Pulmonary Edema of Environmental Origin*

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Fifty-five patients with chemical intoxication evoking pulmonary edema were seen in the past several years. In addition, environmental pulmonary edema from heroin intoxication, edema associated with cerebral trauma and that due to post-traumatic pulmonary insufficiency were also encountered. Most patients recovered. Treatment included inhalational therapy utilizing 40-60 percent oxygen with intermittent positive pressure breathing, endotracheal intubation or tracheostomy in the most severe problems. Digitalis and diuretics may be beneficial in a limited number of patients. Corticosteroids and hexamethylenetetramine are effective in specific types of intoxications. Morphine sulfate and other narcotic agents are to be avoided in those patients with respiratory depression due to hydrogen sulfide, hydrogen cyanide, ozone, carbon monoxide and heroin intoxication. As previously mentioned, assisted or controlled ventilation may be of considerable benefit in the latter problem. Most of these patients should be treated in intensive care units and appropriate monitoring of the cardiopulmonary system should be implemented, since the majority of these patients are acutely ill.

Severe pulmonary edema of noncardiac origin is an emergency clinical problem that is encountered rather infrequently in daily practice. However, due to environmental and sociologic factors, the incidence appears to have recently increased in some areas of the country. Furthermore, as in edema of cardiac origin, urgent and proper treatment is essential for survival.

In our experience, industrial sources account for the largest etiologic segment of pulmonary edema. Some of the more common causative chemical agents include nitrogen dioxide, ozone, beryllium salts, cadmium oxide, the halogens, hydrogen sulfide, polyvinyl derivatives and toluidine compounds. Specific chemical atmospheric concentrations are required before significant illness is produced by noxious agents. These have been well defined by the American Conference of Government Industrial Hygienists in 1962.

Moreover, of importance are other environmental causes of pulmonary edema that we have recently encountered, including drug intoxication (heroin), edema associated with cerebral trauma and pulmonary edema associated with posttraumatic pulmonary insufficiency. Cerebral lesions notoriously involve the brain stem and foci around or in the quadrigeminal plate. Systemic fat emboli are associated with pulmonary edema in a rather high percentage of patients.

In the past several years, we have encountered a number of patients with intoxication from various chemicals. The intoxicants include phosgene, hydrogen sulfide, diborane, chlorine, and antimony pentachloride.

Carbon monoxide poisoning arising from excessive smoke inhalation in one patient and auto exhaust fume intoxication in a second patient, resulted in fatal atelectasis in the former and pulmonary edema in the latter.

Zirconium tetrachloride and antimony pentachloride have evoked severe pulmonary edema. The latter metallic chlorides have induced varying degrees of bronchopulmonary damage subsequent to a malfunction of reactors. Our patient study includes the cases as shown in Table 1.

Materials and Methods

All patients had chest x-ray films and electrocardiograms. Routine laboratory studies included a complete blood cell

<table>
<thead>
<tr>
<th>Chemical</th>
<th>No. Cases</th>
<th>Use Or Source</th>
</tr>
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<tbody>
<tr>
<td>Borons (diborane)</td>
<td>35</td>
<td>high energy fuels</td>
</tr>
<tr>
<td>Hydrogen sulfide</td>
<td>8</td>
<td>mercaptans</td>
</tr>
<tr>
<td>Chlorine</td>
<td>3</td>
<td>solvents, mercury</td>
</tr>
<tr>
<td>Phosgene</td>
<td>4</td>
<td>herbicides</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>2</td>
<td>suicide,  home fires</td>
</tr>
<tr>
<td>Antimony pentachloride</td>
<td>3</td>
<td>2 deaths*</td>
</tr>
</tbody>
</table>

*Result of use.

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count, fasting blood sugar and fasting urea, urinalysis and serology. Peripheral venous pressures were measured in patients initially studied in the series, and central venous pressures were taken in patients with either hypotension or shock, utilizing the antecubital or subclavial venous approaches.

Most patients also had arterial blood gas studies consisting of arterial pH, arterial carbon dioxide pressure (Pco\textsubscript{2}), and oxygen tension (Po\textsubscript{2}). The Astrup method was used to analyze these gases. Serum potassium, sodium, chloride and carbon dioxide determinations were also performed in most patients. Blood levels of carbon monoxide were determined by the spectrophotometric method. Central venous oxygen saturation determinations were performed in the past year in four patients, using the Instrumentation method.

All subjects in our series received inhalation therapy utilizing various dosages of oxygen, depending on the degree of hypoxia. In addition, some patients received digitalis and diuretic therapy. To prevent the possibility of pneumonia and other respiratory infections, antibiotics were administered to most patients.

All patients with boron intoxication survived, whereas there were two deaths from hydrogen sulfide and two from antimony pentachloride poisoning.

**Discussion**

The toxic agents in this study include diborane, chlorine, phosgene and hydrogen sulfide. Diborane, with a chemical formula of B\textsubscript{2}H\textsubscript{6}, was used experimentally as an intermediate agent in the formation of high energy rocket fuels in the early 1960's. Phosgene was utilized in the manufacture of a new experimental herbicide. Accidental tank leaks accounted for a number of cases of intoxication from this gas. Hydrogen sulfide exposure occurred during the manufacture of sodium hydrogen sulfide, a product used in the tanning industry. Other cases of toxicity were noted during the production of mercaptanes. The latter compounds serve as components of rubber and lubricants. Chlorine intoxication occurred while processing sodium chloride and hydrochloric acid, which are used as solvents and serve as catalysts in the manufacture of liquid mercury and mercury chloride.

Most cases of intoxication seen in our experience have resulted from acute exposure to gaseous agents. As a group, such chemical compounds are classified as: (1) irritants; (2) asphyxiants; and (3) volatile agents.\textsuperscript{7}

Chlorine gas in low concentrations induces damage primarily by irritating the mucosa of the nose and throat because of the solubility of this gas in water.\textsuperscript{6} Greater concentrations, in the range of 40 to 60 mg per cubic meter (40 to 21 parts per million) over a one-half to one-hour period, are hazardous, giving rise to severe pulmonary congestion and edema. Chemically, this is due to the hydrolysis of chlorine to hydrochloric acid in the parenchymal lung tissue, thereby inducing a chemical alveolitis and capillaritis. In the full blown picture, severe edema and bronchopneumonia occur. The threshold concentration of chlorine has been adopted by the American Society of Governmental Industrial Hygienists as one part per million or 3 mg per cubic meter.

Phosgene, with the chemical formula of COCl\textsubscript{2}, produces irritation of the conjunctiva, nasal and pharyngeal membranes at atmospheric concentrations of two parts per million.\textsuperscript{7} At higher dosage levels, bronchial, bronchiolar and alveolar inflammatory reactions ensue as a result of direct irritative effect.\textsuperscript{7} The threshold limit of phosgene is one part per million for an eight-hour period.

Hydrogen sulfide, a frequent by-product of sewage debris, is a colorless gas, somewhat heavier than air, with the odor of rotten eggs. It is a rapid and powerful suspending poison with the toxic effects achieved as low as 50 parts per million (0.005 percent).\textsuperscript{7} In low exposures, toxicity results at the specific local tissue levels in the conjunctiva, cornea and pharyngeal membranes. A more prolonged exposure to low concentrations evokes damage to the respiratory tract, producing an irritative chemically-induced pulmonary edema. The final systemic effect induced by hydrogen sulfide is the development of central nervous system depression associated with respiratory and olfactory paralysis following relatively high exposure to levels of 300 parts per million and higher.\textsuperscript{9}

**Case Reports**

**Case 1**

On Oct 2, 1969 a 44-year-old white man was admitted to the hospital emergency room with complaints of shortness of breath and a persistent cough. He had been exposed to excessive amounts of phosgene gas, and approximately eight hours afterward he awakened ill.

Examination of the thorax revealed diffuse crepitant rales throughout both lungs. Results of gas studies were essentially normal, except for a depressed arterial Po\textsubscript{2} of 65 mm Hg.

Treatment consisted mainly of oxygen therapy by nasal cannula at 6 liters/min, antibiotics and general supportive care. Isoproterenol (Isuprel) with use of intermittent positive pressure breathing unit (Bennett Unit) was added later because of persistent wheezing and rhonchi. This patient completely recovered and was discharged one week later.

Chest x-ray films recorded pulmonary edema, bilaterally.

### Table 2—Mechanisms of Pulmonary Edema

<table>
<thead>
<tr>
<th>No.</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increased capillary endothelial permeability, chemical irritation, anoxia and inflammation</td>
</tr>
<tr>
<td>2</td>
<td>Decreased osmotic pressure—low plasma protein levels</td>
</tr>
<tr>
<td>3</td>
<td>Impaired lymphatic circulation—depressed ventilation</td>
</tr>
<tr>
<td>4</td>
<td>Anaphylactic-release of histamine, serotonin, kinins</td>
</tr>
<tr>
<td>5</td>
<td>Neurogenic-lesions in or around quadrigeminal plate</td>
</tr>
<tr>
<td>6</td>
<td>Venoconstriction—high altitude</td>
</tr>
</tbody>
</table>

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This 39-year-old white man was exposed to metallic chloride on Sept 27, 1971, with second and third degree burns over most of his body. He became acutely ill with respiratory distress 24 hours after admission, Sept 28, 1971.

He was exposed to an undisclosed amount of antimony chloride following a gas leak from a reactor, whereupon antimony pentachloride was released rather than the trichloride. Subsequently, coughing, wheezing and dyspnea occurred and persisted for an indefinite period. Examination of the chest revealed marked moist rales in both bases and mid-lung fields. He gradually worsened, developing pulmonary edema with an arterial PO₂ of 31 mm Hg. With administration of 80 percent oxygen to 107 mm Hg, the PO₂ improved after approximately one and one-half hours.

An emergency tracheostomy was performed Nov 1, 1971, due to persistent progressive respiratory distress (Fig 3). Continued respiratory embarrassment necessitated a laryngoscopy, which revealed granulation tissue in the subglottic area.

A second tracheostomy was performed below the subglottic stricture because of respiratory acidosis, which developed Nov 12, 1971. Subsequently, the patient improved following longterm intensive respiratory care and repeated subglottic and tracheal dilatation.

The patient required a permanent tracheostomy and was discharged 95 days after admission.

**TREATMENT**

All patients in our study received oxygen therapy in 40 to 60 percent concentrations, and most were given this modality of treatment with intermittent positive pressure breathing. Some patients also required assisted or controlled ventilation with either endotracheal intubation or tracheostomy. In the critically ill patients, the use of oxygen in high concentration (60 to 80 percent) is most essential in order to correct the anoxia. That such concentrations given over short periods are not harmful, is exemplified by several reports, as well as by our own clinical studies. Ethyl alcohol was used in the most severe cases of pulmonary edema of the cardiac type and in edema complicating systemic fat embolism. It was also administered in a few patients with severe chemical pulmonary edema.

Intermittent positive pressure breathing works effectively in several ways in the clinical condition of

**FIGURE 1. Chemical pulmonary edema.**
(Fig 1). Marked improvement was noted five days later (Fig 2).

**CASE 2**

**FIGURE 2. Marked improvement.**

**FIGURE 3. Pulmonary congestion, hyperaeration of upper lung fields.**

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pulmonary edema. Miller and Sproule have shown that it decreases the work of breathing. Courtice has demonstrated improved pulmonary lymphatic circulation after intermittent positive pressure breathing. The transcapillary hydrostatic pressure is also reduced following this form of inhalation therapy. Finally, the role of ethyl alcohol in reducing the surface tension of edematous fluid has been confirmed by many authors. The sedative effect on the central nervous system is also beneficial in allaying tachypnea, but such therapy must be avoided if respiratory depression is already present. Also, in certain types of chemical intoxication caused by irritants, ethyl alcohol may exacerbate the pre-existing inflammatory reaction and therefore should be avoided in these cases.

Obenour et al have documented a decrease in lung compliance in normal animals after the administration of nebulized superinone, whereas ethyl alcohol increased lung compliance in these subjects. However, in induced pulmonary congestion, the above aerosols had no appreciable effect on compliance.

Treatment with digitalis and diuretic agents may be helpful in some patients with edema of noncardiac origin. The latter drugs were used in some cases, prophylactically, but to our knowledge, it is not fully known whether they are beneficial in chemically induced pulmonary edema. In all likelihood, their effect on cardiac function is salutary.

Antibiotics were given to most patients for possible prophylaxis against secondary pulmonary infections. Parenterally administered steroids, advocated by some authors, were not used in our industrial cases.

A recent report on the efficacy of hexamethylene tetramine in the treatment of acute phosgene poisoning is noteworthy. We have had no experience with the new drug, hexamethylene tetramine, which may also be effective in the prevention of progressive pulmonary edema due to phosgene toxicity, according to Stavrikis.

Morphine sulfate and other narcotic agents are to be avoided in those patients with respiratory depression due to hydrogen sulfide, hydrogen cyanide, ozone, carbon monoxide and heroin intoxication. As previously mentioned, assisted or controlled ventilation may be of considerable benefit in the latter problem.

Finally, it is of paramount importance to treat most of these patients in intensive care units. Frequent respiratory, cardiac and central venous pressure monitoring are most essential. Arterial gas studies should be performed and assessed as frequently as deemed necessary clinically. Ancillary supportive treatment by competent intensive care personnel is most important to provide the constant care needed in the vast majority of these patients.

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