to shovel paper bleached with chlorine out of a cellar room, load it onto hand trucks, and transport it to another room. The worker said the odor of chlorine was always present and sometimes was stronger than at other times, but that he knew of no gross exposure. No measurements of airborne chlorine concentration or duration of exposure were reported. No smoking history or record of exposure to other contaminants was presented. In 1924, the worker first noticed the development of a slight cough, associated with sneezing and burning in the eyes. During this period, there were intervals of 1-2 weeks in which he noticed no discomfort; then the coughing and associated symptoms would return for a period of several days. The coughing became increasingly severe. By February 1925, pain was constant in the upper portions of his chest, particularly in his right lung. By August 1925, the patient became dyspneic, the pain in his lungs had increased, and his coughing and bronchitis were marked. During September 1925, after 5 years of digging

paper out of the cellar room, he was forced by his illness to discontinue work and remain at home. His chief complaints at that time were incessant coughing, severe pain in the chest, sore throat, hemoptysis, and the feeling of a "belt around the chest." Examination of his chest in March 1926, 7 months after his last exposure, showed hyperresonance of the left lung, diminished respiratory motility, harsh breath sounds, especially on expiration, distant breath sounds at the base, and occasional dry rales. [36] He was clinically diagnosed as having low-grade bronchitis with emphysema. X-ray examination showed an old tubercular lesion of the upper right lung, an old healed cavity in the upper right lung, and fibrosis in the upper left lung. The intracostal spaces were enlarged, and the density of the lung tissue was definitely diminished throughout the lower lobe of both lungs. The author stated that the patient may have had a decrease in pulmonary function because of chlorine exposure; however, the possibility of deterioration of the lung over time from other causes could not be excluded.

Bates and Christie [37] reported a chlorine exposure in a 59-year-old worker who had been engaged in the remelting of aluminum where liquid chlorine was used under pressure as a fluxing agent. He had been exposed to chlorine on at least five occasions from 1942 to 1960. With each exposure he reported having a temporary cough and shortness of breath, but chlorine concentrations and duration of exposure to chlorine were not given. After the fourth exposure, he developed severe, persistent dyspnea which was brought on by even mild exertion or talking. He did not have a cough. He had a history of diabetes mellitus and myocardial infarction.

It was not stated whether the patient smoked or was exposed to other contaminants potentially damaging to the lungs. Clinical examination of the lungs revealed no abnormalities. A low-grade hypertrophic laryngitis was found, but whether the examination of the larynx was direct or indirect was not reported. With the exception of an increase in the anterior-posterior diameter indicating moderate overinflation and a slight mid-dorsal kyphosis, radiologic examination of the lungs showed no abnormalities. The results of pulmonary function tests showed a reduction in VC and an increase in RV. Airway resistance, which was increased in the patient, was measured unreliably because the patient did not fully cooperate. A low partial pressure of carbon dioxide in the arterial blood (PaCO2) and elevated pH suggested some hyperventilation.

In summary, the above reports [19-37] indicate that exposure to chlorine may cause severe irritation, in some cases resulting in death. Thirteen of the approximately 1,250 exposed persons died. Autopsy following fatalities that resulted from acute exposure to chlorine revealed inflamed bronchi, pulmonary edema, and small foci of bronchopneumonia in the lungs. [19,23]

Nonfatal doses resulted in severe signs and symptoms including dyspnea and cough, expectoration of bloody froth, sensation of tightness in the chest, cyanosis, conjunctival injection, severe headache, nausea and vomiting, and syncope. [22,23,25,27,30] In those persons severely affected, clinical examination and chest X-rays corroborated the presence of pulmonary edema [22,25] and oxygen desaturation. [22,35] One study [34] reported serum enzyme abnormalities in SGOT and SGPT but not lactic

dehydrogenase (LDH). The same study [34] reported sharp transient leukocytosis; less marked leukocytosis was observed in a second study. [22] The absence of any mention of damage to the skin from gaseous chlorine, except in one article, [25] suggests that exposures to chlorine at high concentrations are required for this effect. There were no case reports of exposure to liquid chlorine. The bulk of evidence suggests, albeit follow-up was generally very incomplete, that most persons recover completely and relatively rapidly after massive accidental exposures. [22,26,35] On the other hand, there was some evidence of chronic impairment of pulmonary function following acute exposure. [24,28,33] There is insufficient evidence to conclude that persons chronically exposed to chlorine developed chronic impairment.

All of the reports suffered from a lack of precise data regarding airborne concentrations and exposure durations. Follow-up data on those exposed was generally very limited.

(c) Human Exposure Studies

Ryazanov in 1962 [15] described a "sensory basis" for setting occupational health standards in the USSR. The odor threshold of a group of volunteers ranged from 0.80 to 1.30 mg/cu m (0.3-0.4 ppm) chlorine. One physiologic response that was measured was optical chronaxie, the time necessary for the appearance of a sensation of light when an electrical current of twice the threshold amperage was applied to the eyeball. When air containing chlorine at concentrations of 1.5 mg/cu m (0.5 ppm) was inhaled, the chronaxie was raised just significantly. This was taken as indicating a reflex inhibition of the visual cortex from the olfactory

cortex of excitation by nerve impulses originating in the retina. Another response that was measured was the change in sensitivity to light by the dark-adapted eye. At concentrations of 1.0 mg/cu m (0.33 ppm) chlorine, a detectable change occurred. These observations [15] used very fine alterations in physiology as indications of chlorine effect. The degree to which these minute physiologic alterations represent a significant alteration of the health of exposed workers is poorly understood.

Matt [38] subjected himself along with another human subject to chlorine at various airborne concentrations. Although the concentration of chlorine was given, the magnitude of possible error was not. At the beginning of an exposure to chlorine at 1.3 ppm, the odor of chlorine was hardly noticeable, but after 7 minutes unpleasant burning of the eyes and nose was observed in one subject. At 2.5 ppm, severe burning of the eyes, mouth, and throat was apparent in 5 minutes. Exposure to chlorine at a concentration of 3.5-4.0 ppm produced nasal congestion which could be tolerated for only 16 minutes, and a coughing stimulus that lasted some 18 hours. Although symptoms of irritation were reported at an exposure concentration of 1.3 ppm, Matt concluded that exposure to chlorine at concentrations of 1.0-2.0 ppm would not disturb work.

In 1921, Fieldner et al [39] listed the Chemical Warfare Service chlorine concentrations producing irritation in man. The minimum concentration of chlorine producing irritation in the throat was 15.1 ppm; the lowest concentration causing coughing was 30.2 ppm. The "least detectable odor" was listed at 3.5 ppm. The basis for the determination of these values was not given.

Rupp and Henschler [16] exposed human volunteers to chlorine at various concentrations in two series of experiments. Chlorine was bubbled through liquid paraffin in a flask until the paraffin was saturated. The flask and paraffin were then maintained in a thermostated bath at 21 C. Air was passed at a constant rate through a sintered glass bubbler into the solution. The chlorine-air mixture thus produced was further diluted with air in a mixing flask. Confirmation of the chlorine concentrations produced was obtained by the o-tolidine method of analysis. In the first experiment, 14-20 subjects were exposed to chlorine at fixed concentrations in a test chamber in order to determine the olfactory threshold for chlorine. Concomitant with the measurement of the threshold, certain other observations were made. The duration of exposure at the specified level before symptoms appeared was not given. The authors indicated that they had some difficulty in maintaining constant concentrations of chlorine within the test chamber. A decrease in value occurred between the time the chamber chlorine concentration was set and the time the test subjects entered. Tickling in the nose occurred at concentrations averaging 0.027 ppm and in the throat at concentrations averaging 0.058 ppm. Burning of the conjunctivae was reported at concentrations averaging 0.452 ppm; the response to chlorine at this concentration was clearly felt to be pain by a few subjects (numbers not given) after 15 minutes. The authors, in the second series of tests, exposed subjects to chlorine gas at concentrations slowly increasing from zero to 1.3 ppm over 50 minutes. The number of subjects used for testing with chlorine was not specifically given; however, analogous testing for bromine was done with three test subjects.

Itching in the nose was noted at 0.06 ppm by the first subject after approximately 4 minutes, and at 0.2 ppm by the last subject after approximately 20 minutes. Cough began after 25 minutes when the concentration had risen to 0.5 ppm. When the concentration had risen to 1.0 ppm, after 35 minutes, one subject had a headache. One person had a severe shortness of breath and cough with a violent headache at 1.0-1.3 ppm. Beyond 1 ppm, the stay was felt to be uncomfortable by all test subjects.

Beck [17] experimented with chlorine using chemistry students as subjects. In order to avoid subjective effects in the experimental volunteer subjects, the chlorine concentrations were not arranged in a series of increasing or decreasing steps, but rather selected randomly according to a predetermined plan. The air in the experimental chamber was renewed 22 times/hour. Because of this frequent air exchange, the concentrations decreased only about 5% due to adsorption of chlorine by body surfaces when the subjects entered the chamber. Two overlapping determinations of airborne chlorine concentrations were made as close together as possible.

Upon exposure to chlorine at 0.044 ppm, 5 out of 10 subjects [17] noticed no alteration, 1 was undecided about his perception, and 4 stated that there was an odor. Two out of the four persons who sensed an odor were able to recognize the gas. When the concentration of chlorine increased to 0.09 ppm, all 10 persons noticed an odor, and 7 recognized the gas. Four subjects reported irritation in the upper respiratory passages consisting of tickling and stinging in the nose, a weak cough (one

subject), and increased dryness in the throat.

In another series of tests, [17] an odor was noticed by all 13 subjects at 0.2 ppm and recognized as chlorine by 5. Reports of irritation increased both in number and in intensity as compared with those at 0.09 ppm. Seven subjects reported a slight tickling in the nose and throat; one subject developed a dry, scratchy throat causing a slight cough. Three persons observed slight sensations in the conjunctivae. At 1 ppm, the intensity of these signs and symptoms increased further. Of 10 subjects, only 3 were without signs or symptoms of irritation. Tickling and stinging in the nose were reported in six instances and scratchiness and dryness in the throat in four instances. One subject reported a dull sensation in the teeth and a slight metallic taste; another felt slight pressure in the head together with headache, burning in the conjunctivae, burning of the skin, a distinct taste, coughing, and constriction of breathing (expressed as the sensation of not being able to inhale deeply). Exposure to chlorine at 1 ppm was terminated after 20 minutes because it was judged to be unbearable. One subject complained in all the experiments with chlorine of increasing irritation of the conjunctivae. This was shown not to be caused by air flow drying the conjunctivae.

Additional experiments [17] were performed to determine the effect of humidity on the perception of chlorine. Within 50 minutes, the relative humidity was increased twice within a short period (12-13 minutes) from 56 to 72%, the chlorine concentration remaining unchanged. In one experiment, three subjects were exposed to chlorine at 0.18 ppm; in another, two subjects to chlorine at 0.38 ppm. The introduction of water vapor

increased the temperature 1.5-2 C in the experimental chamber simultaneously with the increase in moisture. The odor of chlorine at both concentrations was noticed by all subjects. At 0.18 ppm, the increase in moisture decreased the odor. When the humidity was then decreased, two subjects noticed an increase in odor, but no clear correlation could be obtained between the variations in humidity and the return of the chlorine odor. At 0.38 ppm, the odor of chlorine was perceived throughout the experiment. Changes in humidity did not have a clear effect on the perception of chlorine at this concentration.

In another experiment, [17] four subjects were exposed in a chamber to chlorine at continuously increasing concentrations from 0 to 1.8 ppm. From 0.3 ppm on, three subjects felt a stinging in the throat. By 0.36 ppm, one subject had a sensation of choking; chlorine at 1.4 ppm apparently caused slight neck pain, substernal pain, and conjunctival irritation in one subject; another subject experienced a slight headache at this level.

In summary, [17] in sensitive subjects, slight irritation in the nose and throat from chlorine appeared at or above 0.09 ppm; at 1 ppm, most subjects felt annoying symptoms, especially in the nose, but also in the throat and sometimes in the conjunctivae. Chlorine exposure at 1 ppm could not be withstood for longer than 20 minutes. With exposure to chlorine at concentrations less than 1 ppm, there appeared a slight adaptation to odor, but the irritation symptoms increased with increasing length of exposure to chlorine at these same concentrations. Changes in humidity did not appear to effect odor perception or symptoms of irritation.

The Dow Chemical Company (CB Kramer, written communication, June 1974) reported the results of subjective responses by their industrial hygienists when sampling workroom atmospheres for chlorine. During sampling periods of 10 minutes or more, the odor of chlorine was perceived by an unspecified number of industrial hygienists at concentrations which averaged 1.1-41.0 ppm. A respiratory response of "minimal," "easily noticed," or "strong" was experienced at concentrations which averaged 1.92-41.0 ppm. "Minimal" or "easily noticed" eye irritation was experienced at concentrations which averaged 7.7-41.0 ppm. It was noted that observations made by the same person late in the day after previous exposure were frequently less discerning than those observations made earlier in the day.

Table XIII-5 summarizes the above mentioned [16, 17, 38] exposure-effect data.

(d) Mutagenicity and Carcinogenicity

The widespread use of chlorination of potable water to kill bacteria [40] has lead to the study of the biochemical mechanism of chlorine-induced alteration of cells. [41-43] In an aqueous milieu such as that found in tissue, molecular chlorine disproportionates rapidly according to the following equation:

$$Cl_2(aq) = H^+ + X^+ + HOCl$$

The equilibrium constant for this reaction in aqueous solutions is 4.2×10^{-4}. [44] Hypochlorous acid, which is formed as a result of this reaction, will react with ammonia and other amines. This reaction results in the introduction of the chlorine radical into the reaction products. [44]

Patton et al [41] have demonstrated that aqueous solutions of hypochlorous acid react with cytosine which is a constituent of the cellular genetic material, deoxyribonucleic acid (DNA). When one gram equivalent weight of hypochlorous acid was reacted with one gram equivalent weight of cytosine under physiologic conditions, a 76% yield of 4-N-chlorocytosine was obtained. When excess hypochlorous acid was reacted with cytosine, several more highly chlorinated derivatives of cytosine were formed. Under acidic conditions, 4-N-chlorocytosine was converted to the more stable 5-chlorocytosine. Prat et al, as cited by Patton et al, [41] isolated the latter compound from DNA treated with sodium hypochlorite.

Using transforming DNA of Haemophilus influenza pretreated with chlorine, Hsu [42] demonstrated that chlorine can interfere with the biologic activity of the macromolecule. Eisenstark, as cited by Shih and Lederberg [43] showed that Bacillus subtilis DNA has a decreased ability to transform cells after chloramine or hypochlorous acid treatment. Shih and Lederberg [43] studied the induction of breaks in the chromosome of Bacillus subtilus following treatment of the organism with chloramine. The number of observed DNA breaks increased monotonically as the dose of chloramine and the treatment time increased. The authors concluded that the DNA breaks induced in vivo were caused by the direct reaction of chloramine with DNA. However, they indicated that it was also possible that chloramine-induced alterations in the functional dynamics of the endonucleolytic DNA monitoring system caused the breaks. Shih and Lederberg [43] also noted that pretreatment of DNA either in vivo or in vitro reduced both the transforming ability of DNA and the cotransduction

of genetic characteristics known to be adjacent on the chromosome.

While observed changes in the cellular genetic material following treatment with chlorinating agents are a matter of grave concern, the available information does not provide any evidence concerning the magnitude of these effects in any higher organism or in humans.

No evidence has been found to indicate that chlorine is a carcinogen. [45]

Epidemiologic Studies

Evans [46] in 1940 reported on chest X-rays taken in the chemical industry over 5 years. A random sample of those exposed to chlorine and hydrogen chloride (no total number given) resulted in a cohort of 35 men exposed for an average of 6.4 years. The substances were handled in a closed system. However, it was reported that low-level concentrations occurred throughout the workday and frequently there were breaks in pipelines and failures in equipment thereby allowing the liberation of unspecified quantities of chlorine and hydrochloric acid gases. Chlorine exposure concentrations were not reported. Short clinical histories of five of those exposed were presented. Three had experienced attacks of respiratory disease during their periods of employment. While employed in the area, one worker was found to have inactive tuberculosis, but it was not apparently affected by continued work in that area. For all 5, it was stated that no X-ray changes were observed.

In 1967, Ferris et al [47] compared the prevalence of chronic respiratory disease in workers exposed to sulfur dioxide, chlorine, and

chlorine dioxide in a pulp mill and a paper mill. The sample from the pulp mill consisted of 147 men who worked in either the chlorine plant, sulfite mill, Kraft plant, or in the chlorine dioxide plant. The sample from the paper mill consisted of 124 men who operated paper machines or were involved in maintenance. The study [47] was conducted over 2 months and included the taking of an occupational history, the use of a standard respiratory disease questionnaire, and the performance of pulmonary function tests for forced expiration (spirometry and peak flow measurement). Standard criteria were used for classification of these data.

Three industrial hygiene surveys [47] were done in the pulp mill between April 1958 and February 1963. Twenty-four samples indicated that chlorine concentrations ranged from trace to 64.0 ppm; only the first survey, accounting for 9 samples, showed any chlorine concentration above trace. No industrial hygiene data were given for the paper mill. In the pulp mill, 73 of the 147 workers were exposed to chlorine for an average of 20.4 years. Nine of the 124 paper-mill workers were exposed to chlorine for an average of 7.5 years. Expected rates of chronic nonspecific respiratory disease were calculated from the rates of the two mill populations pooled for the various categories of age and current smoking habits. The overall expected rates of respiratory disease were then compared with the observed rates to determine whether there was any significant difference between the two mills; the prevalence of chronic nonspecific respiratory disease was 32.5% in the pulp mill and 27.4% in the paper mill. This was not judged by the authors to be a significant

difference. Formulae based on age and height for predicting forced vital capacity (FVC), FEV, and peak expiratory flowrate (PEFR) were calculated for those in the pulp mill and the paper mill; an analysis of variance for testing the equality of regression coefficients (including the constant term) was done on the two equations for each group and, according to the authors, no significant difference was demonstrated.

No difference was noted in results of tests of pulmonary function of 118 pulp-mill workers exposed primarily to sulfur dioxide and the 73 exposed to chlorine or chlorine dioxide. However, when the responses to 12 questions about respiratory symptoms were compared, 3 were answered positively more often by men exposed to chlorine: "gassed at work" ($p < 0.05$), "phlegm past 3 years" ($p < 0.05$), and "shortness of breath grade 3 or more" ($p < 0.01$).

There are problems in interpreting these results, some of which were pointed out by the authors. [47] The industrial hygiene surveys began in 1958; higher chlorine concentrations had probably existed in the past, possibly higher in one mill than in the other, but there were no records. It is also possible that higher levels occurred during the time surveyed, since the sampling was very limited. It is also not clear where sampling had taken place. The authors commented that many men transferred to the paper mill because they disliked the odors in the pulp mill. Because of this, men working in the paper mill may have been more sensitive to irritant gases. Finally, workers were not only exposed to chlorine, but also to sulfur dioxide and chlorine dioxide, although one usually predominated at any given location.

In 1967, Leduc [48] reported studies conducted at the request of 620 employees exposed to various irritant gases to determine effects of chronic exposure. There were 15 workers who were exposed to chlorine. The author questioned physicians in localities where workers were exposed to chlorine, specialists, and industrial physicians of factories with similar risks about their experiences with acute chlorine intoxication and any sequelae, and about their observations of ill effects from chronic exposure to chlorine. Private physicians reported treating 5 cases of acute chlorine intoxication; the author's implication was that all 5 were probably not among the 15 chlorine workers in the group requesting the investigation. The extent of exposure for the five was not quantified. Of the five, one had occasional bronchitis since exposure and one had a 5% disability granted because of bronchitis subsequent to exposure. There were no known sequelae for three; the extent of follow-up was not given. Responses from industrial physicians revealed reports on at least 301 workers; there were 2 fatalities and 2 cases of serious pulmonary edema attributed to chlorine exposure. After acute intoxication, one worker developed a serious allergic colitis which necessitated several months of hospitalization; it was not further characterized.

Capadoglio et al [49] examined all 52 workers employed in a plant for electrolytic production of chlorine and soda. Their average length of service was 10 years. With various frequency, each person experienced the irritating effect of chlorine at high concentrations. None suffered clinically significant incapacity, even temporarily. In 18 determinations of chlorine, the average concentration was 0.298 ppm (SD = 0.181). Another

group of 27 clinically healthy workers who had no current or previous exposure to chlorine, halogens, or other respiratory irritants, served as controls. The 52 exposed and the 27 controls were also classified according to smoking habits yielding 4 categories: exposed smokers, exposed nonsmokers, nonexposed smokers, and nonexposed nonsmokers. Those studied had similar ages and heights.

In comparing the four groups as to VC, FEV 1, RV, DLCO, and helium concentration gradient in a single breath during washout, only the results of the test of DLCO showed a significant difference between exposed and control workers. This value was significantly lower in exposed smokers than in nonexposed smokers ($p < 0.02$), lower in exposed smokers than in exposed nonsmokers ($p < 0.04$), and lower in exposed smokers than in nonexposed nonsmokers ($p < 0.003$). Controlling for smoking, prior accidental exposure to chlorine was associated with a decreasing diffusion capacity. All values were corrected for height and age.

Tawast et al [50] studied 49 workers whose stays in a chlorine mill averaged 12 years. No exposure data were given. The average blood values for hemoglobin, red cell count, and leukocyte count and differential did not differ from those of 39 workers not exposed to chlorine.

During a 3-day study period, Chester et al in 1969 [51] examined all 139 men in a plant producing chlorine and sodium hydroxide by electrolysis of brine. Approximately 99% of the air samples taken in this and similar plants contained less than 1 ppm chlorine (number of samples not given). Fifty-five of the 139 workers had been accidentally exposed one or more times to chlorine at higher concentrations and had required oxygen therapy

at least once during their employment. Posterior-anterior chest films were abnormal in 56 of 138 men. The degree of exposure or length of employment of these 56 was not given. One man had a mottled infiltrate in the right apex most consistent with active tuberculosis. Extensive pleural reaction, pulmonary fibrosis, and a high-right diaphragm with plate-like atelectasis and discrete densities in the right lower lobe were separately noted in three other men. Only one subject had abnormal ventilatory function. All but 7 of the 56 revealed evidence of parenchymal or hilar calcifications that were considered to be consistent with old granulomatous disease. Evaluation of a standard respiratory questionnaire revealed that there was no significant difference between the prevalence of symptoms in those exposed to chlorine who smoked, and in those nonsmokers not exposed to chlorine. A significant difference in maximal midexpiratory flow was seen, however, when chlorine and smoking were considered as additive noxious agents (Table III-3). The authors stated that before chlorine could be indicted as a specific health hazard, a detailed study of the smoker-chlorine cohort would have to be made.

Accidental exposure was defined by the authors as one occurring at least once in the history of each worker and severe enough to require oxygen therapy. The prevalence of such exposure in smokers correlated positively with a decrease in MMF ($p < 0.02$). Ages of smokers accidentally exposed averaged 42.5 years, while those with no exposure averaged 35.7 years. The authors felt that this age difference was insufficient to explain the difference in MMF.

TABLE III-3

MAXIMAL MIDEXPIRATORY FLOW VALUES IN SMOKING AND NONSMOKING WORKERS WITH ACCIDENTAL CHLORINE EXPOSURE

Smoking	Exposed			Nonexposed		
	No.	Mean	SD	No.	Mean	SD
yes	46	3.57	1.03	56	4.13	1.33
no	12	4.10	0.76	25	4.36	1.18

From reference 51

During the course of this survey, [51] two subjects were exposed to chlorine and were treated with oxygen. One subject was observed 24 and 48 hours after this acute exposure; the other was observed immediately and then again 24 hours after exposure. The data for these two subjects revealed acute obstructive ventilatory defects with rapid clearing within 24 hours in the second subject and clearing in the first subject at 48 hours.

This prevalence study [51] indicated that workers accidentally exposed to chlorine suffered a greater reduction in pulmonary function than did those who were exposed only to chlorine at the levels usual for their work situation. Since the function studies were not expressed as percentages of normal or predicted values, no conclusions could be drawn about the effect of chlorine at lower airborne concentrations.

In 1970, Patil et al [52] studied 25 chlorine-producing plants in the United States and Canada. Air sampling at representative locations within each plant was done every 2 months throughout the study year. In addition

to the air analysis, each plant assigned its employees a job classification and described the work experience of each classification in relation to actual or potential chlorine exposure. TWA exposure data were calculated for each worker on an 8-hour basis.

A total of 600 male workers from diaphragm-cell plants constituted the total work force considered to have been exposed to chlorine throughout their employment in cell rooms. [52] Because of lack of exposure data on 268, the study population for determining dose-response relationships was 332 workers. The control group of 382 consisted of workers from many of the same plants who were not routinely exposed to chlorine. There were no other control groups. TWA exposures to chlorine ranged from 0.006 to 1.42 ppm, with a mean of 0.15 ppm. All but 6 of the 332 workers had TWA exposures less than 1 ppm and only 21 had TWA's above 0.52 ppm. The average number of chlorine-exposure years for all diaphragm-cell workers was 10.9. Employees with 10-14 years' experience constituted the single largest group, and this group also contained the most workers exposed to more than 0.52 ppm chlorine. There was no correlation between the chlorine concentration and the number of years a person was so exposed.

The exposed and control groups described above were well-matched with respect to age, ranging from 19 to 69 years; 60% of the workers were 30-49 years old. [52] The mean age of the two groups combined was 31.2 years. About 60% of the workers in both groups smoked at the time of the study. In order to determine whether a significant number of workers with occupational exposure to chlorine had retired due to causes related to chlorine exposure, health data were collected on workers not involved in

the study who had terminated employment. No patterns were evident, and it appeared that most workers had resigned or were reassigned for reasons unrelated to health.

The following observations [52] were reported. Chlorine workers showed a higher incidence of history of tooth decay ($p = 0.025$) than controls, but there were far less actual observed abnormalities of teeth and gums of chlorine workers as seen by the examining physician than those reported: out of 332, 98 actually had abnormal teeth and gums. The authors reported no significant dose-response relationship.

Medical histories of the prevalence of frequent colds, dyspnea, palpitation, and chest pain showed no dose-response correlation; however, values were not given. [52] Chest X-rays were evaluated for 544 workers exposed to chlorine. Of these, 21.3% had abnormalities, compared with 26.8% among the controls. Most of these abnormalities, 75%, represented hilar or parenchymal calcifications. Pleural and diaphragmatic abnormalities accounted for 11.4%. No neoplasia or serious acute pulmonary diseases were reported. No significant dose-response correlation was found when chlorine exposure was related to VC, MVV, FEV, and forced expiratory volume at 3 seconds (FEV 3) values. There was, in summary, no evidence of permanent lung damage attributable to chlorine at the levels reported.

Of the 329 ECG's from 332 workers, 9.4% were abnormal as compared to 8.5% in controls; the number of ECG's taken in each group was not given. [52] The incidence of fatigue (undefined) was greater in workers exposed to chlorine at concentrations greater than 0.5 ppm, but there was no apparent correlation below 0.5 ppm. Nervousness, headache, insomnia, and

shyness showed little relationship to chlorine exposure. Anxiety and dizziness showed moderate correlation with exposure level ($p = 0.020$). Histories of neurologic illness and use of alcohol were unrelated to chlorine levels. There was no correlation of exposure with either tremors or abnormal reflexes. The gastrointestinal system and skin showed no dose-related effects. Leukocytosis ($p < 0.05$) and low hematocrits ($p < 0.017$) exhibited some relation to chlorine exposure. In summary, with the exceptions of anxiety, dizziness, leukocytosis, and lower hematocrits, dose-related effects were not found at exposures ranging from 0.006 to 1.42 ppm chlorine.

The use of prevalence studies, such as those reported in the foregoing reports, [51,52] to define the relationship between chronic exposure to chlorine and the development of symptoms or signs, suffers from certain conceptual as well as methodologic difficulties. The exposure pattern, even excluding acute episodes, may be variable over time. The results of air-monitoring performed during a study do not necessarily reflect chlorine exposure prior to the study. Acceptance of volunteer workers for medical examinations may produce a group of those exposed to chlorine potentially different from the pool of all exposed workers. The pulmonary function effects attributed to exposure to chlorine closely resemble those produced by smoking and by other respiratory irritants, some of which commonly occur in combination with chlorine; adjustment for all of those known exposures is difficult, and the possibility remains that unknown exposures exist. Selection of subjects to represent some defined group may pose problems. Complete follow-up information is difficult to

secure. Analysis of sufficient air samples to calculate TWA's for each exposed employee is rarely done. Some of the adverse effects of chlorine exposure are subtle and thus require fairly large studies to make them visible.

In spite of these difficulties, the authors [46-52] in the seven studies described did attempt to document chronic changes following chlorine exposure by means of prevalence studies. Three [46,47,50] concluded there were no observable effects by the methodology used. Chester et al [51] found that previous accidental exposure to chlorine in workers who smoked was associated with a decreased MMF. Patil et al [52] noted some apparent dose-response relationships, but none involving the respiratory tract. Leduc [48] uncovered two cases of pulmonary edema and two fatalities attributed to chlorine by industrial physicians. Capodaglio et al [49] found a lower DLCO in persons who reported having had previous accidental exposure at work. None of the seven epidemiologic studies made any measurements which would clarify whether or not small airway disease had occurred.

Animal Toxicity

In 1920, Underhill [53] described effects of chlorine on dogs. Animals not subjected to any previous testing were exposed to chlorine gas for 30 minutes at 50-2,000 ppm. They first showed general excitement, as indicated by restlessness, barking, urination, and defecation. Irritation was distinctly visible, as indicated by the blinking of eyes, sneezing, copious salivation, retching, and vomiting. Later, their respiration

became labored with frothing at the mouth. Although the dogs frequently drank large quantities of water, they refused food. With increased concentrations of chlorine, the respiratory distress increased until death occurred, usually within 24 hours, apparently from asphyxiation. Table III-4 shows that at a chlorine concentration of 800 ppm half the animals died within 3 days, while at 900 ppm exposure 87% died within this time.

Animals which died after 3 days were classified as "delayed" deaths. The animals so classified did not exhibit the signs of acute exposure, ie, labored and distressed breathing, for more than 1 or 2 days. They showed signs of loss of appetite, extreme depression, and weakness. In the majority of cases, deaths classed as "delayed" resulted from secondary factors, chiefly bronchopneumonia following the subsidence of acute pulmonary edema. The author considered "the minimum lethal toxicity of chlorine gas under the conditions of the experiment" to occur between 800 and 900 ppm chlorine.

Underhill [53] conducted further experiments on 40 of 43 dogs surviving the first gassing (Table III-4) with chlorine. He reported 53 original survivors, as shown in Table III-5; however, his tabular data presented only 43 survivors. The discrepancy was not explained.

Two interpretations of these results were suggested by the author: the first gassing either rendered the animals less susceptible to the effects of subsequent exposure or killed the weaker individuals. When the deaths from the first gassing were added to those from the second gassing, the final percentage of dying was practically identical with the original standard toxicity figures, a finding supporting the second hypothesis.

TABLE III-4

MORTALITY IN DOGS EXPOSED TO HIGH CONCENTRATIONS OF CHLORINE

	Concentration of Chlorine, ppm													
	50-250		400-500		500-600		600-700		700-800		800-900		900-2000	
	N*	%	N*	%	N*	%	N*	%	N*	%	N*	%	N*	%
Deaths														
1st day	0	0	0	0	0	0	4	19	3	17	12	52	10	71
2nd day	0	0	1	6	1	10	5	24	4	22	6	26	3	21
3rd day	0	0	0	0	1	10	0	0	2	11	2	9	0	0
Delayed deaths	1	11	4	24	2	20	5	24	2	11	1	4	0	0
Recoveries	8	89	12	70	6	60	7	33	7	39	2	9	1	7
Total number exposed	9		17		10		21		18		23		14	

*N is the number of dogs calculated from percentages and total exposed.

From reference 53

In 1920, Winternitz et al [54] examined 326 dogs at post mortem which had been gassed with chlorine. The dogs were those which had died in the course of the study conducted by Underhill [53]. The salient features of pathologic changes in dogs dying within the first 24 hours after gassing (acute deaths) included severe injury to the mucous membranes of the upper

TABLE III-5

MORTALITY IN DOGS REEXPOSED TO CHLORINE

Concentration of Chlorine at First Gassing (ppm)	No. of Dogs Surviving First Gassing	Concentration of Chlorine at Second Gassing (ppm)	No. of Dogs Exposed	No. of Acute Deaths	No. of Delayed Deaths
Less than 200	8	738-882	6	5	0
400-600	19	750-860	15	9	1
600-800	13	643-1065	12	2	1
800-900	10	809-851	7	2	0

From reference 53

respiratory tract with irregular dilation and contraction of the bronchi resulting in alternating patches of acute emphysema and atelectasis in the lungs. All tissues of the respiratory tract showed extreme congestion and edema. An acute inflammatory reaction began within a few hours of exposure, developing into pneumonia. Animals autopsied 2-5 days after gassing, (delayed deaths) showed an increase in the intensity of inflammation and development of lobular pneumonia which was frequently complicated by abscess formation and gangrene. Bronchiolar spasm was most pronounced in this group. Dogs in a group autopsied 5-15 days post mortem (late deaths) suffered pulmonary damage of a severity between that of the dogs in the delayed death group and that of the recovered dogs. Death of dogs in this group was usually due to pulmonary infection, pneumonia, and bronchitis, the most striking feature of which was the tendency of the inflammatory exudate to organize. This was cut short by the death of the animal.

Animals surviving for 15-193 days after gassing [54] showed marked emphysema, which was associated with an organizing exudate in the bronchioles, "bronchiolitis obliterans." The bronchioles sometimes contained a small amount of purulent exudate, but the larger mass of exudate was organized, composed of fibroblasts and blood vessels with some mononuclear cells. Not infrequently, the lung tissue surrounding such a bronchus showed an organizing pneumonia. Aside from the areas of organizing pneumonia which were found around the bronchi, the alveoli were, in many places, filled with a cellular exudate. This exudate was not composed of polynuclear leukocytes, or red cells, but almost entirely of large mononuclear cells with watery, vacuolated protoplasm similar to the desquamated cells frequently found in the more chronic forms of pneumonia in man.

Winternitz et al [54] thought that the patchy distribution of alveolar damage as seen in these animal studies represented effects of chlorine which reached the terminal sacs through airways that were not occluded by spasm.

Faure et al [32] studied 35 guinea pigs exposed to chlorine at 200 ppm for 15-30 minutes, repeating the pathologic observations of Winternitz et al. [54] The clinical reactions of the animals were not given.

Barbour [55] found that four dogs exposed to chlorine at concentrations of 24-30 ppm for 30 minutes showed clinical signs of "irritation," but that they returned to an apparently normal condition immediately after removal from the chamber. During the gassing, lacrimation and profuse salivation usually occurred as well as mild

retching and vomiting. The effects upon pulse and respiratory rates were variable. When exposed to chlorine at 180-200 ppm for 30 minutes, three dogs showed the irritant effects described above followed by general depression of muscle activicy and dyspnea before the gassing was terminated. No evidence of bronchitis or edema was obtained and the animals became apparently normal again after a few hours. When chlorine at 800-900 ppm was used, it killed at least 85% of the dogs which were exposed for half an hour. It is not clear how many dogs were exposed at this concentration. These studies were also carried out to assess the possible effect of chlorine on body temperature. At 24-30 ppm, there were rises in body temperature which averaged 0.8 C and lasted 3-24 hours during gassing of four dogs. At 180-200 ppm, the three dogs had decreases in temperature which averaged 0.7 C during gassing. Return to normal began promptly; the average duration of hypothermia was 6 hours. At 800-900 ppm, the temperature drop in 20 dogs averaged 1.0 C/half hour. The temperature continued to fall at the same rate for another 1 1/2 hours, after which it declined more gradually until death ensued. After being gassed at 800-900 ppm, dogs were unable to regulate their body temperatures when exposed at moderately high external temperatures (35-40 C) or at low ones (ordinary room temperatures), a range over which ungassed animals maintained their normal temperature.

Gunn [56] found that exposing cats and rabbits to chlorine at concentrations of 1 part/5,000 parts (200 ppm) to 1 part/10,000 parts (100 ppm) produced a reflex constriction of the bronchi lasting about 1 minute. The rate of respiration increased concomitantly.

Bell and Elmes [57] used specific pathogen-free 14-week-old rats (SPF rats) to determine whether chlorine exposure at 40 ppm for 3 hours daily for a total of 43 hours (discrepancy not explained) had any immediate effect or altered the effect of exposure to chlorine at 117 ppm at age 30 weeks (3 hours daily until about half had died, 29 hours). They presented the details about the exposure in another paper. [58] At 40 ppm, exposed rats coughed, sneezed, and huddled together; after 3 hours, their noses were running and sometimes blood-stained. Exposure to chlorine at 40 ppm did not make death from chlorine at a subsequently higher concentration (177 ppm) more likely.

A second experiment [57] compared the effect of chlorine at high concentrations on SPF rats and those with spontaneously occurring lung diseases. Female SPF and diseased rats were exposed as separate groups to chlorine at 118 ppm for 3 hours followed by 14 hours at 70 ppm. Male SPF and diseased rats were exposed initially to chlorine at 34 ppm for 3 hours daily with incremental increases to 170 ppm; the total duration for male rat exposures was about 60 hours at a mean chlorine concentration of 90 ppm. It was concluded that the presence of preexisting lung disease increased the likelihood of death from exposure to chlorine at high concentrations ($p < 0.01$). In diseased animals, the cellular response to heavy exposure was much more severe than that in SPF animals. Proliferation of goblet cells and aspiration of mucus were more intense and extensive in the diseased stock following exposure to chlorine. In animals dying during exposure, diseased rats had a significantly higher incidence of emphysema than did SPF stock. The most noticeable difference between

the two groups lay in the reactions of the alveolar part of the lungs to the aspiration of bronchial mucus and debris. In both experiments, the SPF animals showed no increase in number of polymorphonuclear cells, while in 11 of the 29 diseased animals dying during exposure there were extensive areas of acute inflammation with infiltration by polymorphonuclear leukocytes in relation to the aspirated mucus; in another 10, there were smaller patches of acute pneumonia.

Arloing et al [59] exposed guinea pigs to chlorine at 5 mg/cu m (1.7 ppm) for 5 hours daily over 87 days. There were four groups of animals as follows (no numbers or tests of significance were given): (1) exposed first to tubercle bacilli and then to chlorine, (2) first to chlorine and then to tubercle bacilli, (3) given tubercle bacilli but no chlorine, and (4) given chlorine but no tubercle bacilli. The method of achieving this concentration of chlorine was cited [60] but not given in detail. The animals were described as tolerating it perfectly well. Of the animals exposed only to chlorine, all survived over 300 days. There was considerable overlap between the survival times of the first three groups of animals (Table XIII-4), but regardless of how the tubercle bacilli were administered (subcutaneously, into ganglia or conjunctivae, or into trachea), the average length of survival decreased when the animals breathed chlorine.

In a series of experiments evaluating the effects of mixtures of mercury vapor and chlorine gas, Viola and Cassano [61] compared the toxic effects of mercury vapor alone with the effects of a mixture of chlorine gas and mercury vapor. Eighty Wistar rats (average body weight of 250 g)

were divided into two equal groups and exposed separately 5 hours/day, for 5 days/week, during a period of 3 months. The first group was exposed to airborne mercury at a concentration of 4.5 mg/cu m and the second group was exposed to airborne mercury at the same concentration mixed with 1-3 ppm chlorine. After about 6 weeks of exposure to mercury vapor (first group), the rats revealed hyperexcitement, sometimes followed by ataxia and tremor. The rats exposed to airborne mercury vapor mixed with chlorine gas showed mild dyspnea, cough, and diarrhea in the second week. After 2 months of treatment, 10 of the 40 rats in the first group and 4 of 40 rats in the second group had died. In an earlier experiment, [61] the authors had demonstrated a fourfold reduction of the mercury vapor concentration in a closed chamber when chlorine gas was added. A fine precipitate, stated to be mercurous chloride--a reaction product of mercury and chlorine gas--was visible on the floor of the chamber and was thought to have accounted for the mercury vapor reduction.

The authors [61] concluded that the addition of chlorine gas to an atmosphere containing mercury vapor not only reduced mercury absorption, but resulted in a different distribution of the metal in the body, thought to be due to the formation of mercurous chloride. The latter conclusion was supported by autoradiographic studies in which radioactive mercury vapor showed a much different distribution pattern in rats when compared with orally administered radioactive mercurous-203 chloride.

The preceding animal studies were not especially helpful in elucidating the effects of exposure to chlorine at low concentrations. Two studies [53,55] provided data indicating a mortality rate in dogs of 85-87%

after exposure to chlorine at concentrations of 800-900 ppm; one study [53] suggested a chlorine LC50 for dogs of 800 ppm after 3 days following a 30-minute exposure to chlorine. The remaining studies, [32,54,56,57,59,61] with one exception, [59] either did not provide any data on chlorine concentrations, or the concentrations were 40 ppm and higher. Arloing et al [59] exposed guinea pigs to chlorine at 1.7 ppm, 5 hours/day for 87 days. Guinea pigs challenged with tubercle bacilli, with and without a chlorine challenge, were compared with guinea pigs exposed to chlorine alone. In all cases, the animals challenged with either the tubercle bacillus or chlorine alone survived longer than animals exposed to both; and, animals exposed first to chlorine and then to tubercle bacilli died sooner than those first exposed to tubercle bacilli and then to chlorine; this suggests that an increased susceptibility to infection may occur after an exposure to chlorine.

Correlation of Exposure and Effects

All the historical studies [9-12] and case reports [19-37] -- and the epidemiologic studies [46-52] with the exception of the publication by Patil [52] -- share a common deficiency when one attempts to quantify an exposure they described. Even when air sampling had been done, the values for chlorine concentration were available only during a limited period of the worker's total exposure, while any chlorine effects could also be assumed to represent the impact of unknown amounts of additional exposure in the past. Nonetheless, epidemiologic inferences, supplemented by limited studies of acute human exposures, allow some correlations to be

made between exposure levels and effects.

Rupp and Henschler [16] observed that human adults suffered discomfort when the chlorine concentration had risen from zero to 1.3 ppm during 50 minutes. At 1.3 ppm, one subject had severe shortness of breath, cough, and a violent headache. For other subjects, cough began when the chlorine concentration had risen to 0.5 ppm. Itching in the nose occurred in subjects exposed to 0.2 ppm for 4-20 minutes, and headache was experienced at 1.0-ppm exposure after approximately 35 minutes. [16] Beck [17] was unable to continue the experiment beyond 20 minutes when one subject in 10 exposed to chlorine at 1 ppm complained of headache, burning in the conjunctivae and skin, a distinct taste, coughing, and a sense of not being able to inhale deeply. Tickling and stinging in the nose were reported by six others, and four had scratchiness and dryness of the throat. When the concentration of chlorine was gradually increased from zero, one of four subjects considered 0.42 ppm as the limit of "what might be required" of experimental subjects. The details of this individual's symptoms were not given. The same subject had the sensation of choking at 0.36 ppm. Three of the four subjects experienced stinging in the throat at 0.3 ppm. Among 13 subjects exposed to chlorine at 0.2 ppm, 7 reported slight tickling in the nose and throat, 1 had a slight cough, and 3 reported sensations in the conjunctiva.

Matt [38] reported that exposure to chlorine at a concentration of 1.3 ppm resulted in an unpleasant burning in the eyes and nose of one subject after 7 minutes. Exposure at 2.5 ppm resulted in severe burning of the eyes, mouth, and throat after 7 minutes.

The much higher thresholds of discomfort (15.1 ppm) and olfaction (3.5 ppm) determined by Fieldner et al [39] are unsupported by adequate documentation. Ryazanov [15] determined 0.3-0.4 ppm to be the threshold concentration for detection of the odor of chlorine by man. Rupp and Henschler [16] found that 51 of 60 persons perceived the odor of chlorine at a concentration of 0.104 ppm or less; 7 of 14 persons could detect it at 0.038 ppm. Beck [17] found an odor was perceived by all 10 subjects exposed to chlorine at 0.09 ppm (7 could identify the odor) while at 0.044 ppm, 4 of 10 subjects detected an odor (2 could identify it as chlorine).

According to CB Kramer (written communication, June 1974), the Dow Chemical Company reported subjective responses made by their industrial hygienists when sampling workroom atmospheres for chlorine. During sampling periods of 10 minutes or more, odor was perceived by an unspecified number of industrial hygienists at concentrations which averaged 1.1-41.0 ppm. A respiratory response of "minimal," "easily noticed," or "strong" was experienced at concentrations which averaged 1.92-41.0 ppm during the collection of 41 samples. "Minimal" or "easily noticed" eye irritation was experienced at concentrations which averaged 7.7-41.0 ppm during the collection of five samples. It was pointed out that tests by the same individual made late in the shift after previous exposure were frequently less discerning than those made earlier the same day, implying some degree of fatigue or adaptation of olfaction.

Chronic exposures were evaluated by Ferris et al [47] who observed workers exposed an average of 20.4 years to chlorine concentrations ranging from 0 to 64 ppm without observing any adverse effects from chlorine.

Patil et al [52] found no pulmonary effects in 332 workers from 25 plants exposed for an unspecified number of work-years to chlorine at a mean TWA concentration of 0.15 ppm (range: 0.006-1.42 ppm). Capodaglio et al [49] published data on workers with an average exposure of 10 years to chlorine at concentrations which averaged 0.3 ppm who showed some decrease in diffusion capacity; these decreases were associated, however, with histories of accidental acute exposures of unknown magnitude.

Chemical changes have been observed in the genetic material of bacteria following treatment with chlorinating agents. [41-43] The significance of these changes in relation to human populations has not yet been determined.

No evidence has been found to indicate that chlorine is a carcinogen. [45]