Idiopathic fibrosis of mediastinum: a discussion of three cases and review of the literature

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SUMMARY In two out of three cases of idiopathic fibrosis of the mediastinum there was also retro-peritoneal fibrosis, and in one of them extensive fibrosis of the lungs. One of these, a fit middle-aged man, died suddenly with severe coronary artery stenosis due to fibrosis. The third case was that of a young man with a solitary fibrous mass around the right lower lobe bronchus mimicking a malignant tumour and producing bronchial stenosis. Of the various hypotheses about the aetiology and pathogenesis of the fibrous proliferation, that of an autoimmune process seemed the most likely in these cases.

Idiopathic mediastinal fibrosis is an uncommon condition in which predominantly bland collagenous fibrous tissue proliferates with aggregated 'inflammatory' cells. The mediastinal structures are surrounded, constricted, and sometimes invaded by the fibrous tissue, which may extend to affect other intrathoracic organs. The pattern of involvement of the mediastinum is variable and so therefore are the clinical features.

This paper reports three cases that illustrate many of the features of idiopathic mediastinal fibrosis and discusses its aetiology and association with retro-peritoneal and other similar proliferative fibrous tissue lesions.

Case reports

CASE 1

A young man who had previously been well developed when 12 years old a phlyctenular conjunctivitis with enlargement of the right tonsil and right-sided cervical lymph nodes. His tonsils and adenoids were removed. In October 1948, when aged 17, he was referred with bilateral cervical lymph node enlargement and left-sided phlyctenular conjunctivitis. When admitted to hospital in January 1949 for biopsy of the enlarged lymph nodes he had splenomegaly. The biopsy showed the features of caseating tuberculosis (Fig. 1) but no mycobacteria were found in the section or by guinea-pig inoculation. No fungi were seen in sections stained by periodic acid-Schiff (PAS) stain or Grocott silver impregnation.

He was treated with a course of ultraviolet light and tuberculin on the assumption that he had tuberculosis but clinically his condition was unchanged until June 1950, when he was readmitted to hospital complaining of persistent central abdominal pain. He was slightly anaemic (haemoglobin 11.5 g/dl) and his erythrocyte sedimentation rate (ESR) fluctuated between 56 and 98 mm in 1 h. His cervical, abdominal, and inguinal lymph nodes were enlarged, and biopsy of the cervical group showed bland collagenous fibrous tissue. A tentative diagnosis of sarcoidosis was made and ultraviolet light treatment was stopped. The abdominal pain persisted but the lymph nodes decreased in size.

Rounded opacities in the middle and lower zones of the right lung were seen on x-ray examination late in 1953. By March 1954 these had increased in size and the cervical, axillary, and inguinal lymph nodes were again enlarged. The patient was then complaining of recurrent bouts of haematuria lasting for three to four days. Intravenous pyelography showed bilateral hydronephrosis with diminished dye concentration by both kidneys. The diagnosis was changed to 'sarcomatosis'. The haematuria persisted but there was no further deterioration in his general health during the next three years. In May 1957 he was still mildly anaemic (haemoglobin of 11.3 g/dl), his ESR was 61 mm in 1 h, and his blood urea was for the first time at the upper limit of normal at 9 mmol/l (54 mg/100 ml). The lung opacities had increased in size to occupy most of the right lower zone.

He was given a short course of isoniazid without effect, and during 1958 and 1959 his blood urea con-

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Fig. 1 Case 1. Lymph node biopsy. Multiple confluent giant cell granulomata with central caseation histologically typical of tuberculosis. Haematoxylin and eosin $\times 23$.

tinued to rise. He did not attend for follow-up from the end of 1959 until 1961, when he was admitted to hospital as an emergency. He was now very ill, was dyspnoeic at rest with a persistent cough, and had signs of right-sided pleurisy. His haemoglobin had fallen to 6 g/dl, his ESR was 126 mm in 1 h, and his blood urea 23.4 mmol/l (141 mg/100 ml). He was treated with blood transfusion, oral corticosteroids, and penicillin with sufficient success to be discharged from hospital. In November 1961 he was admitted again as an emergency, cold, sweating, orthopnoeic, and with engorged neck veins and tachycardia. He was treated with hydrocortisone and prednisolone but died after five days.

At necropsy there was bilateral pitting oedema of both legs below the knees. The heart weighed 580 g. The left ventricle was much dilated and hypertrophied. The descending aorta was encased in hard fibrous tissue from 5 cm above the diaphragm to its bifurcation into the common iliac vessels. The fibrous mass was continuous through the diaphragm and reached a maximum diameter of 5 cm (Fig. 2). Both ureters were encased and constricted by the fibrosis beyond the upper 5 cm. There was dilatation of the ureters proximal to their entry into the fibrous mass and gross bilateral hydronephrosis with pyelonephritic abscess formation (Fig. 3). The lower lobe of the right lung contained two discrete, hard, fibrous masses occupying some two-thirds of its

Fig. 2 Case 1. Cross section of aorta. Total diameter of the aorta and surrounding fibrous tissue was 5 cm. Dark areas in the fibrosis are areas of osseous metaplasia.

volume and there was subpleural fibrosis in the interlobar fissures. The right middle lobe was completely replaced by similar stony hard fibrosis mottled with carbon pigment (Fig. 4). A fibrotic mass, ovoid in shape and measuring 6.5 $\times$ 7 $\times$ 2.5 cm, surrounded

Fig. 3 *Case 1. Urinary tract and aorta (hydro-nephrotic kidneys have been resutured to specimen after dissection). Shows narrowing and replacement of aortic wall by fibrosis. Arrows indicate where ureters emerge from the fibrous tissue.*

the distal portion of the aortic arch and was attached to the mediastinal aspect of the pleura covering the left lung. The fibrosis did not affect the left lung, which was congested and oedematous, or the superior vena cava, thyroid, mesentery, or epididymis. The lymph nodes, although generally enlarged, were not fibrosed.

The histology of most of the tissue examined was that of collagenous fibrosis with a scanty cellular component of lymphocytes and plasma cells. Small arteries within the fibrosis contained organised

thrombus or showed intimal hyperplasia with a variable degree of narrowing of their lumina. Residual fragmented elastic tissue was evident in many. Vasculitis, however, was not a feature. The fibrosis around the aorta had replaced the adventitia and the outer zone of the media and contained areas of osseous metaplasia (Fig. 5). The macroscopical finding of acute pyelonephritis with abscess formation was confirmed histologically and a small area of fibrosis was noted in the thyroid. No mycobacteria or fungi were identified in the fibrous tissue.

Fig. 4 *Case 1. Sliced right lung showing discrete fibrous nodules in lower lobe and fibrosis of middle lobe extending into upper lobe. Middle lobe is surrounded by dense fibrous zone and all affected areas show central necrosis superficially resembling caseation.*

CASE 2

A 45-year-old, apparently fit man whose hobby was long-distance walking was found dead by the roadside on 30 December 1975 while on such a walk. He had not complained of any ill health before setting out.

At necropsy the only external feature of note was deep, peripheral cyanosis. The heart was not enlarged and there was no infarction of muscle or ischaemic fibrosis in the myocardium, but the left coronary artery and its branches were surrounded and narrowed by a hard fibrous mass 2 cm in diameter. The artery lumen was reduced to pinhole size. A mass of similar fibrous tissue surrounded the upper abdominal aorta but spared the renal vessels and ureters. The left main bronchus and its branches were surrounded by hard fibrosis with slight extension into the surrounding lung parenchyma and the pulmonary artery. Two fibrous plaques were present on the pleura adjacent to the lower thoracic vertebrae and on the left hemidiaphragm in its posterior middle third. The superior vena cava was not affected but the inferior vena cava was partially surrounded and constricted by fibrosis (Fig. 6).

In view of the clinical information the striking histological feature in this case was the severe narrowing of the left coronary artery (Fig. 7). The lumen

Fig. 5 *Case 1. Area of osseous metaplasia from the aortic wall. H and E $\times 5$.*

Fig. 6 Case 2. Mounted section of aorta (bottom right) and of inferior vena cava (top left). Fibrosis and inflammatory infiltrate extend into wall of inferior vena cava. Darker zone around aorta is the elastic tissue of the media, which is largely replaced by fibrous tissue at its lower edge. Orcein, van Gieson $\times 3$.

was reduced to pinhole diameter proximally and completely occluded distally. A cellular infiltrate of plasma cells, lymphocytes, and histiocytes surrounded the lumen and within this infiltrate there were fibroblasts, producing short collagen fibres, and also fragments of the elastic lamina of the vessel. In general the mononuclear cell component of the process was larger in this case than in the first both at the edges of the fibrosis, around blood vessels and bronchi, and within the fibrous tissue (Fig. 8). The destruction of elastic tissue and invasion of large blood vessels by fibrous tissue and cellular infiltrate was prominent in this case (Fig. 9). The pulmonary artery elastic tissue had been completely destroyed in one area. A number of small arteries were surrounded and infiltrated by lymphocytes, suggesting a vasculitis. An unusual feature in the pleural plaques was areas containing large numbers of thin-walled blood vessels distended with erythrocytes.

CASE 3

A 23-year-old male Sikh who had lived in Britain for 21 years was admitted to hospital on 15 July 1976 as an emergency. He had a two-year history of cough,

worsening over the previous two months. For two months he had been vomiting after coughing or food; had noticed a persistent, low-grade fever; and had lost two stones (12.7 kg) in weight. He had had two episodes of haemoptysis, one nine and the other two months previously. On admission he looked ill. His temperature was 38.3°C . He had a persistent cough, a tachycardia of 140/min, a blood pressure of 130/60 mm Hg, and the right side of his chest was dull to percussion with diminished breath sound conduction. The lower liver edge was palpable and he was tender to deep palpation on the left side of the abdomen. Other systems examined were normal. Chest x-ray examination showed a right-sided pleural effusion, enlarged right hilar lymph nodes, and a calcified mass in the superior mediastinum. A provisional diagnosis of tuberculosis was made but no mycobacteria or other pathogenic organisms were isolated from the sputum or the green purulent pleural fluid which was aspirated. His fever continued and he was given a trial course of PAS and isoniazid without improvement.

At bronchoscopy the right main bronchus was seen to be narrowed by what was thought to be a soft

Fig. 7 Case 2. Coronary artery, showing severe eccentric narrowing by proliferating fibroblastic tissue. Fragmented elastic lamina evident mainly on right of field. Orcein, van Gieson $\times 9$.

Fig. 8 Case 2. Aortic wall, showing area of fibrosis with a whorled pattern and infiltrated by lymphocytes and plasma cells. H and E $\times 23$.

Fig. 9 Case 2. Aortic wall. Elastic fibres split and fragmented with accompanying infiltrate composed predominantly of plasma cells. Orcein, van Gieson $\times 60$.

tumour. After a specimen for biopsy had been taken the patient had a respiratory arrest on the operating table owing to bleeding into the trachea. He was resuscitated but did not regain consciousness until the next morning. The tumour on biopsy was reported to be an 'inflammatory pseudopolyp' with no malignancy. During the second postoperative day the patient remained restless and distressed with a persistent cough. On the third postoperative day he suddenly stopped breathing. Resuscitation attempts were unsuccessful.

At necropsy the right pleural sac was obliterated by dense fibrous adhesions and there was diffuse thickening of the wall of the right lower lobe bronchus by hard, white tissue extending into the adjacent lung. This was presumed to be carcinoma until examination of a frozen section showed dense collagenous fibrosis with no malignancy. The hilar and paratracheal lymph nodes were partially replaced by hard white tissue continuous with that surrounding the right lower lobe bronchus. The fibrous mass measured 4 cm in diameter. It encroached on the right pulmonary artery but did not invade the other major blood vessels of the mediastinum. The right lower lobe was consolidated with pneumonia and the cut surface was yellow. The cardiovascular system was normal and no other structure was affected by fibrosis.

The histology in this case showed a degree of cellular infiltration intermediate between that in the first two cases, but again most obvious at the edges of the fibrosis. Partial replacement of the wall of the pulmonary artery similar to that in case 2 was evident. Areas of cellular fibroblastic proliferation were present around the bronchus and the fibrosis had penetrated between the cartilage plates and along their inner surfaces (Fig. 10). The epithelium of the bronchus had been lost. Peribronchial lymph nodes showed reactive hyperplasia with large numbers of plasma cells in the sinusoids. The consolidation of the lung was due to a lipid pneumonia with large numbers of lipid-filled macrophages distending the alveoli. The reason for these changes was not known.

Discussion

The first description of mediastinal fibrosis is ascribed to John Hunter in 1757 (Barrett, 1958), 150 years before the first recognised account of retroperitoneal fibrosis (Albarran, 1902). The first major review of fibrosis of the mediastinum was by Osler (1903) in a paper on superior vena caval obstruction and covering a period of 50 years. Since Osler's study there have been several reviews of large series of cases, including those of Knox (1925), Keefer (1938),

Fig. 10 Case 3. Bronchial wall. Area between bronchial cartilage on left and lumen on right occupied by proliferating fibroblastic tissue containing lymphocytes and plasma cells. H and E $\times 9$.

Barrett (1958), and Hache *et al.* (1962). Probably the early descriptions included cases due to syphilis and tuberculosis, but with the advent of more precise diagnostic methods a group of patients was recognised in which the fibrosis was not due to either of these diseases. No aetiology has been proved in most cases seen in recent years. They have been given a number of names, including 'idiopathic mediastinal fibrosis' (Barrett, 1958; King, 1963; MacKenzie, 1970), 'chronic fibrous mediastinitis' (Erganian and Wade, 1943; Tubbs, 1946; Nelson *et al.*, 1965), 'idiopathic fibrous mediastinitis' (Hache *et al.*, 1962), or simply 'mediastinal fibrosis' (Goodwin *et al.*, 1972).

The histological features of the fibrosis were similar in my three cases. All the areas sampled were composed of bland, hypocellular, collagenous fibrous tissue often with a whorled pattern and accompanied by occasional foci of cellular fibroblastic proliferation. Foci of infiltration by mononuclear cells, mainly plasma cells and smaller numbers of lymphocytes and histiocytes, were present. Neutrophils and eosinophils were not prominent. Stains for mycobacteria in all three cases and Grocott and PAS stains for fungi in case 1 were negative.

The plasma cell and histiocytic infiltrate was most intense at the edges of the fibrosis, particularly when the process affected large blood vessels, where there

was fragmentation of elastic fibres. Similar but less obvious elastic fragmentation was present in affected bronchi and lung parenchyma. No ingestion of elastic material by macrophages or formation of 'foreign body' giant cells was found.

Recent observations that mediastinal and retroperitoneal fibrosis are histologically similar and may coexist in the same patient, as in my cases 1 and 2, have led to a belief that they are the same pathological process. Also the histological similarity with Riedel's thyroiditis, orbital pseudotumour, sclerosing cholangitis, sclerosing mesenteritis, and multiple dermal fibromata and the finding of these lesions in combination with retroperitoneal and mediastinal fibrosis (Coopersmith and Appelman, 1971; Comings *et al.*, 1967; Turner-Warwick *et al.*, 1966; Mitchinson, 1970) has led to the term 'multifocal fibrosclerosis'. The association between the mediastinal and retroperitoneal lesions, however, is the commonest (Mitchinson, 1970) and, contrary to Barrett's (1958) claim, may be discontinuous or continuous through the diaphragm, as illustrated by cases 1 and 2.

The clinical syndrome of superior vena caval obstruction was for many years regarded as the hallmark of mediastinal fibrosis, and earlier reports of this condition are in reviews of the causes of superior vena caval obstruction (Osler, 1903; Knox, 1925; Keefer, 1938). While this is still a major clinical feature, the description of cases of involvement of

other mediastinal structures—for example, pulmonary artery (Nelson *et al.*, 1965), pulmonary vein (Bindelglass and Trubowitz, 1958), lung (Benfield *et al.*, 1962), bronchus and oesophagus (Hache *et al.*, 1962), and coronary artery (Reed and Stinely, 1959)—have highlighted the variability of clinical presentation.

Attempts have been made to group patients with mediastinal fibrosis into broad clinical categories. For example, a recent leading article (*British Medical Journal*, 1971) divided cases into two groups by age, claiming (1) that the 40 and over age group developed superior vena caval obstruction as the main feature and the fibrosis mainly affected the larger vessels of the mediastinum, and (2) that the 15-30 years age group had hilar fibrosis presenting as a tumour mass, causing pulmonary infection and severe haemoptysis.

Although case 3 fits well into the second group and case 2 showed involvement of medium-sized vessels and slight permeation of the pulmonary artery, case 1 does not fit at all and in none of the three cases was there anatomical superior vena caval obstruction. A review of the literature suggests that this grouping, which may be valid in some instances (Yacoub and Thompson, 1971), is an oversimplification. Cases have been described—for example, some of those cited by Hache *et al.* (1962)—in which the patients were asymptomatic, but I have not found an example of sudden death in a person previously in good health. Case 2 is the more surprising in this respect in that physical fitness was such a feature of the man's life.

My three cases illustrate some of the structures which may be affected by mediastinal fibrosis—in particular, lung, bronchus, pulmonary artery, aorta, and coronary artery—and also the association between retroperitoneal and mediastinal fibrosis in the same patient. I have, however, been unable to find recorded cases that had the extensive lung involvement of case 1 or discrete intrapleural plaques separate from the mediastinal fibrosis. The histological appearances are typical, although no specific reference to elastic damage associated with the cellular infiltrate seems to have been reported.

A complete correlation between clinical and pathological features in these three patients is impossible but certain factors can be linked. The extreme dyspnoea in case 1 may be attributed to the widespread fibrosis of the lung and the rising blood urea and fluid retention to the ureteric obstruction produced by the retroperitoneal fibrosis. Case 2 is more difficult because of the lack of clinical information. Although the sudden death may be attributed to the coronary artery stenosis the lack of antecedent symptoms and of any evidence of previous myocardial damage remains unexplained. The cough,

weight loss, fever, and haemoptysis in case 3 presumably result from the chronic pneumonic consolidation of the right lower lobe secondary to bronchial stenosis.

The aetiology and pathogenesis of mediastinal fibrosis, as reflected in the term idiopathic, are unknown. Many speculative hypotheses have been advanced for the idiopathic fibrous lesions and are summarised in reviews by Ross (1968), MacKenzie (1970), and Mitchinson (1970). Many of these hypotheses have been concerned with the retroperitoneal form of the disease—for example, leakage of urine leading to fibrosis (Hinman, 1960) and infection after inflammatory bowel disease (Chisholm *et al.*, 1954). These have been inadequate to explain the more widespread involvement by a disorder which can justifiably be regarded as systemic, both from the coexistence of lesions in different organs in the same patient and the overall histological similarity. A less constrained approach is therefore necessary to explain this systemic disorder. Factors that are not limited to one system or area of the body should be considered, such as the following. (1) The fibrosis results from a chronic infection, especially tuberculosis, histoplasmosis, or syphilis. (2) Repeated trauma followed by organisation in a haematoma produces fibrosis. (3) Fibrosis follows an inflammatory process in adipose tissue—that is, a systemic form of Weber-Christian disease. (4) The condition is iatrogenic and results from an adverse reaction to a drug. (5) The fibrosis represents a self-limiting sclerosing malignancy. (6) An abnormal immune response, either hypersensitivity to a 'foreign' material or autoimmunity, leads to excessive fibrous replacement of damaged tissue.

Infection by *Histoplasma capsulatum* and mycobacteria has been a recurrent theme in the American literature on mediastinal fibrosis. Goodwin *et al.* (1972) reviewed 38 cases in which *H. capsulatum* and *M. tuberculosis* were thought to be the causative organisms and reported a further six cases. In all but one of the six no organisms were isolated on culture and their presence was inferred from microscopy or serological testing. The absence of cultural proof is a consistent finding in cases that are thought to be due to infection and is the major criticism of hypotheses which regard infection as a cause of the fibrosis. Goodwin *et al.* (1972) imply that the lesions which they are describing are identical with those of idiopathic mediastinal fibrosis, but they describe caseation as a constant feature and fibrosis which tends to occur as concentric bands around the caseation. These histological features are not those usually regarded as typical of idiopathic mediastinal fibrosis and the cases presented in this paper support this view. However, in case 1, where caseating lymph

node granulomata were seen in the original biopsy, tuberculosis cannot be excluded as an initiating factor. Tuberculosis and histoplasmosis may be responsible for a number of fibrotic lesions of the mediastinum and lung or even the retroperitoneal space, but in most cases reported, especially those with more widespread disease, there is no evidence for either of these causes. There is likewise no consistent evidence for syphilis as a factor in the aetiology of idiopathic fibrosis, although some cases with positive serological tests for syphilis have been reported and, in the third case described by Tubbs (1946), there was symptomatic improvement in a patient with positive Wasserman and Khan reactions after penicillin and bismuth treatment.

The second and third alternatives have largely been discounted. Lack of haemosiderin pigmentation within the fibrosis and lack of antecedent history of trauma have excluded it as a cause. The suggestion that an inflammatory process in adipose tissue similar to Weber-Christian disease could be an explanation (Mitchinson, 1965) has been retracted by this author (Mitchinson, 1970) for lack of histological corroboration.

The suggestion that the fibrosis is iatrogenic stems mainly from the finding by Graham (1964, 1967) that methysergide therapy was associated with an increased incidence of retroperitoneal and mediastinal fibrosis. But not all patients with mediastinal and retroperitoneal fibrosis are taking methysergide. Most have no consistent drug history. Also the withdrawal of methysergide does not always result in regression of the fibrosis (Schwartz and Dunea, 1966) and therefore, even if this drug is the initiating factor in some patients, there is possibly some other reason for the fibrosis extending.

Sclerosing malignancy is an unlikely explanation in the absence of residual tumour tissue in the cases reported. Hou-Jensen *et al.* (1973) reported a case of a proliferating histiocytic lesion of the mediastinum and retroperitoneal space in which 'burnt out' areas mimicked idiopathic fibrosis histologically. In most cases studied, however, the histiocytic component has not had malignant features. Of some interest is the case reported by Alpert and Jindrak (1972) of a patient with retroperitoneal fibrosis and sclerosing cholangitis associated with reticulum cell sarcoma in whom the tumour growth paralleled the spread of fibrosis. These authors suggest an analogy with carcinoid syndrome and the production of endocardial fibrosis, postulating a fibrogenic product of the reticulum cell sarcoma in their patient. Most reports of 'idiopathic' fibrosis are of cases without tumour, and certainly none was found in my three cases.

Mitchinson (1972) suggested that hypersensitivity

to the leakage of atheroma plaque material or other allergen from damaged aortic wall may be the initiating event in the fibrosis. He drew attention to the fact that most mediastinal and retroperitoneal fibrotic lesions are periaortic, and presumably similar leakage may take place from arteries in any of the other organs affected by proliferating fibrous lesions. Atheroma was not a major feature in any of my three cases and no lipid material was identified outside the wall when the fibrosis affected large blood vessels.

The alternative approach relating to an immunological cause is that the condition is autoimmune or is a collagen disease. Occasional cases with raised serum proteins and ESR and a syndrome resembling rheumatoid arthritis (Mitchinson, 1970) support this possibility. To date most attempts to find an abnormal antibody have been directed to those of organ specificity (Turner-Warwick *et al.*, 1966) and not towards tissue specific antibody. Recently, however, Iversen *et al.* (1975) have demonstrated deposits of IgG, IgM, and IgA on the surface of collagen bundles in a patient with retroperitoneal fibrosis taking methyldopa. The significance of this observation is not clear. It may simply be another antibody in patients taking methyldopa, such as that associated with the positive Coombs test, which does not always produce a haemolytic anaemia.

The prominent plasma cells admixed with lymphocytes and histiocytes in my three cases provide some circumstantial support for an autoimmune hypothesis. Also the greatly increased number of plasma cells in the regional lymph nodes of case 3 suggests increased stimulation of antibody production, although this may be simply a response to local infection. The association of the cellular infiltrate with damaged elastic fibres found in all three cases poses the question whether the antigenic stimulus is an alteration in elastic tissue. This elastic damage is similar to that found in pulseless disease, where giant cells and granulomata are not an essential part of the histological picture and plasma cell infiltrates are often prominent (Nasu, 1963), and also in certain cases of 'giant cell' arteritis. No phagocytosis of elastic tissue was found in any of these three cases.

In conclusion, my three cases illustrate many of the well documented features of idiopathic fibrosis of the mediastinum and some that are less usual. The evidence for this condition being part of a systemic disease is considerable but the aetiology remains unknown, although a small number may be due to infection and drug side effects. The autoimmune hypothesis is an attractive one but even if proved will explain only the mechanism and not the initiating factor. The three cases raise the possibility of the antigen being a component of elastic tissue and the field of tissue-specific antibodies may merit further

investigation. Even when the pathogenesis of this condition is understood many questions may still need to be answered—not least, why is the condition selective for certain apparently unrelated sites and why does the fibrosis spread so widely in a given area?

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