BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 13 1960

CHRONIC DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS*

BY

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The name "chronic diffuse interstitial fibrosis of the lungs" indicates a condition defined in morbid anatomical terms. Literally and without restriction it could be applied properly to a wide range of conditions, some of which would normally be included in other diagnostic categories. For instance, the late stage of sarcoidosis, widespread chronic pulmonary tuberculosis, dust diseases of the lung, and the end-results of some chronic inflammatory changes include an element of interstitial fibrosis; though in many of them the changes in the interstitial tissue are not widespread or predominant. If we exclude cases which can reasonably be included in one of these diagnostic categories we shall be left with a group in which widespread lung changes characterized by the progressive development of fibrosis in the interstitial tissue of the lung cannot be explained as the result of an otherwise recognized pathological process. It is this group which I shall discuss. Though it seems unlikely that all the cases in the group so defined are due to the same cause, experience shows that at least a large proportion of the group is constituted by cases which present a syndrome recognizable with confidence on clinical, radiological, and physiological features.

In order to put certain matters of terminology into perspective, reference must be made first to a group of cases described as "acute interstitial fibrosis of the lungs" by Hamman and Rich (1944). These four cases were all in young adults. They ran an acute course with fever, the total duration of the disease from onset to death from right ventricular failure ranging from six weeks to six months. In none of them was clubbing of the fingers recorded. Histologically they were characterized by the following changes. In the alveoli there was some oedema, with red blood cells and a few leucocytes and enlarged epithelial cells. Some alveoli were lined by a hyaline membrane. In places there was necrosis of alveolar and bronchiolar walls. There was extensive progressive proliferation of fibrous tissue in the interstitial tissue. In places the alveolar contents were undergoing organization. In three out of four cases there was an excess of eosinophils in the interstitial tissue. Thus, the syndrome described by Hamman and Rich was both pathologically and clinically an acute process.

Present Series

The more chronic type of diffuse interstitial fibrosis of the lungs which is the present subject of discussion is in my experience, and also judging from the cases reported in the literature, much more frequent than the acute type described by Hamman and Rich. I have had 26 cases under my own care in the past eight or nine years up to the beginning of the year 1959. These 26 cases were equally divided between the two sexes. They were in an older age-group than the acute cases of Hamman and Rich. Their ages at the onset of symptoms ranged from 23 to 68 years, with a mean of 53½ years; only three of them were under the age of 50. We obtained direct histological evidence in 13 of these. The other 13 conformed so closely to all aspects of the typical picture which I shall describe that I felt justified in including them in the group, more especially since in no case in which I have been confident of this diagnosis has it been disproved by subsequent histology, either biopsy or post-mortem.

The typical clinical history in this more chronic type starts with the leading symptom of gradually increasing breathlessness on exertion. This dyspnoea may take quite a long time to develop to a degree which constitutes a serious disability. Several of my patients had noticed increasing breathlessness for two to three years before they consulted a doctor for the first time about it. The patients have a cough, which, though generally either dry or productive of only a little nondescript mucoid expectoration, may be troublesome. They, like everyone else, are liable to intercurrent respiratory infections, which may cause the sputum to become purulent because of secondary bacterial infection; but this is incidental and not part of the typical picture, and may be controlled by suitable antibacterial treatment. Clubbing of the fingers may be an important symptom. I call it a symptom because some of my patients have complained of it, and one noticed the change in the shape of her fingers several years before she became breathless. In other cases clubbing ranks only as a sign, found on physical examination. At the time of my first examination clubbing was classified as severe in seven, moderately severe in eight, slight in five, and absent in six; in two of the latter it developed later under observation. It usually assumes the classical drumstick form. I have not observed pulmonary osteoarthropathy in any of these cases. Cyanosis is invariable in the moderately advanced disease, and at this stage is evident even at rest, becoming deeper after exertion. Earlier in the disease, at a stage when they are not yet cyanosed at rest, patients may become cyanosed after exercise.

Physical examination shows signs which in most cases make an important contribution to diagnosis. First, the patient may be seen to be cyanosed, especially after exercise, and the fingers may be clubbed. As he lies at

*An open lecture given at the Institute of Diseases of the Chest on June 3, 1959.

rest on the couch, hyperventilation may be sufficient to be noticed as a clinical sign. On examination of the chest there are characteristic showers of fine-to-medium rales during inspiration over the lower parts of the lungs, extending upwards to a variable level, and persisting after cough and at repeated examinations. In some cases, where the changes are predominantly basal, there may also be found impairment of percussion note and alteration of breath sounds towards a bronchial quality over the bases of the lungs at the back of the chest.

This combination of symptoms and signs constitutes a striking clinical picture; and a middle-aged or elderly person who, having previously been well, complains of progressive dyspnoea on exertion over the preceding few years, has a cough perhaps troublesome but usually unproductive, may be cyanosed especially after exercise, has gross clubbing of the fingers, has rales at the bases of the lungs, has no obvious cardiac abnormality, and is not constitutionally ill, can be suspected with some confidence of suffering from chronic diffuse interstitial fibrosis of the lungs.

Physical and Radiological Findings

The physiological picture correlates well with the clinical and morbid anatomical picture. The changes are mainly those of a defect of diffusion between the alveolar air and the alveolar capillaries. At first the ventilatory function is relatively little reduced and may be normal. The total lung capacity is usually somewhat reduced, with a proportionate reduction in its subdivisions, presumably from reduction in the volume of the peripheral air-spaces by the thickening of the alveolar walls. In spite of this, the maximum voluntary ventilation may at first be within the normal range. The volume expired in the first second of a forced expiration, which correlates well with maximum voluntary ventilation, is also normal, and constitutes the normal proportion (more than 70%) of the total forced vital capacity, indicating that airway obstruction plays no part in the dyspnoea. Whereas a normal adult has a resting ventilation of no more than 7–8 l./min., these patients may be ventilating even at rest at 15–16 l./min., and on exercise they hyperventilate even more, so that the ventilatory cost of exercise is high. Their arterial oxygen saturation is reduced, in the earlier stages only after exercise, but later at rest and even further after exercise.

The arterial carbon-dioxide tension is normal or even low. Appropriate tests will show reduction in diffusing capacity of the lungs. The test most commonly used is the uptake of carbon monoxide, which is much reduced even in the earlier stages. The combination of a reduced carbon-monoxide uptake with a normal or only slightly reduced ventilatory function leads inescapably to the conclusion that there is a serious defect of diffusion across the alveolar membrane. This physiological picture has been described as alveolo-capillary block or alveolar respiratory insufficiency (Baldwin, Cournand, and Richards, 1949). Later in the disease the ventilatory capacity becomes reduced, with progressive reduction in maximum voluntary ventilation and in volume expired in one second, and there may be secondary changes suggestive of emphysema—that is, of dilatation of peripheral parts of the air passages, in the form of an increase in the proportion of the total lung capacity which constitutes the residual capacity.

Radiologically the chief features are shadowing of nodular or reticular pattern predominantly at the bases but also sometimes extending throughout the lungs, involving both lungs but not necessarily symmetrically. The quality and distribution of these changes is rather variable from case to case, as is discussed below.

The course of these chronic cases is usually slowly downhill, but some patients seem to have quite prolonged remissions of progression of the disease. By this I mean that the disease sometimes ceases to progress and the patient remains at a steady level of disability for a number of years.

The first two cases illustrate the more chronic type, and the third an acuter type of the disease.

Case Reports

Case 1.—A clergyman aged 69, whom I first saw in February, 1951, had been becoming increasingly breathless on exertion for four years. His only other symptom was a cough which produced about 15 ml. of mucoid sputum daily. On examination I noted cyanosis, gross drumstick clubbing of the fingers, and constant rales at the bases of both lungs. Fig. 1 shows the radiographic appearance of the lungs, with coarse mottling giving a somewhat honeycombed appearance, mainly at the bases. Physiological studies showed a total lung capacity of 4.4 l., considerably less than the expected figure, with a residual capacity of 1.9 l., constituting a normal proportion of the total lung capacity, and a maximum breathing capacity of 103 l./min.,

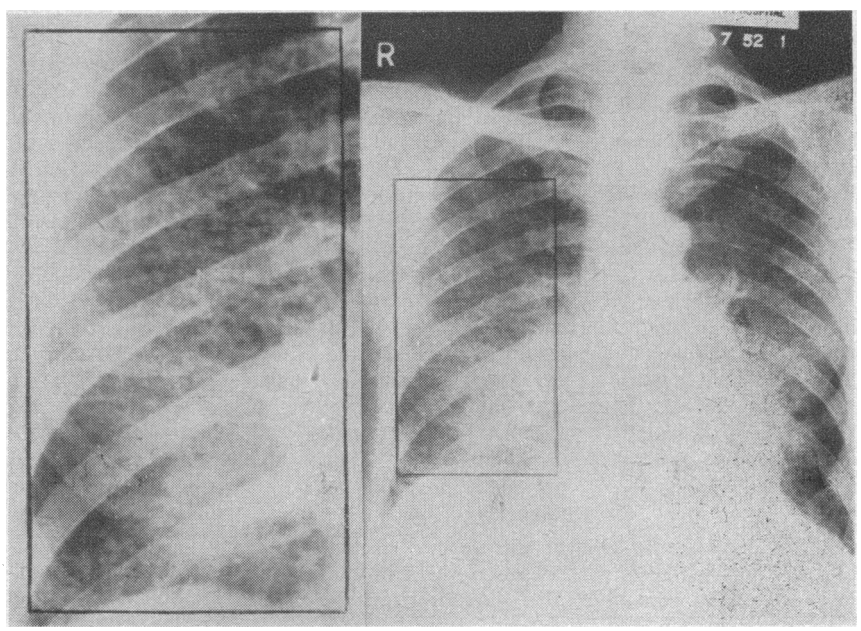

FIG. 1.—Case 1. Radiograph of chest. The area outlined is shown on a larger scale for detail.

well within the normal range for a man of 69. The ventilation at rest was 15 l./min.—a high figure—and the arterial oxygen saturation was only 86% at rest and fell to 65% on exercise. This patient received only simple symptomatic treatment. He survived for a total period of seven years from the beginning of his symptoms and died in February, 1954, at the age of 72 as a result of an intercurrent respiratory infection. During the last three years of his life there was little change in the severity of his symptoms.

Case 2.—This patient, a housewife, was aged 57 when I first saw her in 1954. Since January, 1953, she had been feeling tired and breathless and had lost a little weight. When I first saw her about the beginning of 1954 she was afebrile and had clubbing of the fingers, which she herself had noticed to be coming on for a few months. There were fine rales at the bases of both lungs. Radiologically there was a diffuse, rather fine mottling at the bases of the lungs, more on the left than on the right (Fig. 2). A lung biopsy showed thickening, increased cellularity and fibrosis of the alveolar walls, with some mononuclear exudate and rather prominent epithelial cells in some of the alveoli, She has been observed for six years from the onset of the

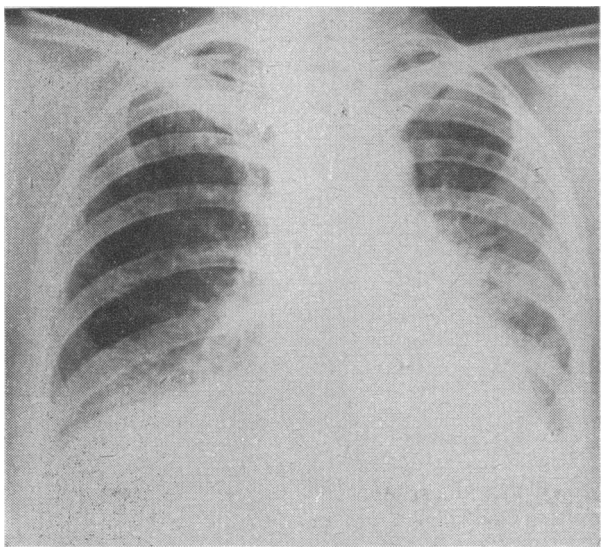

FIG. 2.—Case 2. Radiograph of chest, January, 1954.

symptoms and 5½ years from the biopsy, with only occasional symptomatic treatment. She is still breathless on exertion, has clubbed fingers, but is carrying on and seems no worse over the past few years. Radiologically there has been progression of the changes to honeycombing throughout the left lung and possibly also at the base of the right lung (Fig. 3).

Three of my 26 cases might be regarded as intermediate between the very chronic type, of which Cases 1 and 2 are examples, and the acute type described by Hamman and Rich ; but all three of these patients still survive for periods ranging from 1½ to 4½ years from the beginning of their symptoms. Their ages when their illnesses began were 25, 40, and 50 years ; the younger two were the youngest in the whole series of 26 patients.

Case 3.—A 50-year-old housewife, when I first saw her in September, 1957, had noticed for four months rather rapidly increasing breathlessness and a slight unproductive cough. She was afebrile. The fingers were slightly clubbed, and constant rales were audible at the bases of both lungs. Radiologically there was a rather featureless shadowing over the lower half of both lungs which closer inspection showed to be made up of a very fine nodular pattern (Fig. 4).

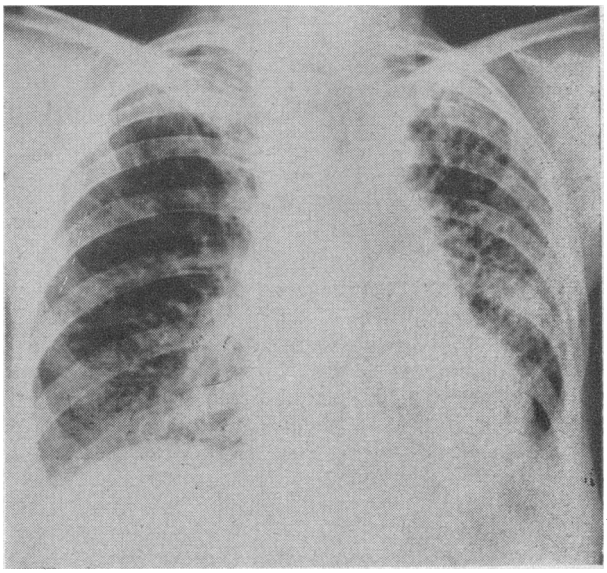

FIG. 3.—Case 2. Radiograph of chest, November, 1958. "Honeycombing" has developed in the left lung.

Lung biopsy showed great thickening of the alveolar walls with a great increase in reticulin and a considerable amount of actual fibrous tissue, and some mononuclear and epithelial cells in the alveoli. Physiologically the pattern of deranged function was characteristic, with a moderately reduced maximum voluntary ventilation of 57 l./min., and a carbon-monoxide uptake of 5.7 ml./min./mm. Hg, less than half the lower limit of the normal range. The disease was progressing rather rapidly, and for this reason she was treated with prednisolone. This is the only case in the whole series in which there is evidence of something approaching a remission from the use of a corticosteroid, persisting after withdrawal of the hormone. After two weeks' treatment with 30 mg. of prednisolone daily there was substantial clearing of the radiographic shadows with considerable symptomatic relief. The dosage of prednisolone

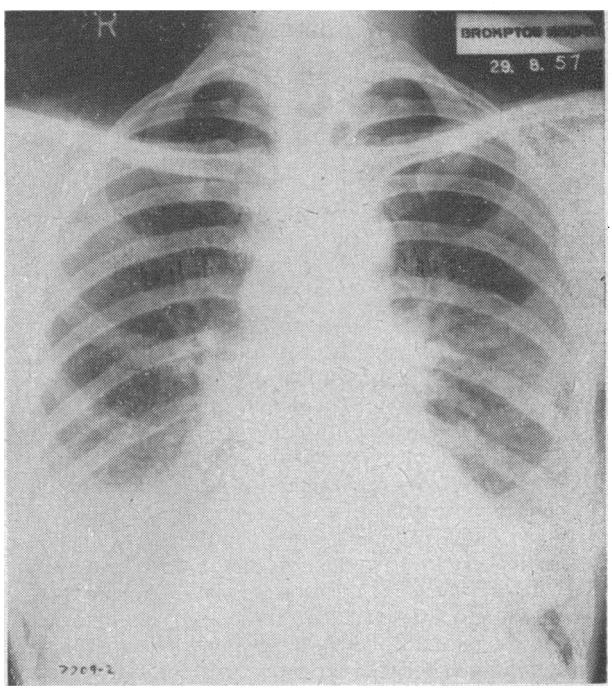

FIG. 4.—Case 3. Radiograph of chest, August, 1957.

was gradually reduced, and after over a year's treatment with 15 mg. daily the drug was withdrawn gradually in February, 1959. To date (June, 1959) the symptomatic and radiographic remission has been maintained. But the diffusing capacity for carbon monoxide has improved only slowly, up to 7.1 and later up to 10.9 ml./min./mm. Hg, still well below the normal range.

Histology

The essential features of the histology of these more chronic cases can be quite briefly stated. Within the affected alveoli there may be some mononuclear exudate and proliferation of lining cells, which may fill some of them. The alveolar walls are thickened with chronic inflammatory cells, fibroblasts, and young fibrous tissue, and suitable staining shows considerable reticulin proliferation. Other changes in the alveoli, such as hyaline membrane, organization of exudate, and the presence of eosinophils, have been described, but are inconstant, and if present may not be prominent. In the late stages the fibrous tissue in the more affected parts of the lung condenses down, so that the lung presents a honeycombed appearance, in which completely destroyed and condensed lung tissue contains cyst-like air-spaces which are all that is left of the respiratory part of the broncho-pulmonary tree. At this late stage the hypertrophy of the cells, possibly of bronchiolar origin, which line the air-spaces may in places become exuberant to form several layers of hypertrophic epithelium. This gives rise to an appearance closely resembling that produced in the alveoli by the so-called pulmonary adenomatosis or alveolar-cell carcinoma. In one patient changes of this sort were found at necropsy in at least three lobes.

In one of my patients there were changes in the liver of rather unusual character, which do not seem to have been reported previously. This was a woman aged 41, who, when I first saw her in January, 1958, had been becoming progressively more breathless on exertion for one year. In the chest radiograph there was fine mottling over both lungs, mostly at the bases. A lung biopsy showed characteristic changes of interstitial fibrosis, with typical thickening of the walls of the alveoli, which contained epithelial cells and mononuclear cells. Because sarcoidosis had been suspected before she was referred to me a liver biopsy had been performed. This showed normal liver cells, but the portal tracts were densely infiltrated with lymphocytes, some histiocytes and fibroblasts, and a few polymorphonuclear neutrophils and plasma cells. There was some formed fibrous tissue.

It is of interest that the sister of another of my patients, Case 3 above, came into hospital under my care in 1954 with an obscure illness of which hepatomegaly was a feature. Exhaustive investigation failed to elucidate the nature of this illness, but a liver biopsy showed infiltration of the portal tracts with a nondescript granuloma of similar character. Both the symptoms and the granulomatous change in the liver have been controlled with continued administration of corticosteroids but relapse on reduction of the dose below the equivalent of 50 mg. of cortisone daily. Though there is at present no evidence that these liver changes are related to interstitial fibrosis of the lungs, I record these two observations, because they may at some future time be seen to fit into a pattern at present not evident.

Radiology

I have already mentioned that the radiographic appearances are variable. Fig. 5 shows a coarse mottling fairly uniform throughout the lungs of a man aged 63, in whom the diagnosis was confirmed histologically after death. Fig. 4 (Case 3) shows a much finer mottling, again fairly uniformly distributed, which might perhaps be described accurately as stippling. Fig. 2 (Case 2) shows a very fine stippling giving a rather cloudy appearance involving predominantly the

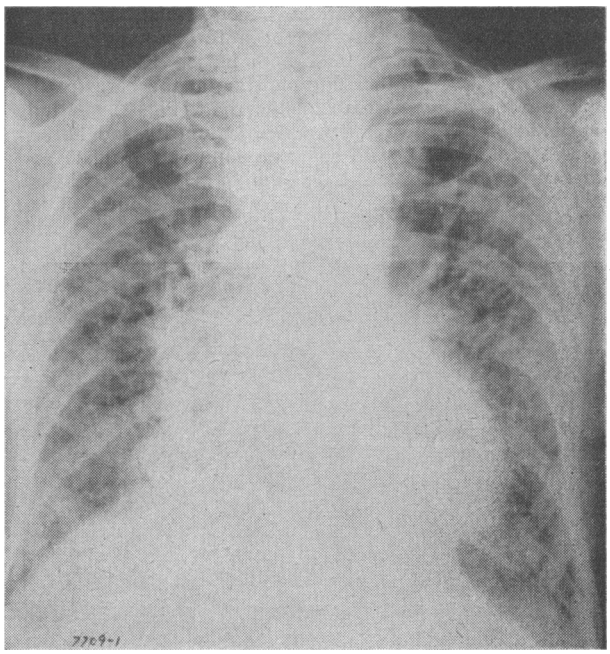

FIG. 5.—Radiograph of chest of a man aged 63, showing coarse type of mottling due to diffuse interstitial fibrosis.

bases of the lungs, especially the left, and proceeding over the course of four years to the development of "honeycombing" (Fig. 3). Fig. 1 shows a mottling of intermediate character, mainly in the middle and lower zones of the lungs, with some early "honeycombing."

Chronic diffuse interstitial fibrosis of the lungs shares with other conditions causing fibrosis at and beyond bronchiolar level some interesting bronchographic appearances. The bronchi seem to maintain an undiminished calibre much further out towards the periphery than usual, and the peripheral zone up to 5 mm. wide which normally remains unfilled is much narrowed. These appearances are shown in Fig. 6. which may be compared with the normal, shown in Fig. 7. Reid and Simon (1958) have shown that this unfilled peripheral zone represents the lung tissue beyond terminal bronchiole level. The bronchographic appearances in interstitial fibrosis of the lungs thus seem to be due to the condensation of the respiratory part of the broncho-pulmonary tree, which is evident pathologically in the later stages of this disease.

Aetiology

Various possibilities have been advanced in discussions of the causation of "idiopathic" diffuse interstitial pulmonary fibrosis. It has been suggested that the acute cases might be a response to some form

of chemical irritant. We know that exposure to nitrous fumes, for instance, may produce not only an acute illness with pulmonary oedema, but sometimes also the gradual development of a condition which has been described as "bronchiolitis fibrosa obliterans" with fibrosis in the peripheral parts of the lungs. The analogy is very imperfect, since bronchiolitis is not a feature of chronic interstitial fibrosis. Nevertheless the hypothesis that a fibrosis of this sort might be a response to a chemical irritant must be considered. It can be rejected both because of the absence of a history of exposure to chemical irritants and because there is usually no acute episodes at the beginning of the chronic illness. None of my patients has been engaged in an occupation involving any evident risk.

The possibility that diffuse interstitial fibrosis might be the result of some sort of chronic viral infection has been considered. But against this there is the fact that in viral pneumonias the greatest damage is at bronchiolar level. Delayed resolution of an acute pneumonia, especially a viral pneumonia, has been considered, but seems unlikely in view of the absence of an initial acute stage; and it seems inconceivable that any such process could occur so widely as to produce changes as generalized as those of chronic diffuse interstitial fibrosis. Moreover, in delayed resolution of acute pneumonia there is intra-alveolar organization with the characteristic appearance of fibroblasts growing through the interalveolar pores, which is not paralleled in chronic interstitial fibrosis.

The resemblance of some aspects of the chronic fibrosing changes that may occur in the lungs of hypertensive patients who have been treated for a long time with hypotensive drugs has been noted. The resemblance here is, I think, fortuitous. In the "hexamethonium lung" the most prominent change appears to be intra-alveolar organization of fibrin-rich oedema, and interstitial fibrosis is less constant and less prominent.

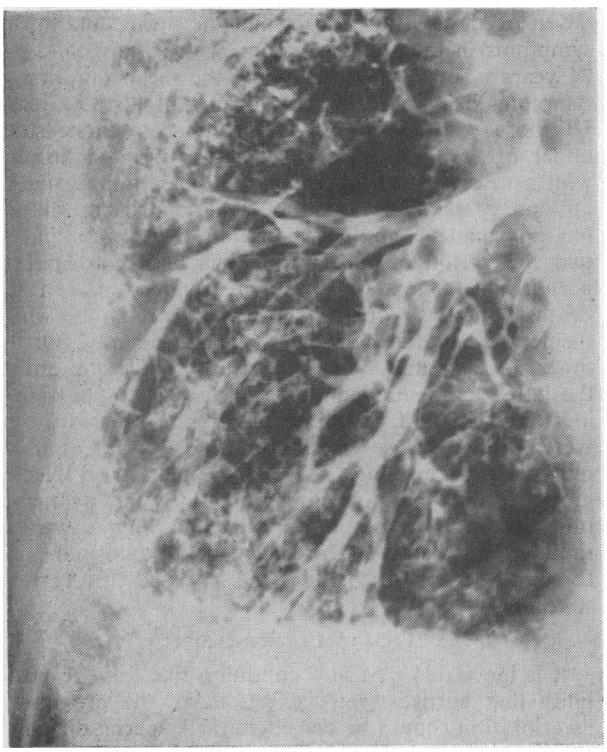

FIG. 6.—Bronchogram in a patient with chronic interstitial fibrosis of lung, showing great condensation of peripheral part of bronchopulmonary tree and diminution of normal peripheral unfilled zone.

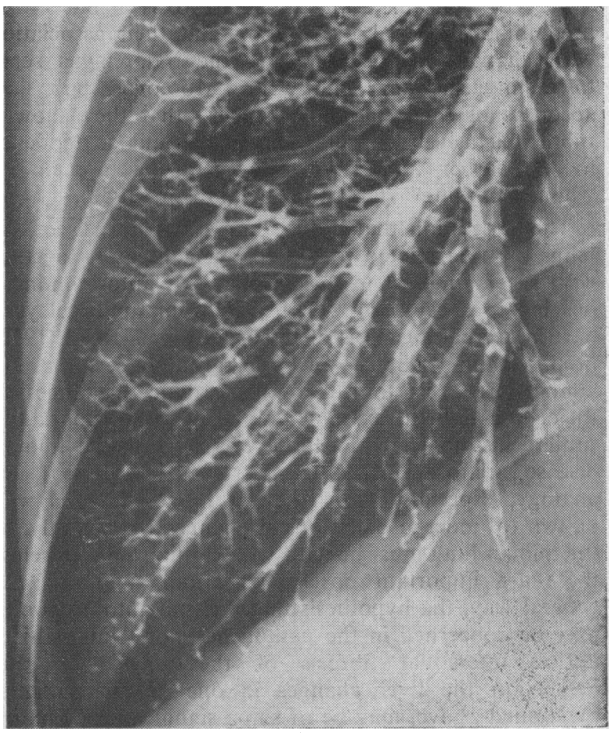

FIG. 7.—Normal bronchogram for comparison with Fig. 6.

Andrews (1958) has described an interstitial fibrosis of the lung caused by obstruction of pulmonary veins, with some features resembling those seen in "idiopathic" interstitial fibrosis; but in the many reported cases of the latter condition in which necropsy has been performed no venous obstruction has been mentioned.

The possibility of a relationship with the so-called collagen diseases must next be considered. A number of cases have been recorded in which lung changes indistinguishable from the description given above have accompanied typical rheumatoid arthritis. Rubin and Lubliner (1957) in their survey of 15 personally observed patients included one who also had rheumatoid arthritis. I have observed three patients with rheumatoid arthritis who had lung changes, confirmed histologically in two, indistinguishable from those of diffuse interstitial fibrosis; these three are not included in the 26 on which my main description is based. I have excluded them because they are distinguished from the main group not only by the presence of rheumatoid arthritis but also by a positive Rose–Waaler differential sheep red-cell agglutination test. In all my patients with chronic interstitial fibrosis without rheumatoid arthritis in whom this test has been carried out it has been negative. There is thus not only clinical but laboratory evidence differentiating between these two groups.

In scleroderma with visceral manifestations—better called progressive systemic sclerosis—changes may develop in the lungs which are not very dissimilar from

those of chronic interstitial fibrosis; but their predominantly basal distribution and their association with changes in the skin and the oesophagus serve to distinguish them clinically. Moreover, published accounts of their pathology suggest that they show a more exclusively fibrotic character and a tendency to the earlier and more prominent development of "honeycombing" (Orabona and Albano, 1958).

The suggestion that diffuse interstitial fibrosis of the lungs may be related to the collagen diseases, together with recent interest in the problems of auto-immunity, has led to speculation whether auto-immunity plays a part in the pathogenesis of this syndrome. Read (1958) prepared in rabbits an anti-rat-lung serum, and administered this to rats. This produced changes in their lungs which, examined serially, were remarkably similar histologically to those observed in the human disease, diffuse interstitial fibrosis. Argument by analogy, especially from the rat lung, which is well known to undergo pathological changes very readily, to the human lung must be used with caution; nevertheless these are important observations, and support, in a general way, the hypothesis that a tissue auto-immunity may be concerned in the pathogenesis of "idiopathic" diffuse interstitial fibrosis of the lungs. In this connexion the liver changes in one of my patients, mentioned above, may be of some significance; Luxton and Cooke (1956) have reported liver changes in Hashimoto's disease of the thyroid, a condition in which the importance of auto-immunity has been established.

Differential Diagnosis

Most of the types of widespread fibrosis which may be caused by recognizable agents can be distinguished from "idiopathic" diffuse interstitial fibrosis on consideration of the total clinical, radiological, and physiological picture. Among these, dust diseases may cause confusion in all respects save the occupational history; clubbing is rare in most industrial lung diseases, but may be prominent in asbestosis, Sarcoidosis should be distinguished without much difficulty; in sarcoidosis, dyspnoea is associated with the late fibrotic stage when usually there is local contraction of fibrous tissue, most often into the middle zones of the lungs, with emphysema at the bases and at the apices, an appearance quite unlike that seen in interstitial fibrosis. As a generalization it may be said that in sarcoidosis radiographic shadows in the lungs precede and in the early stage are out of proportion to dyspnoea, whereas in interstitial fibrosis dyspnoea in the early stage is out of proportion to the radiographic changes. Moreover, clubbing is usually absent in sarcoidosis, and very rarely even of moderate degree. Typical histological changes may be found in easily accessible tissues such as lymph nodes, skin, or liver.

Differential diagnosis from the lung changes which may occur in some of the collagen diseases may in some instances be largely a matter of definition of terms. The relevant practical points are mentioned above in the discussion of aetiology.

It may be difficult to differentiate between diffuse interstitial fibrosis and the various forms of "honeycomb lungs" (Oswald and Parkinson, 1949). This is a convenient general term for a group of cases characterized by widespread formation of small cysts in the terminal parts of the bronchopulmonary tree. Such changes, throughout the lungs, may be associated with two general systemic diseases—mesodermal dysplasia, of which tuberous sclerosis, adenoma sebaceum, and subungual fibromata are other detectable features (Dawson, 1954), and non-cholesterolaemic xanthomatosis, of which eosinophilic granuloma of bone is another possible manifestation; but in many cases the process causing the lung changes remains obscure. In these various forms of honeycomb lungs progression of the disease is usually extremely slow, and in the early stages the radiographic changes may be present without symptoms and generally are more striking than the symptoms; unless there is severe and prolonged secondary bacterial infection with purulent sputum, clubbing is not observed; spontaneous pneumothorax is frequent; and some of the associated features noted above may be found.

Though lung biopsy may be required to establish a diagnosis of diffuse interstitial fibrosis beyond doubt, in many instances consideration of these points may enable the diagnosis to be sufficiently well based for clinical purposes; and in general it may be said that the need for biopsy varies inversely with the confidence with which the characteristic clinico-radiological picture is recognized.

Prognosis

Both from my own experience of these 26 cases and from published reports it seems that on the whole the acuteness of the disease and the rate at which it progresses tend to vary inversely with age; the older the patient the more likely is it to be only slowly progressive, or even to enter a stationary phase. Fourteen of my patients have received only symptomatic treatment, and, in some cases, antibiotics to control episodes of secondary bacterial infection. The mean age of these patients at the onset of their symptoms was 60 years. Seven of these 14 are dead, and the mean duration of symptoms in them was 4½ years, with a range of 1½ to 7½ years. Seven are still living; the mean duration of symptoms being 5 years, with a range of 1½ to 8½ years. Of those who are still living, four seem to be static under observation; one has recently been in hospital with a severe attack of congestive heart failure due to pulmonary hypertension and right ventricular failure, but has made a good response to treatment; and in two the period of observation has been too brief to permit any estimate of rate of progression. Of the deaths, one was due to bronchial carcinoma which seemed to have developed quite independently, but the other six were due to the interstitial fibrosis; in one of the latter, as mentioned above, histological appearances indistinguishable from those of alveolar-cell carcinoma were present in several parts of the lungs, but no metastases were found. These 14 patients are a selected group, in that they were those in whom under observation the condition did not appear to be progressing very rapidly, and there therefore seemed to be no indication for an attempt to modify the course with corticosteroids.

Trial of Corticosteroids

It is inevitable that in a condition like this the possibility that corticosteroids might delay the progressive deterioration should be considered. A special difficulty, over and above the general difficulties and anxieties entailed by the use of corticosteroids in chronic disease, has been observed in this group of cases. Once one of these patients has been established on a cortico-

steroid withdrawal of the hormone may prove impossible, for even a reduction in dosage may give rise to an acute and possibly uncontrollable exacerbation of symptoms. Three cases of this sort were reported by Peabody, Buechner, and Anderson (1953) in the United States.

Though I have proceeded with considerable caution in the use of corticosteroids in these cases, one of my patients had a mild episode of this sort. This was a woman who was so disabled by dyspnoea that she was unable to move from her bed, so that in spite of the known difficulties I felt justified in seeing whether she could be helped by corticosteroids. We gave her cortisone, starting with small doses and gradually increasing to 100 mg. daily, on which she improved moderately. After three weeks the dose was reduced to 75 mg. daily. Ten days later she became acutely ill with extreme dyspnoea, cyanosis, slight fever, and an increase in the shadowing in the lungs, especially on the right. Fortunately, she recovered from this episode when the dosage of cortisone was increased, and we were later able to reduce the dose very gradually, so that now, three years later, she is still living, though very breathless, taking 10 mg. of prednisolone daily. Because of the danger of such acute exacerbations on reduction of dosage, I think it reasonable, if corticosteroids are used in one of these cases, to start with a small dose and gradually increase it, until either there is a tolerable degree of improvement or it is clear that no improvement will ensue. In the latter event, even more than usual caution in reduction of dosage is required.

It must be remembered that in these patients, once corticosteroid treatment has been started, it is likely to be needed for the rest of the patient's life; and this entails all the hazards of long-term treatment with corticosteroids. To quote an example: a woman aged 56 who had been becoming progressively more breathless for one year because of diffuse interstitial fibrosis of the lungs started corticosteroid treatment in June, 1956, with moderate relief of symptoms. The dose could not be reduced below the equivalent of 50 mg. of cortisone, because such reduction caused desperate dyspnoea. In February, 1958, she complained of backache, and was found to have severe osteoporosis of the spine. In this case we are on the horns of a therapeutic dilemma: the osteoporosis demands the withdrawal of corticosteroids, yet complete withdrawal would undoubtedly lead to death from respiratory insufficiency.

It will be clear from this discussion of the difficulties that corticosteroids should be used in these cases only for certain special indications. In the more chronic form of the disease the possibility of benefit beyond some amelioration of symptoms seems to be slight. If the patient is so disabled that he is incapable of leading any sort of useful life, so that it seems worth while exposing him to a dangerous treatment for the sake of giving him a limited period of more tolerable life, then it is justifiable to face the risks and try the effect of corticosteroids. The more acute type, often seen in younger patients, may be treated with less hesitation, both because their untreated course seems to be more rapidly and uniformly downhill and because, in a few of them, remission both of symptoms and of radiographic changes may occur under treatment and even be maintained, at all events for a time, after gradual withdrawal of the corticosteroids. Such cases have been recorded by others (Harris, Preuss, Goldman, and Friedman, 1957; Read and Holland, 1959), and one of my patients seems to be now in such a remission. But such a favourable response is rare. In the chronic cases with long-standing and only slowly progressive fibrosis, my experience suggests that corticosteroids do not produce any fundamental change in the course of the disease.

Effects of Corticosteroid Treatment

Twelve of my patients have received corticosteroid treatment. In one (Case 3 above), treatment has been withdrawn after 15 months, and she is still free from symptoms and radiographic abnormality five months later, though, as noted below, her diffusing capacity is still abnormal. One experienced limited improvement on corticosteroid treatment, which was withdrawn after 13 months; six months later the radiographic shadowing was still slightly less dense than before treatment, and she claimed to be less dyspnoeic, though there was no improvement in the objective physiological tests of respiratory function. Three showed limited improvement, which is maintained only so long as corticosteroid treatment is continued; to date one has been treated for three years and is now receiving 10 mg. of prednisolone daily, and two have been treated for 18 months and are receiving 10 mg. and 15 mg. of prednisolone daily. In two of these the improvement has been mainly subjective, with slight improvement in physiological tests, but no change in radiographic appearances. The third, a man who was 25 years old at the beginning of his illness, has shown a greater improvement in the physiological tests and some improvement in radiographic appearance, but he has developed a moderately severe Cushing's syndrome.

Two patients have received corticosteroid treatment for three years and one year respectively, and are still surviving with only slight subjective improvement and no physiological or radiographic change; but it is impossible to withdraw the hormone because of increased dyspnoea on reduction of dosage below a critical level. One of these is the patient with osteoporosis of the spine mentioned above. One patient was treated for 16 months in a similar unsatisfactory way, and died out of hospital; no precise information is available about the mode of death. In four patients corticosteroids produced no improvement, and after two or three months were withdrawn without ill effect. Three of these survive 2½, 2½, and 1½ years later, but are slowly deteriorating; and one died with progressive dyspnoea 20 months later.

Some physiological observations are available in 10 of the patients who received corticosteroids. Tests of ventilatory function before and after treatment are available in seven. In three the results were within the normal range before treatment and did not change during corticosteroid treatment; in four, a reduced maximum voluntary ventilation or equivalent measure was increased from a mean of 37 l./min. to 62 l./min. The carbon-monoxide uptake, which correlates best of the normally available tests with disability in cases of this sort, has shown only moderate improvement while the patients are receiving corticosteroids. In six patients in whom results before and during treatment are available, the mean figure for carbon-monoxide diffusing capacity at rest by the steady state method was 8 ml./min./mm. Hg before and 10 ml./min./mm. Hg during treatment. In four in whom results are available also

after cessation of treatment the mean figures are 8 before, 12.9 during, and 6.5 after treatment. These figures fit well with the clinical impression that, while an exceptional case treated early in the disease may show a more favourable response, all that can be expected of corticosteroid treatment is that it may suppress the progress of the disease process and certain of its symptoms, and that the favourable effects, if any, do not usually continue after cessation of treatment.

Successful treatment of these cases will probably have to await more complete knowledge of their aetiology. At present, in our study we are in the preliminary stage of collecting information and building up an accurate description of every aspect of them. To go back to a point mentioned earlier, I think that at the moment it may be obscuring important issues to call the whole of this group the Hamman–Rich disease or Hamman–Rich syndrome. If those words mean anything, they would imply that the chronic cases represented a chronic reaction to the same noxious process, whatever it may be, to which the original cases described by Hamman and Rich were an acute reaction. This may or may not be found eventually to be true; but in our present state of ignorance the use of a form of words which assumes tacitly that it is true implies the uncritical acceptance of so many unproved hypotheses that it only confuses our thought, and this should certainly be avoided. For this reason I prefer to refer to this fascinating group of cases in the chronic stage by the purely descriptive name, chronic diffuse interstitial fibrosis of the lung of undetermined aetiology.

Summary

Twenty-six cases of chronic diffuse interstitial fibrosis of the lungs have been observed during a period of nine years. Their clinical, radiological, and physiological features are described, and an account of the morbid histology, based upon studies in 13 of them, is given. The prognosis is discussed, and the effects of corticosteroid treatment in 12 cases are described.

In this lecture, which was intended to recount my own experience, I have not attempted a formal review of the extensive literature. Good reviews have been published by Grant, Hillis, and Davidson (1956) and by Rubin and Lubliner (1957). I have previously published a brief account of 12 of my cases (Scadding, 1956).

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RESPIRATORY SYMPTOMS, BRONCHITIS, AND VENTILATORY CAPACITY IN MEN

AN ANGLO-DANISH COMPARISON, WITH SPECIAL REFERENCE TO DIFFERENCES IN SMOKING HABITS

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Reid (1956) has drawn attention to the striking difference in the crude mortality rates (per million) from bronchitis in Great Britain (838) and in Denmark (33). Christensen and Wood (1958) concluded that these differences were most unlikely to be caused solely by diagnostic differences in the two countries. They suggested that, as the cigarette consumption in England and Wales was about double that in Denmark, this might be an important factor causing the difference.

Dr. A. L. Cochrane suggested that Bornholm might be a suitable place to make a direct comparison with the surveys made in South Wales and Scotland of respiratory symptoms (Higgins, 1957; Higgins and Cochran, 1958) because the island has been the centre of a number of successful epidemiological studies (Olsen, 1943; Fremming, 1951; Dencker and Felbo, 1958). In South Wales (Vale of Glamorgan) and in Scotland (Annandale) the populations were defined by private census, and a random sample of men aged 55–64 were asked to collaborate. In Bornholm one of us (H. C. O.) has for a number of years called up age-defined groups for examination as part of the programme for the control of tuberculosis, using the civil population lists. The response has been excellent, and it seemed probable that if men aged 55–64 were sampled from the town list of Rønne (where the principal tuberculosis dispensary in the island is situated) we might expect a response as good as that achieved by Dr. Higgins (over 90%).

Bornholm is an island of about 588 square km. situated in the Baltic, 200 km. off the east coast of Zeeland, the largest Danish isle. It forms one of the administrative counties of Denmark and has a population of 48,959. About half the population live in the country and the remainder in the few small towns, the largest of which is Rønne, on the west coast.

Most of the population are directly or indirectly employed in agriculture or fishing, but there is an important granite industry, and a large factory making fire-bricks, glazed tiles, and drain-pipes.

Rønne has a population of 13,200; it is the commercial centre of the island and a fishing port. It is a strikingly clean and well-kept town and has no slums or visible atmospheric pollution. The average temperature in February is 32.2° F. (0.1° C.), and in July 61.4° F. (16.3° C.). This is only a little colder in winter and a little warmer in summer than the Vale of Glamorgan and Annandale. At the turn of the