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Systemic idiopathic fibrosis and systemic Weber-Christian disease

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SYNOPSIS Idiopathic retroperitoneal fibrosis is represented as one of the manifestations of a widespread disease, systemic idiopathic fibrosis. Some evidence is presented which suggests its origin as an inflammatory disease of adipose tissue. Although relatively rare, the idiopathic diseases of adipose tissue and its blood vessels are worthy of closer study.

In 1948 Ormond reported two cases of unheralded anuria due to idiopathic retroperitoneal fibrosis. Previous documentation of the condition had been scanty, but since then over a hundred similar cases have been reported. The patient, usually an adult, at first has only vague symptoms such as abdominal discomfort, anorexia, loss of weight, or nausea. The diagnosis is made usually only when signs of ureteric obstruction appear later in the illness.

At operation there is mechanical obstruction to the ureters by a mass of exuberant retroperitoneal fibrous tissue. Freeing the ureter from the mass almost always results in relief of the obstruction and cure of the symptoms. The purpose of this paper is to review some aspects of the pathology of this and similar conditions, and to draw attention to evidence which suggests a possible pathogenesis.

IDIOPATHIC RETROPERITONEAL FIBROSIS

In the typical case of idiopathic retroperitoneal fibrosis the fibrous mass found at operation is of variable extent within the limits of the fascial planes enclosing the kidneys, ureters, and great vessels (Mitchell, 1950) (Fig. 1). It usually obstructs both ureters and surrounds the great vessels. Occasionally there is obstruction of the aorta or its branches (*e.g.*, Hackett, 1958) or the inferior vena cava (*e.g.*, Schneider, 1964).

An uncommon variant is 'periureteritis plastica'. The fibrosis in these cases is localized in the immediate vicinity of the ureter causing a fancied resemblance to a garden hose (Vest and Barelare, 1953). The cause is unknown, and may not be the same as that of idiopathic retroperitoneal fibrosis.

SYSTEMIC IDIOPATHIC FIBROSIS

In recent years there have been many reports of

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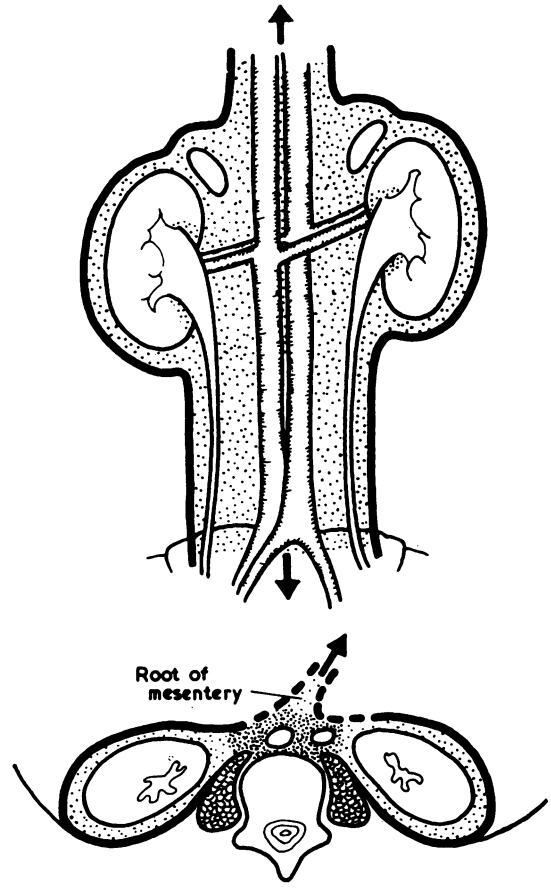

FIG. 1. *Fascial boundaries of retroperitoneal tissues (partly after Mitchell, 1950). The condensation of the connective tissue in the mid-line around the great vessels is not a barrier to extension of idiopathic fibrosis and Weber-Christian disease.*

idiopathic fibrosis affecting also tissues outside the usual anatomical limits. Tubbs (1946) was the first to describe simultaneous involvement of mediastinal tissues. Raper (1955) and Clouse (1964) mentioned extension of the fibrosis forwards into the mesentery of the small intestine. Raper (1956) first reported involvement of the lower end of the common bile duct and adipose tissue surrounding the spleen. The pelvis is sometimes infiltrated, and obstruction of the sigmoid colon was present in the case described by Iozzi and Murphy (1957). Reed and Stineley (1959) described a case with fibrosis around the coronary arteries.

In most of these sites idiopathic fibrosis has also been reported in the absence of conspicuous retroperitoneal involvement. Examples include idiopathic mediastinal fibrosis (Barrett, 1958), 'pericystitis plastica' (Hewett and Headstream, 1960), and retractile mesenteritis (Tedeschi and Botta, 1962). It therefore seems possible that these conditions are closely related to idiopathic retroperitoneal fibrosis, and may share a common cause.

Thus the concept has arisen of a disease which may affect many parts of the body, not exclusively involving the retroperitoneal tissues, and frequently accompanied by systemic signs such as disturbance of the albumin-globulin ratio, elevation of the E.S.R., and anaemia (Pugh, 1960; Que and Mandema, 1964); hypertension may result from renal involvement (Blanc, 1951). When necropsy evidence is available in more cases of idiopathic fibrosis it is likely that this concept will be strengthened.

AETIOLOGY OF SYSTEMIC FIBROSIS

The fibrosis is found in sites normally occupied by connective tissue, mainly adipose tissue. The absence of neoplastic characteristics and of disease of neighbouring organs (notably the urinary tract) has led to the view that the fibrosis is the result of inflammation of the connective tissue. Most reports have pointed out the presence of non-suppurative inflammation of adipose tissue near the fibrosis, and in two cases the histological evidence was strongly suggestive of gradual healing by fibrosis of an inflammation of adipose tissue (Hamburger, Richet, and Ducrot, 1957; Margoles and McQueeney, 1960).

Not only is the cause of the inflammatory process obscure, but it is also apparently silent clinically. There are many possible causative agents, and the idiopathic fibroses may therefore be heterogeneous. Little is known of inflammatory diseases affecting internal adipose tissue, but study of the superficial adipose tissue of the breast and panniculus adiposus is helpful in providing analogies which suggest a possible cause for systemic idiopathic fibrosis.

INFLAMMATION OF SUPERFICIAL ADIPOSE TISSUE

The adipose tissue of the breast and panniculus adiposus is frequently exposed to cold, heat, trauma, and the introduction of foreign materials; it is also easily accessible to clinical examination and biopsy. As a result, the inflammatory lesions of superficial adipose tissue and its blood vessels have been the subject of detailed study and elaborate classification, a simple version of which follows:—

1 Due to physical agents, *e.g.*, 'traumatic fat necrosis,' 'cold panniculitis'; 2 due to pancreatic enzymes, *e.g.*, in pancreatitis, carcinoma of the pancreas; 3 due to infection, *e.g.*, tuberculous erythema induratum; 4 idiopathic, *e.g.*, in collagen diseases, erythema nodosum, nodular vasculitis.

The histological appearances of all these inflammatory conditions are fairly similar, probably partly due to the prolongation of the inflammatory response caused by liberation of lipids and enzymes from the adipose tissue cells (Panabokké, 1958). The result is a chronic 'granulomatous' appearance and healing by fibrosis is usual.

Most of these causes of superficial adipose tissue inflammation have been considered as causes of idiopathic systemic fibrosis (*e.g.*, Coppridge, Roberts, and Hughes, 1955). Trauma, pancreatic disease, and infection have at present been rejected because of lack of evidence. Extravasation of urine has also been frequently suggested as a cause, especially since the recognition of 'peripelvic urine granuloma' (Hamperl and Dallenbach, 1958), which is a localized inflammation of adipose tissue apparently due to small leakages of sterile urine from the renal pelvis. However, this seems inadequate to explain a widespread disease, and there is no supporting histological evidence.

There remain for consideration the idiopathic inflammatory diseases of adipose tissue. Vasculitis of variable severity is commonly found in these lesions and may, in some instances, be the primary abnormality. Weber-Christian panniculitis is one such disease, and is of particular relevance to the present discussion because involvement of internal adipose tissue other than the panniculus has been described with increasing frequency in the last 20 years. Its possible relationship with idiopathic fibrosis has, however, received scant attention (Coppridge, *et al.*, 1955; Charnock, Riddell, and Lombardo, 1961).

WEBER-CHRISTIAN PANNICULITIS AND SYSTEMIC WEBER-CHRISTIAN DISEASE

Weber-Christian panniculitis has been well recognized for about 30 years, although the first case was

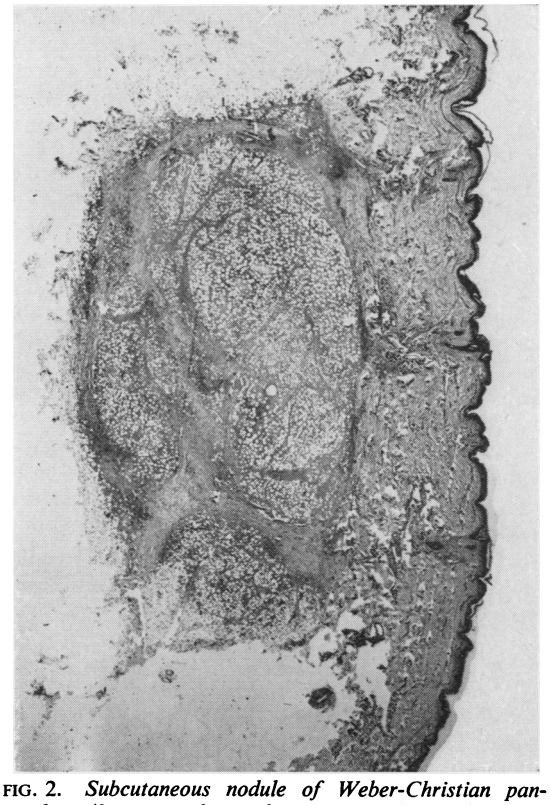

FIG. 2. *Subcutaneous nodule of Weber-Christian panniculitis (haematoxylin and eosin, × 7) (Milner and Mitchinson, 1965).*

described as long ago as 1891. The typical patient is an adult who complains of nodules in the subcutaneous adipose tissue which after a variable time, usually weeks or months, regress only to be succeeded in many cases by similar lesions elsewhere in the panniculus adiposus. Fever usually accompanies each crop of nodules. The histological appearance (Fig. 2) is one of pleomorphic inflammatory cell infiltration of the subcutaneous adipose tissue, often especially around interlobular septa and blood vessels. The infiltrate usually consists mainly of mononuclear cells, sometimes including foamy macrophages; giant cells and polymorphonuclear neutrophil leucocytes are usually scanty. Necrosis of local adipose and connective tissue is almost always seen, and is usually followed by fibrous repair.

The cause is unknown, although many suggestions have been made (Hallahan and Klein, 1951; Beerman, 1953). Some form of allergy or auto-allergy may be implicated.

The natural history of the disease is usually benign, but some of the patients have died from intercurrent disease; in 13 necropsies evidence has been found that internal adipose tissue other than the panniculus has been affected by the same inflammatory process. The 'systemic' lesions are clinically silent, or almost so, and have usually been found only at necropsy (Milner and Mitchinson, 1965).

SYSTEMIC WEBER-CHRISTIAN DISEASE AND SYSTEMIC IDIOPATHIC FIBROSIS

There are several facts which suggest a relationship between systemic Weber-Christian disease and systemic idiopathic fibrosis.

There is a striking correspondence in anatomical distribution of these conditions. Systemic Weber-Christian disease is usually found within the retroperitoneal fascial compartment (Figs. 1 and 3) but frequently also involves other sites including the mediastinum, perisplenic tissues, and mesentery. Occasionally adipose tissue around the bowel, pericardial adipose tissue, and the region of the urinary bladder neck have been affected. As far as I am aware all areas of the body affected by systemic idiopathic fibrosis have also been involved in reported cases of systemic Weber-Christian disease.

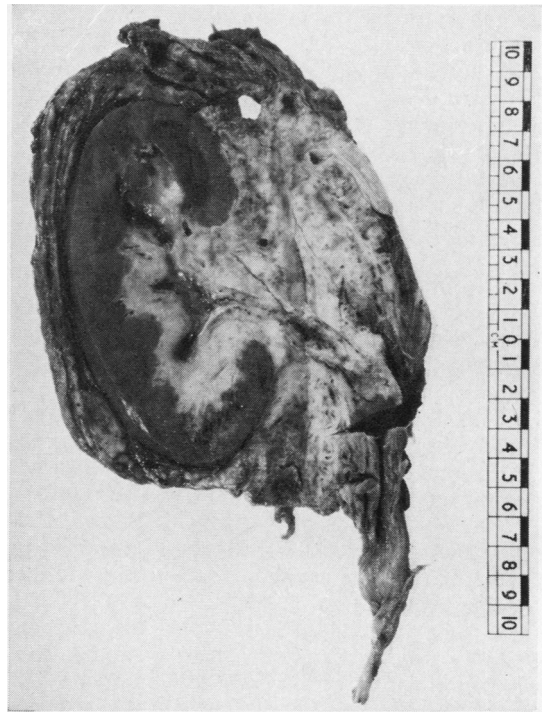

FIG. 3. *Anterior half of left kidney, ureter, and surrounding tissue in systemic Weber-Christian disease (Milner and Mitchinson, 1965).*

The second point of resemblance is that organs contiguous with the diseased adipose tissue are similarly affected in both disorders. Veins running through the affected area are often inflamed and thrombosed in systemic Weber-Christian disease and may be invaded and organized in systemic idiopathic fibrosis. The kidney, ureter, lymph nodes, nerves, and skeletal and cardiac muscle are occasionally infiltrated superficially; the suprarenal capsule and the peritoneum seem to be resistant to both processes.

The late, fibrotic stage of a nodule of Weber-Christian panniculitis often differs only slightly in its histological appearance from idiopathic fibrosis. Lymphocytes are the predominant infiltrating cells within and near the fibrotic areas.

A condition similar or identical to Weber-Christian disease has been described affecting only the mesentery, in the absence of nodules in the subcutaneous adipose tissue. It has been called 'isolated mesenteric lipodystrophy' (Herrington, Edwards, and Grossman 1961) or 'mesenteric panniculitis' (Grossman, Kaplan, Preuss, and Herrington, 1963). The view has been expressed that localized fibrosis of the mesentery, seen in 'retractile mesenteritis' is the result of healing of this form of Weber-Christian disease; retractile mesenteritis may be indistinguishable from mesenteric involvement in systemic idiopathic fibrosis.

Slight degrees of hypothyroidism are common in Weber-Christian disease (Bendel, 1949); necropsy reports have mentioned chronic thyroiditis with thyroid antibodies (Milner and Mitchinson, 1965) or atrophy and fibrosis of the thyroid (Schoen, Reingold, and Meister, 1958). Hypothyroidism is not uncommon in systemic idiopathic fibrosis, and there is some evidence that Riedel's struma, thought by some to be the result of Hashimoto's disease (Vaux, 1938), is associated and may share a common cause with systemic idiopathic fibrosis (De Courcy, 1942; Haché, Woolner, and Bernatz, 1962; Bartholomew, Cain, Woolner, Utz, and Ferris, 1963; Hardmeier and Hedinger, 1964). The possibility that autoallergic disease of the thyroid may progress to fibrosis, in association with development of systemic idiopathic fibrosis from systemic Weber-Christian disease, is worthy of particular attention.

'Sclerosing cholangitis' is the name given to a condition in which there is biliary obstruction due to fibrosis of unknown cause around the biliary tree, sometimes extending into the intrahepatic biliary tracts. It has also twice been reported as coincident with systemic idiopathic fibrosis (Haché, Utz, and Woolner, 1962, Bartholomew *et al.*, 1963). In one necropsy report of systemic Weber-Christian disease, there was around the extra and intra-hepatic bile ducts a granulomatous inflammatory process similar to that seen in the adipose tissue elsewhere in the body (Arnold and Bainborough, 1963). This process might, like mesenteric panniculitis, heal by fibrosis and may therefore produce a histological appearance indistinguishable from sclerosing cholangitis.

Peculiar lung lesions have been described in three examples of systemic Weber-Christian disease (Schoen *et al.*, 1958; Arnold and Bainborough, 1963; Milner and Mitchinson, 1965). Although similar or fibrotic lesions have not been described in systemic idiopathic fibrosis, the coincidence of vague and transient pulmonary signs with idiopathic retroperitoneal fibrosis was thought by Hoffman and Trippel (1961) to support some type of allergic origin for the fibrosis.

Inflammation of small arteries and arterioles is a common finding in systemic Weber-Christian disease and occasionally also in systemic idiopathic fibrosis. Indeed in both conditions widespread arteritis has been suggested as the cause by those who have seen examples of the widespread forms of the disease (*e.g.*, Kay, 1963).

DISCUSSION

Both systemic idiopathic fibrosis and systemic Weber-Christian disease are conditions in which adipose tissue is predominantly but not exclusively involved. They appear to spread to various parts of the body in a similar way; and allergy or autoallergy, perhaps associated with arteritis, have been suggested as possible causes for both.

The similarities are striking, but of course inconclusive. First, to conclude that either disease is a disease of adipose tissue because adipose tissue is predominantly affected might be as naïve as to conclude that rheumatoid arthritis is a disease of synovium.

Secondly subcutaneous lesions, a feature of all cases of systemic Weber-Christian disease so far described, are absent in idiopathic systemic fibrosis. However, it is likely that systemic Weber-Christian disease would not be recognized by clinician or perhaps even pathologist in the absence of subcutataneous lesions. Exceptions are systemic Weber-Christian disease producing symptoms (of which 'mesenteric panniculitis' may be an example) and systemic Weber-Christian disease in its late stage of fibrosis, producing secondary effects on nearby organs.

Thirdly the sex incidence is different, systemic fibrosis affecting more males than females, Weber-Christian disease more females than males.

However, the hypothetical linkage of the two diseases is profitable if only to emphasize the wide-

spread changes which may occur in idiopathic systemic fibrosis, in particular its possible association with Riedel's thyroiditis. Viewed in this perspective, similarities to allergic or auto-allergic conditions become apparent; and questions are raised of relationships with other fibrotic conditions, *e.g.*, Peyronie's disease, Dupuytren's contracture, keloid, pulseless disease, idiopathic pulmonary fibrosis, and pseudo-tumour of the orbit. In addition it becomes apparent that comprehensive investigation and particularly detailed post-mortem examination is indicated in all cases of idiopathic fibrosis.

Finally, and perhaps most important, is the exposure of our ignorance of the pathogenesis of not only systemic Weber-Christian disease but also the other similar diseases of adipose tissue and its blood vessels. Similarities to the 'collagenoses' are evident; but many more clinical, necropsy, and experimental observations are needed to elucidate a group of disorders which demand attention not only for their own sake, but also for the better understanding of all the diseases of mesenchyme.

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The author is at present collecting data on cases of idiopathic fibrosis in characteristic distribution, and would be grateful for opportunities to examine clinical and pathological material from any source.

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