CHAPTER 17

Scleroderma

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The term scleroderma was first used by Gintrac in 1847, but clinical conditions probably corresponding to scleroderma had already been mentioned much earlier in the literature. Thus Zacuti not only first described the condition clearly in 1634, but also recognized the visceral involvement.

Scleroderma is a disease in which the clinical picture is dominated by skin changes; in addition to visceral disorders, signs of neurological defect are almost constant. The cause of the disease remains obscure. At present, scleroderma is assigned to the group of collagenoses. Although the course of the disease in the circumscribed form known as morphea is favourable and restoration sometimes is the rule, the generalized form of diffuse scleroderma or progressive systemic sclerosis leads to death after an average of 10–20 years through a variety of complications, especially those affecting the lungs, kidneys, myocardium and gastrointestinal tract.

Patients with scleroderma are usually treated by dermatologists or, if visceral disorders predominate, by specialists in internal medicine.

The complications affecting the nervous system tend to receive too little attention, although lesions of muscles and peripheral nerves are constantly present while signs of cerebral and spinal cord lesions are seen in advanced cases. The terminal stage of scleroderma is usually marked clinically by acute cerebral failure in the setting of an endotoxic coma.

The incidence of scleroderma is generally underestimated, but represents about 1–2% of cases seen in a dermatology department (Korting and Holzmann 1967a). The clinical picture of scleroderma, however, has an interest for social medicine also. Medical historians have noted that Paul Klee suffered repeated attacks of scleroderma, painted features of scleroderma in his pictures, and himself demonstrated in a self-portrait the classical features of scleroderma.

DEFINITION

Two forms can be distinguished by the signs and symptoms and by the course; these are the progressive and circumscribed or localized forms, the latter being also known as morphea. The progressive form of scleroderma is, as the name implies, progressive with a variety of visceral manifestations accompanying the progressing skin changes. The lungs, kidneys, upper gastrointestinal tract and myocardium are particularly affected. Circumscribed scleroderma or morphea is a benign disorder which in most cases leaves only traces.

In both forms, the age distribution lies between 40 and 60 years. Whereas in morphea there is no significant sex prevalence, (according to Korting

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and Holzmann 1967a, the proportion of affected women to men is 1:1.5), in progressive scleroderma there is a marked preponderance of females, with a sex distribution of 3 to 1 (Tuffanelli and Winkelmann 1961; Korting and Holzmann 1967a).

The duration of illness in progressive scleroderma lies between 5 and 20 years. Ten or 15 years ago the illness invariably leaded to death, at an average age of 46.2 years (Schuermann 1959; Tuffanelli and Winkelmann 1961; Gottron and Korting 1963). Patients with circumscribed scleroderma are affected for periods ranging from a few months to a few years, and expectation of life is not diminished (Korting and Holzmann 1967a).

DIFFERENTIAL DIAGNOSIS

A number of differential diagnostic factors need to be taken into account in scleroderma because of its classification within the collagen diseases and also from the viewpoint of enzymology.

Etiologically, dermatomyositis and lupus erythematosus must be differentiated within the collagenoses. Table 1 indicates the sex distribution, age, earliest manifestation, average duration of illness, average age of death, involvement of visceral organs, and pathogenesis in general. As the table shows, there is a predominance of females in all three collagen diseases. The first signs in dermatomyositis and acute lupus erythematosus appear earlier, in fact in middle age, whereas scleroderma begins from the fifth decade on, apart from the paediatric forms. The duration of illness is shortest in dermatomyositis, but the average age at death is lowest (46 years) in scleroderma. Visceral involvement is prominent in scleroderma. Table 1 sets out the differences in pathogenesis which range from neurovascular causes in scleroderma through enzyme disorders in dermatomyositis to immunological disturbances in acute lupus erythematosus. Sleroderma is characterized by an increased incidence of other malignant diseases, although dermatomyositis may also be combined with malignant neoplasms.

TABLE 1

Comparison of sex preference, age at onset, duration of course, visceral involvement and presumed pathogenesis of sclerodermia, dermatomyositis and lupus erythematosus. (Modified from Margraues et al. 1948; Schuermann 1959; Korting et al. 1962; Gottron and Korting 1963; and Korting and Holzmann 1967.)

	Sclerodermia	Dermato-myositis	Lupus erythematosus
Sex preference	♀	♀	♀
Average age at onset	40–60 years	20–30 years	30 years
Average duration of clinical course	6 years	12 months	6 months
Visceral involvement	kidney, myocardium, upper gastrointestinal tract, lungs	myocardium, sceletal muscle	joints, serous membranes kidney, myocardium
Pathogenesis	neurovascular	enzymological	abnormal antibody

Morphologically, there are a number of diseases of the skin which resemble scleroderma, and can appear either in generalized or localized form. These include Buschke's scleroedema adultorum, Werner's syndrome (progeria adultorum), the sclerodystrophies and even rheumatoid arthritis. In the circumscribed form of scleroderma the differential diagnosis includes in particular chronic dermatitis atrophicans. Raynaud's syndrome presents a differential diagnostic problem especially in the early phase of scleroderma.

Etiology of scleroderma

As Rodnan emphasized 'the etiology of PSS (progressive systemic sclerosis) is still obscure, but during the past few years the demonstration of a variety of serological abnormalities and of certain cellular immune reactions in a high percentage of patients has given rise to the suspicion that immunological mechanisms play an important role in the pathogenesis of PSS'. As indicated above, scleroderma is assigned to the groups of collagenoses. This group includes a number of clinical conditions which possess a morphological similarity based on changes in the intercellular ground substance of the connective tissue but have a different etiological basis. To

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this group belong for example the Ehlers–Danlos syndrome and the mucopolysaccharidoses, but especially acute lupus erythematosus and dermatomyositis. Among all these diseases, particular symptoms predominate.

The question of inheritance is of prime importance in cases of scleroderma but opinions on this are sharply divergent. In recent years, however, there is a tendency to accept a multifactorial type of hereditary transmission (Jörgenson 1965). The consequence of this may be the appearance of molecular protein structures genotypically determined and predisposing to certain pathological changes. The haptoglobins should be mentioned in this connection; their carbohydrate moiety is probably synthesized in the connective tissues. They are finally deposited in the ground substance of collagenous connective tissue and probably have an influence on the stability of connective tissue fibres (Jayle 1956; Mathis et al. 1963). In human subjects in contrast to animals, these haptoglobins not only show marked polymorphism (Baitsch 1961) but are also very subject to hormonal influences (Wuhrmann and Märki 1963). Thus, in relation to the distinct predilection of the disease for the female sex, the fact that the serum concentration of haptoglobins falls with oestrogens and rises with androgens, should be stressed (Korting and Holzmann 1967a). However, no specific changes in haptoglobins or other serum proteins have been demonstrated in scleroderma (Korting and Holzmann 1967a), nor are there any characteristic and reproducible immunopathological changes. Although these authors have described immunoelectrophoretic changes, increases and decrases in gammaglobulins, decrease in albumin, etc., the pattern of protein disorders is on the whole nonspecific and in the final analysis related to the acuteness and extension of the disease (Fleischmajer 1964; Brehm 1965; Stachów and Jabłońska 1965; Fanconi 1966). Equally nonspecific are the rise in Sabin–Feldman titre (Dymowska and Mazurkiewicz 1965) probably caused by nonspecific antibodies, the appearance of LE cells (Myer et al. 1967) and antinuclear factors (Meyer et al. 1966), and the delay in skin response to autologous leucocytes (Tuffanelli 1964). The latter changes are more common in lupus erythematosus, and only occasionally seen in scleroderma. They are transient phenomena and related to auto-sensitization that can occur with all kinds of disease. Some authors have also demonstrated antibodies against collagen (Beck et al. 1963) but these findings were very irregularly present in progressive scleroderma and also observable in other disorders of connective tissue. Finally, the demonstration of fluorescent antibodies in serum has given no reliable indication as regards pathogenesis (Fisher and Rodnan 1960). It might be added that not only collagen, but also its individual fractions such as denatured collagen, can give rise to specific antibody formation, which will in turn prevent fibre formation from soluble collagen in vitro (Watson et al. 1954; Paz et al. 1963).

In order to gain information about collagen and its physiological and pathological structure, a substance has been studied which occurs almost exclusively in collagen in high concentrations. This substance, hydroxyproline, is also present, mostly combined with peptide, in serum, plasma and urine. Only a very small percentage occurs as the free amino-acid (Meilmann et al. 1963; Laitinen et al. 1966; Nusgens and Lapiere 1973). Comparison of the two values yields information about the momentary metabolic situation of collagen. However, the sensitivity of serum or urine estimations of hydroxyproline depends on the dietary intake of collagen, for example in the form of gelatin (Dull and Henneman 1963). The values are also age-specific and determined by bone growth or loss of collagen synthesis with age (Korting and Holzmann 1965; Grassmann et al. 1965). Because of these factors, correlation of a raised hydroxyproline level with different skin diseases is impossible (Korting and Holzmann 1967a; Nusgens and Lapiere 1973). This is particularly true of scleroderma, in which values are usually normal. The only exception to this is the exudative-inflammatory initial phase, rather often seen clinically. There is, however, a definite relationship to rheumatic diseases, especially respecting the acuteness and extent, and also to diseases of bone (Hartmann 1966). This is due to the high proportion of osteoid collagen (about 55% of total collagen) and its higher turnover rate than that of connective tissue collagen (Gould et al. 1960).

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In addition to hydroxyproline, Korting and Holzmann (1967a) were able to demonstrate by fractionated protein precipitation and electrophoresis a collagen-like protein which behaves like the alpha-beta globulin fraction (Frey et al. 1965). These findings suggest that there is a collagen fraction soluble in serum. It is apparently uncertain as yet what place collagen-like protein occupies in collagen metabolism, but there are indications of a correlation with the metabolically active fraction of collagen. Collagen-like protein is probably an intermediate product in renal transport (Morsches et al. 1967).

In contrast to hydroxyproline, collagen-like protein depends neither on dietary factors nor on age (Le Roy and Sjoerdsma 1965) but is significantly increased in episodic and progressive diseases of bone and connective tissue. The concentration is said to be lowered in scleroderma (Korting and Holzmann 1967a).

In association with the deficiency of proteolytic enzymes succinate dehydrogenase and alkaline phosphatase (Steigleder et al. 1963), the concentration of collagen-like protein in serum (Holzmann et al. 1967b) and of hydroxyproline in urine are indications of disordered and retarded collagen metabolism (Korting and Holzmann 1967a).

Symptoms and signs of scleroderma

In both forms of scleroderma, the skin changes are prominent in the clinical picture. The latter shows distinct differences both in location and in appearance. In the progressive form, the accompanying visceral symptoms and signs are well to the fore, whereas in circumscribed scleroderma or morphea only the muscular involvement is apparent clinically. The main difference between the two forms lies with the clinical course.

SYMPTOMS AND SIGNS OF PROGRESSIVE SCLERODERMA

In the initial stage of the progressive form the patients complain of tiredness, exhaustion, headache with a sensation of pressure, feverishness, increased sweating, seldom lacrimation and salivation; mental symptoms include insomnia and depression. In this stage there is often an erythema with telangiectases.

The first typical complaints are of fainting and of circulatory deficiencies in the fingers and toes which at first are discontinuous and resemble the lesions in Raynaud's syndrome (Pratesi et al. 1976). The skin changes later lead to fingertip necroses resembling ratbites. After a phase, lasting for years, like a scleroedema, a stage of induration is reached.

Visceral involvement is frequently first made apparent by mucosal changes with pigment disorders in the oral and genital areas. These may take the form of hyperpigmentation or depigmentation, and the affected areas may be linear or patchy; they end in sclerosis of the affected mucosa.

Parallel to the skin changes, early injury to muscle is observable, mainly under the primarily damaged skin areas. During the course of the disease the muscular atrophy and skin lesions are related in their shape and location; this fact is partly responsible for the characteristic appearance of patients with scleroderma (Fig. 1a).

The involvement of internal organs begins independent of the skin changes but mostly in the same time. Myocardial lesions and fibrotic changes in the lung parenchyma are prominent. Vascular lesions develop in the kidneys, and mucosal lesions in the gastrointestinal tract, especially in the oesophagus.

Lesions of the peripheral nerves, which particularly affect the terminal reticulum and are manifest clinically as a polyneuritis, and disorders within the central nervous system (CNS) due to changes in the supportive tissue and vessels, also appear later than the skin lesions. Additional secondary lesions affecting the peripheral nervous system, spinal cord and brain result from malnutrition and malabsorption. Finally, in the terminal stage of the progressive form of scleroderma there are endotoxic lesions of the brain, spinal cord and peripheral nerves.

SYMPTOMS AND SIGNS OF CIRCUMSCRIBED SCLERODERMA (MORPHEA)

As mentioned above, morphea tends to be an episodic disease which only occasionally becomes

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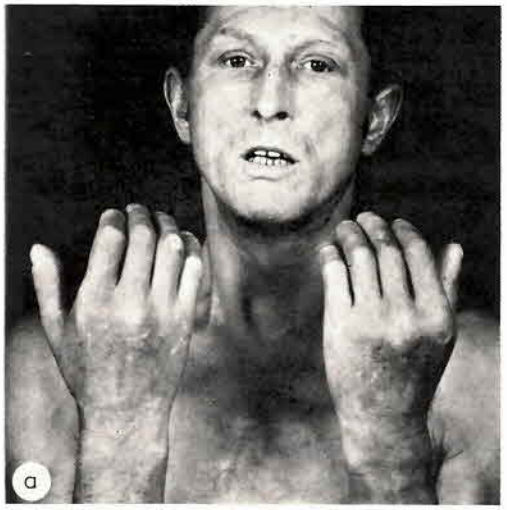

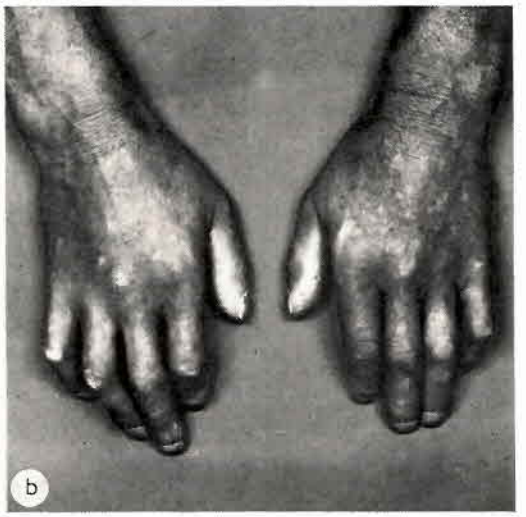

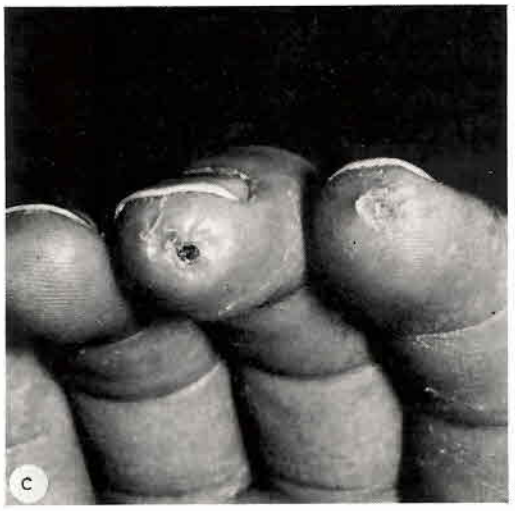

Fig. 1. (a) Sclerodermatous tightness of the acral and facial skin leading to immobility of the fingers and microstomy. (b) Sclerodactyly with necrotic lesions over interphalangeal joints and mattled hyper- and depigmention. (c) Typical 'rat bite' necrosis of fingertips.

generalized or is transformed into a progressive scleroderma. Symptoms and signs usually develop within a few weeks and may last for several years. A wide variety of preceding conditions, some of which may be related etiologically, has been reported (trauma, burns, febrile infections, stress situations and neuritis).

SKIN CHANGES IN SCLERODERMA

The main aids to the differential diagnosis of the two forms of scleroderma and their subgroups are assessment of the skin lesions and their development. The prognosis and therapeutic approach depend entirely on this.

Skin changes in progressive scleroderma

The most important distinction is between a form affecting the extremities with a better prognosis and the rheumatoid arthritic type, also designated as malignant scleroderma by Stava in 1959. Whereas the form affecting the fingers and toes begins like a Raynaud syndrome, the first skin lesions in the rheumatoid arthritic form tend to appear on the trunk and the proximal parts of the limbs.

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The form affecting the extremities begins with coldness and cyanosis of the fingers and toes either continuously or episodically (Pratesi 1976), followed by formation of necrotic areas on the fingertips resembling ratbites (Fig. 1c). After a rapid transition through a scleroedema-like phase and a phase of induration with an increase in consistency of the dermis giving a waxy appearance with a mirror-like sheen, the dermis becomes fused with the firm tissues underneath and lastly firmly attached with the bone, thus greatly impairing motility (Fig. 1b).

Changes in the distal parts of the limbs result from these developments. The so-called Madonna fingers arise, to which deformities resembling birds' claws may be added. In the end stage a fixed flexion deformity on the fingers is present. These changes are also known as sclerodactyly. During the further course of the disease similar skin changes also take place in the face; these are first expressed by loss of mimicry and later by contraction of the mouth.

In the rheumatoid arthritis-like form there is at first a very rapid crop of spots on the trunk and proximal parts of the limbs. These later unite to form larger foci. Rarely, in addition, telangiectases, punctate haemorrhages, or lentil-sized nodules form (Lipschütz 1913) or even bullous or ulcerative lesions. Vitiligo-like patches of depigmentation may appear or areas of hyperpigmentation, the latter of so-called quilloche character. It is also very common, especially in women, to find calcified deposits in the skin; Gottron (1937) and also Brehm and Heinzel (1964) have suggested that circulatory disorders are responsible for these. Growth of hair also seems to be disturbed, and in addition to an alopecia or pseudopelade (Grupper 1965) may appear on the trunk. In contrast, an increase in hair growth on the limbs has been observed (Leinwand et al. 1954).

Skin changes in scleroderma circumscripta (morphea)

Three distinct groups can be recognized clinically in circumscribed scleroderma, the discoid form (scleroderma en plaques), the linear or band form (coup de sabre) and the small focal variants. In general, all three forms show a characteristic development, with subacute erythema at the beginning. This shows progressive blanching towards the centre with a so-called lilac ring. The next stage is one of induration with a phase of scleroderma lardacea followed by atrophy. When the lilac ring is dominant and the induration regresses, the expression scleroderma liliacée pure (forme liliacée non indurée) has been used (Gougerot et al. 1936). If there is no induration, the condition is called morphea plana atrophicans. This is very similar to the atrophodermia of Pasini and Pierini.

Special forms worthy of mention include subcutaneous scleroderma, in which there are palpable deep subcutaneous infiltrates. Weissenbach and Bash (1938) described a tuberose, and Unna (1931) a keloid-like scleroderma. It very rarely appears in transitional stages to a bullous form. The latter, known as morphea bullosa or pemphigoid morphea, is due to added lymph stasis, especially in the lower limbs. Subepidermal blisters form as a result of an increase in interfibrillary oedema (Alkiewicz and Sowinski 1963). The bullae may also ulcerate. It is notable that this form of morphea favours the female sex. If typical bullae remain absent but a honeycomb formation develops, Nekam (1936) has suggested the term pseudobullous scleroderma.

As stated above, three clinical groups exist in morphea. In the first, the discoid form, the term is self-explanatory. The second, linear or band form is mostly found in the paramedian area of the forehead, more rarely on the limbs. Since it occurs mainly in children, limb growth may be endangered especially if a scleroderma annularis or mutilans is present with subsequent strangulation and mutilation. The course is also different from that in other forms in that development is slower and the tendency to regression less. The increased incidence of spina bifida occulta with this form is notable, but there is no definite connection with a particular segmental innervation. The linear form of morphea is very commonly combined with Romberg's facial hemiatrophy but the two do not form a diagnostic unit, since hemiatrophy may follow an encephalitis or trauma (Tuffanelli et al. 1966).

The small focal variants of morphea show mul-

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tiple disseminated changes, sometimes with grouped areas of induration but sometimes with only a lilac ring in miniature. Very rarely are these varieties generalized.

In addition to the above skin lesions, conspicuous symptoms and signs include increased loss of hair, telangiectases, diminished sweat and pilomotor reactivity and pruritus, as well as hypoaesthesia, hyperaesthesia and paraesthesiae, especially in the affected skin areas.

Histological findings in scleroderma

No essential differences between progressive scleroderma and morphea can be demonstrated by light and electron microscopy. However, in morphea there are definite indications of muscle involvement in the form of sclerosis, myositis and atrophy in the adjacent muscle layers (Bolgert et al. 1962; Bureau et al. 1963; Jabłońska 1963; Témime et al. 1963; Hadida et al. 1964). Linear scleroderma is also accompanied by bone atrophy, hyperostosis and osteoporosis.

Light microscopical examination of the integuments reveals no essential difference between the circumscribed and the progressive forms of scleroderma, but the blood vessels are less affected in morphea. In the foreground of the microscopically visible changes, are sclerosing and homogenizing processes in the collagen bundles (Unna 1931).

Whereas in morphea the first sclerotic changes are in the dermis, perivascular sclerosis is the primary event in acrosclerosis (sclerosis of the distal extremities) according to Ishikawa et al. (1967).

Towards the edge of the lesions are accumulations of cells, with lymphocytes, histiocytes, and fibrocytes prominent and mast cells and plasma cells rare (Fig. 2).

The connective tissue appears relatively a cellular and run parallel to the surface while the collagen fibres remain undamaged and therefore appear to be relatively increased, especially in progressive scleroderma. There is only mild splitting and fracture (Winer 1955). Later, the changes re-

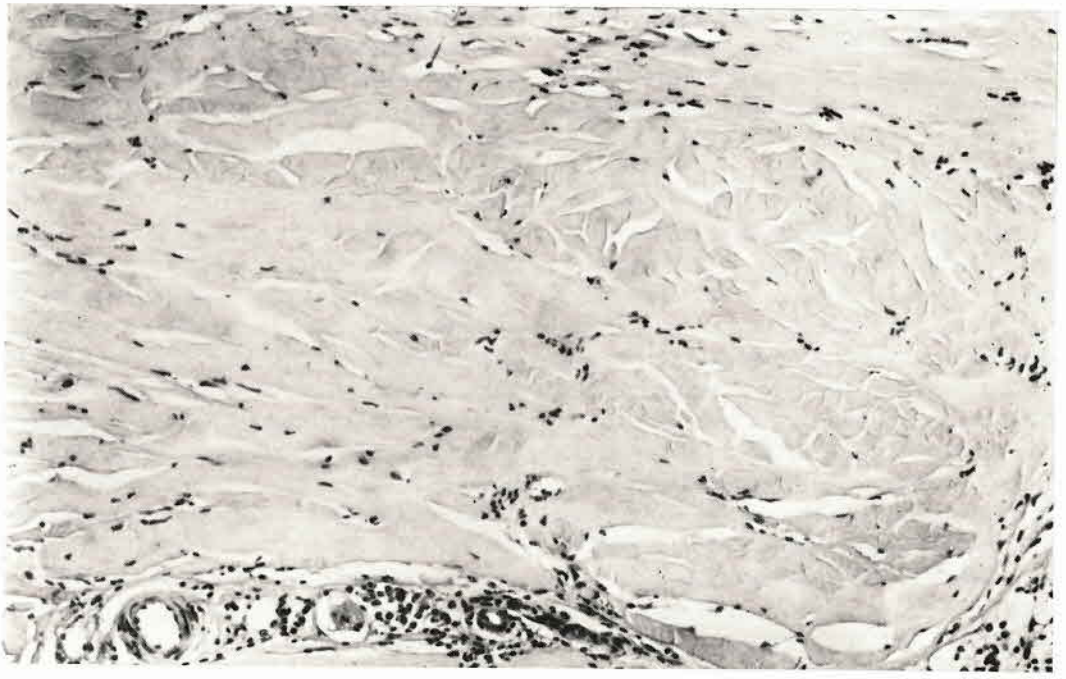

Fig. 2. Sparse perivascular lymphocytic infiltrates, increase and homogenization of collagen bundles and a reduction of the number of fibroblasts.

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gress in the epidermal-subepidermal area, with ectasia and cystic dilatation of the lymph spaces. Pressure atrophy affects the skin appendages such as sweat glands and sebaceous glands. In contrast, the hair follicle musculature appears to be very resistant and seems pseudohypertrophic.

In the early stages, the vessels are dilated, more obviously in the progressive form than in morphea, while later, thickening of the walls including the vasa nervorum takes place so that a typical absence of capillaries increasing with the depth of the stratum papillare, becomes evident (Kurban et al. 1964). In the epidermis, the only notable features are mild loosening of the rete and a decrease in melanin pigmentation towards the periphery of the lesions.

Neurohistologically, there is in morphea a close connection between the dendritic cell elements of the epidermis and the Schwann cells of the terminal reticulum in the nervous system (Ishikawa and Klingmüller 1964). This is probably based on a reactive increase in Schwann cells (John 1949; Ormea 1952) with simultaneous increase in the dendritic cell elements in the epidermis. In addition, Schwann nuclei are multiplied in the major plasma spaces, while there are indications of destruction in the receptor areas, both in the affected and in the healthy skin (Pawlowski 1963). Similar changes in the terminal reticulum are seen only in the foci of lichen sclerosus et atrophicus (Zierz and Kantner 1958).

Histochemically, the dermal-epidermal junction shows slight PAS reaction, while in the area of the superficial and deep skin vessels in the sclerotic areas, there is a demonstrable PAS-alcian blue reaction. This very probably represents a deposition of acid mucopolysaccharides in the vascular region. Braun-Falco (1957) has suggested that the latter are also laid down between the fibrils in the collagen fibres, but this is more likely to occur in the acute phases.

Under the electron microscope, the collagen fibrils mostly have a normal structure (Rupec and Braun-Falco 1964) as regards periodicity and transverse striation. However, an increased incidence of thinner but otherwise unremarkable fibrils is observable as an ultramicroscopical substrate to the sclerosis (Korting et al. 1965).

EXTRACUTANEOUS MANIFESTATIONS OF SCLERODERMA

The characteristic of scleroderma is the involvement of certain internal organs, particularly the lungs, heart, circulatory system and gastrointestinal tract (Vlk and Dolinsky 1974). Nevertheless, other organs such as the liver, kidneys, skeleton and musculature, as well as the sense organs, (eyes, ears) and the central and peripheral nervous system, may be affected. There is no correlation between severity and extent of skin disease on the one hand and visceral involvement on the other. In fact, organs may be involved before the skin changes appear (progressive systemic sclerosis sine scleroderma, Rodnan and Fennel 1962).

Changes in visceral organs in scleroderma

The lungs, cardiovascular system and gastrointestinal tract are particularly affected and most frequently the liver and kidneys. Involvement of these organs and systems leads to a series of secondary effects that can seriously influence the course of progressive scleroderma by causing metabolic disorders, malnutrition and ischaemic injury. The appearance and course of skeletal and muscular complications are both subject to laws of their own in both forms of the disease. This is also true of the CNS, which is of course most affected by secondary lesions.

Lung involvement. In approximately 24–25% of patients (Tuffanelli and Winkelmann 1961; Fischer 1963), a diffuse interstitial lung fibrosis with typical radiological (Getzowa 1945) and spirometric findings (Fischer 1963) develops, even in the initial stages of the disease. Parallel to this, a pulmonary hypertension develops which may lead to a right-sided cardiac hypertrophy (Sackner et al. 1964).

After a history of recurrent pleurisy, the patient develops typical symptoms and signs of pulmonary fibrosis with dyspnoea and demonstrable change in total and vital capacity, and in maximum breathing capacity with normal minute volume and diffusion capacity. Residual volume is within normal range or slightly reduced. These disorders are an expression of constriction, rig-

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idity and disturbance of diffusion in the lungs. The radiograph shows linear changes at first; later there is reticular shadowing with small or large cystic translucencies.

Cardiovascular involvement. Estimates of the incidence of cardiac involvement in scleroderma patients vary between 9 and 21% (Oram and Stokes 1961; Tuffanelli and Winkelmann 1961). The commonest signs are disorders of rhythm together with right axis deviation of the QRS complex and low voltage in the electrocardiogram (ECG), as well as the symptoms of cardiac failure with hepatomegaly and dyspnoea (Hurly et al. 1951; Stava 1958; Demidova et al. 1971). Oedema is rather uncommon and not too obvious in view of the skin sclerosis. At autopsy, fibrinous pericarditis as well as myocarditis and valvular sclerosis may be present (Middleton 1962; Sackner 1966; Cosh 1972).

In progressive scleroderma, the changes in the vascular system take the form of an acute or subacute arteritis, most marked in the deep tissue layers of the internal organs (Cosh 1972). The changes in the digital, coronary and cerebral arteries are especially striking, closely resembling a thrombangitis. An acute necrotizing arteritis is common in the area of the renal arterioles.

Peripheral circulatory disorders can be demonstrated technically in the fingers and legs in diffuse scleroderma, but do not appear as primary vascular lesions in localized scleroderma (Munter 1963).

The cardiovascular disorders in scleroderma lead to a series of secondary and tertiary lesions in the nervous system, especially circulatory disorders in the brain and spinal cord. Histologically, there is an arteritis with thickening and homogenization or hyalinization of the arteriolar walls and consequent narrowing of the lumen. Under the electron microscope, thickening of the basal membrane is particularly marked (Holzmann et al. 1967a).

Renal involvement. Apart from the development of renal hypertension, renal symptoms and signs usually appear in the terminal weeks of the disease. A terminal uraemic state may be induced by an acute pyelonephritis (Kreysel 1966). Bourne et al. (1960) described a patient in acute uraemic coma with midbrain and medullary signs, in whom severe vascular changes in the brain were later demonstrated.

In addition to the changes of pyelonephritis, there are pathological signs of a malignant nephrosclerosis with mucoid impregnation (Urai et al. 1958; Hoerini 1960).

Gastrointestinal involvement. Visceral manifestations of progressive scleroderma in the gastrointestinal tract are quite commonly observed. In one series, gastrointestinal involvement was found in up to 90% of cases, but there were differences in location. The oesophagus is most commonly affected (over 50%, according to Tuffanelli and Winkelmann 1961), and patients complain of dysphagia and retrosternal pain. Lesions in the rest of the gastrointestinal tract lead to anorexia, epigastric pain, vomiting, constipation, and sometimes to symptoms of ileus.

Radiologically, disorders of motility (Tatelman and Keech 1966) and localized areas of dilatation above isolated strictures (Olsen and Schlegel 1973) are demonstrable.

Pathologically, the oesophagus shows areas of epithelial thickening and of epithelial deficiency with fibrosis of the submucosa and muscularis. In the gastrointestinal tract, the most obvious finding is of a smooth, atrophic mucosa with otherwise fairly similar changes in the wall (Orabona and Albano 1959). These changes are of special importance because as a result there may be disorders of secretion with consequent malabsorption and digestive dysfunction and its sequels (Cliff et al. 1966; Bjerregaard and Jgaard 1976). This is of particular significance in relation to lesions of the peripheral and CNS.

Involvement of liver, pancreas and spleen in progressive scleroderma. Various authors have reported involvement of the liver (Boyd et al. 1954; Tuffanelli and Winkelmann 1961; Sackner 1966; Korting and Holzmann 1967a). Hepatomegaly alone may be simply due to right heart failure, but if there is also a demonstrable liver fibrosis this may be due to widespread sclerosis or to malnutrition and malabsorption (Ormea and Aprà 1955; Bartholomew et al. 1964). Symptoms and

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signs of liver involvement are characterized by the liver parenchymal insufficiency. The most evident laboratory finding is a change in serum proteins (Jablońska and Szczepanski 1975).

Pancreatic involvement with focal induration and fibrosis is very rare, as is intimal fibrosis of pancreatic arterioles (Piper and Hellwig 1955). This may lead to the appearance of a diabetes mellitus (Fleischmajer et al. 1970).

Splenic involvement becomes manifest in the form of a Banti syndrome with sharp pain in the side, sensation of fullness, splenomegaly, hypochromic anaemia, leucopenia, thrombopenia and lymphopenia, and gastrointestinal haemorrhage. These are followed by subicterus, ascites, raised temperature and cachexia.

Histologically, there is sclerosis of the splenic pulp, and vascular changes in the media and adventitia, together with collagen deposition and periarterial fibrosis (Skouby and Teihun 1950; Yarchumian and Kleinerman 1959).

Involvement of sense organs

In the sense organs, affection of the eye and of the hearing apparatus is known but the vestibular apparatus seems not to be touched.

Ocular involvement. Ophthalmologically, keratoconjunctivitis sicca (Bessi et al. 1972) and individual pareses of ocular muscles have been described; the latter are partly based on a myasthenic disorder (Mukuno 1971; Arnett and Michels 1973; Egerer and Fanta 1976). In addition, bilateral luxations of the lens can occur (Sackner 1966).

At an age roughly between 40 and 50 years, bilateral cataracts usually develop; these take the form of a presenile radial cortical cataract (Gärtner et al. 1967). Multiple areas of vitreous destruction have been described (Gärtner et al. 1967), while degenerative foci and arterial occlusions appear in the retinal area (Sacks 1976).

Involvement of the hearing apparatus. Because of the rigidity of the drum and suspensory ligaments of the ossicles, a conductive deafness develops. It has been debated (Brandstetter and Koehler 1953) whether the sensory epithelium of the organ of Corti atrophies and the connective tissue of the tectorial membrane is involved. Changes in th voice, due to thickening of the squamous epith lium of the vocal cords (Rossier and Hegglin Volkmann 1954) and caused by increasing dry ness of the mouth, has been reported and bilater parotid swellings have been described (Kortin and Holzmann 1967a).

Changes in the musculoskeletal system

Musculoskeletal changes can be demonstrated i a high percentage of cases. Involvement is preser in at least 50% of patients with progressiv scleroderma.

Changes in the skeletal system. Scleroderma frequently accompanied by osteolysis and atroph in the bones of the extremities and by dissociate bone absorption in the terminal phalanges. Ma donna fingers are also commonly simulated b thickening of the proximal soft parts due to pachydermatosis. Arthropathies with destructio amounting to mutilation are especially seen i small joints (Rodnan 1962). These arthropathies scleroderma can be grouped into pseudoarthr pathies with inflammatory periarticular and in flammatory polyarthritic changes (Freneau 1962).

Changes in the muscles. Clinically, the commone features are those of a primary myopathy. Th muscle atrophy may precede muscle weaknes and the atrophic appearance may be enhanced b the disappearance of the subcutaneous fatty ti sue and by atrophy due to inactivity. Especially the progressive form of scleroderma, there a often features resembling myasthenia and the may in some circumstances be confined to ind vidual muscles or muscle groups (Korting an Holzmann 1965).

Neurologically, there are no changes in reflex unless a peripheral neuron has been injured. O the sensory side, dysaesthesias and hypaesthesi may be demonstrable but it is never possib to relate these to a segment and seldom to peripheral nerve. Sensory change is usually co fined to an altered skin area (Herrman

The silent enzymes such as SGOT, SGPT, 196

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aldolase, CPK and myokinase are mostly elevated and certainly of differential diagnostic value, including phosphoglucose isomerase which shows significantly raised serum values (Holzmann et al. 1967c). There is increased creatine excretion in the urine (Epstein and Ayres 1937). A creatine tolerance test shows definite rise in serum creatine and lowered creatinine excretion in the urine (Debreczeni and Ládanyi 1969).

The electromyogram (EMG), which is abnormal in about 50% of cases (Sollberg et al. 1967), and the clinical findings are not always correlated. In areas quite definitely clinically and histologically involved, the EMG findings may be insignificant or doubtfully pathological (Weidner and Braun-Falco 1968), but there may also be definite signs of myositis. In contrast, there may be areas without clinically obvious change where there are massive indications of a myopathy (Hausmanova-Petrusewicz and Komińska 1961). There is no fundamental difference between the localized and diffuse forms of scleroderma but the EMG changes in the former tend to be confined to the immediate neighbourhood of the foci. The clinical and EMG findings suggest that there is a primary disease of muscle in scleroderma, but the presence of polyphasic tracings makes a so-called silent peripheral denervation also debatable (Sollberg et al. 1967).

Histologically, a discrete myositis can be demonstrated (Leinwand et al. 1954). However, in isolated cases, myositic changes of such a massive nature have been seen as to make one think of a combination with a dermatomyositis. The muscle fibres show hyalinization, vacuolization and swelling (O'Leary et al. 1955). Transverse striation is lost and the sarcolemmar nuclei are significantly increased (Adams et al. 1962). Under the electron microscope, mitochondrial damage, virus-like particles and proliferated muscle nuclei are visible (Kudejko 1966). In addition, there is general connective tissue proliferation with thickening of arterioles and venules (Michalowski and Kudejko 1966).

Involvement of the peripheral nervous system in scleroderma

Symptoms and signs suggesting a peripheral nerve lesion are rare in the initial stage of scleroderma. If they are present they should be taken to represent sequels of a mild neuropathy or neuritis. There are very frequent indications of cranial nerve involvement, especially pupillary changes such as miosis, diminished light reflex, sensory disorders in the trigeminal area, and facial palsy (Kintzen 1952). Trigeminal neuralgia and also sensory neuropathy in the trigeminal area have been described (Beighton et al. 1968). A facial hemiatrophy may follow; this however is almost exclusive to localized scleroderma (Götz and Schuppener 1969).

As the scleroderma progresses, the lesions in the peripheral nervous system become increasingly obvious. This is a consequence of the often severe changes in such viscera as the lungs, heart, vascular system, liver, kidneys and gastrointestinal tract and the resulting circulatory, endotoxic metabolic and digestive-absorptive disorders. A few cases have been reported, however, in which a severe polyneuritis was in aetiological relation to a scleroderma first appearing years later (Richter 1954).

Electrically, the typical findings are of an initially sensory and later sensorimotor neuropathy.

Histologically, nerve fibre degeneration is demonstrable which may be confined to peripheral nerves or to autonomic ganglia or may involve both. Marked features are the extensive infiltration of the perineurium with collagenous tissue and the changes in the vasa nervorum. The intima proliferates, leading to vessel occlusion, there are nonuniform changes in the walls with massive deposition in the elastica, and collagen hyperplasia of the connective tissue of small arteries, capillaries and veins with metachromasia and scattered mast cells (Zülch 1959).

Involvement of the CNS

In both forms of scleroderma, clinical symptoms and signs of spinal cord and brain involvement can be demonstrated. In general, lesions of the brain and spinal cord can be shown to be secondary, or tertiary as a consequence of disorders of digestion, but the situation of the CNS with special reference to facial hemiatrophy is not entirely clear.

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Neurological features of spinal cord lesions. During the course of scleroderma, symptoms and signs typical of degeneration in columns of the spinal cord may appear. Pseudotabetic features are particularly common and are sometimes combined with cerebral and peripheral deficits (Lee and Haynes 1967). In addition to signs of columnar lesions, there are often indications of focal intramedullary changes in the form of pareses, disorders of sensation and disorders of micturition (Schmitt 1967). The cerebrospinal fluid (CSF) is almost always normal, an important point in differential diagnosis of disseminated disease (Hofmann and Steger 1959).

Pathological examination reveals either isolated or combined demyelination of the anterior, lateral and posterior columns as well as multiple intramedullary foci. The latter often correspond segmentally with the circumscribed skin changes (Hofmann and Steger 1959). It should be emphasized, however, that in many cases in spite of extensive clinical findings, the pathological appearances are unobtrusive. In such cases, a circulatory disorder may be the cause of the clinical defects (Zülch 1959).

Neurological features of brain lesions. Brain damage may manifest itself either as a slowly increasing diffuse collection of symptoms and signs with organic brain syndrome, signs of disintegration and general increase in reflexes or as typical focal symptoms and signs which may be multiple. In their development, the latter may imitate all manner of lesions. There may be spastic hemipareses, a variety of sensory disorders, signs of extrapyramidal lesions such as akinesis and rigidity (Benos et al. 1970), and midbrain or brain stem syndromes (Kissel et al. 1950; Gordon and Silverstein 1970). In some cases there may even be signs of tentorial or foraminal constriction of the brain stem with symptoms and signs of an acute midbrain and bulbar syndrome as a result of increase in intracranial volume due to oedema of the brain, massive haemorrhage or diapedetic bleeding (Gordon and Silverstein 1970).

Epileptic attacks are mostly associated with metabolic disorders such as uraemia (Bourne et al. 1960; Gordon and Silverstein 1970). These should be distinguished however from the combination of facial hemiatrophy, morphea and epileptic attacks, mostly Jacksonian (Wartenberg 1927; Harnack 1962).

Hemiatrophies are almost exclusively associated with localized scleroderma. They develop in youth and must be clearly distinguished from Romberg's hemiatrophy, which is not associated with any dermatological or neurological symptoms and signs. In most cases, the hemiatrophy is confined to the face. The skin changes may be limited to sclerodacyly but cases have been reported with circumscribed patches of scleroderma confined to a quadrant of the body (Korting and Korte 1958) or with irregular areas of atrophy (Driesen et al. 1966; Götz and Schuppener 1969). Transition to a total hemiatrophy of the body is possible (Hartwig 1965). If the atrophy is contralateral to the sclerodermal changes, the condition is known as atrophia cruciata (Zetterström 1955; Korting and Ruthner 1954; Benedetti and Cordaradi 1959; Götz and Schuppener 1969).

The electroencephalogram (EEG) is abnormal in 40% of cases of progressive scleroderma (Sollberg et al. 1967), with instability of frequency and predominance of rapid waves. Other nonspecific and symmetrically distributed signs may first be elicited after hyperventilation. In about 60% of cases of localized scleroderma, there are intermittent and diffusely distributed, flat slow waves (Stava and Stein 1961; Sollberg et al. 1967). With a combination of morphea and hemiatrophy, focal abnormalities in the EEG are almost constant, and these may be ipsilateral or contralaterial to the atrophy (Harnack 1962; Hartwig 1965). This is also true of convulsive patterns.

Angiographic investigations often reveal stenosis or occlusion of major arteries in the neck with corresponding symptoms and signs (Kö... 1970) or even occlusion of intracranial arteries (Stava 1958; Lee and Haynes 1967; S... 1972).

In cases with combinations or morphea, hemiatrophy and epilepsy in particular, dilatation of the ventricular system can be demonstrated by encephalography or ventriculography. Either ipsilateral or contralateral lateral ventricle is involved, with the IIIrd ventricle and the interpeduncular cisterna (Korting and Ruthner 1954; Hartwig 1965). Computed axial tomogr...

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should be able to provide better information about this in future.

The changes in the vessels are the most prominent pathological feature. These especially affect the small arteries and arterioles of the cerebral cortex and the corpus striatum. There is fibrinoid degeneration of the collagen with numerous fibroblasts and massive endothelial proliferation, with or without thromboses which may even occlude the affected vessel (Stork 1972). Not only the smaller vessels but also the major ones such as the anterior, middle or posterior cerebral artery, internal carotid artery, or basilar artery may show intimal proliferation with thrombosis and consequent brain infarction (Stava 1958; Bourne et al. 1960; Lee and Haynes 1967; Köhler 1970). Particularly in the terminal stage of scleroderma, there is development of brain oedema, increased diapedetic bleeding, and signs of tentorial or foraminal herniation due to increased intracranial volume with brain stem haemorrhage (Gordon and Silverstein 1970).

In the syndrome of hemiatrophy, morphea and epilepsy, in addition to brain atrophy with prominent dilatation of the lateral ventricle, IIIrd ventricle and interpeduncular cistern, there are changes in the thalamus, usually contralateral. Histologically, there are inter alia coagulation necroses, pale areas, round cell infiltrates and amyloid granules in the paraventricular and optic nerves, tuber cinereum and mammillary bodies. Similar changes are observable in the spinal cord and the ipsilateral superior cervical ganglion.

MENTAL CHANGES IN SCLERODERMA

Mental changes related to scleroderma may be coincidental or may arise through enhancement of certain characteristics in a pre-existing personality. The concept of the sclerodermal personality has thus developed (Stava 1958). The patient, usually a woman, is withdrawn, anxious, fearful and introverted. The appearance of skin lesions naturally induces corresponding behavioural and experiential reactions.

Psychiatric precursors of scleroderma include the so-called neurasthenic states with prominent autonomic symptoms such as excessive sweating, changes in temperature sensation and digestive disorders as well as depressive mood changes (Jansen 1949; Erbslöh 1961; Tumulty 1968).

As the disease progresses, a phase of amentia (Piper and Helwig 1955) as a transitional syndrome (Wieck) leads to an organic brain syndrome (Gordon and Silverstein 1970), mostly showing frontal lobe cortical symptoms (Hochleitner 1966). Psychoses appear in about 10%, mainly in the late stage (Piper and Helwig 1955). Delusions are common with paranoid content (Imberciadori 1956). Hallucinoses (Saucet et al. 1962) or schizophrenic developments are fairly rare (Richardson 1955). It is noteworthy that psychotic symptoms may regress with regression of the scleroderma (Senseman 1967).

Although individual cases have been described in which a psychosis preceded the appearance of skin lesions, this is probably a chance association (Saucet et al. 1962).

Disorders resembling scleroderma

In differential diagnosis of scleroderma, a number of clinical conditions must be considered which may be generalized like progressive scleroderma or localized like the circumscribed form.

DISORDERS RESEMBLING GENERALIZED SCLERODERMA

In the group of diseases resembling generalized scleroderma, two conditions in particular must be distinguished. These are Buschke's sclerodema adultorum and Werner's progeria adultorum. Scleroedema adultorum usually begins around the age of 20 and favours the female sex. The disease is said to be very often (90%) preceded by infections of the respiratory and gastrointestinal tracts. It is less commonly preceded by experience of some injury such as brain and head injury (Abramowitz and Andrews 1947) or of a neuritis (Hoffmann 1924). The disease lasts between a few months and 10 years (Curtis and Shulak 1965; Fleischmajer and Lara 1965). The lesions in the organs mostly return spontaneously to normal (Keining and Dorner 1950). In only 10% pericarditis, mediastinal, fibrosis and alternation of the kidneys persist.

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The skin develops patchy erythematous lesions, often with an uneven surface and waxy consistency. On the cheeks and sides of the neck, the lesions shelve at the edges and are alabaster coloured or a waxy brown (Sellei 1928). The hands are almost always spared. Rarely there are small or larger spots of so-called mobile erythema. Patients complain of either excessive or scanty sweating, localized itching and lowered temperature sense for cold in the affected areas (Reichenberger 1964).

In the mucosal areas, macroglossia develops (Schuermann 1959a) and leads to dysphagia. Occasionally, the periorbital region is involved in scleroedema (Breinin 1953).

Apart from the typical skin lesions, a large variety of symptoms and signs indicate involvement of internal organs and muscles. There are disorders of cardiac rhythm with corresponding ECG changes (Fleischmajer and Lara 1965), pleurisy and hydrocele formation (Reichenberger 1964).

Hepatomegaly and nephropathy (lipid nephrosis) have also been reported. In the muscles there are trough-shaped or boat-shaped areas of atrophy, and signs of joint involvement appear. More remarkable is the appearance sometimes of ocular muscle pareses as the first sign of scleroedema adultorum (Spängler et al. 1973). Transient loss of visual field has also been described (Merlenender and Zand 1935).

Among the laboratory findings, an increased erythrocyte sedimentation rate and the appearance of leucocytosis, lymphocytosis and monocytosis (may be combined with a pernicious anaemia) are worthy of mention. The serum level of iron may be lowered (Reichenberger 1964), while dysproteinaemias, hypercholesterolaemia and a raised basic metabolic rate have been reported. Creatine excretion in the urine is increased (Brehm and Cabré 1963). While the CSF shows little change (Bradford et al. 1966), the EMG almost always shows changes indicative of myopathy (Reichenberger 1964).

Light microscopy reveals oedematous infiltration of the skin from the middle of the cutis to the subcutis, especially in the neighbourhood of the vessels, follicles and sweat gland excretory ducts. Hyaluronidase can be demonstrated in the cavities (Braun-Falco 1952). The elastica is intact. There is also a slight degree of vasodilatation with increase in basal cell pigment and increased numbers of lymphocytes, plasma cells and mast cells (Reichenberger 1964; Fleischmajer and Lara 1965). The electron microscope reveals an increase in thin collagen fibrils with a great deal of surrounding cement substance, which is partly adherent (Teller and Vester 1957). Histologically the peripheral nerves show metachromatic swelling resembling that in dermatomyositis or pellagra (Helfland 1938).

Peripheral skeletal muscles (and rarely the ocular muscles) show interstitial accumulations of cells together with definite signs of myolysis (Brehm and Cabré 1963; Robinow 1963; Reichenberger 1964; Spängler et al. 1973). There is interstitial oedema of the myocardium as well as swelling and degeneration of individual muscle fibres.

Werner's syndrome or progeria adultorum (Thannhauser 1945) represents an ulcerative scleroatrophy. It is mainly familial (recessive heterozygotic) and appears in men after the age of 20 years. Consanguinity is abnormally common in the affected families (Klein and Franceschetti 1964; Thiers et al. 1964). The disease progresses slowly with disappearance of fat and musculature beginning at the extremities; over the affected areas the skin is tense and atrophic with pigmentary displacement.

An inherited enzyme defect (Petrohelos 196 or a disorder in synthesis of an enzyme syste (Boyd and Grant 1959) has been postulated.

A typical skin lesion is the development premature baldness with brittle hair (Knoth et 1963) progressing later to total alopecia, togeth with nail dystrophy (Boyd and Grant 1959) a disorders of sweat gland function. Torpid troph ulcers (Bohnenstengel 1963) and warty, usua plantar hyperkeratoses, form later.

Patients with progeria adultorum have a cha acteristic phenotype. They are small in stat with a bird-like face and show reduction development of the higher and highest br functions together with disinhibition of aff (lowered IQ, sluggish or irritable reactions). T primary and secondary sex characters are poo developed. There may be gynaecomastia in in

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vidual cases (Zaun 1962). The affected males have a feminine hair pattern (Kansky and Franzot 1963). There is simultaneous disorder of sexual and gonadal function (Kansky and Franzot 1963).

Ophthalmologically, there may be bilateral juvenile cataract (Knoth et al. 1963), keratopathy and retinitis pigmentosa. In 40% of cases there is diabetes mellitus with hyperlipaemia (Kansky and Franzot 1963). There are corresponding vascular lesions in the form of arteriosclerosis with massive stenoses and occlusions, affecting inter alia the carotids (Perloff and Phelps 1958). Hypertension, left heart failure and myocardial infarction appear (Perloff and Phelps 1958). The extremities may become gangerenous. Disorders of liver, parenchymatous function with aminoaciduria, thyroid malignancy (Kansky and Franzot 1963), lymph node swelling and splenomegaly have also been observed.

Neurologically, in addition to diffuse disorders of cerebral function and degenerative signs there are focal findings corresponding to the vascular occlusions present in any particular case; EEG findings are nonspecific, sometimes with focal changes (Jablońska and Segal 1959). Pathological changes in the EMG related to myopathies or myositis have been reported (Thiers et al. 1964).

Under the light microscope, the skin shows an atrophic, poorly defined epithelial band with hyperkeratosis, granulosis, acanthosis and increase basal cell pigmentation (Bohnenstengel 1963; Kansky and Franzot 1963). The subepidermal structure is very homogenous (Knoth et al. 1963). In the middle zone of the dermis, the elastica shows increased entanglement and entwining (Winer 1955) with a focal atrophy in places (Knoth et al. 1963). Around the vessels there are capsules of collagen tissue and infiltrates (Kansky and Franzot 1963; Knoth et al. 1963). Endangitic lesions exist only in the deeper layers of the subcutaneous tissue (Field and Loube 1960). The electron microscope reveals large quantities of granular material overlying the collagen fibrils; the granules degrade readily with trypsin (Korting and Holzmann 1967a).

Patients with progeria adultorum have a particularly marked tendency to develop malignant tumours, 40% of which are sarcomas (Knoth et al. 1963).

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Generalized lesions resembling scleroderma also appear in childhood in the form of sclerema neonatorum (Korting 1958) and Rothmund's or Thomson's congenital dystrophy. The latter is classified with the congenital poikilodermas. So-called scleropoikiloderma (Arndt and Jaffé) amounts to a Rothmund syndrome without cataract. Clinically, the marked sclerodermal lesions are prominent, while atrophy is in contrast only slight.

So-called sclerodystrophies may be due either to metabolic disorders or pathological deposits. These include scleromyxoedema and scleroderma amyloidosum of Gottron. In scleromyxoedema, a secondary sclerofibrosis arises though primary mucinous deposits in the skin. In this disease, cerebral infiltrates of mucin may also form with corresponding neurological deficit. Lesions like those of scleroderma have also been reported in porphyria cutanea tarda and carcinoid syndrome.

Rheumatoid arthritis may take a so-called pseudosclerodermatous course. In these cases there are indications of delicate atrophy and small spots of pathological pigmentation, but the typical fusion of skin and subcutaneous tissue with bone is absent, and visceral lesions are extremely rare. Caution is necessary in the differential diagnosis from scleroderma since rheumatoid factor tests are positive in 15–20% of cases of the latter.

DISORDERS RESEMBLING CIRCUMSCRIBED SCLERODERMA

Chronic atrophic acrodermatitis shows lax as well as tense atrophic changes in the skin. Contradictory views are held about its relationship to scleroderma. Possibly a lax skin atrophy appears with primarily cellular inflammation and a tense atrophy with primarily exudative inflammation (Szodoray and Daróczy 1960). The skin atrophy described by Pasini and Pierini corresponds closely to so-called scleroderma plana atrophicans.

Lipoid necrobiosis (Oppenheimer–Urbach) shows areas of erythema the size of the palm of a hand, which are at first brownish-red but later become pale and indurated with central depressions. They are permeated with telangiectases. Histologically, the lesions show granulomatosis and necrobiosis.

Special relationships between circumscribed scleroderma, progressive scleroderma, and the Raynaud phenomenon

Scleroderma is essentially due to a circulatory disorder which may be caused peripherally or centrally according to the site of the nerve irritation, and may therefore manifest itself more peripherally or diffusely (Gottron 1937). Transitional cases lying between the two forms are exceedingly rare (Curtis and Jansen 1958).

One essential difference between circumscribed and progressive scleroderma lies in the presence of the Raynaud phenomenon. The latter appears in the initial stage of progressive scleroderma, and at a later stage in a few particularly severe cases. In 90% there is a symptomatology of Raynaud phenomenon, which cannot be ascertained neither clinically or enzymatically and with plethysmography. The diagnosis is only proved by the incidence of nuclear antibodies. It is extremely rare in the circumscribed form (Lawrence 1946).

The Raynaud phenomenon is characterized by very variable symptoms which depend on intermittent closure of digital arteries. Histologically, there is filiform thinning of the digital arteries (Servelle 1954). The vascular lesions are identical in the Raynaud syndrome and in progressive scleroderma (Gohrbrandt 1948). In contrast, in the circumscribed form a lilac ring is the only inflammatory phenomenon, and this is not a variable but a permanent sign.

Vasomotor disorders are a prominent feature of progressive scleroderma, and are clinically expressed as an increase in sensitivity to cold and bouts of stiffness in individual fingers. After some intervening trauma the first episode of spasm appears with transition to an asphyxial or cyanotic situation in the digital circulation, while an initially somewhat raised blood pressure simultaneously falls (Gottron 1937).

These signs may exceptionally appear unilaterally (Spillmann 1935) but are usually symmetrical, tend to affect the second to fourth fingers, and sometimes also involve the nose, cheeks and tongue.

The cause may well be the same in some forms of scleroderma and in the Raynaud syndrome (Gougerot et al. 1950; Mufson 1953). It has even been suggested that patients with Raynaud's disease actually develop symptoms and signs o scleroderma later (Ratschow 1955). Moreover, i progressive scleroderma, a form can be distin guished with particularly marked Raynaud sign and intensive involvement of viscera (Piper an Helwig 1955).

Although about 90% of patients in a dermato ogy department have been observed to develo their scleroderma after a Raynaud syndrome, it i advisable in every case of the syndrome to co sider the possibility that a scleroderma may b developing (Farmer et al. 1961).

Therapy of scleroderma

Since scleroderma is a connective tissue diseas the use of drugs affecting this system must co into consideration first in therapy. It must ho ever be emphasized that in principle no speci therapy for progressive or circumscribed scler derma is known.

The effect of corticosteroids on connecti tissue metabolism has been known for years. Bo fibroblasts and mast cells are reduced in numb by corticosteroids and their growth is inhibit (Baker and Abrams 1955; Junge-Hülsing a Hauss 1960). Intracellular collagen formation fibroblasts decreases (Porter 1951), while the m cells become vacuolated and their mucopo saccharide granules clump together and lose th staining properties (Asboe-Hansen 1966). vestigation of the collagen content of the skin revealed a fall in neutral, saline-soluble colla (Houck and Jacob 1963), and in particular an crease in insoluble collagen after prednisone ministration. This is explained by an accelera transition from soluble to insoluble colla (Kühn et al. 1964). In addition, mucopolysacc ride synthesis (Mancini et al. 1960; Whiteho and Boström 1962) diminishes with simultane increase in the degree of polymerisation (Su blad et al. 1954). This leads to a diminution spreading effect and of membrane permeabi (Junge-Hülsing 1965).

The indications for the use of corticoster are the presence of the acute exudative phas progressive scleroderma and in addition,

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presence of a myositis (Winkelmann et al. 1968; Winkelmann et al. 1971), a markedly destructive arthritis (Tuffanelli 1972) and severe finger ulceration. Favourable therapeutic effects have also been reported in extensive morphea (Jablońska and Szczepanski 1975).

Progesterone administration is also known to influence connective tissue. Progesterone inhibits collagen fibre formation (Harkness and Harkness 1954). Very irregular fibrils appear and the whole of the connective tissue is greatly loosened (Harkness and Harkness 1954; Fainstat 1962; Vogel and Ther 1963). However, collagen synthesis is scarcely affected by progestagens, and the transition from soluble to insoluble collagen is delayed (Holzmann et al. 1965a, b). For this reason, progestogen administration raises the proportion of soluble collagen (Korting and Holzmann 1967b). Since the latter is particularly sensitive to tissue proteases, increased degradation of neutral soluble collagen can be demonstrated (Morsches et al. 1966). The result is a rise in collagen-like protein in the serum. Inhibition of synthesis of acid mucopolysaccharides has also been discussed (Zachariae and Thorsae 1966; Holzmann et al. 1968).

It has been a point of discussion if progesterone administration leads to demonstrable improvement in skin and bone lesions. The possibility of using peptides with a releasing hormone function, such as thyroid releasing hormone (Jackson and Reichlin 1978), should also be mentioned.

The chelating agent D-penicillamine acts preferable on heavy metals with an affinity for sulphur (Eyring and Engleman 1963) or -SS- compounds, which are split (Crawhall and Thompson 1965). The effect of D-penicillamine on collagen is shown by a significant rise in the fraction soluble in metallic salts together with a fall in insoluble collagen level (Uitto et al. 1970). This may be the consequence of increased collagenase activity, since the inhibiting enzyme cysteine is itself inhibited (Nimni and Bavetta 1965). If D-penicillamine is employed, its side-effects, especially those on the blood cell count and kidneys and the production of urticaria, must be watched for. It is usually given in conjunction with vitamin B_6 (Werner and Weinmann 1966; Rosenberg and Hayslett 1967; Fulghum and Katz 1968).

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Instead of D-penicillamine, penicillin itself either in the form of procaine penicillin or as the diethylaminoethyl ester of penicillin hydroiodide, is very often given (Jablońska and Szczepanski 1975). It is assumed that panicillin acts through its degradation product, penicillamine. The advantages of this treatment are that the drug is nontoxic and can be given by mouth. Success has been reported particularly in morphea (Jablońska and Szczepanski 1975).

Another chelating agent, EDTA (ethylene diamine tetraacetic acid) reduces the calcium content of the skin in scleroderma (Keech et al. 1966). In combination with pyridoxine and nicotinamide, it is also thought to influence abnormal tryptophan metabolism (Birk and Rupe 1962) and also enzymatic co-factors (Jablońska and Szczepanski 1975). A therapeutic effect is clinically evident especially in the exudative phase of scleroderma (Langhof and Zabel 1962). Recent publications emphasize in particular its effect on acroscleroderma (Jablońska and Szczepanski 1975). Long-term control studies have however shown disappointing results.

Apart from the above, a number of other drugs have been tried out in the treatment of scleroderma. Among them is vitamin E (tocopherol) which has a stabilizing effect on lysosomes (Miller and Smith 1966) and inhibits collagen synthesis.

EACA (ε-aminocaproic acid), originally used in rheumatoid arthritis, retards the transformation of plasminogen to plasmin and therefore retards fibrinolysis (Burks 1963); however, if it has any effect in scleroderma, this must be a subjective one (Hall and Scott 1966). Except for the relief of joint pain, the above is also true of indomethacin (Indocid) (Fleischmajer and Goldstein 1966).

Opinions are divided on the effectiveness of para-aminobenzoic acid (PABA) (Sitch and Trofimova 1971; Tuffanelli 1972), which increases the activity of monoamino oxidase in connective tissue and inhibits serotonin (Zarafonetis et al. 1950).

Noteworthy results have been reported from the employment of hyaluronidase in both forms (Petter and Bellmann 1971). Hyaluronidase has a depolymerising action on the ground substance of connective tissue and inhibits the synthesis of collagen fibres.

Equally good results, especially in progressive and linear scleroderma, have been reported with Madecassol (extract of Centella asiatica) which inhibits the synthesis of mucopolysaccharides and collagen (Boris and Stevenson 1965). Only in occasional cases has success been reported from the employment of colchicine (Alarcón-Segovia et al. 1974) which inhibits the incorporation of proline in skin collagen (Ehrlich and Bornstein 1972).

Especially when the Raynaud phenomenon is combined with diffuse scleroderma, low molecular dextran (Holti 1965; Pringle et al. 1965) may improve the microcirculation and thus ameliorate symptoms (Gelin and Ingelman 1961; Bygdamen and Eliasson 1967).

The administration of vasodilators is indicated only if there are particularly marked vasomotor manifestations early in the disease. Results have been contradictory with reserpine, which lowers activity of hypothalamic sympathetic centres (Willerson et al. 1970; Siegel and Fries 1972). Alpha-methyldopa has given promising results especially in acroscleroedema but has the disadvantage of high toxicity (Varadi and Lawrence 1969).

The malabsorption that results from severe visceral involvement can be influenced by small doses of erythromycin and tetracycline. These improve intestinal peristalsis, reduce diarrhoea and improve the absorption of vitamin B_{12} and D-xylose (Kahn et al. 1966). In addition, it is advisable to administer vitamins, especially of the B group, and to prescribe an appropriate diet.

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