

Chapter 9

TOXIC INHALATIONAL INJURY

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SUMMARY

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INTRODUCTION

Pulmonary toxic inhalants have been a military concern since the Age of Fire. Thucydides, in 423 BC, recorded the earliest belligerent use of a toxic inhalant. The Spartans used a burning mixture of pitch, naphtha, and sulfur to produce sulfur dioxide that was used in sieges of Athenian cities.¹ There is scant reference in the literature to further military use of toxic inhalants until World War I. In early 1914, both the French and Germans investigated various tear gases, which were later employed. By early 1915, the German war effort expanded its gas research to include inhaled toxicants. As a result,

on 22 April 1915, at Ypres, Belgium, the Germans released about 150 tons of chlorine gas along a 7,000-m battlefront within a 10-minute period. Although the exact number of injuries and deaths are unknown, this “new form” of warfare produced a degree of demoralization theretofore unseen.² Although phosgene and chlorine have not been used militarily since 1918, vast amounts are produced annually for use in the industrial sector. The potential for accidental or deliberate exposure to a toxic inhalant exists, and military personnel should be prepared.

TOXIC INHALATIONAL INJURY

Physical Aspects

Airborne (and consequently inhaled) toxic material may be encountered in gaseous or particulate form (Exhibit 9-1). Airway distribution of toxic

inhalants as a gas or vapor follows normal respiratory gas flow patterns. The central airways exchange gases with the environment as a result of the mechanical aspects of breathing. Each breath dilutes central airway gas with newly inhaled gas.

EXHIBIT 9-1

DEFINITIONS OF AIRBORNE TOXIC MATERIAL

Gas	The molecular form of a substance, in which molecules are dispersed widely enough to have little physical effect (attraction) on each other; therefore, there is no definite shape or volume to gas.
Vapor	A term used somewhat interchangeably with gas, vapor specifically refers to the gaseous state of a substance that at normal temperature and pressure would be liquid or solid (eg, mustard vapor or water vapor compared with oxygen gas). Vaporized substances often reliefs and hence may have a combined inhalational and topical effect.
Mist	The particulate form of a liquid (ie, droplets) suspended in air, often as a result of an explosion or mechanical generation of particles (eg, by a spinning disk generator or sprayer). Particle size is a primary factor in determining the airborne persistence of a mist and the level of its deposition in the respiratory tract.
Fumes, Smokes, and Dusts	Solid particles of various sizes that are suspended in air. The particles may be formed by explosion or mechanical generation or as a by-product of chemical reaction or combustion. Fumes, smokes, and dusts may themselves be toxic or may carry, adsorbed to their surfaces, any of a variety of toxic gaseous substances. As these particles and surfaces collide, adsorbed gases may be liberated and produce local or even systemic toxic injury.
Aerosol	Particles, either liquid or solid, suspended in air. Mists, fumes, smokes, and dusts are all aerosols.

Gas moves by convection into the peripheral airways (airways of 2-mm diameter) and then by diffusion to the alveolar-capillary membranes. Consequently, there is a much slower dilution of gas at this level. Therefore, toxic inhalants reaching this level may have a more profound effect due to greater relative duration of exposure.

Particles (such as those present in mists, and in fumes, smokes, and dusts) present a more complex distribution pattern because the particle size affects its deposition at various levels of the airway. Such factors as sedimentation and impact rates also control particle deposition. Therefore, heavier particles may settle in the nasopharynx or upper airways, whereas lighter or smaller particles may reach more-peripheral airways. Once they have impacted, particles are susceptible to a variety of respiratory defense mechanisms. These mechanisms determine the efficiency with which particle removal progresses, thereby determining the particle's ultimate degree of adverse effects.

Clinical Effects

Toxic inhalants may cause damage in one or more of the following ways:

- Asphyxiation may result from a lack of oxygen (eg, as in closed-space fires) or by interference with oxygen transport (eg, by cyanide, which compromises oxygen uptake by preventing its transport to cellular metabolic sites).
- Topical damage to the respiratory tract may occur due to direct toxic inhalational injury to the airways or alveoli. Cellular damage with consequent airway obstruction, pulmonary interstitial damage, or alveolar-capillary damage ultimately compromises adequate oxygen-carbon dioxide exchange. Some substances are relatively more toxic to the central airways, whereas others are more toxic to the peripheral airways or alveoli.
- Systemic damage may occur as a result of systemic absorption of a toxicant through the respiratory membranes (eg, leukopenia following mustard inhalation) with consequent damage to other organ systems. Effects on other organ systems may be more obvious than the respiratory effects of exposure (as with mercury).
- Allergic response to an inhaled toxicant may result in a pulmonary or systemic re-

action, which may be mediated by one or more of a variety of immunoglobulins. Secondary by-products of this reaction may cause cellular destruction or tissue swelling; consequently, oxygen-carbon dioxide exchange may be compromised, and there may be systemic inflammatory damage.

Physiology

The ultimate effect of a particular toxic inhalant on the respiratory system or the whole organism is the result of a complex interaction of multiple factors, including the intensity of exposure, condition of exposed tissues, and intrinsic protective and reparative mechanisms.

Intensity of Exposure

The intensity of exposure variable is partially affected by the physical state and properties of the toxicant. Heavier-than-air gases are particularly affected by environmental conditions; for example, warm environments increase the vaporization of some substances (such as mustard), making inhalational toxicity more likely. Increased humidity increases particle size by hygroscopic effects. Increased particle size may decrease the respiratory exposure to a toxicant because larger particles may precipitate prior to inhalation, or they may be collected preferentially in the upper airways, which have better clearance mechanisms.

The intensity as well as the site of exposure is partially affected by the toxic inhalant's degree of water solubility: more soluble toxicants (such as chlorine) primarily affect the upper airways and the more central airways. Despite the relatively high rate of airflow in central airways, the more soluble toxic gases are almost entirely deposited there. The less-soluble gases tend to produce effects in the peripheral airways or alveoli. In peripheral airways, air motion is relatively slow, occurring primarily by molecular diffusion. Foreign substances (such as cigarette smoke and toxic gases) that have not been trapped at more-central sites tend to remain longer in the peripheral airways. These substances may induce a surprising degree of damage due to their prolonged effect.

The intensity of exposure is commonly measured by multiplying the concentration (C , in milligrams per cubic meter) of a substance by the time of exposure (t , in minutes); the product is known as the Ct ; the units of measurement as $\text{mg} \cdot \text{min}/\text{m}^3$. Precise measurement of the toxicant's concentration at the

site of topical effect is not possible. An inhaled breath of toxic inhalant is mixed into a greater volume of airway gas (containing oxygen, nitrogen, carbon dioxide, and water vapor). The distribution of that breath then depends on such variables as speed of inhalation, depth of inhalation, and even body position during inhalation. Additionally, the duration of exposure, particularly in a combat setting, may be exceptionally difficult to assess. Finally, little attention is paid to the additional variable of depth and frequency of respiration (minute ventilation). This variable is highly affected by the exercise state or metabolic rate of the soldier. Deeper and more frequent breathing during combat may expose the airways to a greater amount of toxic inhalants compared to the exposure of an individual at rest.

Because of difficulties in accurately measuring C_t , the threshold limit value (TLV) of a substance is used more often; a thorough discussion of TLV can be found in another volume in the *Textbook of Military Medicine* series, *Occupational Health: The Soldier and the Industrial Base*.³ Calculations are made of a maximum allowable exposure to a toxicant, typically expressed for a 15-minute or an 8-hour period. This calculation makes the development of environmental standards and alarm detection systems somewhat simpler. The TLV should not, however, be considered a definition of a safe level. The concept of safe level wrongly implies that exposure to toxicants below that level has no effect. Rather, the TLV should be considered an expedient method of defining the statistical risk of injury resulting from an exposure. As biological and medical testing techniques undergo revision, toxic inhalants are often found to have histological or physiological effects in experimental animals at levels well below the established TLV. Therefore, rather than defining a "safe" level of a toxicant, the TLV may simply describe a level at which there is no recognized biological effect.

Condition of Exposed Tissues

Preexisting airway damage (such as that caused by prior toxic inhalant exposure) may seriously compromise the respiratory system's normal protection and clearance mechanisms. Specifically, there may be depletion of critical enzyme systems. Cigarette smoking may severely compromise airway function with respect to both airway patency and clearance mechanisms. Hyperreactive airways (asthma in varying degrees) are seen in up to 15% of the adult population. Toxic inhalant exposures

may trigger bronchospasm in these individuals. This bronchospasm may delay the clearance of the toxicant, interfering further with gas transport. The development of an acute interstitial process (eg, phosgene-related pulmonary edema) may also trigger bronchospasm. Individuals with any of the following characteristics should be considered likely to develop bronchospasm as the result of a toxic inhalant exposure:

- prior history of asthma or hay fever (even as a child),
- prior history of eczema, or
- family history of asthma, hay fever, or eczema.

Individuals with hyperreactive airways will benefit from bronchodilator therapy and possibly from steroids after exposure to a toxic inhalant. This statement, however, does not constitute an endorsement for routine steroid use in all toxic inhalational injuries.

Evaluation of Injury

Individuals exposed to a toxic inhalant should be carefully examined by medical personnel who are well versed in military medicine in the area of pulmonary injury. Obtaining a medical history and examining an exposed individual require the examiner to have an extensive knowledge of military toxicology and a thorough background in the fundamental aspects of medical practice. Casualties with toxic inhalational injuries present with a history that is characteristically different from that of most injuries; the cause-effect relationship may be particularly difficult to assess. The possibility of delayed effects caused by toxic inhalants cannot be overemphasized. Evidence of physiological damage may not become apparent for 4 to 6 hours after a lethal exposure (eg, to mustard or phosgene). If such an exposure is suspected, the patient must be observed for at least 4 to 6 hours. Even if there is no obvious injury noted during the observation period, the patient must be carefully reassessed before being discharged from the medical system.

History

Collecting historical data from the casualty is a critical aspect of assessing and treating toxic inhalational injury. Careful questioning of an exposed individual will often greatly simplify the diagnosis and therapy of the injury.

- **Environment.** Were explosions observed? Was there obvious smoke? If so, what color was it? Was the smoke heavier than air? What were the weather conditions (temperature, rain, wind, daylight, fog)? Were pools of liquid or a thickened substance in evidence?
- **Protective Posture.** What was the level of mission-oriented protective posture (MOPP)? Was there face mask or suit damage? Did the face mask fit adequately? When was the filter changed? How well trained was the soldier in using the appropriate protective posture, in making clinical observations, and in choosing appropriate therapy? Were other factors present (eg, consumption of alcoholic beverages, exposure to other chemicals, psychiatric status)?
- **Prior Exposure.** Was there prior exposure to other chemical agents? Is the individual a cigarette smoker? (For how long? How recently? How many?)
- **Pulmonary History.** Is there a prior history of chest trauma, hay fever, asthma, pneumonia, tuberculosis, exposure to tuberculosis, recurrent bronchitis, chronic cough or sputum production, or shortness of breath on exertion?
- **Cardiac and Endocrine History.** Is there a history of cardiac or endocrine disorder?
- **Acute Exposure History.** What were the initial signs and symptoms?
 - **Eyes.** Is there burning, itching, tearing, or pain? How long after exposure did symptoms occur: minutes, hours, days?
 - **Nose and sinuses.** Was a gas odor detected? Is there rhinorrhea, epistaxis, or pain? How long after exposure did symptoms occur: minutes, hours, days?
 - **Mouth and throat.** Is there pain, choking, or cough? How long after exposure did symptoms occur: minutes, hours, days?
 - **Pharynx and larynx.** Are there swallowing difficulties, cough, stridor, hoarseness, or aphonia? How long after exposure did symptoms occur: minutes, hours, days?
 - **Trachea and mainstem bronchi.** Is there coughing, wheezing, substernal burning, pain, or dyspnea? How long after exposure did symptoms occur: minutes, hours, days?
 - **Peripheral airways and parenchyma.** Is

there dyspnea or chest tightness? How long after exposure did symptoms occur: minutes, hours, days?

- **Heart.** Are there palpitations, angina, or syncope? How long after exposure did symptoms occur: minutes, hours, days?
- **Central nervous system.** Is there diffuse or focal neurological dysfunction?

Physical Examination

Physical examination may be particularly difficult in the event of combined toxic and conventional injuries; therefore, it is essential that medical personnel note the following conditions:

- **Reliability.** Is the casualty alert and oriented?
- **Appearance.** Is he anxious or tachypneic?
- **Vital Signs.** What are his weight, blood pressure, pulse, and temperature?
- **Trauma.** Is there a head injury? Are there burns in the region of the eyes, nose, or mouth?
- **Skin.** Are there signs of burns, erythema, sweating, or dryness?
- **Eyes.** Is there conjunctivitis, corneal burns or abrasion, miosis, or mydriasis?
- **Nose.** Is there erythema, rhinorrhea, or epistaxis?
- **Oropharynx.** Is there evidence of perioral burns or erythema?
- **Neck.** Is there hoarseness, stridor, or subcutaneous emphysema?
- **Chest.** Is there superficial chest wall trauma, tenderness, crepitation, dullness, or hyperresonance? Are crackles present? This measurement should be made by asking the patient to hold a forced expiration at residual volume for 30 seconds, then listening carefully at the lung bases for inspiratory crackles. Is wheezing present? This examination should be undertaken by listening for wheezes bilaterally in the chest both posteriorly and anteriorly under circumstances of forced expiration.

Laboratory Measurements

Sophisticated laboratory studies are of limited value in the immediate care of an exposed, injured individual. The following studies are of some predictive value in determining the severity of exposure and the likely outcome.

Chest Radiograph. The presence of hyperinflation suggests toxic injury of the smaller airways, which results in air being diffusely trapped in the alveoli (as occurs with phosgene exposure). The presence of “batwing” infiltrates suggests pulmonary edema secondary to toxic alveolar capillary membrane damage (as occurs with phosgene exposure). Atelectasis is often seen with more-central toxic inhalant exposures (such as with chlorine exposure). As radiological changes may lag behind clinical changes by hours to days, the chest radiograph may be of limited value, particularly if normal.

Arterial Blood Gases. Hypoxia often results from exposure to toxicants, such as occurs following exposure to chlorine. Measurement of the partial pressure of oxygen (P_{O_2}) is a sensitive but nonspecific tool in this setting; both the central and peripheral effects of toxic inhalant exposure may produce hypoxia. At 4 to 6 hours, normal arterial blood gas (ABG) values are a strong indication that a particular exposure has little likelihood of producing a lethal effect. Typically, carbon dioxide elevation is seen in individuals with underlying hyperreactive airways; in this circumstance, it is thought that bronchospasm is triggered by exposure to the toxic inhalant.

Pulmonary Function Tests. A variety of airway function measures and pulmonary parenchymal function measures can be performed in rear-echelon facilities. Initial and follow-up measurements of the flow-volume loop, lung volumes, and the lung diffusing capacity for carbon monoxide ($D_{L_{CO}}$) are particularly useful in assessing and managing long-term effects of a toxic inhalant exposure. Although such laboratory studies are of minimal value in an acute-care setting, flow volume loop measures may document a previously unrecognized degree of airway obstruction. A degree of reversibility may also be demonstrated if bronchodilators are tested at the same time. Substantial airway obstruction may be present with little clinical evidence. In all cases of unexplained dyspnea, regardless of clinical findings, careful pulmonary function measurements should be undertaken. Ideally, these studies should be performed in an established pulmonary function laboratory and would include $D_{L_{CO}}$ and ABG measurements. These studies should also be performed during exertion if dyspnea on exertion is noted that cannot otherwise be explained by pulmonary function studies performed at rest.

GENERAL THERAPEUTIC CONSIDERATIONS

Further Exposure

A soldier's exposure to toxic inhalants is limited by removing him from the environment in which the toxicant is present. Careful decontamination serves to limit reexposure to the toxicant from body surfaces or clothing. Furthermore, decontamination reduces the risk of secondary exposure of other personnel.

Critical Care Concepts

Life-threatening pathophysiological processes arising from toxic inhalants usually develop in the upper airway, where laryngeal obstructions can cause death in a few minutes, and in the lower respiratory tract, where bronchospasm can cause death almost as rapidly. Severe bronchospasm may indicate exposure to a nerve agent. If there is any possibility that exposure to nerve agents has occurred, the use of one or more of the three Mark I Auto-Injector kits that are provided to all military members (see Chapter 5, Nerve Agents) should be considered an urgent part of initial therapy. Like the airway and breathing, cardiac function must likewise be assessed immediately.

Adequate control of the airway is important in all toxic inhalant exposures. Exposure to centrally absorbed toxic inhalants (such as chlorine) and to fires may be particularly dangerous, insofar as laryngeal or glottal edema may rapidly compromise upper airway patency. Evidence of perinasal or perioral inflammation indicates the need for more careful investigation of the oropharynx for erythema. Subsequent laryngoscopy or bronchoscopy may be of particular value and should be undertaken along with preparations for expedient intubation. The presence of stridor indicates the need for immediate airway control.

Primary failure of respiration after exposure to toxicants other than nerve agents suggests a severity of exposure that requires intensive medical support; at this point, a triage decision may be needed. The presence of wheezing indicates severe bronchospasm, which requires immediate therapy. The presence of dyspnea necessitates careful observation of the patient for at least 4 to 6 hours, until severe, potentially lethal respiratory damage can be reasonably excluded.

Primary failure of cardiac function, like respiration, is a grave sign after exposure to toxicants other

than nerve agents. Cardiac rate and rhythm abnormalities are often seen after toxicant exposure. These abnormalities are often transient and improve once the casualty is removed from the toxic environment and is provided with supplemental oxygen. Hypotension is a grave prognostic sign if not immediately reversed by fluid and volume resuscitation and intensive medical care.

Clinical Abnormalities

Clinical abnormalities that may lead to respiratory failure can also be observed after pulmonary toxic inhalational injury. These include hypoxia, hypercarbia, pulmonary edema, which are all signs of possible toxic inhalant exposure; and infection, which is a frequent complication, particularly in intubated patients.

Oxygen supplementation should be provided to maintain a P_{O_2} greater than 60 mm Hg. Very early application of positive end-expiratory pressure (PEEP) is important, with progression to intubation and positive pressure ventilation if PEEP fails to normalize the P_{O_2} . Note that PEEP application may precipitate hypotension in individuals with marginally adequate intravascular volume (such as those with conventional trauma or pulmonary edema) or in individuals previously treated with drugs that have venodilating properties (such as morphine or diazepam). Particular attention to anemia is necessary if hypoxia is present.

An elevation of the partial pressure of carbon dioxide (P_{CO_2}) greater than 45 mm Hg suggests that bronchospasm is the most likely cause of hypercarbia; therefore, bronchodilators should be used aggressively. If the patient has a prior history of clinical bronchospasm, steroids should be added immediately; steroids should also be considered if the patient has a history of hay fever or eczema and obvious bronchospasm with the current exposure. Occasionally, positive pressure ventilation may also be necessary. Interstitial lung water (early pulmonary edema) may trigger bronchospasm in individuals who are otherwise hyperreactive (such as those with "cardiac" asthma). Steroids are not primarily useful in this circumstance.

Pulmonary edema noted after a toxic inhalant exposure should be treated similarly to adult respiratory distress syndrome (ARDS) or "noncardiac" pulmonary edema. The early application of PEEP is desirable, possibly delaying or reducing the severity of pulmonary edema. Diuretics are of limited value; however, if diuretics are used, it is use-

ful to monitor their effect by means of the pulmonary artery wedge pressure measurement because excessive diuretics may predispose the patient to hypotension if PEEP or positive-pressure ventilation is applied.

Toxic inhalant exposures typically cause acute fever, hypoxia, elevated polymorphonuclear white cell count, and radiologically detectable infiltrates. These changes should *not* be taken to indicate bacteriological infection during the first 3 to 4 days postexposure. Thus, routine or prophylactic use of antibiotics is not appropriate during this period.

Infectious bronchitis or pneumonitis commonly supervenes 3 or more days postexposure to a toxic inhalant, particularly in intubated patients. Close observation of secretions, along with daily surveillance bacterial culture, will permit the early identification and specific treatment of identified organisms.

Steroid Therapy

Systemic steroid therapy has been considered for use in certain toxic inhalational exposures. U.S. Army Field Manual 8-285, *Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries*,⁴ suggests a benefit in phosgene exposure, but human data supporting this approach are scanty. There is some support in the literature for steroid use in exposure to zinc/zinc oxide and oxides of nitrogen. However, there is no other strong support in the literature for the treatment of other specific toxic inhalations with systemic steroids.

A significant percentage of the population has a degree of airway irritability or hypersensitivity, as exemplified by persons with asthma. These individuals are likely to display heightened sensitivity or even bronchospasm, nonspecifically after an inhalational exposure. The use of systemic steroids would be indicated in this population if their bronchospasm were not readily controlled with more routine bronchodilators. Systemic steroids may, if used in this setting, be required for prolonged periods, particularly if superinfection should supervene.

Inhaled steroids may be less effective than systemic steroids in circumstances of acute exposure—especially if later infected. Inhaled steroids appear most useful as an adjunct to the gradual reduction or weaning or both from a systemic steroid use.

EXERTION AND TOXIC INHALATIONAL INJURY

“The extra amount of oxygen needed in the exertion could not be supplied and the results showed at once.... [M]en who had been comfortable while lying became rapidly worse and sometimes died suddenly if they walked or sat about,”^{5(p424)} wrote Herringham in his article describing gassed casualties in World War I.

There is scant, primarily anecdotal, information relating to the effects of exercise postexposure to toxic inhalants. During World War I, attempts to assess the effects of toxic inhalant exposure on exercise tolerance were severely constrained by a limited understanding of basic exercise physiology and by limited technological capacity. Some early observations in exercise-limited victims of gassing included observations of limited “depth of respiration” and tachycardia after “mildest exercise”^{6(p3)}; and a heartbeat that “rises more than normal for given exercise...returns to normal more slowly after exercise [seen in 116 of 320 gassed patients].”^{7(p10)}

As a result of the World War I experience, it was clear that cardiorespiratory damage resulting from toxic inhalant exposures could severely limit exercise capacity. Of primary concern, however, was whether exercise undertaken after a toxic inhalant exposure could, in some way, exacerbate the effects of that exposure and thus increase the morbidity or mortality of exposed individuals. This was a particularly practical concern in light of the military needs to return soldiers to active duty as soon as possible and to require soldiers to participate (insofar as they appeared able) in their own evacuation.

Toxic inhalant exposures may produce direct pulmonary effects, indirect cardiac effects, and other systemic effects (eg, central nervous system [CNS] effects of mercury inhalation). Severe damage to those systems will be readily apparent; however, identification of lesser damage may require increasingly sophisticated examination. Minor organ dysfunction is best identified during stress; that is, an organ system that is functioning near its maximum capacity is more likely to demonstrate physiological limitation than a system that is functioning under conditions of rest. The principle of organ stress as a method of functional assessment is well recognized. Both cardiologists and endocrinologists have devised stress testing methods that allow earlier and more sensitive demonstration of cardiac and endocrine limitations. Systems with small de-

grees of physiological limitation are much more likely to display such limitations during stress than at rest. Conversely, an organ system that is impaired may become so dysfunctional during stress that it exceeds its compensatory mechanisms (and those of other support systems) and fails, with resulting catastrophic consequences for the organism as a whole.

The normal human body is designed to function at a wide range of activity. Normal cardiopulmonary reserves permit a 25- to 30-fold increase in oxygen delivery to working muscles. Other compensatory mechanisms permit transient activities even beyond these limits. Ultimately, however, any activity requires adequate oxygen delivery and carbon dioxide extraction for cell function. A damaged cardiorespiratory system that is unable to accomplish normal oxygen-carbon dioxide exchange will first appear limited at the extreme of exertion. Maximum exercise capacity will be restricted. With increasing damage to the cardiorespiratory system, exercise capacity becomes further limited until symptoms (eg, dyspnea or orthopnea) appear even at rest.

Although oxygen-carbon dioxide exchange may be adequate at rest (oxygen delivery of approximately 250 mL/min), the requirements of oxygen delivery during exercise (up to 5,000 mL/min) cannot be met if there is cardiorespiratory damage: with cardiorespiratory damage, cellular hypoxia results during exercise. Anaerobic mechanisms are transiently effective but are inadequate to provide energy for extended periods of time, and metabolic acidosis ensues. Ordinarily the metabolic acidosis (lactate-predominant) causes enough discomfort and discoordination of activity to limit the exertion. Lactate is then cleared from the circulation and excreted from the body as carbon dioxide. However, should respiratory limitation also be present, then excess carbon dioxide load is not readily exchanged. A respiratory acidosis is superimposed. Acidosis develops more rapidly than systemic buffer systems can accommodate it. The resulting hydrogen ion excess compromises myocardial contractility, increases pulmonary artery resistance, and causes peripheral venous dilation. Cardiac output then diminishes relative to metabolic needs.

Furthermore, a diminished intravascular blood volume—which is secondary to losses to the extravascular space, particularly to lung paren-

chyma—and increased intrathoracic pressure (air trapping secondary to bronchospasm) reduce venous return. This contributes to a further, severe compromise of cardiac output. Hypotension then exceeds other compensatory mechanisms (such as tachycardia), with further restriction of oxygen delivery to metabolizing tissue. Finally, more intense acidosis occurs and, ultimately, death supervenes.

Interactions of Pulmonary Toxic Inhalants and Exercise

Airway resistance may increase because of toxic inhalational injury, resulting in increased work of respiration. Air trapping secondary to increased airway resistance increases intrathoracic pressure. Increased work of respiration and decreased venous return result in exercise limitation. Ventilation–perfusion abnormalities of disordered airway function limit oxygen delivery and carbon dioxide clearance, which also compromises exercise tolerance.

Acute, short-term changes in interstitial function secondary to pulmonary edema, or long-term changes secondary to interstitial inflammation or fibrosis subsequently limit diffusing capacity, a particularly exercise-sensitive portion of the gas exchange system.

During exercise, the airways and the alveoli have greater exposure to a toxicant because of increased ventilation. Hyperventilation may itself induce mild bronchospasm, delaying toxicant clearance from the lung periphery. Already limited oxygen delivery may be critically compromised by exercise,

resulting in systemic hypoxia (including cerebral, cardiac, renal, and hepatic systems).

With regard to interstitial mechanisms, increments of pulmonary arterial pressure with increased cardiac output may aggravate capillary leaks, increasing interstitial edema. Inflammatory cells may accumulate in the interstitium, creating local toxicity as they degenerate.

Therapy

After a toxic inhalational exposure, exercise may further compromise the patient. Hypoxia is a primary factor. Oxygen supplementation is necessary at rest and especially during exercise. Exercise may aggravate the effects of toxicant exposure and should be limited or restricted if possible.

Toxicant exposure may produce pulmonary abnormalities which result in dyspnea. Clinical or laboratory testing may fail to confirm this symptom in the early hours postexposure; hence examination of the patient must also take place at 4 to 6 hours postexposure, if no abnormalities are initially identified.

Dyspnea may be present long after the chest radiograph, physical examination, and resting values for ABG return to normal. Exercise evaluation of these individuals (with ABG readings as a necessary part of that evaluation) must be undertaken to understand the exposed individual's complaints. Failure to make these measurements in a soldier complaining of exercise limitation displays a lack of understanding of both toxic inhalant exposures and basic exercise physiology.

HISTORICAL WAR GASES

A variety of chemical agents were used as toxic inhalants during World War I; of these, several are considered current threats. Some toxicants have current military relevance either because of their presence in stockpiles or because of their current or recent use in military operations in other countries. Other toxicants exist in large quantities as a result of their industrial use. Because of the military's preparedness in managing large-scale exposure to toxicants, such as poisonous gases, military assistance may be required in the event of a major accident involving toxic inhalants.

The following section discusses chlorine and phosgene, the two war gases that were used during World War I. Although they are not considered

current threats, under the right conditions they could pose a threat to military personnel.

Chlorine

Chlorine is a dense, acrid, pungent, greenish-yellow gas that is easily recognized by both color and odor. Because of its density and tendency to settle in low-lying areas, this gas is hazardous in closed spaces. Because the gas has a characteristic odor and its odor threshold is well below acute TLVs, chlorine is said to have good warning properties. However, chronic exposures are thought to lead to a progressive degradation of the odor threshold. As a result, workers with frequent or long-term occupa-

tional exposures to chlorine are at greater risk of inhalational damage in later years.⁸⁻¹⁰

Clinical Effects of Exposure

An almost characteristic initial complaint of chlorine exposure is that of suffocation: the inability to get enough air.¹¹ Typically, low exposures produce a rapid-onset ocular irritation with nasal irritation, followed shortly by spasmodic coughing and a rapidly increasing choking sensation. Substernal tightness is noted early. Complaints are particularly evident in individuals who have a history of hyperreactive airways (asthma). Minimal to mild cyanosis may be evident during exertion, and complaints of exertional dyspnea are prominent. Deep inspiration produces a typical persistent, hacking cough.

Moderate chlorine exposures result in an immediate cough and a choking sensation. Severe substernal discomfort and a sense of suffocation develop early. Hoarseness or aphonia is often seen, and stridor may follow. Symptoms and signs of pulmonary edema may appear within 2 to 4 hours; radiological changes typically lag behind the clinical symptoms. There may be retching and vomiting, and the gastric contents often have a distinctive odor of chlorine. Figure 9-1 shows the chest radiograph of a chemical worker 2 hours postexposure to chlorine: note the diffuse pulmonary edema without significant cardiomegaly. This patient experienced severe resting dyspnea, diffuse crackles on auscultation, and had a PO_2 of 32 mm

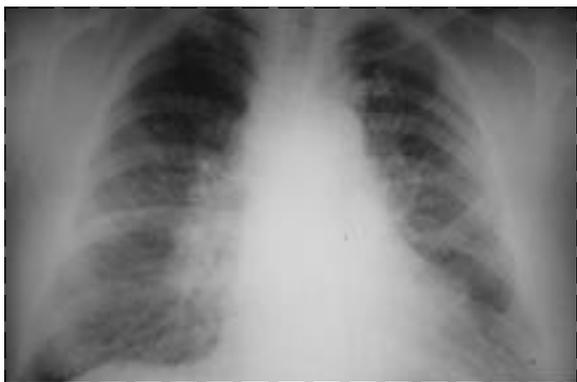


Fig. 9-1. The chest radiograph of a 36-year-old female chemical worker 2 hours postexposure to chlorine inhalant. She had severe resting dyspnea during the second hour, diffuse crackles/rhonchi on auscultation, and a PO_2 of 32 mm Hg breathing room air. The radiograph shows diffuse pulmonary edema without significant cardiomegaly.

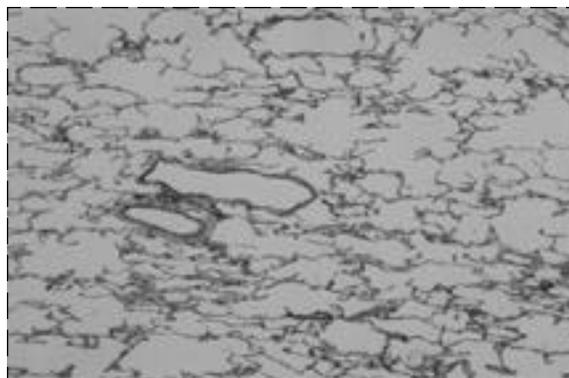


Fig. 9-2. A section from a lung biopsy (from the patient whose chest radiograph is seen in Figure 9-1) taken 6 weeks postexposure to chlorine. At that time, she had no clinical abnormalities and a PO_2 of 80 mm Hg breathing room air. The section shows normal lung tissues without evidence of interstitial fibrosis/inflammation. Hematoxylin and eosin stain; original magnification $\times 100$.

Hg breathing room air. Figure 9-2 is a section of lung biopsy taken from the same worker 6 weeks postexposure. The section shows no residual injury from the chlorine exposure. The patient's PO_2 was 80 mm Hg breathing room air.

Intense toxic inhalant exposures may cause pulmonary edema within 30 to 60 minutes. Secretions from both the nasopharynx and the tracheobronchial tree are copious, with quantities of up to 1 L/h reported.¹² Severe dyspnea is so prominent that the patient may refuse to move. On physical examination, the chest may be hyperinflated. Mediastinal emphysema secondary to peripheral air trapping may dissect to the skin and present as subcutaneous emphysema. The sudden death that occurs with massive toxic inhalant exposure is thought to be secondary to laryngeal spasm.¹³

Therapy

There is no chemically specific prophylactic or postexposure therapy for chlorine inhalation; therefore, postexposure therapy is directed toward treating the observed physiological signs and symptoms. Most deaths occur within the first 24 hours and are caused by respiratory failure.

Individuals who survive a single, acute exposure generally demonstrate little or no long-term pathological or physiological sequelae. Individuals with underlying cardiopulmonary disease or those who suffer complications (such as pneumonia) during therapy are at risk for developing chronic bronchi-

tis or (rarely) a gradual and progressive bronchiolitis obliterans. Chronic bronchitis was thought to be common after World War I chlorine inhalant exposures. Current assessment of these gassed individuals suggests that their chronic or progressive illness is more likely to have resulted from a combination of inadequately treated complicating infections and cigarette smoking than from the destructive effects of a single, acute exposure.^{14,15}

Secretions are typically copious but generally thin; mucolytics are not required. Careful attention to the appearance of secretions will assist in the early identification of bacterial superinfection, which may be associated with secretions that are other than clear or white.

Bacterial superinfection is commonly noted 3 to 5 days postexposure. Early, aggressive antibiotic therapy should be directed as specifically as possible against identified organisms. Careful, frequent Gram's stains and cultures of sputum are used to identify a predominant organism. Persistent fever, infiltrates, or elevated white blood cell count in the presence of thickened, colored secretions should prompt the institution of a broad-spectrum antibiotic (such as ampicillin or a cephalosporin). The choice of antibiotic should be based on local experience with either community-acquired or nosocomial organisms. Antibiotics are not used prophylactically in this setting; such therapy would only serve to select a resistant bacterial population in the injured individual.

Bronchospasm is an early and prominent complication of chlorine exposure. Aggressive bronchodilator therapy (a combination of adrenergic agent and theophylline) is appropriate. Steroids are used if the patient has a history of hyperreactive airways. Bronchodilators are used at least until the antibiotics are discontinued and there is no further evidence of clinical response (eg, as indicated by laboratory testing). Steroid doses should be tapered as rapidly as clinical circumstances warrant after the first 3 to 4 days of (uncomplicated) recovery. Superinfection may complicate prolonged steroid therapy.

Hypoxia improves as the bronchospasm improves, and long-term oxygen supplementation is rarely required. If long-term oxygen supplementation is needed, a search for other causes of hypoxia should be undertaken. Early institution of positive airway pressure (such as using a PEEP mask) may be useful. Positive pressure ventilation may be necessary if PEEP is insufficient to maintain PO_2 greater than 60 mm Hg. Occasional reports of subcutaneous emphysema after chlorine exposure should not

be considered a contraindication to using PEEP or positive pressure ventilation.^{16,17}

Generally, the patient gradually recovers from his acute injury in 36 to 72 hours, depending on the degree of exposure. Delay in recovery may be the result of superinfection. Pleural effusions of up to 600 mL have been identified, generally in association with pulmonary edema. Areas of pneumonic consolidation may be evident on the chest radiograph.¹⁶ Follow-up studies of acute toxic inhalant exposures have generally demonstrated that patients who had no acute complications developed no significant long-term effects.¹⁵ Pulmonary function and respiratory symptoms in individuals with repetitive, long-term, or low-dose toxic inhalant exposures have been reviewed in a number of reports.¹⁸ Although accurate records are difficult to maintain and, consequently, the data may be somewhat difficult to interpret, long-term or multiple, low-dose toxic inhalant exposures appear to produce no significant physiological defects when the results are corrected for smoking.¹⁸

Clinical Summary

Long-term complications from chlorine exposure are not found in those individuals who survive an acute exposure. There is little or no evidence that significant long-term respiratory compromise occurs, unless there has been a superimposed bronchitis or pneumonitis. The toxic effects of chlorine in the absence of superinfection are relatively short lived. Bronchospasm may require prolonged therapy, occasionally with steroids. There is little evidence for significant long-term pathophysiological abnormalities with either acute, severe chlorine exposure or repetitive low-dose, long-term exposures. A patient's failure to demonstrate substantial recovery within 3 to 4 days should prompt an investigation for the possible presence of bacterial superinfection or other complicating features.

Phosgene

Phosgene (military designation, CG) appears at usual battlefield temperatures as a white cloud whose density is due, in part, to hydrolysis. The gas is heavier than air and at low concentrations has a characteristic odor of newly mown hay. At higher concentrations, a more acrid, pungent odor may be noted. An odor threshold of 1.5 ppm has been reported but does not apply to all observers. This odor threshold is inadequate to protect against toxic inhalant exposures to this substance. Furthermore, a

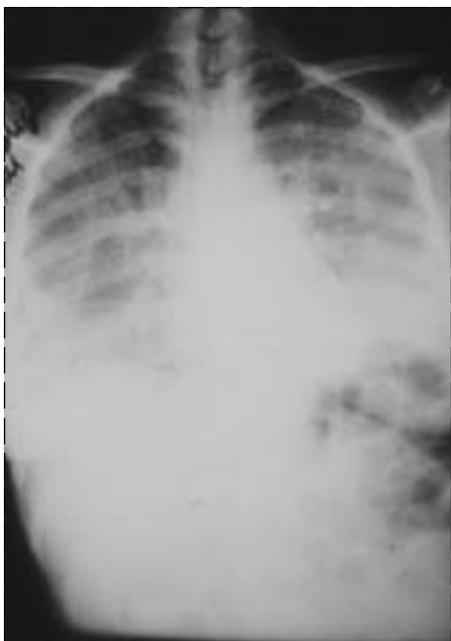


Fig. 9-3. The chest radiograph of a 42-year-old female chemical worker 2 hours postexposure to phosgene. Dyspnea progressed rapidly over the second hour; Po_2 was 40 mm Hg breathing room air. This radiograph shows bilateral perihilar, fluffy, and diffuse interstitial infiltrates. The patient died 6 hours postexposure.

relatively rapid nasal adaptation limits the usefulness of odor as a detection mechanism.¹⁹ Synonyms for phosgene include carbonyl chloride, D-Stoff, and green cross.

Clinical Effects of Exposure

In the first 30 minutes following exposure to phosgene, low concentrations may produce mild cough, a sense of chest discomfort, and dyspnea. Exposure to moderate concentrations triggers lacrimation and the unique complaint that smoking tobacco produces an objectionable taste.²⁰ High concentrations may trigger a rapidly developing pulmonary edema with attendant severe cough, dyspnea, and frothy sputum. Onset of pulmonary edema within 2 to 6 hours is predictive of severe injury. High concentrations may produce a severe cough with laryngospasm that results in sudden death; this could possibly be due to phosgene hydrolysis, which releases free hydrochloric acid at the level of the larynx.²¹

In the first 12 hours after toxic inhalant exposure, depending on the intensity of exposure, a substernal tightness with moderate resting dyspnea and

prominent exertional dyspnea become evident. These symptoms are often a prelude to the characteristic development of pulmonary edema. Initially small, then greater, amounts of thin airway secretions may appear. The delayed and insidious onset of severe pulmonary edema often has resulted in a casualty's being medically evaluated and discharged from the medical facility, only to return some hours later with severe and occasionally lethal pulmonary edema. The chest radiograph of a female chemical worker 2 hours postexposure to phosgene (Figure 9-3) shows bilateral perihilar, fluffy, and diffuse interstitial infiltrates. A section of the lung (Figure 9-4) from the same patient shows nonhemorrhagic pulmonary edema with few scattered inflammatory cells.

An individual may remain relatively asymptomatic for up to 72 hours after inhalant exposure. During that time, dyspnea or pulmonary edema may be triggered by exertion (see the preceding section, Exertion and Toxic Inhalational Injury).

Therapy

Pulmonary edema is the most serious clinical aspect of phosgene exposure and begins with few, if any, clinical signs. Consequently, early diagnosis of pulmonary edema requires that careful attention be paid to the patient's symptoms of dyspnea or chest tightness. The presence of these symptoms in a setting of possible inhalant exposure requires ex-

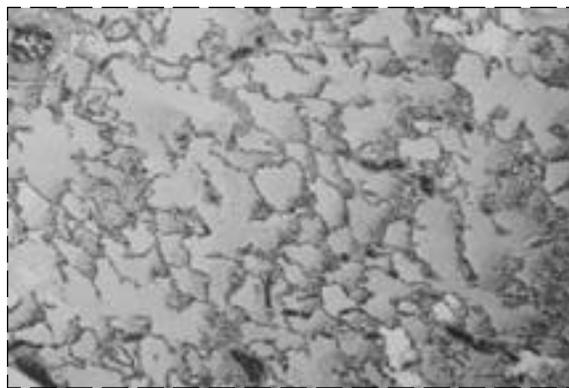


Fig. 9-4. A lung section of the patient whose chest radiograph is seen in Figure 9-3. This patient died 6 hours after exposure to phosgene; the biopsy section was taken at postmortem examination. The section shows nonhemorrhagic pulmonary edema with few scattered inflammatory cells. Hematoxylin and eosin stain; original magnification $\times 100$.



Fig. 9-5. The chest radiograph of a 40-year-old male chemical worker 2 hours postexposure to phosgene. The patient experienced mild resting dyspnea for the second hour; however, his physical examination was normal with a P_{O_2} of 88 mm Hg breathing room air. This radiograph is normal.



Fig. 9-6. The same patient seen in Figure 9-5, now 7 hours postexposure to phosgene. He had moderate resting dyspnea, a few crackles on auscultation, and a P_{O_2} of 64 mm Hg breathing room air. This radiograph shows mild interstitial edema.

peditions auscultation, chest radiograph, and ABG measurements.

If abnormal, these measurements mandate close observation and support at the intensive care level. If the measurements are normal, they all must be repeated 4 to 6 hours after the suspected exposure; only then can an individual be released to a lower medical priority status. Abnormality of any one of those measures, in the absence of other explanation, should prompt institution of therapy for noncardiac pulmonary edema. At the early stages of treatment, therapy should include positive airway pressure with early application of the PEEP mask. Later application of positive pressure ventilation through intubation may be required if the PEEP mask fails to maintain adequate arterial P_{O_2} .

Figures 9-5 and 9-6 are the chest radiographs of a male chemical worker 2 hours and 7 hours, respectively, postexposure to phosgene. The chest radiograph taken 2 hours postexposure was normal. The patient presented with mild resting dyspnea, but otherwise his physical examination was normal. The same individual, 7 hours postexposure, presented with moderate resting dyspnea and a few crackles on auscultation. His chest radiograph showed mild interstitial edema. Figure 9-7 is a lung section from this patient, who died 4 years later from unrelated causes. These tissues are normal, and there is no evidence of interstitial fibrosis.

Diuretics may be of minor value in reducing capillary pressure and consequently decreasing the rate

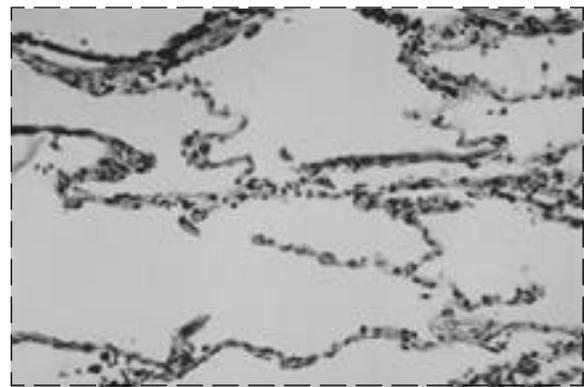


Fig. 9-7. A lung section from the patient whose chest radiographs are shown in Figures 9-5 and 9-6, who died 4 years later from causes unrelated to his exposure to phosgene. This section shows normal lung tissues without evidence of interstitial fibrosis or inflammation. Hematoxylin and eosin stain; original magnification $\times 400$.

of fluid loss through a (presumptively) damaged alveolar–capillary membrane. It should be kept in mind that intravascular volume reduction (such as that induced by diuretics) may lead to serious hypotension if positive pressure ventilation is required. Steroids have not been found to be clinically useful in treating phosgene-induced pneumonitis. There has been some discussion in the literature concerning the use of hexamethamine tetramine. However, reliable comparative data supporting this therapeutic intervention are not available.^{22–24}

Clinical Summary

The toxic effects of phosgene in the absence of superinfection or other complications are relatively short-lived. There is little evidence of significant long-term pathophysiological abnormalities with either acute, severe phosgene exposures or repetitive, low-dose, long-term exposures. A patient's failure to demonstrate substantial recovery within 3 to 4 days should prompt an investigation for the possible presence of bacterial superinfection or other complicating features.²⁵

SMOKES AND OTHER SUBSTANCES

Smokes and obscurants comprise a category of materials that are not used militarily as direct chemical agents. They may, however, produce toxic injury to the airways. The particulate nature of smokes may lead to a mechanical irritation of the upper and lower airways—therefore inducing bronchospasm in some hypersensitive individuals (eg, those with asthma). Certain smokes contain chemicals with a degree of tissue reactivity that results in damage to the airways. A discussion of obscurant smokes is followed by a discussion of certain explosion-related (oxides of nitrogen) or pyrolysis-related (perfluoroisobutylene) substances that are important in military practice.

Zinc Oxide

During World War I, the difficulties experienced by the Allies in using white phosphorus as an obscurant smoke led both the French and the U.S. Chemical Warfare Service to search for other smokes; zinc oxide (military designation, HC or HC smoke) is an outgrowth of that search. HC contains equal percentages of zinc oxide and hexachloroethane, with approximately 7% grained aluminum. The material is currently formulated for use in smoke pots, smoke grenades, and artillery rounds.

On combustion, the reaction products are zinc chloride and up to 10% chlorinated hydrocarbons such as phosgene, carbon tetrachloride, ethyl tetrachloride, hexachloroethane, and hexachlorobenzene. In addition to these products, hydrogen chloride, chlorine, and carbon monoxide are also produced. As the zinc chloride particles form, they hydrolyze in ambient water vapor to produce a dense white smoke. The toxicity of this chemical agent is generally attributed to the topical toxic effects of zinc chloride. However, carbon monoxide,

phosgene, hexachloroethane, and other combustion products may also contribute to the observed respiratory effects, depending on the circumstances of the munitions ignition.²⁶

Clinical Effects of Exposure

Since World War I, there have been numerous reports of accidental exposures to the combustion products of HC. Depending on the intensity of the exposure, a wide range of clinical effects occurs; exposures as brief as 1 minute may lead to death.

Low-dose toxic inhalant exposures are characterized by sensations of dyspnea without subsequent radiological, auscultatory, or blood gas abnormalities. These patients should be watched carefully for 4 to 6 hours postexposure (see the earlier discussion on phosgene); however, severe clinical sequelae are uncommon.

Moderate exposures to HC are characterized by severe dyspnea, which may show a relatively rapid clinical improvement during the first 4 to 6 hours. Because the chest radiograph is typically unremarkable at this time, the patient is often inappropriately discharged. These patients usually return to the medical facility within 24 to 36 hours complaining of rapidly increasing shortness of breath. By that time, the chest radiograph typically demonstrates dense infiltrative processes, which clear slowly with further care. Moderate to severe hypoxia may persist during the period of radiological abnormality.

After exposure, the chest radiograph is characteristically unremarkable within the first hours despite severe clinical symptoms, which include rapid respirations and severe dyspnea. An elevated temperature is often noted within the first 4 to 6 hours and may remain over the ensuing days. At 4 to 6

hours, the chest radiograph begins to show a dense infiltrative process that is thought to represent edema. However, bronchopneumonia may supervene in the following days; a long-standing, diffuse interstitial fibrosis may become evident, with only very gradual recovery.^{27,28}

Figure 9-8 is the chest radiograph of a 60-year-old male 8 hours postexposure to HC; it shows diffuse, dense, peripheral pulmonary infiltrates. The patient presented with moderately severe resting dyspnea and diffuse coarse crackles on auscultation. Taken 14 weeks postexposure, Figure 9-9 is a section from an open lung biopsy from the same patient. Diffuse interstitial fibrosis with inflammatory cells are evident. This patient presented with a persistent, moderate resting dyspnea. At this point, the patient had not been treated with steroids.

Exposures to very high doses of HC commonly result in sudden, early collapse and death, which are thought to be due to rapid-onset laryngeal edema and glottal spasm with consequent asphyxia. Exposures to high but nonlethal doses typically produce very early, severe hemorrhagic ulceration of the upper airway. Such exposures may also produce a relatively rapid onset of pulmonary edema.

Prolonged, severe exposures typically result in relatively rapid onset of severe dyspnea, tachypnea, sore throat, and hoarseness. A characteristic paroxysmal cough often produces bloody secretions. An acute tracheobronchitis may lead to death within hours.

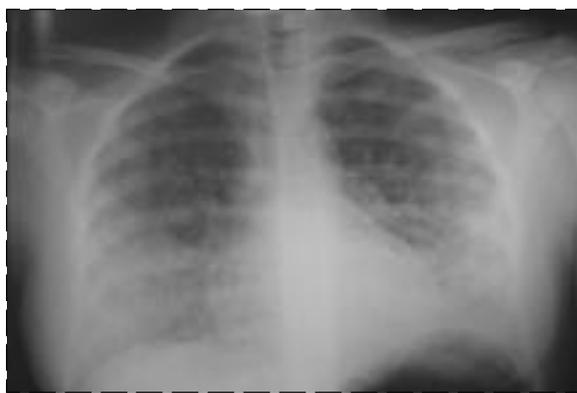


Fig. 9-8. The chest radiograph of a 60-year-old male sailor who inhaled zinc oxide (HC) in a closed space, taken 8 hours postexposure. He had moderately severe resting dyspnea during the seventh and eighth hours, diffuse coarse crackles on auscultation, and a P_{O_2} of 41 mm Hg breathing room air. The radiograph shows diffuse dense peripheral pulmonary infiltrates.

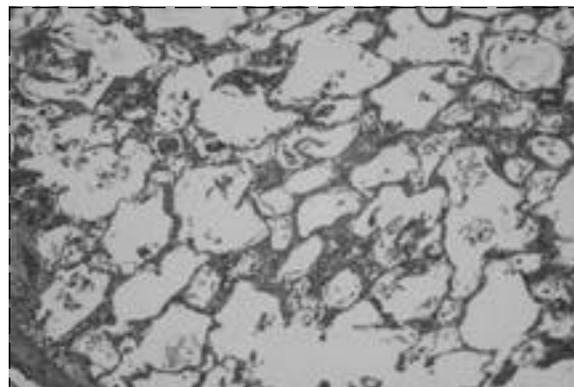


Fig. 9-9. A section from an open lung biopsy of the patient whose chest radiograph is shown in Figure 9-8, 14 weeks postexposure to zinc oxide (HC). He had persistent moderate dyspnea at rest and a P_{O_2} of 61 mm Hg breathing room air. Steroids had not been used. The section shows diffuse interstitial fibrosis with few inflammatory cells. Hematoxylin and eosin stain; original magnification $\times 400$.

Therapy

There is no chemically specific prophylactic or postexposure therapy for exposure to HC. Routine clinical support for specific complaints of acute tracheobronchitis and noncardiac pulmonary edema has been detailed previously (see the section titled General Therapeutic Considerations). Systemic steroid therapy is thought to be useful in treatment of the inflammatory fibrosis seen with this disorder.²⁹⁻³²

There are no reports of the clinical efficacy of chelating agents; however, the use of such agents as British anti-Lewisite (BAL) and calcium ethylenediaminetetraacetic acid (CaEDTA) has been suggested because of their capacity to reduce serum zinc levels. After acute exposure, however, long-term pulmonary function testing is indicated until the patient's condition is stable by that measurement. The continued presence of exertional dyspnea 2 to 3 months postexposure implies further development of interstitial fibrotic changes. Exercise testing would be of value to obtain a more accurate assessment of the degree of oxygen transport limitation. There are no data evaluating the use of long-term steroid therapy in the treatment of interstitial disease secondary to HC inhalation.²⁹⁻³²

Clinical Summary

Although most patients with zinc chloride inhalational injuries progress to complete recovery, a

smaller group of approximately 10% to 20% of exposed individuals may go on to develop fibrotic pulmonary changes. Both groups show early clinical recovery, making it difficult to distinguish patients who are likely to recover from those who are likely to develop more permanent changes. Early steroid use may modify the intensity of pulmonary reaction and the resulting fibrosis; therefore, steroids appear indicated in the acute therapy of zinc oxide exposure.

Phosphorus Smokes

Phosphorus occurs in three allotropic forms: white, red, and black. Of these, white phosphorus was used most often during World War II in military formulations for smoke screens, marker shells, incendiaries, hand grenades, smoke markers, colored flares, and tracer bullets.

White phosphorus is a very active chemical that will readily combine with oxygen in the air, even at room temperature. As oxidation occurs, white phosphorus becomes luminous and bursts into flames within minutes. Complete submersion in water is the only way to extinguish the flames. Vapors from white phosphorus are toxic; however, because these vapors quickly oxidize into phosphorus pentoxide and phosphoric acid, they are harmless to humans and animals at usual field concentrations.

Clinical Effects of Exposure

At room temperature, white phosphorus is somewhat volatile and may produce a toxic inhalational injury. Over a period of years, repetitive exposures can result in systemic poisoning.³³ At warmer temperatures, a slow oxidation to phosphorus trioxide (P_2O_3), which smells like garlic, can occur. At still higher temperatures (approximately 32°C [90°F]) and with adequate air exposure, dense white clouds of phosphorus pentoxide (P_2O_5) result from the combustion of phosphorus.

In moist air, the phosphorus pentoxide produces phosphoric acid. This acid, depending on concentration and duration of exposure, may produce a variety of topically irritative injuries. Irritation of the eyes and irritation of the mucous membranes are the most commonly seen injuries. These complaints remit spontaneously with the soldier's removal from the exposure site. With intense exposures, a very explosive cough may occur, which renders gas mask adjustment difficult. There are no reported deaths resulting from exposure to phosphorus smokes.

Because of the toxicity associated with the manufacture of white phosphorus and because of its field risks, a gradual shift to red phosphorus (95% phosphorus in a 5% butyl rubber base) was undertaken after World War II. The British smoke grenade (L8-A1-3), which used red phosphorus, produced adequate field concentrations of smoke and functioned as an effective tank screen. Oxidation of red phosphorus produces a variety of phosphorus acids that, on exposure to water vapor, produce polyphosphoric acids. These acids may produce mild toxic injuries to the upper airways that result in a cough and irritation. There are no reported deaths resulting from exposure to red phosphorus smokes.

Therapy

Phosphorus smokes are generated by a variety of munitions. Some of these munitions (such as the MA25 155-mm round) may, on explosion, distribute particles of incompletely oxidized white phosphorus. Contact with these particles can cause local burns, and systemic toxicity may occur if therapy is not administered. Therapy consists of topical use of a bicarbonate solution to neutralize phosphoric acids and mechanical removal and debridement of particles. A Wood's lamp in a darkened room may help to identify remaining luminescent particles.

Clinical Summary

The principal form of toxicity of absorbed elemental phosphorus, a destructive jaw process (phossy jaw), has been virtually eliminated by using (a) less white phosphorus in all industrial settings other than the military and (b) efficient adjunctive dental screening of exposed individuals for periods of up to 2 years postexposure. Careful dental screening consists of regular radiological assessment of the mandible for characteristic lesions, early and aggressive treatment of those lesions, and absolute prohibition of further phosphorus exposure.³³

Sulfur Trioxide–Chlorosulfonic Acid

Sulfur trioxide–chlorosulfonic acid (military designation, FS smoke) consists of 50% (weight/weight) sulfur trioxide (SO_3) and 50% (weight/weight) chlorosulfonic acid [$SO_2(OH)Cl$]. FS smoke is typically dispersed by spray atomization. The sulfur trioxide evaporates from spray particles, reacts with moisture in the air, and forms sulfur acid, which condenses into droplets that produce a dense

white cloud. The highly corrosive nature of FS smoke in the presence of moisture resulted in the army's abandoning its use.

Clinical Effects of Exposure

Contact with liquid FS smoke produces a typical mineral acid burn of exposed tissues. Exposure to the smoke—which constitutes exposure to sulfuric acids—produces irritation of the eyes, nose, and exposed skin and complaints of cough, substernal ache, and soreness. After a severe exposure to FS smoke, a casualty demonstrates profuse salivation and an explosive cough, which could render respirator adjustment difficult. The highly irritative nature of the substance acts as an adequate warning, however, and prompts an immediate evacuation from the smoke cloud.

Therapy

Severe exposures (sufficient to give rise to the rapid onset of symptoms) may require therapeutic intervention similar to that for chlorine exposure. Individuals with highly reactive airways are particularly at risk. In the event of triggered bronchospasm, these patients would benefit from aggressive bronchodilator use; consideration should also be given to the early use of steroids as well as positive-pressure ventilation.^{4,29,34}

Titanium Tetrachloride

Titanium tetrachloride (military designation, FM smoke) is a corrosive substance typically dispersed by spray or explosive munitions. A dense, white smoke results from the decomposition of FM smoke into hydrochloric acid, titanium oxychloride, and titanium dioxide. Because titanium tetrachloride is extremely irritating and corrosive in both liquid and smoke formulations, FM smoke is not commonly used.

Exposure to the liquid may create burns similar to those of mineral acids on conjunctiva or skin. Exposure to the dense, white smoke in sufficient concentration may produce conjunctivitis or cough. There are no reports of exposure-related human deaths, nor are data available regarding pulmonary function assessment in extensively exposed individuals. Individuals with hyperreactive airways would be expected to develop bronchospasm with exposure to this substance.

Aggressive bronchodilator therapy and, possibly, steroid therapy should be considered.⁴

Nitrogen Oxides

The oxides of nitrogen (military designation, NO_x), particularly nitrogen dioxide, are components of photochemical smog. Their concentrations in smog are generally thought to be low enough to be of no significant clinical concern for the normal, healthy individual.³⁵

There are four forms of nitrogen oxide. The first is nitrous oxide (N₂O), which is commonly used as an anesthetic; however, in the absence of oxygen, it acts as an asphyxiant. The second is nitric oxide (NO), which rapidly decomposes to nitrogen dioxide in the presence of moisture and air. Nitrogen dioxide exists in two forms: NO₂ and N₂O₄. At room temperatures, nitrogen dioxide is a reddish brown vapor consisting of approximately 70% N₂O₄ and 30% NO₂. Injuries from this toxic inhalant are seen most often in nonmilitary settings of silage storage.^{36,37}

In a military or industrial setting, nitrogen dioxide occurs in the presence of electric arcs or other high-temperature welding or burning processes, and particularly where nitrate-based explosives are used in enclosed environments (such as tanks and ships). Diesel engine exhaust also contains substantial quantities of nitrogen dioxide.³⁶⁻³⁹

Clinical Effects of Exposure

At NO_x concentrations of 0.5 ppm or less, individuals with preexisting airways disease show no clinical effects postexposure. At 0.5 ppm to approximately 1.5 ppm, individuals with asthma may note minor airway irritation. Concentrations of 1.5 ppm may produce changes in pulmonary function measurements in normal individuals, including airway narrowing, reduction of diffusing capacity of the lung, and widening of the alveolar-arterial difference in the partial pressure of oxygen (P_{AO₂} - P_{aO₂}) gradient.

This level of toxic exposure may occur with little initial discomfort. The soldier may ignore the resultant mild coughing or choking. Because of rapid symptomatic accommodation to this cough, continued exposure may occur. A lethal exposure can occur within 0.5 hour, with the soldier only experiencing a minimal sense of discomfort.

The clinical response to NO_x exposure is essentially triphasic. In phase 1, symptoms appear more or less quickly, depending on the intensity of exposure. With a low dose, initial eye irritation, throat tightness, chest tightness, cough, and mild nausea may appear. Once the casualty is removed from the source of exposure, these symptoms disappear

spontaneously over the next 24 hours. However, at 24 to 36 hours postexposure, a particularly severe respiratory symptom complex may appear suddenly; exertion seems to be a prominent precipitating factor. There may be severe cough, dyspnea, and rapid onset of pulmonary edema. If the patient survives this stage, spontaneous remission occurs within 48 to 72 hours postexposure. More intense exposures produce a relatively rapid onset of acute bronchiolitis with severe cough, dyspnea, and weakness, without the above-mentioned latent period. Again, spontaneous remission occurs at approximately 3 to 4 days postexposure.⁴⁰

Phase 2 is a relatively asymptomatic period lasting approximately 2 to 5 weeks. There may be a mild residual cough with malaise and perhaps minimal shortness of breath, and there could be a sense of weakness that may progress. The chest radiograph, however, typically is clear.

In phase 3, symptoms may recur 3 to 6 weeks after the initial exposure. Severe cough, fever, chills, dyspnea, and cyanosis may develop. Crackles are identified on physical examination of the lung. The polymorphonuclear white blood cell count is elevated, and the partial pressure of carbon dioxide (P_{CO_2}) may be elevated as well.⁴¹ The chest radiograph demonstrates diffuse, scattered, fluffy nodules of various sizes, which may become confluent progressively, with a butterfly pulmonary edema pattern and a prominent acinar component. At this point, pathological study demonstrates classic bronchiolitis fibrosa obliterans, which may clear spontaneously or may progress to severe, occasionally lethal respiratory failure. The fluffy nodular changes noted in the chest radiograph typically show no clinical improvement. Pulmonary function testing may show long-term persistence of airways obstruction.^{37,42,43}

Therapy

There is no chemically specific prophylactic or postexposure therapy for NO_x inhalational injury. Current therapy consists of intervention directed at specific symptoms (see the earlier discussion titled General Therapeutic Considerations). Pneumonitis appears to complicate the initial pulmonary edema relatively early; nevertheless, the use of prophylactic antibiotics is not indicated.

The use of steroids early in phase 3 has been reported; and although controlled studies are not available, these reports strongly suggest the value of steroid therapy in modifying the bronchiolitis obliterans that develops in the third stage.⁴² Despite

therapy, persistent limitation of airway function is typically seen, as demonstrated by long-term abnormalities in pulmonary function.⁴⁴

Clinical Summary

Exposure to NO_x may produce a variety of delayed and severe pulmonary sequelae that are not readily predicted from early clinical or laboratory data. Careful, long-term observation appears to be important. Steroid therapy may be a useful therapeutic tool.

Organofluoride Polymers: Teflon and Perfluoroisobutylene

Teflon (polytetrafluoroethylene, manufactured by Du Pont Polymers, Wilmington, Del.) and other similar highly polymerized organofluoride polymers (eg, perfluoroethylpropylene) enjoy widespread use in a variety of industrial and commercial settings. Because of their desirable chemical and physical properties (eg, lubricity, high dielectric constant, chemical inertness), organofluoride polymers are considered important and are used extensively in military vehicles such as tanks and aircraft. The occurrence of closed-space fires in such settings has led to toxicity studies of the resultant by-products created from incinerated organofluorines. Inhalation of a mixture of pyrolysis by-products of these substances produces a constellation of symptoms termed polymer fume fever.

A primary high-temperature pyrolysis by-product of these substances is perfluoroisobutylene (PFIB). Inhalation of this material may produce a "permeability" or "noncardiac" type of toxic pulmonary edema very much like that produced by phosgene.

General Description of Polymer Fume Fever

Teflon pyrolysis occurring at temperatures of approximately 450°C produces a mixture of particulate and gaseous by-products; in 1951, Harris⁴⁵ was the first to describe polymer fume fever, the clinical syndrome that resulted from inhaling this mixture. Within 1 to 2 hours postexposure, a syndrome known as polymer fume fever appears. Often mistaken for influenza, polymer fume fever causes malaise, chills, fever to 104°F (40°C), sore throat, sweating, and chest tightness. Once the patient is removed from the site of exposure, the symptoms spontaneously and gradually disappear over 24 to 48 hours without any specific treatment. The patient typically

has no long-term complaints or sequelae.⁴⁶ Much of this symptomatology may be due to a millipore-filtrable particulate. Animal studies have shown an alleviation of symptoms with filtration of the pyrolyzed materials⁴⁷ and restoration of symptoms with parenteral injection of the filtered material.⁴⁸

Polymer fume fever may be induced by smoking Teflon-contaminated cigarettes (the burning tip temperature reaches 884°C⁴⁶). Smoking contaminated cigarettes can also induce the signs and symptoms of pulmonary edema. Onset of pulmonary edema is typically rapid (2–4 h), mild in degree (rarely requiring oxygen supplementation as part of treatment, and rapidly remits (clears within 48 h).⁴⁹

As Teflon is pyrolyzed at a higher temperatures, more variety and higher concentrations of organofluoride by-products are noted.⁵⁰ Among these, PFIB is found to be the most toxic (Exhibit 9-2), with an LC₅₀ (ie, the vapor or aerosol exposure [concentration • time] that is lethal to 50% of the exposed population) of 1,500 mg • min/m³ (in comparison, the LC₅₀ of phosgene is 3,000 mg • min/m³).⁵¹

Clinical Effects of Exposure to Perfluoroisobutylene

Inhalation of PFIB is followed by a very rapid toxic effect on the pulmonary tissues (see the section below titled Clinical Pathology), with microscopic changes of perivascular edema evident within 5 minutes.⁵² Exposure to a very high concentration of this colorless, odorless gas may produce early conjunctivitis⁵³; in animal studies, it has produced sudden death (“lightning death” reported by Karpov, which occurred within 1 min).⁵⁴ No such sudden human deaths have been reported.

Less-intense exposures to PFIB are followed by a clinically asymptomatic period (clinical latent period) of a variable duration. During this period, normal biological compensatory mechanisms control the developing pulmonary edema until those compensatory mechanisms are overwhelmed. The length of this interval depends on the intensity and duration of exposure and on the presence or absence of postexposure exercise. Recent animal studies of PFIB inhalation strongly support World War I anecdotal human observations (with phosgene) that the resulting toxic pulmonary edema appears earlier and with more intensity when the casualty is required to exercise postexposure. It may be that increased pulmonary blood flow increases the permeability of the already damaged alveolar-capillary membrane.⁵⁵

The clinical latent period for PFIB injury is 1 to 4 hours (compared with 1–24 h for phosgene). Sub-

EXHIBIT 9-2

PROPERTIES OF PERFLUOROISOBUTYLENE (PFIB)

Chemical formula:	(CF ₃) ₂ C=CF ₂
Molecular weight:	200
Boiling point at 1 atm:	7.0°C
Gas density (dry air, at 15°C and 760 mm Hg = 1.22 g/L):	8.2 g/L
Colorless	
Odorless	
Very slightly soluble	

Data source: Smith W, Gardner RJ, Kennedy GL. Short-term inhalation toxicity of perfluoroisobutylene. *Drug and Chemical Toxicology*. 1982;5:295–303.

sequent symptoms of pulmonary edema progressively appear: initially, dyspnea on exertion; then orthopnea; and later dyspnea at rest. Radiological signs and clinical findings of pulmonary edema progress for up to 12 hours, then gradually clear with complete recovery by 72 hours. Typically, there are no long-term sequelae^{49,56–59}; however, two deaths have been reported.^{53,60} The death reported by Auclair et al⁵³ occurred after very severe pulmonary edema (requiring intubation), hypotension, and ultimately, Gram-negative superinfection.

Four reports on the long-term effects of PFIB exposure are available. Brubaker⁵⁶ reported a decrement in DL_{CO} 2 months after a single exposure. Capodaglio et al⁶¹ reported that 3 of 4 exposed individuals showed pulmonary function test (PFT) abnormalities 6 weeks to 6 months postexposure. Paulet and Bernard⁶² reported four workers with abnormal PFTs and DL_{CO}s during the 4 months following exposure. Williams et al⁶³ reported an individual with pulmonary interstitial fibrosis after multiple episodes of polymer fume fever.

Clinical Pathology of PFIB Inhalation

PFIB primarily affects the pulmonary system. Although animal studies occasionally report disseminated intravascular coagulation and other organ involvement, these effects only occur with sub-

stantial pulmonary injury, suggesting that systemic hypoxia is a major factor.⁶⁴ No human studies report organ involvement other than the respiratory system.

Pathological data on acute human exposure to PFIB are not available; however, pathological data on animals show both histological and ultramicroscopic changes occurring within 5 minutes of exposure.⁵² Interstitial edema with alveolar fibrin deposition progresses rapidly over the next 24 hours, then gradually subsides until the patient is fully recovered. At 72 hours, a type II pneumocyte hyperplasia is seen (interpreted as consistent with known reparative processes). Although some long-term animal pathological changes have been reported,⁵⁴ most animal studies do not identify such long-term changes.

Human long-term pathological data are available in only one reported case: a 50-year-old female experienced approximately 40 episodes of polymer fume fever—typically occurring from smoking contaminated cigarettes. Eighteen months after her last episode, progressive exercise dyspnea was noted. A cardiopulmonary physical examination, chest radiograph, and ABG were all normal. Pulmonary function testing supported a provisional diagnosis of alveolar capillary block syndrome (decreased DL_{CO} , increased exercise $PAO_2 - PaO_2$ gradient, and minimal airway disease). Death occurred from an unrelated cause. The autopsy provided histological evidence of moderate interstitial fibrosis with minimal chronic inflammatory cell infiltrate.⁶³ Only two human deaths from pyrolysis products of polymerized organofluorides have been reported.^{53,60}

During World War I, the number and types of pulmonary toxicants available to the military increased substantially. At least 14 different respiratory agents were used, as well as obscurants (smokes), harassing agents (chloracetone), and vesicants (mustard) that could cause pulmonary injury. Today, only a handful of these toxicants still exist in stockpiles around the world, but several, such as chlorine and phosgene, are currently produced in large quantities for industrial purposes. Whether produced for military or industrial uses, these chemical agents pose a very real threat to military personnel.

Toxic inhalational injury poses a 2-fold problem for military personnel:

Therapy

There is no recognized prophylactic therapy for human PFIB exposure. Animal studies suggest that increasing pulmonary concentrations of oxygen free-radical scavengers containing thiol groups may be of value; *N*-acetyl cysteine has been found effective.^{65,66} No postexposure medical or chemical therapy that effectively impedes or reverses the effects of this toxic inhalational injury is known.

Specific therapy for the observed “noncardiac” pulmonary edema symptoms has been derived from clinical experience with ARDS. Pulmonary edema responds clinically to application of positive airway pressure. PEEP/CPAP (continuous positive airway pressure) masks are of initial value. Intubation may be required.

Oxygen supplementation is provided for evident hypoxia or cyanosis. Expeditious fluid replacement is mandatory when hypotension is present. Combined systemic hypotension and hypoxia may damage other organ systems. Bacterial superinfection is sufficiently common to warrant careful surveillance cultures. There is no literature support, however, for use of routine prophylactic antibiotics.

Steroid therapy for PFIB exposure has been reported in only two instances—both for the same worker.⁴⁹ The fact that recovery may be spontaneous and rapid makes it difficult to decide whether steroid use improves recovery.

Laboratory studies clearly support the observation that rest subsequent to exposure is useful. Because the intensity of injury and the duration of the clinically latent period are both affected by exercise, bed rest and litter transport are preferred.

SUMMARY

1. No specific therapy exists for impeding or reversing toxic inhalant exposures.
2. Toxic inhalational injury can cause large numbers of casualties that can significantly burden medical facilities.

The pathophysiological processes that develop in the upper and lower respiratory tract can greatly incapacitate a casualty or result in death within minutes of exposure. It is therefore imperative that adequate control of the casualty's airways be maintained. Medical personnel should look for hypoxia, hypercarbia, and pulmonary edema, all of which are signs of possible toxic inhalant exposure. Infectious bronchitis or pneumonitis (particularly in in-

tubated patients) is a frequent complication. The importance of chronic health problems that occur postexposure to toxic inhalants is a contentious subject because of the nebulous signs and symptoms that mimic degenerative diseases, such as emphysema, common to the general population.

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