Chemical Pneumonitis Due to Exposure to Bromine Compounds*

Allen Kraut, M.D.;* and Ruth Lilis, M.D., F.C.C.P.

A 60-year-old laboratory technician developed pulmonary infiltrates consistent with chemical pneumonitis following accidental exposure to a mixture of hydrogen bromide and phosphorus tribromide. A protracted clinical course ensued consistent with bronchiolitis obliterans. These problems may have been avoided if the potential for subsequent damage had been realized at the time of the initial exposure. Health personnel must be aware of the potentially delayed effects of accidental exposures to respiratory irritants.

Chemical pneumonitis, a potentially fatal condition, can be caused by exposure to a number of gases or fumes. Toxic effects of exposure to halogen gases, particularly chlorine, have been well described. Although bromine is a more potent respiratory irritant than chlorine, it is not mentioned in some of the frequently consulted texts which list the causes of acute toxic pulmonary edema, chemical pneumonitis, and/or bronchiolitis obliterans. Hydrogen bromide, reported to be approximately one third as toxic as bromine, is also not mentioned in these sources. In reviewing the last 20 years' literature, we were unable to find reports of inorganic brominated compounds causing pulmonary disease in humans. In order to remind physicians that this may occur during accidental exposures, we wish to report the occurrence of chemical pneumonitis in a worker exposed to bromine compounds.

Case Report

A 60-year-old female laboratory assistant had worked for the previous 17 years with chemists in the flavor research department of a chemical company. Her work consisted of mixing various chemicals and solvents under a local exhaust hood. A uniform was routinely worn; respiratory protective equipment was available in case of emergency. She had never smoked nor had she had a history of lung disease.

In February 1986, experiments began in the laboratory with bromine (Br2), phosphorus tribromide (PBr3), and hydrogen bromide (HBr). On February 13, due to an unexpected reaction while mixing HBr and PBr3, she was splashed on the face, chest, and hair. Vapor escaped from under the exhaust hood and liquid spread on the floor of the laboratory. The subject remained in the room for five to ten minutes before proceeding to the company nursing station to receive local treatment for the chemical burn on the left side of her forehead, cheek, and neck. No medical follow-up was arranged. The laboratory was closed for four hours after which she returned to clean the room. At that time, she complained of dry cough, light-headedness, and slight congestion in her throat. She continued to work a normal schedule, and according to her, no further unexpected exposures occurred.

During the next two weeks, the subject experienced increasing shortness of breath and was referred to the company physician. On examination, he reported bibasilar crackles. Chest x-ray film (Fig 1)

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Table 1—Pulmonary Function Test Results

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<th>Date</th>
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*All TLCs were determined with a body plethysmograph except for the one obtained on 12/16/86 when the single breath dilution method was used.

Figure 1. PA chest x-ray film—Feb 28, 1986.

showed bilateral lower lobe infiltrates and a diagnosis of chemical pneumonitis was made. The patient was advised to stay home, stay away from smoke, and avoid getting respiratory infections.

Over the next three days, the shortness of breath and cough worsened, and the subject developed chest tightness. A second physician was consulted who arranged hospitalization. On admission, she was afebrile, had a respiratory rate of 20 per minute, heart rate of 90 beats per minute, and blood pressure of 110/70 mm Hg. A small degree of inflammation was noted in the posterior oropharynx. Crackles were heard over both lung bases and under the right clavicle. The remainder of the physical examination was normal. Chest x-ray film revealed bilateral lower and right upper lobe pneumonitis. Pulmonary function test (PFT) results showed a restrictive pattern (Table 1). White blood cell count was 16,000/mm3. Arterial blood gas values on room air were Po2 84, CO2 28, and pH, 7.45. The ANA value was normal. A diagnosis of chemical pneumonitis was made, and therapy was instituted with oral prednisone, 40 mg daily. Her chest roentgenogram had partially cleared by March 12, and three days later, the patient was discharged on a two-week tapering regimen of prednisone. On March 30th, she returned to the emergency room complaining of "congestion in her chest" and shortness of breath. These symptoms were attributed to a "severe flu syndrome." A chest x-ray examination was not performed.
Over the summer, the subject did not work with brominated compounds, but was exposed to other known respiratory irritants including various alkalis, aldehydes, and acids. She recalled coughing while handling some of these compounds. A one-week history of increasing shortness of breath culminated in readmission to the hospital on September 17 with additional complaints of weakness, myalgia, and fever. No other respiratory symptoms were present. Aside from a temperature of 38.5°C, the physical examination results were normal. Bilateral patchy pneumonitis with new infiltrates in both right upper and right mid-lung fields was seen on chest roentgenogram (Fig 3). A concurrent asymptomatic urinary tract infection was again diagnosed. The WBC was 15,800/cu mm, and PPD reaction was negative. The urinary tract infection was treated with gentamicin. Defervescence occurred in two days. Bronchoscopy showed no inflammation or secretions. Transbronchial biopsy from the right upper lobe showed focal fibrosis and a circumscribed nodule with crushed nuclei resembling lymphocytes. All immunoglobulin levels were normal. The PFTs again showed a restrictive defect. Chest x-ray film had almost normalized ten days after discharge. The discharge diagnoses were hypersensitivity pneumonitis of unknown etiology and urinary tract infection.

In December 1986, the subject came to the Occupational Medicine Clinic at Mount Sinai Medical Center complaining of shortness of breath on climbing two flights of stairs. No other respiratory symptoms were present. She had not been allowed to return to work as her treating physician had recommended that she not be exposed to chemicals. With the exception of a respiratory rate of 20 per minute, physical examination was normal. Chest x-ray findings were normal. Pulmonary function testing revealed normal flows, decreased TLC and diffusing capacity of 62 percent predicted. Urinalysis showed 5 to 8 WBCs/HPF; CBC and SMA 12 results were normal.

**DISCUSSION**

Bromine has a multitude of industrial applications, the largest present use being production of the anti-knock agent and fumigant, ethylene dibromide. Others include manufacture of fire retardants, flameproofing materials, and intermediate compounds in the production of film, dyes, and inks.7

Bromine and hydrogen bromide are potent irritants of the oral mucosa, nose, eyes, and respiratory tract. The irritative effects of bromine are so pronounced that human volunteers could not tolerate a concentration of 0.9 ppm of bromine for longer than five minutes.4 Some,4 but not all,6 animal experiments have shown bromine to be more toxic than chlorine. Mice exposed to bromine had periods of early (first four days) and delayed (one to two weeks) mortality, while exposure to chlorine resulted only in early mortality.8

Delayed mortality after bromine exposure was associated with peribronchiolar abscesses and thought to be due to the comparatively deeper tissue penetration and damage caused by bromine. Bromine may penetrate deeper into tissues than chlorine due to its greater solubility. In animals surviving the acute poisoning, histopathologic findings revealed persistent bronchiolar and bronchial spasm and delayed healing.9

The patient described first developed pulmonary infiltrates, consistent with chemical pneumonitis, after acute exposure to HBr and PbBr2. The natural course of the effects of acute overexposure to bromine compounds is uncertain as documentation of their human toxicity is limited. In this case, a protracted illness ensued with incomplete resolution of the pulmonary infiltrates. Relapses occurred in March and May 1986; another occurred in September possibly after
exposure to other respiratory irritants. By December 1986, the chest x-ray film had normalized, but the patient was found to have a diffusion abnormality consistent with the interstitial pulmonary fibrosis detected on transbronchial biopsy. The close temporal association between the initial exposure to the brominated compounds and the development of the pulmonary infiltrates strongly implicates the accidental exposure as the cause of the initial episode of chemical pneumonitis. The subsequent recurrence of respiratory symptoms and pulmonary infiltrates without documented resolution of the initial chemical pneumonitis suggest bronchiolitis obliterans. Nevertheless, the possibility of other mechanisms cannot be totally excluded.

This case illustrates the importance of close medical follow-up after major exposures to known respiratory irritants. Bromine and brominated compounds, similar to oxides of nitrogen and phosgene, can cause delayed toxic pulmonary edema 24 to 48 hours after exposure. No precautions were taken in this case to prevent this life-threatening possibility. Chemical pneumonitis developed and progressed over the ensuing two weeks. Prednisone has been used to treat symptomatic chemical pneumonitis,11,12 whether the earlier institution of such treatment would have prevented the development of the later complications remains an unanswered question in the absence of controlled clinical trials.

Bronchiolitis obliterans is the probable mechanism for the relapses in this case. Bronchiolitis obliterans is a well known, potentially fatal complication of toxic irritant gas exposure. The typical course, most often reported after nitrogen dioxide exposure, is recurrence of shortness of breath two to six weeks after the acute pneumonitis has resolved.11,12 Lower levels of exposure to a variety of respiratory irritants can lead to a more delayed and less severe form of this disease with intermittent symptoms persisting for months. Spontaneous resolution can occur; however, it may take up to six months for the chest x-ray film to clear. Healing may not be complete and diffuse interstitial pulmonary fibrosis can develop.12 Pathologic confirmation is not available in this case, but the clinical course and roentgenographic abnormalities are strongly suggestive of bronchiolitis obliterans.

Although no acute overexposure was reported prior to the September relapse, the patient had not totally recovered either symptomatically or on chest roentgenogram when she returned to work in July 1986. This most probably made her more susceptible to the toxic effects of the variety of irritant chemicals she worked with after July. Recurrent chemical pneumonitis or bronchiolitis may have caused this episode.

A second point illustrated by this case is the importance of worker and physician knowledge of potential occupational hazards. The patient was not told of any of the potential problems associated with exposure to the brominated compounds when she began working with these materials. On her return to work in July 1986, she was exposed to other known respiratory irritants; had this been realized, the pulmonary complications which occurred in September may have been averted. She had not resumed work after this last episode as her physician recommended she not be exposed to chemicals. Her employer, a chemical company, claimed she therefore could not work. Although the patient should not work around respiratory irritants, a job at the plant was found that would not place her at risk of such exposure. Broader understanding by management workers and health care personnel of the potentially adverse effects of chemical exposures would create a safer workplace and limit the disability and cost of occupational disease in our society.

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Ipratropium in Patients with COPD Receiving Cholinesterase Inhibitors*

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Three patients with chronic obstructive lung disease (COPD) and myasthenia gravis whose pulmonary symptoms were worsened by therapy with cholinesterase inhibitors were improved by inhaled ipratropium bromide. Two had increases in FEV₁ (18 percent, 35 percent) and specific conductance (106 percent, 31 percent) and reductions in dyspnea. The third had no change in airflow with ipratropium, but improved due to decreased bronchial secretions

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