PULMONARY MANIFESTATIONS IN THE SYSTEMIC COLLAGEN DISEASES*

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During the past decade, interest in the so-called 'systemic collagen diseases,' which are more accurately described as connective tissue diseases, has spread and increased. The present concept of them requires a brief explanation by way of introduction.

It is generally understood that the connective tissues of the body arise from the mesenchyme, and constitute most of the supporting structures which themselves include various serous membranes. Connective tissue varies in composition in different sites, but is usually composed of bundles of fibres (collagenous material) embedded in mucoid ground substance (composed of mucopolysaccharides). Robb Smith (1954) has described the modern concept of disease of collagen but the term was used by Klemperer (1950) to mean all the extra-cellular components of connective tissue. Klemperer held that the term referred to the fact that alterations of the extra-cellular portions of the connective tissue were prominent and systemic in various diseases. It would seem to embrace, as Banks (1941), among others, has suggested, such hitherto undifferentiated conditions as disseminated lupus erythematosus, polyarteritis nodosa, scleroderma, rheumatic fever and rheumatoid arthritis. Klemperer considered these were related clinically and pathologically, as diffuse vascular and mesenchymal diseases. The typical lesion common to the group is 'fibrinoid change in connective tissue.' Klinge, in 1933, first reported its occurrence in relation to rheumatic fever, believing that its pathogenesis was an allergic tissue reaction, and that fibrinoid degeneration of connective tissue was a characteristic lesion in tissue hypersensitivity. To many observers, there is no doubt that

the unifying principle for the systemic collagen diseases is the assumed allergic aetiology of these conditions, and the role of hypersensitivity in human disease is being explored and extended, particularly in relation to this group of diseases.

The similarity of their histopathology would suggest a common pathogenesis, but a unitary concept for the widely differing clinical manifestations is upheld by some observers, and not accepted by others.

There would, however, appear to be some unity of vascular pathology founded upon an apparently uniform and diffuse arteritis. These diseases often show some common clinical manifestations, viz. fever, polyarthralgia, polyarthritis, anaemia, high sedimentation rate and, to a lesser extent, purpura, a Raynaud phenomenon, polyserositis, renal and pulmonary lesions. Of recent years, the development of steroids has opened the gate to further therapeutic possibilities.

I propose to confine my attention to the pleural and pulmonary lesions, which are fairly common in diffuse collagen disorders, and which have interested me for some years. In such conditions, one encounters changes varying from pleural effusions, partial consolidation, widespread reticulation, miliary mottling to chronic fibrosis and sclero-cystic lung disease (Ellman and Cukrowski, 1954). These lesions must be integrated with the systemic clinical picture which involves the whole of general medicine.

Let us, therefore, first review the pleural and pulmonary lesions of *disseminated systemic lupus erythematosus*, and illustrate some of them by case records. The natural history of the disease, a review of the literature, the clinical picture of the acute, subacute and more chronic discoid type (with the latter little or no constitutional disorder) have been admirably described by Cohen and Cadman (1953), who stress the close relationship and gradation between these three types. I am interested in the general aspects of this subject are

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FIG. 1.—L.E. cells in the peripheral blood.

referred to this comprehensive paper with its record of 16 cases of the disease. Osler, in 1895, recognized not only the systemic manifestations of the disease, but the fact that pleuro-pulmonary lesions were among the visceral changes. Pleural lesions, both dry and moist, are indeed quite common, but pure 'lupus pulmonary parenchymal lesions' can and do occur, and have to be carefully differentiated from secondary pulmonary bacterial infections which may complicate the terminal stages of the disease.

Various types of lung parenchymal involvement were observed in 46 of 105 cases studied by Harvey *et al.* (1954). Israel (1953), recognizing that the pulmonary manifestations of systemic lupus erythematosus may occasionally dominate the clinical picture, urged the importance of careful search for the typical L.E. cells in the peripheral blood or marrow. These were first described by Hargraves *et al.* (1948). The typical L.E. cell, which is more commonly found in acute cases, consists of a large mature polymorphonuclear neutrophil containing within its cell membrane round or oval homogeneous (inclusion body) material. The segments of the nucleus are displaced to the periphery, and only a thin crescent of cytoplasm can be seen. Around the edge of the mass 'rosettes,' aggregates of polymorphonuclear neutrophils surrounding masses of homogeneous material, are frequently found, in association with cells. The absence of L.E. cells from one single preparation is of little significance.

We have encountered these cells in acute pleural, pericardial and synovial effusions (Fig. 1).

In cases that have come to autopsy, the lupus lung lesions are found to simulate closely those in 'rheumatic pneumonia,' polyarteritis nodosa, the so-called 'anaphylactic pneumonitis,' and the lungs in 'serum sickness,' with such histological changes as focal necrosis of the alveolar walls with capillary thrombi, areas of organizing interstitial pneumonia and haemorrhage and metaplasia of the bronchial epithelium.

A brief comment on the clinical and radiological aspects of three cases is perhaps instructive.

Case 1. S.W., typist, aged 35, with a 17-year history of R.A., experienced in 1950 a sudden severe inspiratory pain in the left chest; she became rapidly dyspnoeic and developed a high pyrexia (temperature range 99-104.6). She was admitted under my care with high swinging temperature, tachypnoea and acute swelling of the knees. She was wasted, her face and breasts showed marked erythematous patches and many small telangiectases. She had marked cyanosis of the lips and fingers. The breath sounds were diminished at both bases, especially the right, crepitations were very audible at the left base and pericardial friction was well heard at the base of the heart. X-ray examination of the chest showed a right basal effusion with bilateral basal reticulation (Fig. 2). There was an effusion into both knees, and a rheumatoid type of arthritic lesion. Blood cultures were negative. There was a polymorphonuclear leucocytosis. Antibiotics had no effect on the high pyrexia. L.E. cells were found in the marrow and blood, and, in view of the grave condition of the patient, she was given ACTH (90-60 mg. per day) which had to be discontinued on the ninth day, despite subjective improvement, because of a purpuric rash on the buttocks and over the lumbar spine, and because of a rise in temperature. It was then decided to try the effect of 100 mg. of cortisone per day. Her rash disappeared rapidly, the temperature subsided, and she improved remarkably. The lungs, however, showed little change clinically or radiologically. She subsequently kept reasonably well, with occasional recurrences, which always responded to cortisone until she developed a progressive renal lesion for which steroids produced no remission, and she died on January 14 of this year.

Case 2. J.M., female, aged 32. She complained of sudden onset of swelling of the right knee and the proximal interphalangeal joints of both hands in November, 1952. In April, 1954, she was admitted to hospital with left basal pleurisy. Subsequently, she had transient attacks of polyarthritis and Raynaud's disease. On August 12,

FIG. 2.—X-ray chest from Case 2 of disseminated lupus erythematosus (D.L.E.) showing elevation of diaphragm, right basal effusion and reticulation at the bases.

1955, she was admitted to my chest unit as an emergency, with high pyrexia. Investigation revealed pain in the chest, pleurisy at the left base, pericarditis, severe anaemia, marked leucopenia, no thrombocytopenia, normal plasma proteins, although electrophoresis showed a slight excess of gamma globulin. Blood culture and blood agglutinins were negative. The left basal pleurisy and pericarditis were confirmed radiologically, and were associated with a characteristically high diaphragm. No L.E. cells were found in the blood or marrow on repeated examinations, until mid-September, when she was given 100 units of ACTH daily, with rapid systemic improvement. In October a butterfly transient erythematous rash over the face was observed. The dose was gradually reduced to 15 units of Gel every third day. On December 17, 1955, the equivalent dose of delta cortisone (prednisone) was administered, and she was discharged from hospital on December 31 on a maintenance dose (10 mg.) of this drug every third day. She remains entirely free from symptoms.

Disseminated Lupus Erythematosus

Case 3. V.B., housewife, aged 29, complained on April 6, 1953, of vaginal bleeding, following four months of amenorrhoea. Fourteen days later she complained of persistent vomiting; she had marked swelling of her face, and was very anaemic with a haemoglobin of 50 per cent. The erythrocyte sedimentation rate was 80. On April 13 she developed an erythematous butterfly rash on the

face. She had a left basal effusion with some consolidation of the left upper lobe (Fig. 3). She was gravely ill with high pyrexia and signs of meningeal irritation. L.E. cells were found in the peripheral blood. She responded well to full doses of ACTH in hospital; her lung and other lesions subsided (Fig. 4). Subsequently she was given maintenance doses of oral cortisone as an out-patient. This was discontinued in November, 1953, since when her condition has been good. No L.E. cells have been found in the blood, and in November, 1955, she had no anaemia and her E.S.R. was normal. I am indebted to my colleague, Mr Philip Harvey, under whose care this patient was, for permission to include this case.

In all three cases involvement of the pleura occurred; in two of them with accompanying effusion, which is usually small, but was certainly moderate in Case 2. In all three cases the episodes of pleurisy occurred at various periods during the illness.

The striking feature in Case 1 was the tachypnoea during the febrile stage, the progressive dyspnoea and cyanosis, the persistent crepitations at the bases, and the evidence of acute pulmonary insufficiency. There were some very dramatic remissions between 1950 and the time of her demise on January 14, 1956. Fever, anaemia, leucopenia, polyarthritides, polyserositis, skin lesions on the face and breasts, and terminal nephritic lesions characterized her illness at various periods. This case, like many others, illustrates the marked elevation and fixation of both diaphragms with

FIG. 3.—X-ray chest from Case 3 showing left basal effusion with some consolidation of the left upper lobe.

areas of plate-like atelectasis where crepitations are heard in abundance. For the most part, the clinical and radiological signs are basal. The differential diagnosis between tuberculous pleurisy and lupus pleurisy and virus and bacterial lung lesions is of clinical significance. In reaching a diagnosis, failure to respond to antibiotics and a good response to steroid therapy is helpful. I have been amazed at the clinical improvement in the pleural and pulmonary lesions in the early stages of the acute disease, usually within the first week of the initiation of steroid therapy. In keeping with the experience of most observers, the more acute the disease, the better the response to steroid therapy, the introduction of which has, as Cohen and Cadman indicate, proved to be a landmark in the history of the condition. Further, like Cohen and Cadman, it has been my experience that of all the collagen diseases, systemic lupus erythematosus secures the most favourable response to steroid therapy. Cortisone, delta cortisone and ACTH in sufficient dosage may all induce therapeutic remissions of varying lengths, but they do not cure the condition, although the patient is subjectively much more comfortable. Some regression of the pulmonary signs, although rarely complete, may occur, as well as a fall in temperature and an improvement in the sedimentation rate and the anaemia. The development and persistence of renal involvement is, in my experience, a bad sign.

The literature of lung changes in disseminated

FIG. 4.—X-ray chest from Case 3 showing good resolution following steroid therapy.

lupus erythematosus has received attention elsewhere (Ellman and Cudkowicz, 1954).

Pulmonary Polyarteritis Nodosa

Although the disease was described almost a hundred years ago by Kussmaul and Maier, it is little more than ten years since it was diagnosed clinically, and now at least 50 per cent. of cases are diagnosed ante-mortem. The pathological lesion is that of a patchy, inflammatory, necrotizing arteritis with fibrinoid necrosis, involving all coats of the small and medium sized arteries and reflected by symptoms dependent on the specific organs involved. The weakened and necrotic arterial wall may granulate and form multiple small aneurysms which sometimes give rise to palpable swellings beneath the skin or mucous membrane. The clinical manifestations may be a constitutional illness with local manifestations resulting from arterial occlusion. Toxic manifestations and multiple infarctions will account for the widespread polymorphic nature of the disease.

The onset is often acute, with high pyrexia which fails to respond to antibiotics. Almost any system may be involved, including the kidneys, heart, lungs, nervous system, joints and alimentary tract. As Grant (1940) has stated, a complete list of symptoms of the established disease would cover almost the whole field of

medicine. The pulmonary manifestations to which we shall confine our attention are of considerable clinical interest, and may present problems in differential diagnosis.

Lung changes may precede those in other organs by months or even years, and the clinical presentation may be that of 'asthma,' bronchitis, pleurisy or pulmonary infarction, or a pneumonic or broncho-pneumonic episode of miliary pattern. The lesion may closely simulate pulmonary tuberculosis, as was the case in at least three cases to be described here, and may go on to fibrosis, bronchiectasis, caseation and even cavitation.

G. A. Rose (1956) has carefully investigated for the Medical Research Council some 110 cases of polyarteritis nodosa, and some 40 cases have presented with a pulmonary manifestation which has usually manifested certain features not characteristic of polyarteritis as a whole. These are generally associated with high blood eosinophilia, nasal granulomata and pathologically a range of necrotizing and granulomatous lesions not demonstrably related to the arteries.

Klinge (1931), Wegener (1936) and others have reported combined necrotizing granulomatous lesions in the lungs, kidneys, nose, etc., which are borderline types of polyarteritis, sometimes with massive necrosis in the lungs. In some cases foci of necrosis surrounded by palisaded cells with joint lesions have been interpreted as rheumatoid lesions. Indeed, necrotizing arteritis and giant cell formation in the lungs has been thought by Pagel (1951), in a paper on polyarteritis nodosa and the 'rheumatic diseases,' to represent a close relationship. The radiological picture can vary from scattered areas of consolidation to miliary infiltration, fibro-caseous disease closely simulating that of pulmonary tuberculosis, and pleural effusion, usually in combination with a pleural eosinophilia. As already noted, Rose (1955) has shown that the pulmonary cases may precede systemic polyarteritis nodosa by periods varying from one to seven years, and the high blood eosinophilia of our own cases has also been observed. He classified this group under the title 'eosinophilic polyarteritis,' and there would appear to be considerable clinical support for this designation or that of pulmonary polyarteritis, where the presenting lesion is pulmonary in type.

My experience of a limited number of cases originating with symptoms in the respiratory tract, frequently asthmatic in nature, has shown that eosinophilia was almost invariable and that bronchial or pulmonary lesions were common. In such cases, pulmonary polyarteritis should certainly be suspected, and the relationship of this type of polyarteritis with that of pulmonary

eosinophilia (Crofton *et al.*, 1954) appears very close.

Case 1. A.E., housewife, aged 41, seen by me in 1943. She presented with attacks of breathlessness and wheeziness, polyarthralgia, petechiae on the face, chest and fingers, and bouts of bloody diarrhoea. She was febrile, the chest symptoms were predominant and a competent radiologist had reported tuberculous infiltration of the right upper zone in response to which an enterprising general practitioner was about to induce a right artificial pneumothorax. The patient, however, had second thoughts, and I was asked to see her in consultation. It is true that the lung infiltration would, on radiological appearances, have been compatible with pulmonary tuberculosis, but the history and clinical examination showed such pleomorphic changes that I unhesitatingly called for further investigations before instituting the A.P.

To summarize: The fever, anaemia, a leucocytosis of 33,000 with an eosinophilia of 61 per cent., an E.S.R. of 41 and the findings already noted were responsible for the diagnosis of polyarteritis nodosa on clinical grounds. The diagnosis was subsequently confirmed by Sir Arthur Hurst and Professor Witts, a course of N.A.B. was recommended and this produced a temporary remission. The lung infiltration resolved, but was later followed by a pericardial effusion.

Case 2. P.T., housewife, aged 40, complained of polyarthralgia and polymyalgia of several years' duration. She had left-sided pleurisy in 1951. She was admitted to sanatorium in September, 1955, following an attack of influenza, as a case of acute pulmonary tuberculosis with radiological evidence of infiltration and cavitation in the left upper zone, the infiltration extending into the left middle zone.

In view of the acute lesion, she was immediately put on a course of daily streptomycin, 1 g., and PAS, 20 g., without any real improvement. Numerous sputum examinations were negative. The history showed that for the previous 18 months she had had a cough with a little mucopurulent sputum as well as nocturnal wheezing for at least six months. Because of this wheezing, her husband insisted on her going to the chest clinic. I saw her in consultation after seven weeks of sanatorium treatment. The sputum was persistently negative for A.F.B. and showed numerous eosinophils and Charcot Leyden crystals. The blood count showed no anaemia, but a leucocytosis of 18,500 with 53 per cent. of eosinophils. Electrophoresis of plasma proteins showed slight excess of gamma globulin. The Mantoux test was positive.

She was admitted to my chest unit. The blood

Polyarteritis Nodosa

Fig. 5.—X-ray chest from Case 2 showing infiltration of left upper and middle zones with cavitation simulating pulmonary tuberculosis with no response to antibiotics.

FIG. 6.—Tomograph of same case showing cavitation in the left upper zone.

FIG. 7.—Same case after four weeks of steroid therapy showing progressive resolution.

FIG. 8.—Chart of same case showing response of eosinophilia to steroids (first cortisone, later prednisone).

eosinophilia persisted and although, apart from the polyarthralgia and myalgia, the lesion was confined to the lung, I regarded this as a case of pulmonary polyarteritis. The response to steroid therapy has been dramatic, producing relief of symptoms, almost complete resolution of the lung

lesion and a dramatic fall in the eosinophilia (Figs. 5-8).

Case 3. S.L., housewife, aged 32. She was admitted to hospital in April, 1955, complaining of breathlessness in paroxysms, wheeziness, sweating, cough and the expectoration of a drachm of mucoid sputum for the past six weeks. She had also lost 2 stone in weight. In November, 1954, she had had an attack of what her doctor called 'asthma' and which lasted two days. She had no further attack until six weeks before admission, when attacks of breathlessness were repeated. She had a high temperature (97-101). There was no significant past or family history.

On clinical examination she looked ill and toxic, she was breathless and wheezy, and there were scattered rhonchi throughout both lung fields. Her sputum was negative for A.F.B. by direct smear and culture, and the agglutinins were negative. The serum proteins showed a total of 4 g. per cent., albumin 2.2 g. per cent., globulin 1.8 per cent., A.G. ratio 1.2 per cent. L.E. cells were not found. The blood count showed a leucocytosis with persistent eosinophilia (see chart).

X-ray of the chest showed scattered infiltration of both lungs. She failed to respond to streptomycin and PAS, and was changed to izoniazid

Fig. 9—X-ray chest (Case 3) showing scattered infiltration in both lungs simulating tuberculosis with no response to antibiotics.

and PAS. Her E.S.R. remained 100. On May 7 1955, she was put on cortisone, 100 mg. daily, and dramatic clinical improvement took place. After 14 days the daily dose was reduced to 75 mg. By July 30, 1955, her E.S.R. had dropped to 3, and her eosinophils were normal, she was asymptomatic and gained 1 stone in weight. She was

FIG. 10.—X-ray chest of same case showing almost complete resolution with cortisone.

FIG. 11.—Chart of same case showing response of eosinophilia to cortisone.

discharged on August 30, 1955, on a maintenance dose of $12\frac{1}{2}$ mg. of cortisone with dipasic 200 mg. t.i.d. She has since been seen at monthly intervals, and remains asymptomatic. She has gained 2 stone in weight (Figs. 9-11).

FIG. 12.—Case 5 showing scattered infiltration in right lung. In upper and mid-zones of left lung with a left basal pleural effusion which showed a pleural eosinophilia as well as a blood eosinophilia.

FIG. 13.—Same case showing some resolution.

Case 4. R.G., housewife, aged 42, was treated for rheumatoid arthritis for 18 years. I first saw her in November, 1953, when she was acutely ill with fever, anaemia, purpura, polyarthritis, a massive pericardial effusion, some basal pleural involvement and, finally, glomerulo-nephritis. We came to the conclusion that she was a case of polyarteritis nodosa with joint, serous and renal changes. L.E. cells were never found in her blood, marrow, joint, or pericardial fluid, and when she eventually died of uraemia autopsy examination showed the characteristic changes, and histology confirmed the diagnosis of polyarteritis nodosa, the lung histology being typical. The interesting feature in this case of apparently long-standing rheumatoid arthritis is its emergence 18 years later as a polyarteritis nodosa.

Case 5. A.K.G., female, aged 55, single, had severe 'asthma' in May, 1954. She was admitted to hospital under my care as a case of pulmonary tuberculosis with severe bronchospasm, anaemia, fever (temperature 102), cough and a tablespoonful of mucopurulent sputum in 24 hours. She had physical signs of a bronchitic nature throughout both lungs and dullness and diminished air entry at the left base, where she had a pleural effusion. X-ray examination showed a transient infiltration in both lungs with a left pleural effusion. The blood count showed a haemoglobin of 70 per cent., a white cell count of 14,600, and an eosino-

FIG. 14.—Same case—almost complete resolution which has been maintained on a maintenance dose of steroid therapy.

phil count of 40 to 18 per cent.; the E.S.R. was 110. The pleural fluid showed a marked pleural eosinophilia. Numerous sputum examinations were negative for tubercle bacilli. There was a past history of polyarthralgia, and the response to ACTH was dramatic. For the past 18 months it has been necessary to keep her on a maintenance dose to avoid relapse (Figs. 12-14).

Pulmonary Scleroderma

Finlay (1891) recognized the association between pulmonary fibrosis and generalized scleroderma; Goetz (1945), in view of the widespread and sclerotic nature of the disease, has used the term 'progressive systemic sclerosis'; Matsui (1924) described three patients with pulmonary fibrosis and scleroderma in whom the total pulmonary artery bed was reduced and the right ventricle was enlarged. Varying degrees of diffuse pulmonary fibrosis, fine nodulation and cyst formation (sometimes almost becoming a honey-comb lung), as well as pleural fibrosis, may all be encountered in this disease. Interstitial thickening of the alveolar basement membranes is commonly recognized.

We have not encountered any case with a pleural effusion clinically or radiologically. Hypertension in the pulmonary circuit was a feature of a few cases. Radiologically, the diffuse mottling and interlacing linear shadows, commencing in the lower zones and advancing to a netlike shadowing in the middle zones, is characteristic. Hilar involvement is uncommon, but occurred in one case, illustrated here with pulmonary hypertension.

Clinically our cases with 'pulmonary scleroderma' have presented with progressive dyspnoea recurring after the disease as a whole had been recognized. All the cases showed sclerodactylia, accompanied sometimes by calcinosis circumscripta, telangiectasis and widespread skin involvement by the time the patient became breathless. The physical signs were comparatively scanty, but chest expansion and vital capacities were diminished. Our experience tallies with that of Lloyd and Tonkin (1948), who described the clinical sequence in scleroderma lung disease as exertional dyspnoea, dry cough and reduction in vital capacity, associated radiologically with diffuse pulmonary fibrosis and, in some cases, fine nodulation, fibrocystic change and pleural fibrosis. The pulmonary fibrosis starts at the bases and may spread to the middle and even the upper zones, leaving the apices almost invariably free. In one of our cases, dermatomyositis and sclerodermatous lesions appeared to merge into each other. Pagel and Treip (1955) have shown how the clinical and histological features of these systemic collagen diseases may sometimes overlap

FIG. 15.—X-ray chest showing gross pulmonary fibrosis.

sufficiently to render differential diagnosis almost impossible. They have suggested that such intermediate forms should be grouped under the name of 'viscero-cutaneous collagenosis.'

In one such case under my care rheumatoid disease with a Felty's syndrome and Sjögren's disease was complicated by a scleroderma merging into dermatomyositis.

Case 1. O.F., housewife, aged 65 (seen by courtesy of my colleague, Dr. Francis Bach). Her history was of 18 years' duration, the onset having been insidious with coldness and hardness of the finger tips. The skin remained normal until four years ago, when she noticed a few 'red spots' on her face, cough and progressive breathlessness, with tightness of the skin of her face and around her mouth and gross pulmonary fibrosis (Fig. 15). She showed a satisfactory response to ACTH. There was nothing abnormal in the sputum; the blood count and E.S.R. were normal.

Case 2. A.S., ex-R.A.F. N.C.O., aged 33, began with Raynaud's disease in 1945, for which he had a bilateral cervical sympathectomy with no appreciable benefit. I first saw him in July, 1950, when he had sclerodactylia, telangiectasis and a widespread skin sclerosis. At this time, he began to complain of breathlessness, his chest expansion was restricted, and within 18 months his vital capacity was reduced from 4.2 to 2.6 litres. The breath sounds were diminished at both bases,

FIG. 16a.—Sclerodactylia with absorption of the terminal flanges.

where fine crepitation and pleural friction could be heard.

Serial X-ray examination of his chest (1950-53) has shown a progressive fibrosis, starting at the bases and gradually spreading to the middle zones with some fine honeycombing, especially at the right base. During his period of observation he had developed dysphagia, nausea, vomiting and diarrhoea, with definite involvement of his gastrointestinal tract, as well as cardiac enlargement. He eventually died of ischaemic heart disease (Figs. 16a, 16b).

Case 3. B.R., male, aged 66, had had scleroderma for over 20 years, with obvious sclerodactylia, widespread skin sclerosis, multiple telangiectasia and dysphagia. At this time he also complained of breathlessness, effort, chest pain and haemoptysis. His lung fields showed bilateral pleural fibrosis, his heart was markedly enlarged, his blood pressure was 220/110, and the pulmonary arteries were very prominent. After repeated attacks of heart failure he died, 22 years after the onset of his disease. Unfortunately, a post-mortem was refused.

Case 4. B.B., housewife, aged 46, was first seen in November, 1952, with swellings of the proximal interphalangeal joints of the hands, and a Raynaud phenomenon as well as early thyrotoxicosis. She came under my care 12 months later when, in addition to these manifestations, she had developed some periarticular thickening of the wrists, and a tendency to clawing of the fingers, which had become progressively worse. Within a year, the skin of her fingers had begun to ulcerate over the

FIG. 16b.—X-ray chest of same case showing a typical area of pulmonary fibrosis in the right lower lobe.

knuckles, and the skin over the front of her chest and around the angles of the mouth had also become tight, so that she had increasing difficulty in opening her mouth.

She soon developed a typical sclerodactylia with calcinosis, dysphagia, early basal lung changes consistent with pulmonary fibrosis. In October, 1954, she developed increasing breathlessness and ischaemic chest pain, and skin and muscle changes in her arms, compatible with dermatomyositis, complicated by a carcinoma of the left breast. She died from heart failure on December 1, 1954, and at autopsy sclerodermatous changes were seen in the heart, lungs, skin and oesophagus. Her response to several courses of steroid therapy was on the whole unsatisfactory.

Pulmonary Manifestations in Rheumatoid Disease

Finally, I must refer to certain pulmonary manifestations which I have encountered in what I prefer to call 'rheumatoid disease.'

We have already noted the complex clinical problems which may arise in patients with merging patterns of some systemic collagen diseases. 'Rheumatoid disease,' whose principal local clinical manifestation is arthritis, is a systemic as well as a local disease. Its systemic nature can be manifested by widespread pathological changes of mesenchymal connective tissue which may occur in various tissues and organs, including the skin, with cutaneous and subcutaneous nodules, muscles, tendons, peripheral nerves, serous structures including the synovia, pleura and pericardium and, in some cases, extending into the lungs and heart.

It is, of course, true that both the pleural and pulmonary lesions in rheumatoid disease are rare. The occurrence of nodular lung and pleural lesions (structurally indistinguishable from the subcutaneous rheumatoid nodule) has been described by Bennet *et al.* (1940), Bagenstoss and Rosenberg (1941, 1943, 1944), Gruenwald (1948), Raven *et al.* (1948), Ellman *et al.* (1954), and Christie (1954). Caplan (1953) described in coalminers a syndrome of nodular lung fibrosis associated in over 50 per cent. of the cases with rheumatoid arthritis. Miall *et al.* (1953) suggested that the prevalence of rheumatoid arthritis was increased where there was a complicating pneumokoniosis. The question of an association between rheumatoid arthritis and pulmonary tuberculosis was raised by Miall (1955), who noted the frequency of tuberculosis in the rheumatoid arthritic group. He suggested from his data that there may be a relationship between the two diseases, due perhaps to some alteration

in tissue reaction, genetic in origin, and possibly a component of the so-called rheumatoid diathesis.

Gough and his colleagues (1955), basing their work on extensive pathological studies, found that, in contrast to ordinary lungs, the pneumokoniotic lungs of coalminers appear exceptionally vulnerable to the rheumatoid process. Gough suggests that they are sometimes more vulnerable than the joints and like Miall and his colleagues, he encountered characteristic X-ray appearances in the chest and lung lesions which seemed typical of the 'rheumatoid' pneumokoniotic type. There were, however, no joint changes and these other manifestations may precede the appearance of joint lesions.

Christie (1954) has shown that rheumatoid disease affects the respiratory tract in the pleura (probably the commonest site), the bronchi, the pulmonary and bronchial vessels and the alveolar walls. The lesions he found in the lungs were as varied and widespread as those in other organs, and ranged from acute exudative foci to chronic scars of loose or dense texture. In size they varied from minute connective tissue buds to a giant nodule 7 cm. in diameter, structurally indistinguishable from the familiar subcutaneous rheumatoid nodule. Much of the fibrosis found by Christie was non-specific, although such areas usually contained more advanced foci, recognizable as rheumatoid nodules.

The respiratory manifestations of rheumatoid disease that we have encountered can be classified as:

- (1) Pleural lesions which may be (a) nodular, (b) diffuse. A dry or wet pleurisy may be encountered.

(2) Pulmonary lesions: (a) nodular, (b) diffuse. The nodular lesions in the lungs and pleura are almost identical histologically with those of the rheumatoid subcutaneous nodules, showing a central fibrinoid necrosis, surrounded by an encircling corona of closely-packed mesenchymal cells, the great majority of which are fibroblasts and external to this is a zone of inflammatory tissue (Collins, 1937). The interstitial changes at the periphery of the nodules closely resemble those that have been described in the diffuse parenchymal lung lesions (Ellman and Ball, 1948; Christie, 1954).

It would appear from the cases encountered that the rheumatoid changes in the lungs or pleura (or both) may occur early or late in the rheumatoid process, and when they occur, they may be silent (when they are not discovered) or symptomatic. The nodules can sometimes be demonstrated radiologically and by tomography. The diffuse pulmonary lesions show a reticular pattern. The diagnosis cannot be made in the absence of arthritis as Spence (1955) has shown,

FIG. 17.—X-ray chest from a case of acute rheumatoid joint disease showing diffuse reticulation of both lungs.

and we would agree with Aronoff and his colleagues (1955) (who have found no example of 'rheumatoid lung' in what they describe as a comparatively small group of patients) that the problem of differential diagnosis of lung lesions in rheumatoid arthritis can be most difficult.

It is important to separate this apparently rare condition from unrelated pulmonary disease, as e.g. pulmonary tuberculosis, the pneumonias, sarcoidosis, carcinoma of the lung, etc. The lung lesions in the systemic collagen diseases already noted must also be carefully eliminated.

The occurrence of nodular lung and pleural lesions is generally accepted. We, like other workers, have also recorded interstitial lung changes, both at autopsy and during life. Using routine chest X-rays for all patients with rheumatoid disease, we have on occasion noted pleural effusions and peripheral lung shadows which the closest possible clinical scrutiny has led us to regard as lung and pleural manifestations of rheumatoid disease. We have suggested that the non-specific interstitial lung changes may represent the end stages of acute lung lesions which at some stage in the patient's life may well have been of the nodular variety (Ellman and Cudkowicz, 1955). Indeed, in view of the presumably asymptomatic nature of some of the pleural and pulmonary

FIG. 18.—Same case showing dramatic response to steroid therapy in lungs (with complete resolution) as well as joints.

FIG. 19.—X-ray chest showing a left pleural effusion.

FIG. 20.—Macroscopic photograph of lung following autopsy showing pleural and pulmonary nodulation and fibrosis.

FIG. 21.—Microphotograph of a section of the lung showing gross pleural thickening and a subpleural rheumatoid nodule radiating into the lung parenchyma and surrounded by fibrosis.

FIG. 22.—Photomicrograph of section of left auricular myocardium and endocardium showing two rheumatoid nodules in the endocardium (multiplied ten times).

FIG. 23a.—Photograph of the hands from a case of acute rheumatoid joint disease.

FIG. 23b.—X-ray hands from same case of acute rheumatoid disease showing active joint changes in the P.I.P. and carpal joints.

nodular lesions, we do not know how commonly these lesions occur nor what are the end-effects upon the adjacent lung in patients who have experienced lung remissions from the rheumatoid process.

Much support for this viewpoint is obtained from the pathological work of Christie (1954) and is confirmed by Spence (1956).

A review of the literature on the pulmonary manifestations of rheumatoid disease and a record

of cases has been given elsewhere (Ellman, 1947; Ellman and Ball, 1948; Ellman and Cudkowicz, 1954).

Through the courtesy of Dr. G. E. Beaumont and G. D. Hadley of the Middlesex Hospital I was recently asked to see two cases (since recorded by Spence, 1955) of the pulmonary manifestations of rheumatoid disease. One was a man, J.H., aged 47, with 14 years of inactive rheumatoid arthritis and subcutaneous nodules.

FIG. 24.—X-ray chest showing widespread infiltration in both lungs.

Symptomless subpleural nodules (seen radiologically in the right mid-zone, 14 mm. in diameter) and very evident on tomography appeared after some 14 years of his illness. The rounded opacities were in close relation to the pleura. Eight months later, when the nodule had increased in size to 17 mm., a pleural effusion, filling the right costo-phrenic angle, developed.

The second case was a man, aged 29, who, after an acute exacerbation of a relatively mild rheumatoid arthritis of six years' duration, developed fever and cough with a diffuse patchy reticulation of both lungs. The response to steroid therapy in both the joint and lung lesions was striking. (Figs. 17 and 18.)

We have records of a large number of cases of this type of lung reticulation.

We have recently recorded (Ellman, Cudkowicz and Elwood, 1954) a case which illustrates the co-existence of multiple subcutaneous rheumatoid nodules, involving the scalp, the left olecranon process, the ulnar borders of both forearms and the ischial tuberosities, with widespread involvement of viscera, including the lungs and pleurae. This was confirmed by autopsy.

The patient, a male, aged 63, had had rheumatoid arthritic disease for 17 years with widespread rheumatoid nodules involving subcutaneous tissue, sclera, dura mater synovia, myocardium, all valves, pericardium, intima of the ascending part

FIG. 25.—Further X-ray of same case showing good resolution following steroid therapy.

of the aorta, the lungs and pleura. These lesions were all associated clinically, in addition to polyarthritides, with a left pleural effusion (Fig. 19), heart block and Jacksonian epilepsy. The initial response to steroid therapy was satisfactory, the subcutaneous nodules showing signs of regression. Eventually, however, the patient succumbed, and came to autopsy. (Figs 20, 21 and 22.)

Rheumatoid Arthritis

Among further cases are the following :

M.H.C., aged 54, male, farm labourer. Ten years' history of transient polyarthritides. In April 1953 he had acute exacerbation of the joint lesions which settled down after three months. In November of that year he developed an acute febrile illness, cough with severe breathlessness and flare-up of his joint lesions. There were widespread physical signs throughout both lungs and an X-ray examination of his chest showed mottling of all zones of both lungs. There was no response to antibiotics. All investigations for tubercle, carcinoma, sarcoid, etc., were negative. A lung biopsy was done for me by Mr. W. Cleland. The sections were examined by Dr. J. W. Clegg and Professor Gough, and showed evidence of fibrosing pneumonitis (non-specific). Joint and lung lesions responded well to steroid therapy. (Figs. 23a, 23b, 24 and 25.)

FIG. 26.—X-ray of hands from a case of active rheumatoid joint disease.

H.L., paint sprayer, aged 59, presented in 1951 with a long-standing history of rheumatoid arthritis, dating to the First World War. He had had a long remission, and this acute exacerbation of his joints responded well to treatment.

Nothing was seen of him again until November 1954, when he developed a severe respiratory infection and acute polyarthritis, (Fig. 26). He had pronounced crepitations at both bases with marked finger-clubbing. X-ray examination of his chest showed a hilar adenopathy with increased reticulation of both lungs, especially at the bases (Fig. 27). All investigations for pulmonary tubercle, carcinoma, sarcoid, etc., were negative.

In February 1955 Mr. Cleland performed a left lateral thoracotomy through the seventh interspace. The lingula appeared fairly normal, but higher up the fissure, the lung fringe exhibited small nodules not much larger than a pinhead. Higher still, the nodular change seemed even more marked. Unfortunately, these nodules were not biopsied, but the lingular biopsy showed a non-specific fibrosis. Professor Gough has informed me (personal communication, 1955) that he has recently had a sudden death in a woman with active extensive rheumatoid arthritis. He found whitish areas in the lung which histologically showed focal nodular changes.

A.L., aged 47, night watchman, has had rheumatoid arthritis for 20 years. In August 1953, he was admitted to my chest unit with an acute exacerbation of his joint lesions, fever, and a cough with 2 ounces of frothy white sputum. He also had progressive dyspnoea and a severe

laryngeal stridor. There was widespread lymphadenopathy, and there were nodules in both olecranon bursae. The lungs showed diffuse reticulation in both mid-zones. The spleen and

FIG. 27.—X-ray of chest from same case showing bilateral hilar adenopathy and basal reticulation.

FIG. 28.—X-ray chest from a case of active rheumatoid joint disease. Diffuse reticulation in both mid-zones.

liver were not felt. Sputum was repeatedly negative for tubercle bacilli, and showed repeatedly some non-haemolytic streps and *M. catarrhalis*. There was no anaemia; there were no L.E. cells

in the blood; the E.S.R. Westergren (50-30); plasma proteins were normal; bronchoscopy and liver biopsy were normal; bronchography showed no evidence of bronchiectasis, and cold agglutination tests were negative.

Investigations showed no evidence of lung carcinoma, tubercle, sarcoid, virus pneumonia or mycosis. The lung and joint lesions finally subsided, but on June 18, 1954, he had a further relapse with intense laryngeal stridor, acute polyarthritis and lymphadenopathy with widespread physical signs in both lungs, expiratory rhonchi throughout both lungs, and basal crepitations. The laryngeal stridor was so pronounced that it necessitated urgent tracheotomy. Careful investigations at the Institute of Laryngology favoured the diagnosis of crico-artenoid arthritis. The joint and lung lesions are now in remission, and the radiological picture of the joints and chest are shown (Figs. 28 and 29).

In conclusion, it would seem, from a review of the literature, that the lung lesions of the systemic collagen diseases are confined in varying degrees to the pleura, the interlobular septa and the alveolar supporting membranes, the smaller bronchi and peri-bronchial tissues, and, in some cases, to the walls of the pulmonary artery. These supporting structures of the lungs receive their blood supply from the bronchial arteries (Coppkowitz, 1952). If it is accepted, as Miller (1949) believes, that a panarteritis underlies the manifestation of collagen disease, the diffuse lung and

FIG. 29.—X-ray of hands and wrists from same case showing advanced rheumatoid joint changes.

pleural changes can be explained by ischaemic changes in the bronchial circulation which is the sole arterial blood supply to these structures.

The close relationship of these diseases and their response to steroid therapy, producing varying degrees of remission, make their diagnosis a matter of clinical significance.

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