STENOSING NON-CASEATING TUBERCULOSIS (SARCOIDOSIS) OF THE BRONCHI

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(RECEIVED FOR PUBLICATION SEPTEMBER 7, 1956)

The purpose of this paper is to describe three cases in which multiple strictures of the bronchi, affecting especially the main bronchi and the proximal parts of the segmental branches, resulted from a chronic granulomatous process of the sarcoidosis or non-caseating tuberculosis type.

CASE REPORTS

CASE 1.—Case 1* is that of a man born in 1923. He was employed in toolmaking and light engineering, involving no dust hazard. In 1940 cervical lymph nodes, presumed tuberculous, were excised. In October, 1951, he developed cough, expectoration, and breathlessness on exertion. In February, 1952, a chest radiograph (Fig. 1) showed shadowing in the right middle lobe and some faint mottling in the upper zones of both lungs, with a rounded shadow at the right hilum suggestive of enlarged lymph nodes. The middle lobe shadow cleared in three months without treatment, but wheezy dyspnoea persisted, with increasing volumes of purulent, occasionally blood-stained sputum. In December, 1952, he had an acute febrile illness with right pleuritic pain. The radiograph showed shadowing in the lower zone of the right lung. He was treated with penicillin, but resolution of the shadows was slow. Bronchoscopy at this stage showed no abnormality, but bronchography showed slight narrowing of the middle lobe bronchus and of some of the basal segmental bronchi on the right side. By now dyspnoea was so severe that he was unable to continue his work as a toolmaker. In October, 1953, he had another febrile illness, associated with collapse-consolidation of the anterior and posterior segments of the right upper lobe. This again cleared slowly after penicillin treatment. Tomography suggested enlargement of the right hilar nodes. At this time his general condition was poor. There was soft stridor, both inspiratory and expiratory. Respiration was laboured with prolonged wheezy expiration, and an inspiratory rhonchus was persistently audible on the right side. No lymph nodes were palpable.

Bronchography in January, 1954, revealed a remarkable appearance of multiple bronchial strictures (Figs. 2 and 3). On the right side the upper lobe bronchus, the main lower bronchus, and several of the basal bronchi were narrowed, and the middle lobe failed to fill. On the left, the apico-posterior and anterior bronchi of the upper lobe were greatly narrowed near their origins, and the lingular bronchus was similarly, though less, affected. There was some dilatation of the affected bronchi beyond the narrowings. Bronchoscopy was difficult because of excessive secretion and bronchospasm, but showed narrowing of the right middle lobe bronchus, from which tissue was taken for biopsy (Fig. 4). This showed great thickening of the bronchial mucosa by granulation tissue undergoing fibrosis, in which there were a number of giant cells and atypical tubercles with very little or no caseation. Twenty-four sputum cultures failed to yield tubercle bacilli. Intradermal injection of 10 T.U. of P.P.D. produced no reaction, but 100 T.U. produced a reaction with induration measuring 25 × 18 mm. Treatment with streptomycin, 1 g., and isoniazid, 200 mg., daily was begun in January, 1954. No clinical improvement being evident after one month of this, cortisone was added in the hope that it might reduce bronchial mucosal swelling and diminish the danger of progressive fibrotic narrowing of the bronchi. The initial dose was 100 mg. daily, reduced after four weeks to 75 mg. and after five weeks more to 50 mg. This dose was maintained until July, 1954, when it was reduced to 37.5 mg. The antituberculosis chemotherapy was changed after three months to isoniazid and p-aminosalicylic acid (P.A.S.), and this, together with 37.5 mg. of cortisone daily, has been continued up to the time of writing. The patient's condition gradually improved during the three months after the beginning of cortisone treatment, although a bronchoscopy at the end of this time still showed bluish granulation tissue and patchy exudate in the right upper bronchus, and the histology of a biopsy specimen of the mucosa was similar to that observed previously. He gained 56 lb. (25 kg.) in weight, and returned to his work as a toolmaker in July, 1954. His vital capacity increased from 2,800 to 4,600 ml., and his maximum voluntary ventilation from 28 to 44 litres per minute. In June, 1955, bronchography was repeated; the appearances were similar to those previously found, but there was some diminution of the stenosis in some of the affected bronchi. The sympto-
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Fig. 1.—Case 1: February, 1952.

Fig. 2.—Case 1: bronchogram, antero-posterior view of right lung.

Fig. 3.—Case 1: bronchogram, left oblique view.

Fig. 4.—Case 1: bronchial biopsy. Haematoxylin and eosin, × 120.
matic improvement has been maintained. In March, 1956, a Kveim test was performed. A small nodule was evident after one month; it was excised for biopsy and showed non-caseating epithelioid cell tubercles.

Case 2.—Case 2 is that of a man born in 1914. He was employed as a clerk. He had been fit and athletic until early in 1951, when he began to cough and expectorate. During the following winter he was obliged to give up playing football because of dyspnoea and wheezing. In February, 1952, he had an acute febrile illness with purulent, blood-stained sputum and pain in the right side of the chest. On examination in April, 1952, respiration was laboured and accompanied by soft stridor, and a persistent rhonchus was audible in the right side of the chest. The radiograph (Fig. 5) showed collapse-consolidation of the right middle and lower lobes, and scattered mottling in the left upper zone. The hilar shadows were prominent on both sides. Treatment with penicillin resulted in little improvement. Six sputa were examined unsuccessfully for tubercle bacilli. Bronchoscopy in April, 1952, showed a rounded, oedematous main carina and reddening of the mucosa of the right upper lobe bronchus, which was narrowed to two-thirds normal size. Just below the middle lobe the right lower lobe bronchus was narrowed concentrically to 1 mm., and its walls were nodular. Biopsy (Fig. 6) from this site showed gross thickening of the bronchial mucosa with active fibrosis, rather atypical tubercles without caseation, and overlying squamous metaplasia. A diagnosis of tuberculous bronchitis was made and he was treated at a sanatorium, where he received streptomycin and P.A.S. for three months and isoniazid and P.A.S. for a further two months. Bronchoscopy was repeated in December, 1952, and showed thickening of the entire bronchial mucosa. Just below the right upper lobe orifice, which was reduced to a small triangular opening, the lower lobe bronchus was narrowed to pencil size; on the left, the main bronchus was narrowed about 2.5 cm. from the carina. Another bronchoscopy in March, 1953, showed increased stenosis of the left main bronchus, where the mucosa bled easily. Biopsy from this site produced a small piece of tissue showing non-specific chronic inflammatory change. The patient remained dyspnoeic and wheezy. Doubt was cast upon the diagnosis of tuberculous bronchitis by the failure to find tubercle bacilli in the sputum (10 smears and one culture), absence of reaction to tuberculin tests (intradermal with 100 T.U. old tuberculin, and Heaf multiple puncture), and the unfavourable response to antituberculosis drugs. Bronchoscopy in September, 1953, showed a narrowed right upper lobe bronchus and smooth strictures of the right lower lobe bronchus to 4 mm. diameter and of the left main bronchus to 6 mm. Bronchography (Fig. 7) confirmed these bronchoscopic findings, and showed also irregular narrowing of the proximal parts of the basal segmental bronchi, especially on the left side; the middle lobe bronchus was not outlined. At this time an intradermal test with 100 T.U. old tuberculin produced
a small reaction, the induration measuring 6 × 5 mm. The sputum was examined for tubercle bacilli six times by microscopy and three times by culture, with negative results. Liver biopsy revealed one follicle of epithelioid cells.

Treatment with cortisone and antituberculosis chemotherapy was begun at the end of October, 1953. The latter took the form of isoniazid and P.A.S. by mouth, which was maintained throughout the period of treatment. One week after this was started cortisone was given in daily dosage of 150 mg. for one week, 100 mg. for three weeks, 75 mg. for one week, 50 mg. for five weeks, 37.5 mg. for four weeks, and then 25 mg. for 76 weeks. All treatment was then (at the end of July, 1955) stopped. Bronchoscopy was repeated two months after the beginning of treatment; the smooth stenoses were still present, but were thought to be less narrow. Symptomatic improvement has been maintained, even after the cessation of treatment. The patient has been able to return to his work. He has had several episodes of fever after upper respiratory infection, associated with transient consolidation, usually in the middle lobe, but these have been well controlled by antibacterial drugs; apart from these, his capacity for exertion and general sense of well-being is much improved.

In September, 1955, a Kveim test produced a well-defined nodule, which on biopsy showed typical non-caseating tubercles. In August, 1956, a routine examination of the eyes showed two small yellow follicles in the lower fornix of the left conjunctiva (Fig. 8). Biopsy of these showed that they consisted of collections of endothelial cells, fibroblasts, giant cells, and a few lymphocytes, the histological picture being that of sarcoidosis.

**Case 3.**—Case 3 is that of a married woman engaged in household duties. She was born in 1904. In 1949 she developed a productive cough, and in 1951 she began to be short of breath on exertion. In 1952 the breathlessness became more severe, with wheezing. A chest radiograph (Fig. 9) showed enlarged right paratracheal lymph nodes and some shadowing in the lung to the right of this. Bronchoscopy was reported to show loss of definition of the right upper lobe orifice, suggesting infiltration of the mucosa. No tubercle bacilli were found in the sputum. In view of the possibility of bronchial carcinoma, thoracotomy was performed in October, 1952; indurated areas were felt in the right upper lobe, and the inferior and right tracheo-bronchial lymph nodes were enlarged, hard, and adherent. Biopsy (Fig. 10) of one of these suggested very chronic tuberculosis showing a central mass of fibrous tissue and some tubercles with little or no caseation at the periphery. The patient was treated with streptomycin and P.A.S. for five months, but the dyspnoea and wheezing became worse. Twenty-two sputum cultures for tubercle bacilli were negative; but, in December, 1953, acid-fast bacilli were seen on microscopy of a sputum smear, but this specimen was not cultured. In February, 1954, bronchoscopy showed
FIG. 9.—Case 3: August, 1952.

FIG. 10.—Case 3: hilar lymph node. Haematoxylin and eosin, ×120.

FIG. 11.—Case 3: cervical lymph node. Haematoxylin and eosin, ×120.

FIG. 12.—Case 3: biopsy of skin nodule. Haematoxylin and eosin, ×120.
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that the right upper lobe orifice was narrow, distorted, and rigid, and nodules of granulation tissue were seen in the posterior segmental division. No material was obtained for biopsy. Acid-fast bacilli were found on microscopy of smears of aspirated bronchial secretions and also of sputum, but cultures yielded no growth. Further treatment with streptomycin and isoniazid was given for four and a half months without improvement in symptoms. In November, 1954, the Mantoux test with 1:100 old tuberculin was twice found to be negative. An enlarged lymph node in the left posterior triangle of the neck was excised and showed non-caseating tubercles (Fig. 11). In January, 1955, soft inspiratory and expiratory stridor was evident. No enlarged lymph nodes were palpable, and liver and spleen were not felt. In the skin of the back, close to the thoracotomy incision, there was a small raised papule, which appeared to have arisen at the site of insertion of a towel-clip at the thoracotomy more than two years earlier. Biopsy of this showed infiltration by epithelioid and giant cells, appearances suggesting sarcoidosis (Fig. 12). The Mantoux test was again negative to 100 T.U. of P.P.D. One sputum culture out of a total of 14 yielded a growth of tubercle bacilli which were found to be of human type and of normal virulence for the guinea-pig. Bronchography (Figs. 13 and 14) showed, on the right side, narrowing of the upper lobe bronchus, apical lower and main lower lobe bronchi, and, on the left, narrowing of the upper lobe and lingular bronchi.

At the end of January, 1955, treatment with isoniazid and P.A.S. was started. Three days later cortisone was added: 100 mg. daily for four weeks, 75 mg. for two weeks, 50 mg. for 11 weeks, 37.5 mg. for 10 weeks, 25 mg. for one week, and 12.5 mg. for one week. While she was receiving cortisone the patient felt much better; her capacity for exertion was improved, she had little wheezing, and she was free from the troublesome cough. Within one week of stopping cortisone in August, 1955, dyspnoea and wheezing returned. Cortisone was therefore administered again from the beginning of October, 1955, starting with 100 mg. daily and reducing the dosage to 75 mg., then 50 mg., by the end of a fortnight. This dose was maintained until July, 1956, when it was reduced to 37.5 mg. These modest doses of cortisone appear to relieve the symptoms in a remarkable way.

DISCUSSION
The similarity in clinical picture of these cases is striking. Cases 1 and 2 occurred in men in the third decade. Their principal symptoms were cough, expectoration, wheezing, and incapacitating dyspnoea. The illness was prolonged and punctuated by recurrent febrile episodes associated with evidence of lobar, segmental or sub-segmental lung consolidation. Case 3 occurred in a woman at the end of the fifth decade; her symptoms were similar, except that she did not suffer from febrile episodes. The severity of the
reduction of the ventilatory function of the lungs before treatment is demonstrated by the figures for maximum voluntary ventilation, which were as follows: Case 1, 29 litres per minute; Case 2, 51 l./min.; and Case 3, 22 l./min. All the patients complained of wheezing on exertion, and in all a soft inspiratory and expiratory stridor could be detected. This additional physical sign distinguished these patients from those with the usual types of bronchitis, asthma, and emphysema.

Radiologically, there was clear evidence of enlargement of hilar lymph nodes in the early stages in Case 3, and suggestive evidence in Cases 1 and 2; no recognizably specific changes were observed in the lung fields, which were relatively clear except during the acute febrile episodes in Cases 1 and 2, when shadows of lobar or segmental distribution appeared for a variable length of time. These were almost certainly the result of collapse-consolidation due to defective drainage of infected secretions from segments supplied by the narrowed bronchi. Bronchography showed widespread changes in all cases. The main bronchi were generally narrowed. The site of greatest constriction was at the level of the origins of some of the segmental bronchi, often with post-stenotic dilatation (Fig. 3). The localization of the strictures at these sites suggests the possibility that in their pathogenesis involvement of the mediastinal and intrapulmonary lymph nodes may be important, either by causing direct pressure or by spread of the granulomatous process from affected nodes to the bronchi.

The bronchoscopic appearances varied with the stage of the disease. At the early bronchoscopies in Case 2 the process appeared active, and the bronchial mucosa was reddened and swollen and bled easily, the whole bronchial tree being involved up to the main carina; narrowing of bronchi was probably due to the swelling of the mucosa. At the later bronchoscopies in Case 2, and at those in Cases 1 and 3, the inflammatory changes appeared less acute and extensive, but nodular swellings of the bronchial mucosa suggesting chronic granulation tissue were present in various sites; and later still the bronchial mucosa might appear fairly normal, with smooth-walled, presumably fibrotic, strictures, as in Case 2, or there might be irregular distortion of the lumen without rigid strictures, as in Case 3. Technical difficulty in bronchoscopy due to spasm and excessive secretion was noted in Cases 1 and 2.

Evidence of the nature of the chronic bronchitis was available from five biopsy specimens (two from Case 1 and three from Case 2). These showed active fibrosis with typical and atypical tubercles, but without obvious caseation. No material was available for the study of the mucosa in Case 3, but biopsy of skin and cervical lymph nodes showed non-caseating tubercles, and it seems likely that the changes in the bronchi were of a similar non-caseating tuberculous character.

In Cases 2 and 3 there was convincing evidence of the failure of treatment by antituberculosis chemotherapy alone, since prolonged administration of adequate combinations of drugs produced no improvement; and in Case 1 there was no response to one month's treatment with isoniazid and P.A.S. before cortisone was administered. All the patients made a good symptomatic response to cortisone. Probably the antispasmodic action of cortisone was important in alleviating symptoms, but there was some evidence that the treatment given produced some effect on the bronchial lesion itself, for in Case 1 bronchography repeated after 17 months' treatment showed some evidence of increase in lumen of some of the narrowed bronchi, and in Case 2 treatment was stopped after 21 months with maintenance of the improvement that had been attained. Whether or not the antituberculosis chemotherapy contributed to these long-term results is uncertain.

Aetiology.—Discussion of the aetiology of these cases raises the disputed problem of the relationship between sarcoidosis and tuberculosis. The similarity in clinical picture, in bronchographic, bronchoscopic, and histological appearances, and in response to treatment between the three cases makes it likely that they were also similar in aetiology; yet they show a confused mixture of features which suggest an aetiological diagnosis of tuberculosis and of others suggesting that they can legitimately be classified as sarcoidosis. Case 2 showed nearly all the features which would be required by the most critical for a diagnosis of sarcoidosis. Atypical non-caseating tubercles were found in the affected bronchi, a non-caseating epithelioid cell tubercle was found in the liver biopsy, and similar histological changes were found in a biopsy from the conjunctiva; a Kveim test was positive histologically; skin sensitivity to tuberculin was low or absent (feeble or no reaction to 100 T.U.) throughout the observed course; and no tubercle bacilli were found in spite of many examinations by culture. Case 1 showed similar histological changes in the bronchi, and a Kveim test was positive histologically; no tubercle bacilli were isolated from many cultures; but the skin was moderately sensi-
tive to tuberculin, 100 T.U. intradermally producing a large reaction.

Case 2 showed histological changes in mediastinal and cervical lymph nodes of a non-caseating tuberculous type compatible with sarcoidosis; similar changes developed in a scar in a manner characteristic of sarcoidosis; the skin persistently failed to react to tuberculin; but the sputum was found on two occasions to contain acid-fast bacilli by direct examination of a smear, and on one occasion by culture, the isolated bacilli being shown to be of human type.

Some of the logical difficulties which confuse discussion of aetiological problems of this type have been outlined by one of us (Scadding, 1950; 1956b). We accept the concept of sarcoidosis as a syndrome whose principal defining feature is the presence in all affected organs of the characteristic histological pattern, and whose definition can include no reference to aetiology. We can therefore refer with logical propriety to “tuberculous sarcoidosis” if, in a case which we believe to conform to the descriptive definition of sarcoidosis, there is satisfactory evidence that the condition is caused by the tubercle bacillus. We consider that Case 3 undoubtedly falls into this group. We have no direct aetiological evidence in Cases 1 and 2, and must therefore place them in the category “sarcoidosis,” without any indication of aetiology. However, we think that they probably are of tuberculous aetiology, both by analogy with Case 3, and from considerations set out elsewhere (Scadding, 1956a and b), which lead us to the opinion that many cases of sarcoidosis in this country are of tuberculous origin.

BRONCHIAL CHANGES IN SARCOIDOSIS.—In a series of 142 cases of sarcoidosis reported by one of us (Scadding, 1956a) there were three in which bronchial biopsy at the stage of hilar lymph node enlargement showed infiltration of a relatively normal-looking mucosa with sarcoid-type tubercles; since bronchoscopy was performed in only a few cases of this series, these figures can give no indication of the incidence of histological changes in the mucosa. There have been few published observations on changes in the bronchi in sarcoidosis. Most of these refer to cases in which enlargement of hilar lymph nodes was associated with infiltration of the mucosa of the main bronchi, macroscopically normal-looking or somewhat thickened and nodular, with non-caseating sarcoid-type tubercles (Benedict and Castleman, 1941, one case; Olsen, 1946, one case; Jacobs, 1949, one case; Harvier, Turiaf, Claisse, and Rose, 1950, one case; Turiaf, Marland, Rose, and Sors, 1952, four cases; Siltzbach and Som, 1952, one case; Grimminger, 1955, two cases). Cowdell (1954) mentions one case in which histological changes of sarcoidosis were found on biopsy of bronchial mucosa, and in which lymph node enlargement appeared later. In one of the four cases of Turiaf and others (1952) and one of Grimminger’s (1955) two cases, the condition was observed to proceed to a stage of fibrotic stenosis. Two cases have been observed for the first time at this stage (Brun and Viallier, 1948; Siltzbach and Som, 1952). Turiaf and Brun (1955) in their monograph on sarcoidosis describe the bronchial changes in seven cases of sarcoidosis, all but one previously published and mentioned above.

In an attempt to determine how frequent is bronchial stenosis of the type observed in our three cases in the fibrotic stage of sarcoidosis, we have performed bronchograms on seven patients at this stage of the disease, in whom there was no clinical evidence of bronchial obstruction in the form of stridor or localized wheezing. In only one of these was there evidence of narrowing of bronchi, and in this case only a little narrowing of the proximal parts of some segmental bronchi. This supports the impression derived from the rather scanty literature that, while infiltration of the mucosa of the larger bronchi in the early stage of intrathoracic sarcoidosis with lymph node enlargement is probably quite frequent, fibrotic stenosis of the type observed in the three cases described in this paper is rare.

SUMMARY

In three patients stenosis of main and segmental bronchi was due to granulomatous changes in their walls, with atypical non-caseating tubercles. These three patients were remarkably similar in clinical picture, but, considered as a group, showed a confusing mixture of features normally regarded as characteristic of sarcoidosis, and others suggestive or diagnostic of tuberculosis. The implications of these findings in relation to the aetiology of sarcoidosis are discussed, and the literature on bronchial changes in sarcoidosis briefly reviewed.

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doi: 10.1136/thx.12.1.10

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