BRONCHIOLITIS FROM NITROUS FUMES*

BY

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The inhalation of noxious fumes causes damage to the air passages and alveolar walls. The response covers a wide range, depending upon the nature of the gas, its concentration in the lungs, and the duration of exposure. Certain irritant gases, notably chlorine and ammonia, have an immediate effect on the upper respiratory tract, with intense burning in the throat, choking, and attacks of laryngeal spasm. Other gases which include nitrous fumes exert a less violent reaction at first but are commonly followed by an acute pulmonary oedema and bronchiolitis. This may be due to the fact that their relative insolubility in water allows deeper penetration of the bronchial tree.

The purpose of this paper is to describe two cases of acute bronchiolitis, following the inhalation of nitrous fumes, that were observed in Sheffield in 1956. One patient died.

CASE REPORTS

Case 1 is that of a man aged 24 years, who was employed as a steel wire cleaner. He had fair health but from an early age had suffered from mild attacks of recurrent bronchitis. This had not caused much incapacity and had never been investigated. The accident occurred on April 4, 1956. He was carrying nitric acid in a rubber bucket when he found that it had sprung a leak. He held the rubber bucket over another bucket of galvanized iron to receive the spillage and the immediate chemical reaction between the acid and metal produced reddish-brown fumes of nitrogen dioxide. It was alleged that he was exposed to the fumes for about 30 seconds. Immediately after the incident he said that he felt no ill effects and he completed his shift before returning home in the early afternoon, when he first complained of feeling unwell. His symptoms consisted of a distressing cough and the production of some mucoid, frothy sputum. He remained at home for five days and then returned to work for one day. He found he could not continue and his doctor was first called on April 11, a week after the actual exposure. A diagnosis of bronchitis was made and he was kept in bed at home until he was admitted to hospital in a mori-

bund condition on April 18. A thorough examination was then impossible, but the clinical picture was one of extreme cyanosis, dyspnoea, and fine rales over the lungs. He was thought to have extensive bronchopneumonia and this appeared to be confirmed by a radiograph which showed soft, discrete opacities throughout the whole of both lung fields with the exception of the right lower lobe (Fig. 1). He survived only a few hours.

NECROPSY.—The examination was made seven hours after death. The body was that of a young adult male of average nutrition. There was no external evidence of disease and no blistering around or within the mouth. The significant findings were confined to the thoracic contents. The larynx showed moderate oedema. The tracheal and bronchial mucosa was congested and there was patchy superficial desquamation. The bronchi of both lungs were filled with thick mucopus. Both pleural sacs showed chronic adhesions. The whole of the left lung and the upper and middle lobes of the right lung showed average anthracotic pigmentation for a resident in an industrial area. They were consolidated and on section

FIG. 1.—Case 1. Chest radiograph taken a few hours before death showing discrete opacities throughout the left lung and the right upper lobe.

*Based on a paper read to the Thoracic Society in Newcastle in July, 1957.

FIG. 2.—Case 2. Chest radiograph on April 11, 1956, showing soft opacities throughout both lungs.

showed widespread small, yellow areas, having the appearance of a generalized bronchiolitis. The right lower lobe was completely free of carbon pigment and of a different texture. It was relatively airless and on section showed extensive chronic cystic bronchiectasis. This was evidently of long duration and unconnected with death. The cardiovascular system was normal apart from terminal right ventricular dilatation. The oesophagus showed a little desquamation of the epithelium, but the remainder of the alimentary tract was normal. Other internal organs, including the brain, were normal.

Microscopical examination of the left lung and the upper and middle lobes of the right lung showed an extensive organizing bronchiolitis, characterized by miliary collections of fibroblasts, plasma cells, and lymphocytes in the centre of which were remnants of bronchioles and bronchiolar epithelium (Figs. 4 and 5). In some areas there was a localized alveolar reaction, the spaces being filled with a polymorphonuclear exudate (Fig. 6), whilst in others the bronchioles were less affected and showed only epithelial desquamation (Figs. 7 and 8). There was no evidence of tuberculosis. An oesophageal ulcer showed minimal round cell infiltration. The liver and kidneys were normal. The appearances were consistent with a diagnosis of obliterative bronchiolitis in an early stage of organization and resembled that which is known to follow the inhalation of nitrous fumes.

Case 2 is that of an electroplater aged 59 years, who was admitted to hospital on April 10, 1956, 17 days after the inhalation of nitrous fumes.

FIG. 3.—Case 2. Chest radiograph on May 2, 1956, showing a linear and reticular appearance.

Since the age of 19 he had developed an electroplating business. He worked with chrome and nickel and in later years cadmium had also been used. He was fully aware of the occupational hazards and had seen that precautions were taken whenever there was a risk of inhaling poisonous fumes. Both he and his workmen wore protective masks on these occasions. He was proud of his health and had never suffered any significant respiratory illness. For this reason a previous physical examination and chest radiograph had not been made.

On March 16 he suffered from a mild upper respiratory tract infection which took a week to subside.

On March 22 and 23 he stripped 22,000 cadmium-lined bolts. On the first day he placed about 200 of these bolts in wire baskets and subsequently dipped them in a mixture of nitric acid one part and sulphuric acid four parts. In this process a reddish-brown gas was given off. About 8,000 bolts were treated in this manner. On the second day he repeated the process with the remaining 14,000 bolts, but used a weaker solution of nitric acid alone.

During these procedures, which were carried out in the yard, he did not wear a mask and relied entirely on the gases being carried away in the atmosphere. He admitted that he must have inhaled a considerable quantity of the brown vapour. There was no immediate distress, but during the remainder of the week he did not feel well, putting this down to the after-effects of his cold.

Seven days after exposure, on the night of March 30, his voice became husky and his chest felt

FIG. 4.—Case 1. Minute foci of obliterative bronchiolitis with associated alveolar reaction. Haematoxylin and eosin. $\times 5$.

tight. His lips and throat were burning and he felt as though he were on fire. An uncontrollable paroxysmal cough developed, and he expectorated a considerable amount of frothy mucus which was frequently streaked with blood. He became feverish and restless with great physical and mental distress from incessant spasms of coughing and from intense dyspnoea. Marked cyanosis developed. He received five daily injections of 600,000 units of procaine penicillin. At no time did his sputum become purulent.

When first seen in hospital, he was afebrile, cyanosed, and distressed by explosive bouts of a wheezy and mostly unproductive cough. Clinical examination revealed a deep chest with weak breath sounds at the bases. Inspiratory rales were audible over both lungs. The cardiovascular and other systems were normal.

A diagnosis of bronchiolitis was made and a chest radiograph on April 11 (Fig. 2) showed soft, irregular opacities throughout both lungs with a suggestion of bullous changes or abscess formation in a few areas. He had a mild fever for three days and was treated with chlortetracycline, 2 g. daily, for five days, reducing to 1 g. for a further seven days. His cyanosis lessened rapidly, and by the end of the first week in hospital the breath sounds over the lower lobes

became normal, although he remained dyspnoeic on the slightest exertion.

With the purpose of limiting the scarring process, cortisone was also given in a dosage of 150 mg. on the first day, then 100 mg. daily for five days, followed by gradual withdrawal over the ensuing eight days.

INVESTIGATIONS.—Culture of the sputum yielded a mixed bacterial growth and repeated examinations failed to demonstrate tubercle bacilli.

The leucocyte count was 14,000 per c.mm., of which 84% were polymorphonuclear neutrophils. The sedimentation rate (Westergren) was 55 mm. in one hour. An electrocardiogram was normal. Serological tests for infection by the influenza and the psittacosis-L.G.V. groups of viruses, by the adenoviruses, and by *R. burneti* were all negative on the 29th day of illness, as was that for agglutination of streptococcus MG.

A second chest radiograph taken one week after admission showed no material change, but subsequent radiographs (Fig. 3) showed progressive clearing of the soft opacities from both lungs but left a fine linear and reticular pattern suggesting an interstitial fibrosis.

FIG. 5.—Case 1. Miliary focus showing bronchiolar desquamation and surrounding reaction. Haematoxylin and eosin. $\times 5$.

FIG. 6.—Case 1. Pneumonic consolidation surrounding an obliterated bronchiole. Haematoxylin and eosin. $\times 170$.

FIG. 7.—Case 1. Early organization of bronchiolar exudate. Haematoxylin and eosin. $\times 100$.

FIG. 8.—Case 1. Early bronchiolar desquamation. Haematoxylin and eosin. $\times 45$.

Despite this, the clinical course was satisfactory and he was discharged from hospital after 14 days and has made a complete recovery. A radiograph eight months later was normal.

DISCUSSION

THE OXIDES OF NITROGEN.—The oxides of nitrogen are nitrous oxide (N_2O), nitrogen trioxide (N_2O_3), nitrogen pentoxide (N_2O_5), nitric oxide (NO), and two forms of nitrogen dioxide (NO_2 and N_2O_4). Gray, Goldberg, and Patton (1954) carried out a series of animal experiments which demonstrated the toxic effects of nitrogen dioxide.

Nitric oxide is a colourless, non-irritating gas which undergoes comparatively rapid oxidation in air to nitrogen dioxide. At body temperature the dioxide exists as a reddish brown vapour consisting of approximately 30% of NO_2 and 70% of N_2O_4 .

Nitrogen dioxide is a moderate irritant and is relatively insoluble in water as compared with chlorine. It may be inhaled into the deeper parts of the lungs where it will react with the water of the respiratory membrane to form nitric and nitrous acids which cause the lesion.

INDUSTRIAL HAZARDS.—Dangerous concentrations of nitrous fumes may arise from the use of nitric acid in a variety of commercial processes, particularly when work is carried out in confined and ill-ventilated spaces.

Nitric acid is used in the dipping of copper, silver, and brass articles and in the manufacture of toluene, metallic nitrates, methyl nitrate, cellulose, nitrocellulose, collodion, and prussian red; in engraving, in the testing of metals, and in the manufacture of certain jewellery and artificial leather; in the commercial production of sulphuric, picric, and chromic acids; and with other acids in descaling and pickling plants for stripping steel sheets after firing and rolling. In these and other processes, irritant fumes are created which may reach a dangerous level if there is inadequate ventilation.

Nitrous fumes may also be liberated from the slow burning or incomplete detonation of nitro-explosives. Many men employed in gun turrets during the two world wars were exposed to a high concentration of these gases, with disastrous results. Occasional cases of poisoning have been reported in the mining and tunnelling industries (Henry, 1939), although fortunately the risk is very small in coal-mines where ventilation is satisfactory. A number of deaths have been notified in the deep gold-mines of India and the Transvaal

(Hunter, 1955). In these instances it is clear that the overriding factor has been poor ventilation.

The most comprehensive description of lung damage from nitrous fumes is that of Nichols (1930). This was based upon experience of a disaster which followed the slow burning of vast quantities of nitrocellulose films in a hospital in Cleveland, Ohio. There were 110 deaths.

A potential danger also exists during work with the electric arc. Welding at the high temperatures created by the arc gives rise to numerous gases. It is generally conceded that the ill effects of inhalation of such fumes can be ascribed wholly or in part to the oxides of nitrogen (Tollman, MacQuiddy, and Schonberger, 1941; La Towsky, MacQuiddy, and Tollman, 1941).

Camiel and Berkan (1944) described the case of a worker who, without a protective mask, was exposed to a high concentration of fumes for a period of four and a half hours while assisting an acetylene welder in the brazing of pipes. They worked in a ship's hold where ventilation was poor. The man continued at work for a further four and a half hours before complaining of dizziness, coughing, and difficulty in getting his breath. Cases of fatal gas poisoning in acetylene welding have been recorded by Koelbel (1938), Maenicke (1937), Mawich (1938), and Williman (1935).

At the present time, nitric acid is used as an oxidizer in rocket fuel, so that an occasional case of poisoning may be expected from this source.

CLINICAL FEATURES.—The initial symptoms vary with the concentration of the gas and the duration of the exposure. Inhalation of a low concentration of nitrogen dioxide provokes mild irritation of the eyes and throat, a dry cough, and tightness of the chest. Occasionally dizziness, nausea, or vomiting may occur. Often a man may continue to work in the contaminated atmosphere, as the appreciation of irritation soon becomes dulled. In that event, irreparable damage to the alveolar epithelium occurs, often without the patient being aware of the dangerous situation. The acute suffocative distress which immediately follows inhalation of chlorine or ammonia is not seen with nitrous fumes.

Nitrogen dioxide in high concentrations, particularly in confined spaces, causes greater discomfort, which rapidly diminishes when the man breathes fresh air. After cessation of exposure, there may be a latent interval of many hours before further symptoms occur. These take the form of increasing dyspnoea and cyanosis, paroxysmal cough and expectoration of frothy sputum. The clinical picture is that of bronchi-

olitis. Auscultation of the lungs at this phase reveals generalized medium and fine rales.

Mild cases recover after a few days of acute respiratory distress. At any time, secondary infection may occur when the retained secretions cause scattered areas of atelectasis and pneumonia. Appropriate treatment may save the patient's life, although recovery is often delayed for many weeks. Severe poisoning causes death from acute pulmonary oedema. Peripheral circulatory collapse rapidly supervenes and at this stage neither oxygen nor measures to combat the state of shock are of any avail.

RADIOGRAPHIC APPEARANCES.—The radiographic changes are in no way diagnostic. In the fulminant case, the patient is usually too ill for chest radiography. Such records as are available reveal the features of acute pulmonary oedema. The shadows clear rapidly if the patient survives.

Less severe exposure is followed after a short interval by irregular soft, mottled shadows throughout the lungs (Camiel and Berkan, 1944). The shadows vary in size from 2 to 10 mm. in diameter and may be interpreted as small areas of collapse or pneumonia. Some of these opacities may become confluent. With effective therapy, rapid resolution of these changes may be expected.

Nichols (1930), Doub (1933), Holland (1937), and Henry (1939) have each described the radiological appearance resulting from acute exposure to nitrogen dioxide and have emphasized that complete resolution is the rule.

TREATMENT.—Immediate removal from the dangerous area is the first consideration. Absolute rest must be imposed for at least 24 hours after exposure, and it is advisable for the patient to be admitted to hospital forthwith (McNally, 1942). At the onset of dyspnoea oxygen should be administered by any method ensuring full oxygenation. It has been suggested that positive pressure respiration may have a place in the treatment of pulmonary oedema (Hardy and Barach, 1945). At the same time, antibiotics are needed in full dosage to prevent the serious consequences of secondary infection.

PATHOLOGY.—Nitrous fumes exert a corrosive action upon the respiratory mucous membrane. Since breathing may proceed without undue distress, due to the relatively low solubility of the gases, the alveolar epithelium invariably suffers severe damage. The naked-eye and histological appearances are those of acute pulmonary oedema. The mucosal lining of the bronchioles is also particularly vulnerable, and the membrane

may be shed in its entirety. Similar damage may affect the remainder of the tracheobronchial tree. Microscopical examination shows that the lumen of the smaller tubes is filled with detritus, consisting of desquamated epithelium, fibres, red cells, and leucocytes invaded by granulation tissue. The muscular and elastic fibres in the walls may show disruption or complete dissolution and there is usually a surrounding alveolar reaction. Should the patient survive the initial onslaught, a patchy atelectasis or widespread bronchopneumonia occurs, which apparently may heal with little or no scarring. Occasionally this acute necrotizing bronchiolitis is followed by partial or complete obliteration of the lumen.

In that event, extreme respiratory distress ensues, leading to the clinical picture of bronchiolitis obliterans, as was evident in the first case described in this report. Becklake, Goldman, Bosman, and Freed (1957) have described two patients who suffered from dyspnoea some months after exposure to nitrous fumes. They considered that the physiological disturbance might be explained by narrowing of bronchial passages as a sequel to acute bronchiolitis.

CONCLUSION.—There is usually no difficulty in making a correct diagnosis provided a history of exposure is given. Most cases develop an acute pulmonary oedema due to the severe damage to the alveolar walls. Very mild cases present as an acute, dry tracheo-bronchitis to which there are no sequels unless a virulent infection supervenes. A third group comprises those patients who do not develop pulmonary oedema, but suffer from a variety of effects based upon an intense generalized bronchiolitis. As a direct result of the corrosive action of the vapour and of added infection the associated lobules become airless and invaded by organisms. What amounts to a chemical bronchopneumonia results. Case 2 of this report is representative of this group and illustrates that full recovery is possible, particularly if appropriate antibiotics are administered to master the secondary infection. On the other hand, necrosis and shedding of the bronchiolar epithelium may be followed by an exuberant granulation tissue and fibroblastic proliferation. These obliterative changes, which are illustrated in Case 1, are usually seen at the time of relapse, some 15 days after exposure.

Nichols (1930) described a group of victims in the Cleveland disaster who showed a phase of clinical improvement followed by a relapse and severe cyanosis. Radiographs of the chest showed

small nodules throughout the lungs. Histologically these were described as foci of interstitial fibrosis, but it is quite as likely, as suggested by McAdams (1955), that these were lesions of bronchiolitis obliterans.

SUMMARY

Two patients are described who suffered from bronchiolitis following the inhalation of nitrous fumes. In one instance, death occurred 14 days after exposure from a generalized obliterative bronchiolitis. The other patient recovered completely after a period of intense dyspnoea and cyanosis.

A brief account is given of some of the known occupational hazards. In view of the extensive use of nitric acid in industry, it seems likely that accidents will continue to occur.

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