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Bronchiolitis fibrosa obliterans

H. S. BAAR[1] AND J. GALINDO

From the Pathology Department, Pineland Hospital, Pownal, Maine

Bronchiolitis fibrosa obliterans, described first by Lange in 1901, is an obliterative process of the bronchioles in which there is extensive damage to the bronchial wall involving all the constituent elements (the epithelium, elastic tissue, and muscle fibres), and the lumen is partially or totally occluded by bronchial exudate organized by fibroblasts and capillaries.

The disease is extremely rare in man. LaDue (1941), for example, made a specific search of this entity in necropsy material and encountered but one case in 42,038 consecutive necropsies. On the other hand, in experimental dogs which had been exposed to war gases, such as phosgene, chloropicrin, and chlorine, Winternitz (1920) found the disease consistently. Even in humans, the majority of described examples are due to the inhalation of poisonous gases. Statements that the disease is not uncommon are based on the confusion of the diffuse widespread disease with an occasional histological finding of a bronchiolus with organized exudate (Ehrich and McIntosh, 1932). The aetiology (McAdams, Jr., 1955; Blumgart and MacMahon, 1929; Amoroso and McNally, 1949; Löblich, 1952) of this pathological entity is clear when it is associated with the inhalation of toxic gases capable of chemically damaging the elements of bronchiolar walls. Among those most commonly reported are oxides of nitrogen (NO_2 and N_2O_4, both of these being readily soluble in water, thus forming nitric acid), war gases such as have been mentioned above, and occasionally other types of gases such as chlorine.

A few examples have been directly related to pulmonary infection, such as infection by Pfeiffer's bacillus (Hübschmann, 1916) or whooping cough (Blumgart and MacMahon, 1929), and occasionally to aspiration of a foreign body (Wegelin, 1908), while a few others have been of unknown or uncertain aetiology in which the patient was neither exposed to toxic gases nor had clinical evidence of pulmonary infection. The latter group has been called 'primary bronchiolitis obliterans' by Löblich (1952). The case presented in this paper would fit into the last category and is remarkable by the absence of any respiratory symptoms except for a few days before death.

Clinically, there is considerable variation in the symptomatology and also in the time lapse between the different symptoms and the underlying aetiology, even if the latter is so definite as inhalation of toxic gases. The initial symptoms are those of chest pain and slight cough. The severity of the cough is related to the amount of bronchial damage, and the respiratory symptoms are dependent on both the bronchial and the pulmonary parenchymal involvement. During the first clinical stage pulmonary oedema may occur, and the expectoration which accompanies cough may be minimal or abundant and may or may not show evidence of blood streaking. After the first episode there ensues a clinical plateau which may last from a few days to as long as one month, during which the symptoms appear to abate or become stationary. However, following this period of *status quo*, dyspnoea appears and becomes progressively worse. Coughing becomes more frequent, expectoration increases, and blood streaking of the sputum is more common. It is during this stage of the affliction that fever, generally of low grade, may first appear. The patient is in obvious respiratory difficulty and cyanosis is usually present. The course of the disease is as a rule a rather chronic one, but after inhalation of poisonous gases death may occur rapidly. In a case described by Darke and Warrak (1958) the patient (case 1) died 14 days after exposure to nitrous fumes, and necropsy revealed the presence of organizing bronchiolar exudate.

The chest radiograph at this time shows scattered miliary densities within both lungs, this picture being reminiscent of miliary tuberculosis. Actually the clinical diagnosis was miliary tuberculosis in several cases (Blumgart and MacMahon, 1929; Assmann, 1934). However, the purified protein derivative (P.P.D.) may be negative and

[1]Present address: 33 Sandon Road, Birmingham, 17, England

culture and animal inoculation are negative for tubercle bacilli.

In spite of a varying period of a clinically stationary condition, the disease follows a clinically relentless course with ever-increasing respiratory difficulties and deepening cyanosis, usually terminating in death in a matter of weeks or months.

At necropsy the picture is that of multiple greyish or whitish nodules, highly suggestive of miliary tuberculosis. However, on close inspection and palpation of the lungs in these areas it becomes evident that the nodules are more white and their consistency much firmer than that of miliary tubercles. Caseation is absent, and with the help of a lens one may discern in some of the nodules an eccentric, tiny lumen. Such lumina, which correspond to those of the bronchioles, are often crescent-shaped. A few or many of the nodules may show no lumina at all. The edge of the nodule is not rounded but rather serrated, this being due to the accompanying peribronchial infiltration and/or fibrosis. In the majority of cases there is no evidence of tuberculosis elsewhere in the body, and the tracheo-bronchial and mediastinal lymph nodes are usually only unspecifically involved. The lungs are congested, voluminous, and quite frequently they are oedematous, oozing large amounts of fluid on section. One may see haemorrhages, usually in bronchial location, which are small in dimensions, generally only a few millimetres. Examination of the bronchioles may show extensive fibrous replacement of all elements of the bronchiolar wall and peribronchial fibrosis or a vascular peribronchial granulation tissue. The bronchiolar lumen may be occluded by a network of closely interwoven fibroblasts which may leave only the previously described eccentric crescentic lumen, or one may see a mushroom-like projection of fibrous tissue attached to the bronchial wall by only a thin, fibrous pedicle. Vascular proliferation within the fibrous tissue is quite prominent in some places and mild in others. The remainder of the pulmonary parenchyma may show fibrosis and compensatory emphysema. A case of typical bronchiolitis fibrosa obliterans will be described which, apart from the rarity of the condition, is remarkable by the absence of any respiratory symptoms in the presence of definite radiological findings.

CASE REPORT

M.R., a white male, was born on 1 September 1908. There was no information concerning his birth or early development. He was admitted to the Pineland Hospital and Training Centre on 22 January 1954. The family history was negative. He was found to have a spastic hemiplegia on the left side with atrophy of the left upper and lower extremities. There was a club foot on the left side. He had a spastic gait and nystagmus. There was a positive Babinski sign on the left side and he had a severe defect of speech, being able to say only a few words. There was a partial stiffening of the left ankle-joint. A tuberculin patch test, done in January 1954, was positive. Chest radiographs, taken repeatedly between 1954 and 1962, were reported as within normal limits.

However, a radiograph in March 1963 showed 'fine mottling of both lung fields'. Though examination of the gastric lavage was negative for tubercle bacilli in culture and in animal inoculation, the radiological picture was suggestive of tuberculosis, and so the patient was put on para-aminosalicylic acid and isoniazid medication. Further chest radiographs showed the same miliary densities apparently unaffected by the antituberculosis therapy, and the differential diagnosis between miliary tuberculosis, 'collagen disease', or sarcoidosis had to be made. An examination for lupus erythematosus cells was negative, and a radiographic examination of the bones of the hand showed none of the changes suggestive of sarcoidosis. During this time the patient was asymptomatic, and there was no shortness of breath and no cyanosis. The laboratory examination showed a total protein of 7·0 g./100 ml., albumin 4·9 g./100 ml., and globulin 2·1 g./100 ml.; albumin-globulin ratio 2·3; calcium 9·7 mg./100 ml.; alkaline phosphatase 4·4 Bodansky units. Examination of the urine was within normal limits; the white blood cell count was 7,000, with 2·1% eosinophils. In April 1963 he sustained a chipped fracture of the twelfth thoracic vertebra and a fracture of the left os ilei. The fractures healed well. In January 1964 the P.P.D. test was positive. He remained symptomless until 12 June 1964, when he became cyanosed and orthopnoeic and died on 16 June.

Since admission in 1954 the patient had been in a large ward with 30 other patients under the supervision of a nurse and two attendants. Careful inquiries after the necropsy ruled out the possibility of accidental inhalation of poisonous gases.

At necropsy the body was that of a strongly built, well nourished white male with 180 cm. body length. All other measurements were corresponding and symmetrical. The pleurae were thin, lustrous, and delicate, and there was no fluid in the pleural cavities nor were pleural adhesions present. The right lung was 810 g. and the left 630 g. in weight. On all cut surfaces of each lung there were numerous pinhead millet- (occasionally lentil-) sized, greyish-white, rather firm, irregularly outlined nodules (Fig. 1). The cut surfaces were overflooded with frothy fluid. The tracheo-bronchial and paratracheal lymph nodes were enlarged; the largest, at the bifurcation, was the size of a hazel-nut. All were soft and, on the cut surfaces, red with greyish spots, but none showed areas of caseation, calcification, or tubercles. The heart was

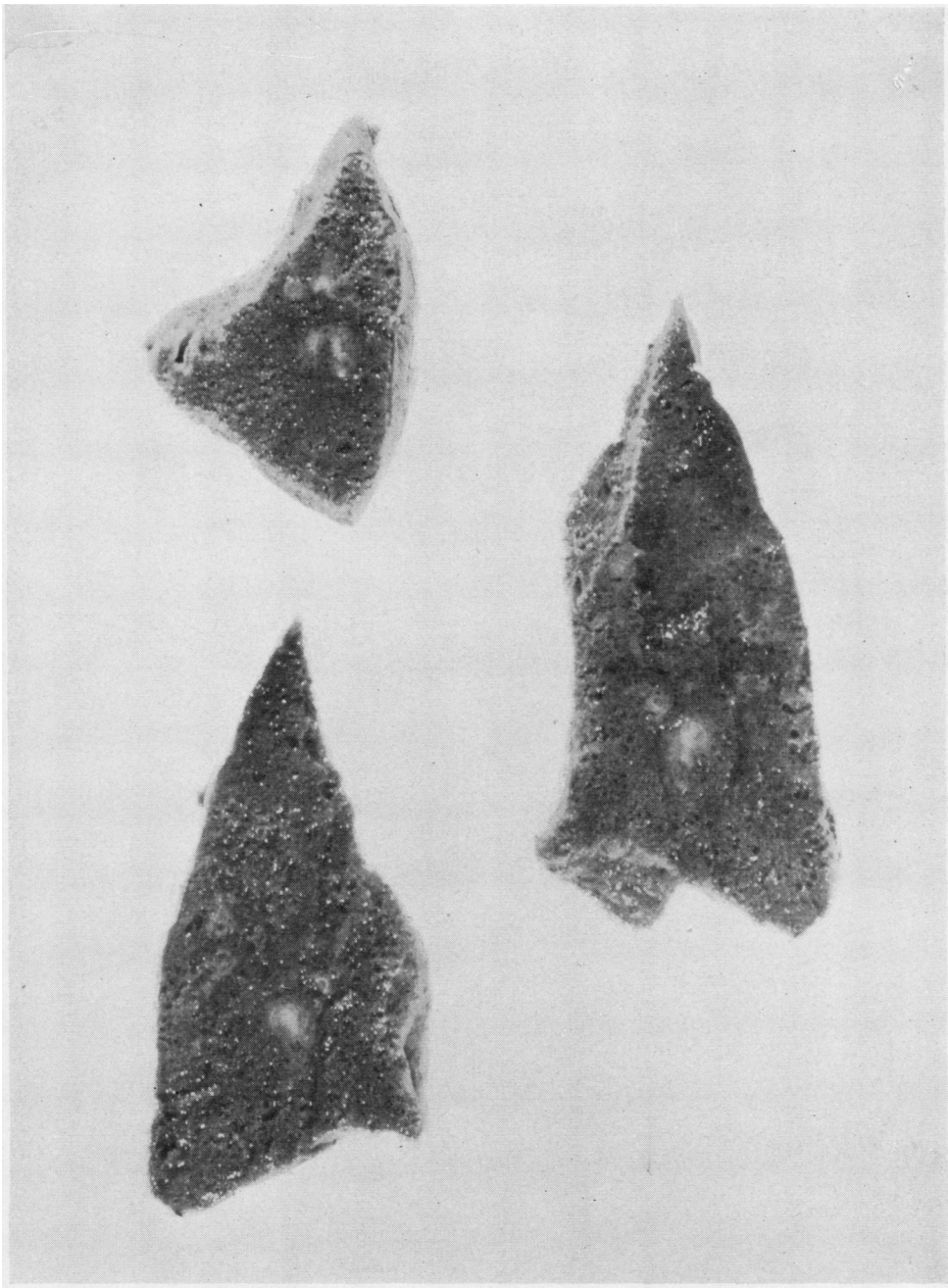

FIG. 1. *Lung sections after formaldehyde fixation showing whitish, circular, indurated areas suggestive of healing miliary tuberculosis.*

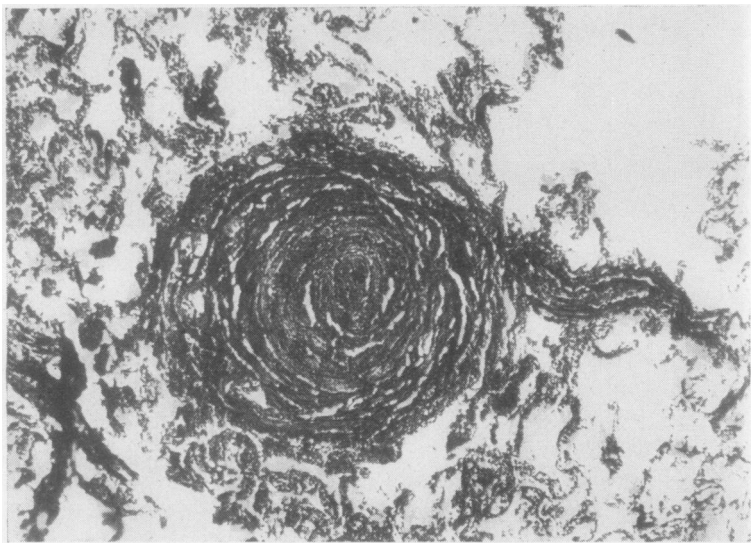

FIG. 2. *A bronchiole appears completely obliterated by fibrous tissue which occurs in concentric rings. Verhoeff-Van Gieson.* ×400.

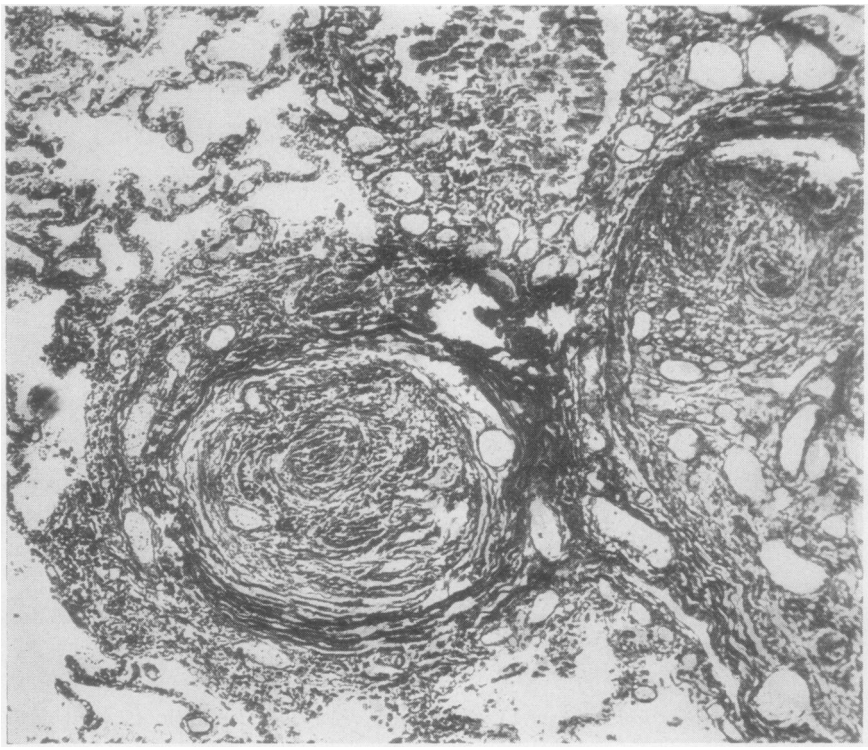

FIG. 3. *Two obliterated bronchioles with lamellar fibrous tissue and vascularization. Verhoeff-Van Gieson.* ×400.

enlarged, 410 g. in weight, with particularly marked hypertrophy of the right ventricle, which had a maximal thickness of 9 mm. There was a severe congestion of the liver, a 'strawberry' gall-bladder, and an atrophy of the left testicle which was 6 g. in weight and situated in the inguinal canal. The brain was 1,100 g. in weight and there was a hemiatrophy present, the right hemisphere of the cerebrum and cerebellum being smaller than the left. The right temporal lobe was shrivelled and contracted, and its pole showed a thin-walled, translucent cyst, 4 cm. in diameter, which extended for 2 to 3 cm. into the depth of the brain. Another similar cyst, 5 cm. in diameter, was present on the vertex just behind the post-central gyrus and close to the median fissure. A coronal section showed atrophy of the central grey matter and a dilatation of the lateral ventricle. There were extensive areas of demyelinization in the centrum semiovale. The other organs were not remarkable.

HISTOLOGY Both lungs were severely hyperaemic and showed extensive areas of atelectasis. In many examined sections not a single normal small bronchus or bronchiolus was seen. A few were dilated, filled with polymorphonuclear exudate, showed deep ulceration of the wall, and were surrounded by a very vascular granulation tissue. Many were seen as circles, completely filled with granulation tissue, which was either vascular or avascular and contained, occasionally, a foreign body giant cell. Occasionally, in the periphery of the ring-structure, columnar epithelium was seen. In the absence of epithelial cells, such structures could be mistaken for arteries with an organized and eventually recanalized thrombus or embolus. The differentiation was, however, clear in Verhoeff-van Gieson stains by the arrangement of muscle fibres and absence of a characteristic elastic membrane (Figs 2 and 3). In some, elastic fibres were absent, in others they were fragmented. Occasionally a polypoid granulation tissue was seen growing into a bronchiolus. The pulmonary arteries showed myoelastic hypertrophy, some with subendothelial cushion-like proliferation of fibrous tissue (Fig. 4) and, occasionally, a complete obliteration of the lumen by a vascular granulation tissue. Such obliterated arteries were easily differentiated from obliterated bronchioli by the presence of a wavy elastic membrane. Obliterated arteries were much rarer than obliterated bronchioli and, in many places, obliterated bronchioli were seen, surrounded by granulation tissue without a spacial relationship to obliterated arteries.

We can therefore not agree with the thesis of Amoroso and McNally (1949) that bronchiolitis

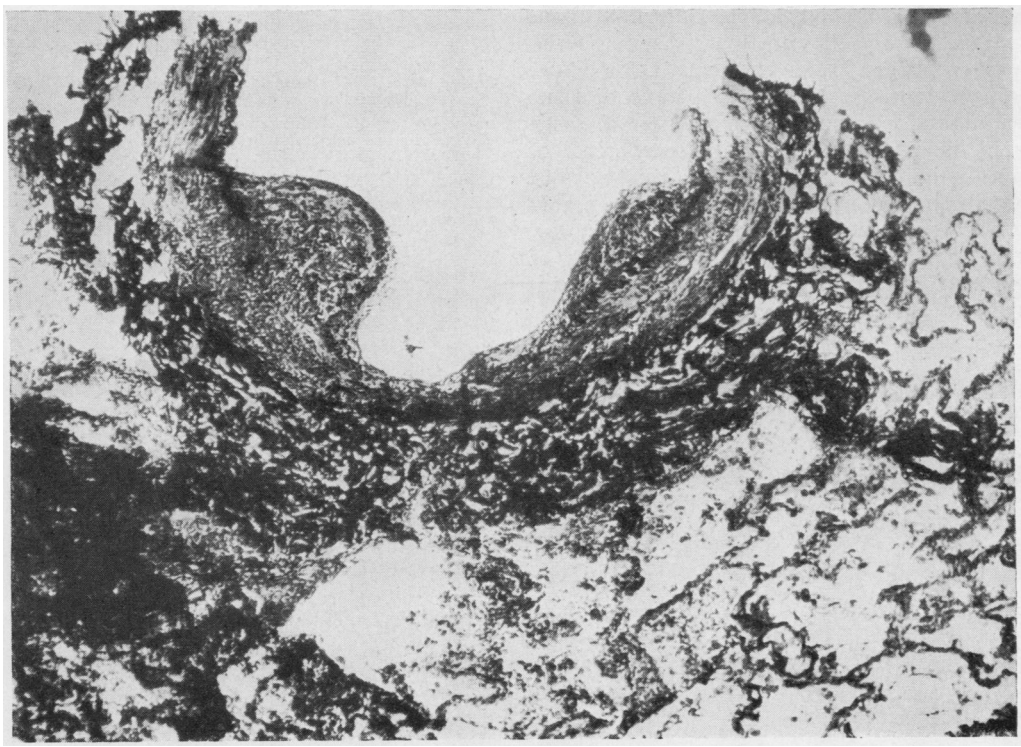

FIG. 4. *Endarteritis obliterans. Verhoeff-Van Gieson.* × 400.

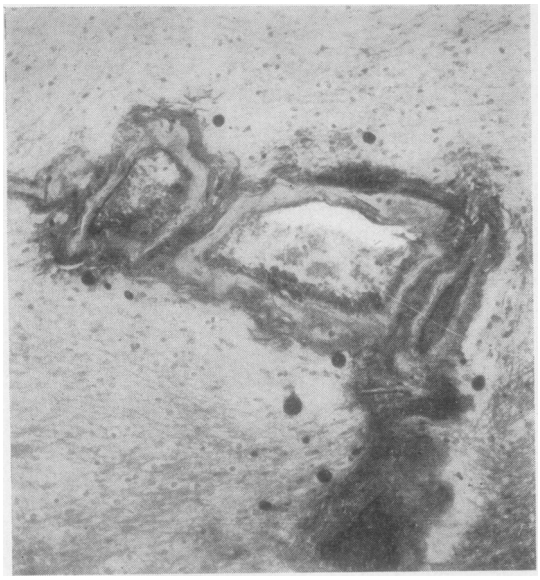

FIG. 5. *Cerebral arterioles showing mucoid degeneration of their wall. H. and E.* ×150

obliterans is secondary to a granulomatous vasculitis. Rather the reverse relationship appears to be indicated. Throughout all the interstitial tissue and within the alveoli were many haemosiderin-laden macrophages. However, there was no diffuse interstitial fibrosis such as is seen in cardiogenic brown induration nor the fragmentation of elastic fibres in the interalveolar septa, characteristic of this and of idiopathic pulmonary haemosiderosis. The brain showed fibrotic changes in the arachnoid, large areas of demyelinization and spongy degeneration, and hyalinization of the walls of arterioles and venules within the atrophic hemisphere (Fig. 5).

SUMMARY

The clinical and pathological findings in a case of bronchiolitis fibrosa obliterans are described. Concentric fibrous obliteration of the lumina of bronchioles resulted in pulmonary hypertensive arteriopathy with proliferation of endothelial cushions and diminution of arteriolar lumina. Respiratory symptoms were absent in this patient.

The spastic paralysis from which he suffered was related to the cerebral lesions of hemiatrophy, ventricular dilatation, and cystic degeneration.

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