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RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF SCLERODERMA

Rien n'est plus bizarre, mais aussi rien n'est plus intéressant que la dégenération cornée du système dermöide.

J. L. Alibert, 1818.

A comprehensive review of scleroderma was presented during these Grand Rounds in January of 1978. Today, I would like to focus on selected areas in which significant new knowledge has evolved in the past five years.

Classification

The term scleroderma embraces a heterogenous group of diseases characterized by localized or generalized induration, atrophy, and fibrosis of the skin and underlying connective tissues. The most popular classification of scleroderma is based on the anatomical distribution of the skin changes and the presence or absence of multisystemic disease.

Table 1

CLASSIFICATION OF SCLERODERMA

1) LOCALIZED FORMS

   a) Morphea
      Plaque-like morphea
      Guttate morphea
      Generalized morphea
   b) Linear scleroderma
   c) Scleroderma "en coup de sabre"

2) CHEMICAL INDUCED-SCLERODERMA-LIKE CONDITIONS

   a) Polyvinyl chloride disease
   b) Trichloroethylene-induced scleroderma
   c) Bleomycin-vinblastine-induced Raynaud's phenomenon and fibrosis
   d) Pentazocine-induced fibrosis
   e) Toxic epidemic syndrome (denatured rape-seed oil)

3) EOSINOPHILIC FASCIITIS

4) PROGRESSIVE SYSTEMIC SCLEROSIS

   a) Classical disease with visceral involvement
   b) CREST syndrome
   c) Overlap syndromes

5) PSEUDOSCLERODERMA

   a) Edematous
      Scleredema
      Scleromyxedema
   b) Indurative
      Carcinoid syndrome
      Phenylketonuria
      Congenital porphyria
      Porphyria cutanea tarda
      Primary and myeloma-associated amyloidosis
      Acromegaly

c) Atrophic
Werner's syndrome
Progeria
Rothmund's syndrome
Acrodermatitis chronica atrophicans
Lichen sclerosus et atrophicus
Lipoatrophy

LOCALIZED SCLERODERMA

The localized forms of scleroderma occur in a small minority of patients. These conditions are self-limiting and not associated with visceral involvement.

CHEMICAL-INDUCED SCLERODERMA-LIKE CONDITIONS

In recent years, several chemicals and drugs have been reported to be associatd with clinical manifestations and tissue lesions resembling scleroderma. As a rule, these manifestations are localized and tend to regress following removal of the offending agent.

Polyvinyl chloride disease. A syndrome characterized by Raynaud's phenomenon and acroosteolysis has been described in workers involved in the process of polymerization of polyvinyl chloride from vinyl chloride gas (1-5). Almost all of the patients reported had been engaged in cleaning of the polymerization chambers for at least one year.

Raynaud's phenomenon occurs in most cases, although few patients have no symptoms but have the roentgenographic evidence of acroosteolysis. It is usually bilateral affecting the hands only. The skin color changes, aching and discomfort associated with hand exposure to cold seem to be no different than the symptoms present in patients with Raynaud's disease or Raynaud's phenomenon associated with collagen vascular diseases. The unusual characteristic of this syndrome is the roentgenologic picture of acroosteolysis. The earliest change found in this condition is the loss of the cortex of one or more of the tufts of the distal phalanges without destruction of the tuft or shaft of the bone. More advanced cases show a small, half-moon cut in the cortex of the tuft of one or more distal phalanges. Finally, there may be complete loss of the tuft and a portion of the shaft of the distal phalanx. In the healing phase, the bone fragments may be joined by fibrous tissue or by new bone.

Other manifestations include scleroderma-like skin thickening, nodular induration of the skin of hands and forearms, synovial thickening of the proximal interphalangeal joints, hepatic and pulmonary fibrosis and occasionally liver angiosarcoma. Wilson, et al, (1) described 31 patients among 3000 workers involved in VC manufacturing and polymerization. Most patients presented with unilateral or bilateral acroosteolysis and Raynaud's syndrome, nine of the thirty-one showed radiological evidence of acroosteolysis without Raynaud's.

Table 2

CLINICAL FINDINGS IN VINYL CHLORIDE WORKERS

	No. of Cases
Acroosteolysis with Raynaud's phenomenon	22
Acroosteolysis without Raynaud's phenomenon	9
TOTAL	31

From Wilson, et al (1)

The pathogenesis of the toxic manifestations of exposure to VC is not known. Jayson, et al, (6) have shown that VC increases collagen synthesis by fibroblasts in vitro. An interesting study by Maricq, et al, (7) demonstrated a high incidence of capillary abnormalities detected by wide-field capillary microscopy. These changes are very similar to the microvascular abnormalities present in patients with scleroderma. These authors examined 44 patients with symptoms related to VC exposure. Seventeen patients in this group showed microvascular abnormalities indistinguishable from those present in patients with scleroderma. Most of these patients with capillary abnormalities belonged to the group showing severe acroosteolysis, Raynaud's

Table 3

CLINICAL FINDINGS IN VINYL CHLORIDE WORKERS

Clinical Manifestations	No. examined	No. with capillary changes
Severe acroosteolysis with Raynaud's	6	4
Scleroderma-like changes with Raynaud's phenomenon	5	4
Liver abnormalities	6	5
Healed acroosteolysis	7	0
Raynaud's phenomenon	9	3
Miscellaneous complaints	11	1
TOTAL	44	17

From Maricq et al. (7)

phenomenon and scleroderma-like skin lesions or liver abnormalities. A second group of workers with a history of exposure to VC but without clear-cut clinical manifestations was also examined. Dilated capillaries were observed in 38 of 108 workers in this group; both the number and distribution of dilated capillaries differed from those observed in most scleroderma patients. Many had isolated, extremely dilated capillaries. No correlation was found between the length of time of exposure to VC and the capillary abnormalities.

Thus, these studies suggest that the capillary abnormalities are not exclusively related to peripheral pathological conditions such as acro-osteolysis, skin induration, or Raynaud's phenomenon, but are also found in subjects with liver abnormalities. The isolated capillary changes in patients without clear-cut clinical findings may represent an early manifestation of exposure to VC.

It is also apparent that idiosyncrasy factors play an important role in the expression to clinical toxicity since most studies have shown that only a small number of workers exposed to VC will develop pathologic changes.

Pathologic manifestations similar to those induced by VC have been reported in isolated cases of exposure to other chlorinated hydrocarbons.

Table 4

CHLORINATED HYDROCARBONS AND SCLERODERMA-LIKE DISEASE

Compounds	References
Trichloroethylene	8
Dieldrin, chlordane, heptachlor	9
DDT, chlorocyclohexane	9

Bleomycin-Vinblastine-Induced Raynaud's Phenomenon and Sclerosis. Administration of bleomycin alone has been associated with two notable side-effects: cutaneous and pulmonary toxicity (10-12). The cutaneous reactions include hyperpigmentation, alopecia, nail changes, vesiculation, and pruritus, and sclerosis of the skin and digital gangrene simulating scleroderma. Sclerosis over the interphalangeal and metacarpophalangeal joints of the hands, lateral aspects of the fingers and palms may be so severe as to restrict the function of the hand. Skin biopsies reveal dense dermal collagen bundles specially around blood vessels and adnexal structures closely resembling the abnormalities found in scleroderma. This picture is usually self-limiting and may resolve spontaneously within two months after termination of therapy.

Raynaud's phenomenon associated with bleomycin plus vinblastine therapy was first reported in 1977 (13). Subsequently, several isolated reports confirmed this association. In a recent retrospective study (12), Raynaud's phenomenon was reported in 37 percent of 60 men treated with the two drugs

for germ cell testicular cancer. Interestingly, there was increased incidence of vasospastic phenomena in cigarette smokers. Nearly 50 percent of the patients showed objective trophic changes of the finger tips and many reported that the ischemic manifestations were severe enough to alter their life-style. Hand arteriograms obtained in two patients showed widespread arterial occlusions and poor distal arterial filling.

Approximately 50 percent of the patients had gradual resolution of symptoms, the other patients have continued to experience persistent vasospastic phenomena each winter. Unfortunately, no capillary microscopy studies are available in this group of patients.

Pentazocine-induced fibrosis. Cutaneous complications associated with pentazocine (Talwin) therapy were first reported in 1971 (14). Four patients developed flat or nodular sclerosis of the dermis at sites of injection. In some cases there were deep ulcerations of the skin. Palestine, et al (15), recently described 17 cases of pentazocine-induced cutaneous changes. The common feature in all patients was sclerosis of the intertegument and subcutaneous tissue with a "woody" consistency. Contractures developed in some cases due to fibrosis of the underlying muscles. Histologic examination of affected tisue revealed severe fibrosis of the dermis and subcutis and fibrous myopathy, with variably severe inflammation ranging from scattered foci of lymphocytes and histiocytes to large organizing granulomas. In six of eight patients examined, prominent thrombosis of small arterioles and venules was found in the deep portions of the dermis and subcutis.

Toxic Epidemic Syndrome (Spain, 1981). An obscure, epidemic disease has been reported by Spanish physicians since May, 1981 (16). Although there is an apparent relation to the sale and consumption of an illegally marketed redistilled denatured rape-seed oil, the cause is still undetermined. The total number of people affected is unknown, although official estimates are in the region of 18,000.

The clinical picture consisted of fever, headaches, cough, dysnea, skin rash, pruritus and myalgia. Eosinophilia was present in 98% of the cases initially. The latter phase of the syndrome is characterized by scleroderma-like skin lesions, sicca syndrome, Raynaud's phenomenon, dysphagia, weight loss, severe motor weakness and muscular atrophy and pulmonary hypertension.

Four months after the onset of symptoms, scleroderma-like lesions began to develop in about 10% of the cases. Ten times more women than men acquired these lesions. The patients developed hard, swollen, often shiny skin disease involving both proximal and distal areas of the limbs. Palm retraction, flexion contractures of fingers, elbows and knees were common. A significant proportion of patients developed Raynaud's phenomenon (28%) and sicca syndrome (74%). The toxic agent has not yet been determined. Anilides found in the oil have been suggested, yet the syndrome induced in animals by such substances does not match the human disease.

EOSINOPHILIC FASCIITIS

Case Report

D.B. is a 26 year-old white male with a nine-month history of stiffness and muscle cramps in both thighs. These symptoms became progressively more severe over a six-month period. Four months prior to this visit, the patient experienced progressive increase in size and induration of both calves. Two months later, the right forearm also became indurated and started to grow in diameter. The patient denied any constitutional symptoms such as fever, loss of weight, generalized weakness, or dyspnea. He acknowledged the possibility that his symptoms may have been preceded by extrenuous exertion. Past history and family history were unremarkable.

Physical examination revealed no significant abnormalities except for diffuse increase in the diameter of both calves and right forearm. There was very hard induration of dermis and subcutaneous tissues. Muscle strength was normal. Neurological examination was within normal limits.

Laboratory findings were unremarkable except for eosinophilia of 16% and polyclonal gammopathy. Electromyography showed no evidence of peripheral nerve or muscle fiber abnormalities.

Skin biopsy revealed subcutaneous tissue abnormalities. There were numerous dilated lymphatics, granulation tissue and numerous plasma cells, lymphocytes, and eosinophils. Collagenous scar tissue was present throughout. Special stains for amyloid were negative. The epidermis and muscle appeared normal.

The patient was treated with Prednisone, 40 mg daily. He has experienced improvement in muscle stiffness and decrease in the severity of cramps. The induration also improved significantly.

In 1974, Shulman (17) described two patients with a condition characterized by painful swelling and induration of the skin and soft tissues mainly localized to the upper and/or lower extremities. These findings were often followed by rapidly progressing contractures due to involvement of tissues adjacent to joints. Raynaud's phenomenon and visceral involvement were absent. The onset of this condition was frequently preceded by an episode of physical exertion.

Table 5

CLINICAL FEATURES OF PATIENTS WITH EOSINOPHILIC FASCIITIS

	Percent
Male/Female	64/36
White/Black	97/3
Sites of Involvement	
Hands	45
Forearms	89
Arms	75
Trunk and neck	43
Thighs	66
Legs	75
Feet	24
Onset after physical exertion	52

From Moore and Zuckner (18)

Laboratory findings revealed striking eosinophilia, elevated erythrosedimentation rate and polyclonal gammopathy. Biopsy of skin showed relative sparing of epidermis and dermis with intense cellular infiltration and thickening due to collagen fiber deposition of the fascia between fat and muscle. The cellular infiltrate consisted of lymphocytes, plasma cells and eosinophils.

Since the initial publication, 58 cases with similar presentations have been reported in the literature (18). As seen in Table 5, the majority of the cases have been white males with a mean age of onset of 44 yr (range 4-88). In over half the cases reported, there was a history of extrenuous physical exertion preceding the rapid onset of symptoms. Subjective complaints consist mostly of pain on motion and stiffness of the affected areas. Muscle cramps have been reported in a significant proportion of cases. Both upper and lower extremities are frequently involved, however, trunk and neck induration also occurred in over 40 percent of the cases.

Eosinophilia of > 400 ml/mm^3 is present in the vast majority of patients. Nonspecific polyclonal gammopathy and elevated erythrosedimentation rate are quite common. Other laboratory abnormalities are only seen sporadically, and their significance is not understood. Rheumatoid and antinuclear factors have been reported in low titers in a small proportion of patients. Muscle enzymes are usually normal, small elevations may be present in patients in whom the deep fascia inflammatory infiltrate overflows into the muscle mass.

Table 6

LABORATORY FINDINGS IN EOSINOPHILIC FASCIITIS

	Percent
Eosinophilia (> 400/mm^3)	92
Hypergammaglobulinemia (> 3.0 g/dl)	73
Elevated IgG (> 2.0 g/dl)	72
ESR (> 15 mm/hr)	68
Rheumatoid factor	11
Antinuclear factor	15

From Moore and Zuckner (18)

As mentioned above, in eosinophilic fasciitis there is a conspicuous absence of systemic involvement. However, hematologic abnormalities seem to be frequently associated with this condition. Recently, bone marrow suppression has been reported in 6 patients with eosinophilic fasciitis (19-22). Four patients developed aplastic anemia and two thrombocytopenia. The pathogenesis of marrow suppression is unclear. Weltz, et al (21), found anti-platelet antibodies and a serum inhibitor of autologous and homologous erythroid stem cells. Hoffman, et al (19), demonstrated an inhibitory factor in their patient's serum against committed erythroid and granulocyte-macrophage progenitor cells.

Table 7

HISTOPATHOLOGIC FEATURES OF EOSINOPHILIC FASCIITIS

Cellular Infiltrate in Deep Fascia

Lymphocytes

Plasma Cells

Histiocytes

Eosinophils

Thickened Fascia with Increased Collagen Deposition

Relative sparing of Epidermis and Dermis

The histopathologic hallmark of this condition is the finding of markedly thickened subdermal fascia associated with a dense infiltrate usually comprised of lymphocytes, plasma cells and histiocytes. Eosinophils are present in about 50 percent of the cases. Not infrequently, perivascular infiltrates of lymphocytes and plasma cells in underlying muscle and fascia have been described. The relative sparing of dermis and epidermis should be emphasized, since a shallow skin biopsy may not include the affected fascia and the diagnosis may be missed.

It is particularly important to differentiate this disease from scleroderma. Unlike scleroderma, the majority of patients with eosinophilic fasciitis experience a complete or near complete remission after a period of 2 to 3 years, usually following corticosteroid treatment.

Treatment outcome has been compiled by Moore and Zuckner (18) in 48 cases. Corticosteroids have been administered at doses ranging from 10 to 100 mg of prednisone with a mean dose of 40 mg daily. Moderate to marked improvement was documented in 44 patients who experienced softening and loosening of skin, better mobility, decreased pain, and diminished contractures. Laboratory parameters showed decreasing ESR, disappearance of blood eosinophilia and decrease in serum globulin levels. Two patients improved on aspirin and physical therapy alone and two had spontaneous remissions.

The etiology and pathogenesis of eosinophilic fasciitis is unknown. The presence of eosinophilia and hypergammaglobulinemia and the occasional association with aplastic anemia and thrombocytopenia support the concept of an immune abnormality as the basis for this syndrome. In spite of its clinical and histopathologic resemblance to scleroderma, there are reasons to consider this condition as a separate entity, particularly because of their vastly different prognosis and response to corticosteroid therapy.

PROGRESSIVE SYSTEMIC SCLEROSIS

Contrasting with the lack of multi-systemic involvement in the localized forms of scleroderma, in Progressive Systemic Sclerosis (PSS) there is symmetrical thickening of the skin with fibrosis and degenerative changes in the synovium, digital arteries, and viscera, notably the oeosophagus and intestinal tract, lungs, heart and kidneys.

PSS is extremely variable in its severity and progression, with a spectrum ranging from widespread skin and visceral involvement to a form characterized by a much more restricted pathology, often confined to the skin of fingers and face and only late evidence of internal manifestations (CREST syndrome). It is particularly important to distinguish the patients with CREST syndrome from those of PSS.

CLINICAL FEATURES OF THE CREST SYNDROME

C alcinosis

R aynaud's Phenomenon

E sophageal changes

S clerodactily

T elangectasia

Anti-centromere antibodies

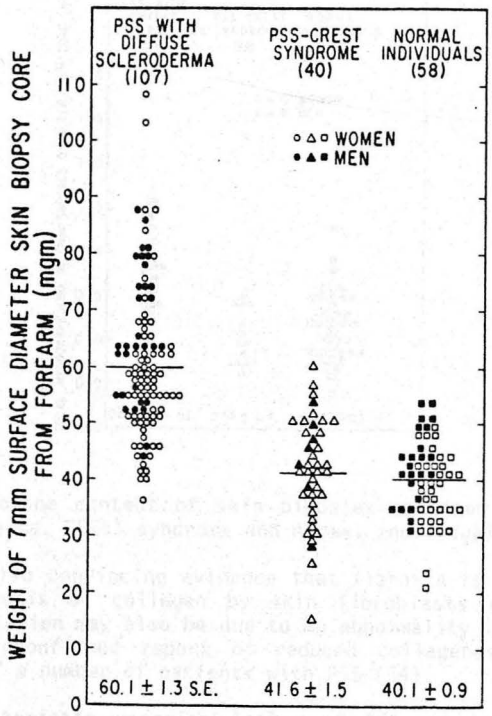
The combination of calcinosis, Raynaud's phenomenon with esophageal changes, sclerodactily and wide-spread teleangectasia is thought to represent a benign variety of PSS associated with a better prognosis than the classic form of the disease (23,24). Most patients experience Raynaud's phenomenon and swollen puffy fingers initially and in a significant proportion, these manifestations remain the sole symptomatology for many years so that these individuals are commonly tagged as having "Raynaud's disease".

Although the lack of visceral involvement in these patients results in a longer life span than the group of patients with diffuse disease (24-26), prolonged observation has shown that the CREST syndrome is not an entirely benign condition. In addition to the development of esophageal pathology indistinguishable from that seen in patients with diffuse disease, these patients develop pulmonary hypertension (27) and primary biliary cirrhosis (28). Moreover, close to one third of these patients have evidence of Sjögren's syndrome or Keratoconjunctivitis sicca (29,30). The clinical impression that this condition may represent a distinct subset has been reinforced by the recent finding of a very high incidence of a specific anti-centromere antibody in most of these patients (see below).

Pathogenesis. The histopathological hallmarks of PSS include sclerosis and thickening of dermis and other connective tissues, and characteristic vascular abnormalities involving small blood vessels. Each has been considered

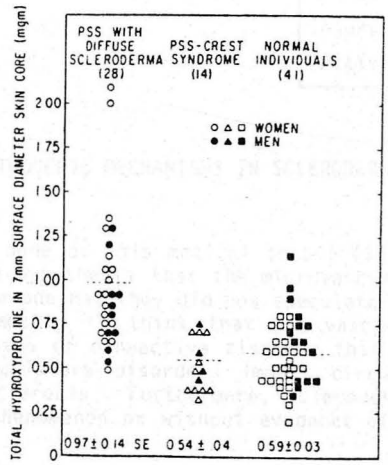
the primary event, however, at this stage of our knowledge it is not possible to point to the initial pathogenic mechanism.

Skin biopsies obtained from the dorsum of the forearm and trimmed of all subcutaneous fat were found significantly thicker and heavier in patients with diffuse scleroderma compared to skin specimens obtained from the same location in patients with CREST syndrome or normal individuals (31).



Weight of skin biopsy cores in patients with diffuse scleroderma, CREST syndrome, and normal individuals (31).

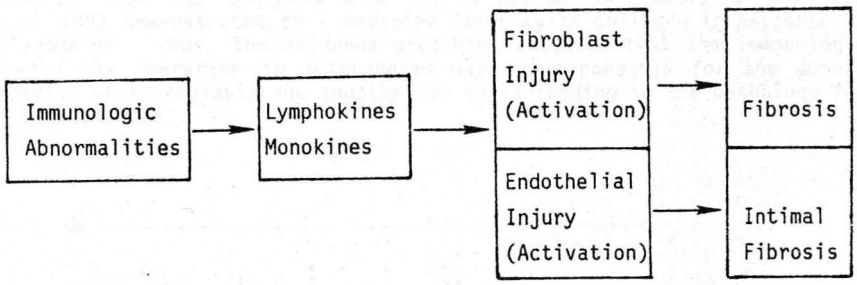
The increased thickness of the biopsy specimens was shown to be due in part to an increase in the total content of dermal collagen as shown by the results of assays of total hydroxyproline content per biopsy specimen. These results correlate with the striking increase of compact collagen fibers in the reticular dermis, a constant finding during the active, indurative phase of the disease.



Total hydroxyproline content of skin biopsies obtained from patients with diffuse scleroderma, CREST syndrome and normal individuals (38).

There is also convincing evidence that fibrosis is the result of overactive biosynthesis of collagen by skin fibroblasts (32,33). Increased collagen accumulation may also be due to an abnormality in degradation since there is one unconfirmed report of reduced collagenase activity in the involved skin of a number of patients with PSS (34).

The characteristic vascular lesion of PSS consists of concentrical proliferation and mucoid thickening of the intima, little change in the media and fibrosis of the adventitia (35-37). In addition, a marked decrease in the number of normal capillaries with a relative increase in the number of larger vessels has been reported (35). Narrowing of the capillary lumen due to endothelial cell proliferation may permit only the passage of erythrocytes, or completely obliterate the vessel (37).



PATHOGENIC MECHANISMS IN SCLERODERMA

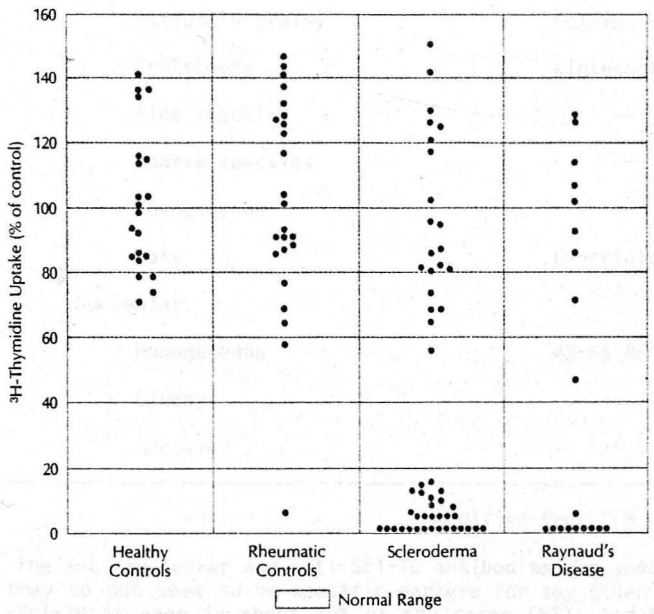
Based on work done at this medical school (35), Norton and Nardo (36) first presented the hypothesis that the microvasculature may be the primary target organ in scleroderma; they did not speculate on the factors involved. Although it is tempting to think that the vascular lesions in PSS lead naturally to sclerosis of connective tissues, this simple mechanism is not tenable. Many circulatory disorders impair circulation to the point of gangrene without sclerosis. Furthermore, scleroderma of the face develops without Raynaud's phenomenon or without evidence of deficient blood flow to that area.

Recent evidence has suggested that abnormal immunologic interactions may be responsible for the generation of factors that stimulate fibroblasts to increase their rate of collagen synthesis (38,39) and induce endothelial cell injury (40,41). A large body of experimental and clinical evidence supports the idea that immunologic mechanisms play a pivotal role in the pathogenesis of scleroderma. Stastny et al (42) had shown that in rats undergoing a chronic graft vs host reaction, scleroderma-like skin changes develop in some animals. Similar findings have been reported in patients following bone-marrow transplantation (43,44).

Sjögren's syndrome and primary biliary cirrhosis has been found associated with scleroderma in a number of cases (29,30). The high incidence of antinuclear antibodies, to be discussed later, constitutes also strong evidence of deranged immune mechanisms in PSS.

The histological changes in scleroderma skin provide additional evidence. In approximately one quarter of biopsy specimens obtained from the forearms of patients with PSS, one encounters accumulation of lymphocytes around blood vessels and in the deeper dermis and subcutaneous tissues (38). These cells have been identified as T-dependent lymphocytes (45,46) suggesting a possible role of cell-mediated immune reactions in the generation of fibrosis. This possibility was first entertained by Johnson and Ziff (47) who showed that lymphokine-containing culture supernatants were able to increase the accumulation of collagen by human embryonic lung fibroblasts. Following

this initial observation, Kondo et al (46) showed that blood lymphocytes obtained from PSS patients were sensitized to skin-antigens and Stuart et al (48) demonstrated cell mediated immunity to collagen in patients with scleroderma. Thus, the evidence presented suggests that the immunological aberrations operative in scleroderma may be responsible for the abnormal behavior of fibroblasts and endothelial cells leading to the pathology found in this disease.



Effect of sera from patients and controls on endothelial cell DNA synthesis (40).

Clinical Significance of Antinuclear Antibodies (ANA) in Scleroderma

It has long been recognized that ANAs are present in scleroderma, but the reported frequencies varied between 40 and 90% (49,50). This is due to the widely different quantities of nuclear antigens present in the cell substrates used to detect the antibodies by indirect immunofluorescence. When continuous tissue culture cell lines are used as substrate, ANAs are now detected in virtually all cases of scleroderma (50,51). Nine different nuclear staining patterns have been recognized (51,52) probably representing different antibody subsets with specificities to different nuclear antigens.

Table 8

ANTINUCLEAR ANTIBODIES IN SCLERODERMA

Pattern	Antigen
Nuclear	
Diffusely grainy	Scl-70
Centromere	Kintechore plates
Fine speckles	--
Coarse speckles	--
Homogeneous	--
Dots	Centrioles
Nucleolar	
Homogeneous	4S-6S RNA
Clumpy	--
Speckled	--

Modified from E.M. Tan (50).

The anti-nucleolar and anti-Scl-70 antibodies are specific for scleroderma, but they do not seem to be specific markers for any given clinical subsets. Anti-Scl-70 is seen in about 20% of the cases (51), and the anti-nucleolar pattern is present in 45% of patients with scleroderma (51,52). It is now well established that the anti-centromere antibody is a serological marker for the CREST syndrome (51-53). Fritzler et al (54) also showed that this autoantibody could predate the appearance of a full blown clinical picture of CREST.

In a recent study by Bernstein et al (52), 21 of 76 sera from PSS patients showed anti-centromere antibody pattern. Nineteen of the 21 (90%) had the CREST syndrome, only 2 sera belonged to patients with diffuse scleroderma. When patients with and without anti-centromere antibody were compared, this antibody was associated with twice the mean duration of disease, twice the frequency of calcinosis, an increased frequency of teleangectasia, little diffuse scleroderma, fever deaths and the absence of renal disease. Pulmonary and gastrointestinal involvement was common in both groups. Of interest was the positive association of serum rheumatoid factor with anti-centromere antibody. By virtue of this association, rheumatoid factor may itself be a useful marker of more benign disease.

Table 9

INCIDENCE OF ANTINUCLEAR ANTIBODY SPECIFICITIES IN SCLERODERMA

Antibody	Incidence Percent
Scl-70	20
Nucleolar	45
Centromere	28

Table 10

COMPARISON BETWEEN SCLERODERMA PATIENTS WITH ANTI-CENTROMERE AND WITH OTHER ANTINUCLEAR ANTIBODIES

	Anti-Centromere	Other Patterns
Mean duration of disease (years)	15.5	7.5
Females (%)	100	67
Calcinosis (5)	71	36
Sclerodactily (%)	90	42
Teleangectasia (%)	90	56
Renal involvement (%)	0	18
Mortality (%)	5	23
Rheumatoid factor (%)	52	11

Modified from Bernstein et al (52).

Thus, the presence of anti-centromere antibody in patients with scleroderma appears to have a similar significance to the association of anti-RNP antibody in patients with mixed connective tissue disease. In both cases, these antibodies are markers for a subset of patients with better prognosis. Further dissection of the auto-antibody specificities in the connective tissue diseases may not only clarify but also reveal some of the pathogenic mechanisms involved.

Microcirculatory Abnormalities

The pathologic hallmarks of scleroderma consist of wide spread vascular abnormalities and fibrosis. As previously mentioned, there seems to be no relationship between the vascular and fibrotic lesions. The fact that Raynaud's phenomenon, a vasomotor disorder is present in approximately 95% of patients with scleroderma, and often precedes this disease by many years points to the important role of the vascular pathology in the pathogenesis of this disease.

Histopathological examination of the affected tissues and organs show the characteristic lesion to consist of concentric proliferation and mucoid thickening of the intima, little change in the media and fibrosis of the adventitia (37,38). In addition, there is a striking decrease in the number of capillaries even in clinically unaffected tissues (35). These findings prompted Norton and Nardo (36) to postulate that the primary vascular abnormality in scleroderma was at the level of the microvasculature, and that the lesions observed in the larger vessels may only represent an extreme expression of a more universal process.

Abnormalities of the microvasculature have been detected by direct inspection of the skin vessels using capillary microscopy techniques. An alteration of cutaneous microvessels was first described by Muller in 1922 (55). Soon after, Brown and O'Leary (56) described the typical changes seen in scleroderma, a decrease in the absolute number of capillary loops, dilation and distortion with an occasional hemorrhage, and reduced flow in the remaining capillary loops. These findings have been confirmed by many investigators. (For review see (57)). However, only recently the capillary microscopy findings have been rigorously correlated with the clinical data by Maricq and LeRoy (39,58,59). These workers use low magnification (X20-100) to cover a relatively large area of skin so that the patterns of microvascular lesions, i.e., abnormal vessels and their distribution among the normal microvessels can be readily observed. Skin microvessels are best observed in the nailfold of the finger because capillaries run parallel to the skin surface at the edge of this fold and a greater length can be observed, whereas only capillary tips can be seen in other areas.

In normal subjects, the capillary pattern varies between fingers of the same person and between different individuals (57). The average nailfold of an average subject seen through a wife-field microscope shows only the tips of the capillaries in the proximal skin and a row of hairpin-like capillary loops along the edge of the fold. Maricq et al (58) have confirmed the earlier reports that the most characteristic microvascular changes seen in the rheumatic diseases are found in scleroderma. They have called this confirmation of findings the "scleroderma-dermatomyositis" pattern because

it is found in 82-95% of patients with these diseases and in a smaller proportion of patients with mixed connective tissue disease.

Table 11

CAPILLARY MICROSCOPY IN SCLERODERMA

Capillary loop dilation and distortion
Focal disappearance of capillaries
Capillary hemorrhages

In patients with scleroderma or dermatomyositis, the size of some capillaries is increased 4-10 times with respect to normal loops. The number of such enlarged capillaries may vary from a few to many per nailfold. In addition, the nailfold area often presents a moth-eaten" appearance because of the presence of many avascular areas along the edge. Capillary hemorrhages are often seen in scleroderma patients, but they are not specific and can be seen in various other diseases and, to a lesser extent, in normal subjects. The characteristic pattern can be identified and correlated blindly with the clinical diagnosis in several connective tissue diseases (59).

Table 12

INCIDENCE OF "SCLERODERMA-DERMATOMYOSITIS" PATTERN

Disease	Percent
Scleroderma	82 - 95
Active Dermatomyositis	100
Mixed connective tissue disease	54
Systemic lupus erythematosus	2

Of interest is the rarity of these abnormalities in systemic lupus erythematosus despite the presence of Raynaud's phenomenon, suggesting that the capillary changes are not an expression of Raynaud's phenomenon per se.

This technique appears to be of particular clinical value as a prognostic indicator of future scleroderma in patients with isolated Raynaud's phenomenon. A prospective study of 35 patients with Raynaud's phenomenon alone, 18 with undifferentiated connective tissue disease and 17 with scleroderma, only the

patients that eventually developed features of undifferentiated connective tissue disease or scleroderma displayed the scleroderma-dermatomyositis pattern capillary morphology on initial examination (60). In addition, only one patient with Raynaud's phenomenon exhibited striking loss of capillaries; this patient died with symptoms of myositis and fulminant pulmonary vasculitis 2 months later.

Thus, this technique may be useful in the diagnosis of scleroderma since the prevalence of capillary abnormalities is second only to the major criterion of proximal scleroderma (61). Moreover, it may help in the differential diagnosis in patients with overlap syndrome in predicting those who are more likely to develop PSS. Finally, the absence of the characteristic pattern in patients presenting with Raynaud's phenomenon in whom no associated disease can be found will increase the likelihood that they may have a benign condition.

Raynaud's Phenomenon (RP)

RP is defined as the paroxysmal ischemic episodes of fingers and toes usually induced by cold exposure or emotional upheaval. This symptom complex should be regarded as a syndrome, since it may be associated with a wide variety of clinical conditions.

Table 12

CLASSIFICATION OF RAYNAUD'S PHENOMENON

Idiopathic

Connective tissue diseases

Vasculitis

Cryoglobulinemia-Cold agglutinins

Obstructive arterial diseases

Occupational

Drug-induced

Cold injury

Neurological disorders

It is also apparent that the pathogenesis of RP may differ according to the underlying condition associated with it. It is therefore important to try to establish in each individual patient if the underlying pathogenic mechanism for the ischemic changes is mainly vasospastic or if vessel occlusion is the prevalent lesion. It is likely that the success or failure of the many treatment modalities available depend in part on whether spasm or vessel occlusion is mainly responsible for induction of the ischemic manifestations.

In scleroderma, over 95% of the patients present with RP and in some cases this symptom precedes by many years the appearance of other clinical manifestations. In concert with the morphologic studies showing arteriolar narrowing and occlusion, several recent arteriographic studies have demonstrated occlusive disease in the digital arteries of patients with scleroderma (62,63). This technique may be particularly useful to delineate the relative importance of vasospasm and organic occlusion in any given patient. It should be emphasized that in many patients, both components can

Table 13

ARTERIOGRAPHIC FINDINGS IN PATIENTS WITH RAYNAUD'S PHENOMENON

Diagnosis	Ischemic Changes	Arteriographic findings		
		Normal	Spasm	Occlusions
Idiopathic Raynaud's (13)	0	2	11	0
Scleroderma (10)	6	0	2	5

Modified from Blunt and Porter (64)

be present so that in order to detect occlusive disease, the digital arteriograms should be preceded by the administration of vasodilators. The importance of either functional or anatomic changes is well demonstrated by the a recent series reported by Blunt and Porter (64). Arteriograms performed in 13 patients with idiopathic RP showed evidence of spasm in 11 and in no case vessel occlusions were demonstrated. In contrast, 5 of 10 patients with scleroderma demonstrated occlusive lesions after administration of intraarterial reserpine. From their work, it is also apparent that some patients with collagen vascular disease may show purely spastic changes early in the disease and extensive occlusive lesions when the procedure is repeated several years later.

To date, a completely satisfactory treatment for RP is not available. This is understandable in view of the very variable pathology underlying this condition. Table 14 lists some of the procedures and drugs used to control this condition.

Table 14

TREATMENT MODALITIES FOR RAYNAUD'S PHENOMENON

Procedure or Drug
Arm whirling
Hypnosis
Sympathectomy
Biofeedback
Hyperbaric Oxygen
Adrenergic Neuronal Blocking Agents
Reserpine
Guanethidine
Methyldopa
α-Receptor Blocking Agents
Phenoxybenzamine
Tolazoline
Prazocin
β-Receptor Stimulants
Isoxsuprine
Terbutaline
Smooth Muscle Relaxants
Griseofulvin
Prostaglandin E_1
Nitrites
Calcium Entry Blockers
Nifedipine
Diltiazem
Miscellaneous
Low molecular weight dextran infusions
Fibrinolytic agents
Captopril

Perusal of the data available in the literature suggests that most of the treatment modalities listed in Table 14 are reasonably successful in patients with idiopathic Raynaud's phenomenon, with little or no ischemic digital lesions and with vasospasm as the major underlying mechanism. Treatment results are not nearly as impressive in patients with secondary RP associated with collagen vascular diseases such as scleroderma where there is frequent evidence of ischemic lesions and probably a major organic occlusive component (Table 15).

A compilation of the results obtained by sympathectomy clearly illustrates the differences in outcome in the different categories of RP. In a controlled study by Farmer et al (65), 46 per cent of the patients treated surgically showed improvement.

Table 15

OUTCOME OF SYMPATHECTOMY IN DIFFERENT CATEGORIES OF RAYNAUD'S PHENOMENON

Category	Patients No.	Cured-Improved Percent	Same-Worse Percent
Raynaud's Disease	236	68	32
Scleroderma	104	29	71

Modified from Blunt and Porter (64)

The control group of scleroderma patients treated medically and followed for a similar period of time demonstrated similar results with 27 percent showing significant improvement. These differences were not statistically significant.

Drugs given by the oral route have been reported to be variably successful in the relief of RP, however, very few controlled trials are available showing objective evidence of relief. Intraarterial infusions of vasodilators are definitely effective in relieving ischemic manifestations and increasing digital blood flow. However, the duration of the beneficial effects is rather short so that this treatment modality is reserved for patients with non-healing painful ischemic ulcers.

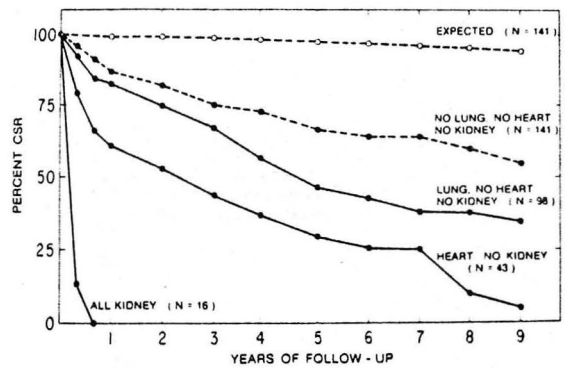
Very recent reports suggest that Captopril may be an effective agent for the control of RP in scleroderma patients. Whitman et al (66) noticed dramatic improvement in six of twelve patients treated with captopril for scleroderma renal disease and malignant hypertension. Ischemic ulcers healed in these patients. These authors noted that there was definite disease progression in the gastrointestinal, cardiovascular, and musculoskeletal systems of three patients while on the drug, despite the beneficial effects on Raynaud's phenomenon and skin ulcers.

A case report by Miyazaki et al (67) is worth mentioning. This patient had Raynaud's disease, unassociated with other connective tissue lesions. After administration of captopril, striking subjective, objective and plethismographic improvement of digital blood flow was observed. Since a pure antagonist of angiotensin II alone did not cause improvement, these authors suggested that the kallikrein-kinin system may play a role in the vasodilator effect of captopril. This agent also inhibits degradation of bradykinin probably increasing its half-life in circulation.

Scleroderma Renal Disease

Scleroderma is a relatively uncommon disease with an incidence of 12 new cases per year per million population. A survey of epidemiologic studies (68) suggest that the 5-year survival rate ranges from 34 to 73 percent, the

upper value probably being the more realistic since the lower values correlate with the proportions of male patients in one series. Thus, it is apparent that males fare worse than females (69) and older patients worse than younger ones (70,71). Most authors agree that involvement of kidney, heart or lung are poor prognostic signs, in that order (68).



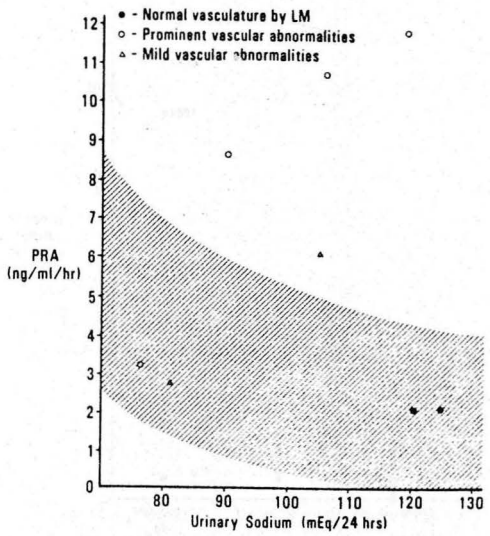
Cumulative survival rate in 309 patients with and without evidence of kidney, heart or lung involvement. From Medsger et al (69).

As a matter of fact, renal involvement is the major cause of death in PSS. In Medsger et al study (69) involving large number of patients, all patients with kidney disease died within 10 months, with 16 of 17 dying within three months. In a large retrospective study by Cannon et al (72), 45% of 210 patients had evidence of renal involvement. Hypertension was present in 24%, proteinuria in 36% and azotenia in 19%. Of the 68 patients that died during the period of study, 82% had renal disease and renal failure was the cause of death in 43% of the patients autopsied. Scleroderma renal crisis with malignant hypertension was fatal in 12 of 15 cases. The three survivors required bilateral nephrectomy for control of hypertension.

It is therefore apparent that in some patients, malignant hypertension or normotensive renal failure can occur rapidly, causing death in a short time. In others, proteinuria, hypertension or azotemia may be present for months or years until an episode of renal ischemia precipitates a crisis of "scleroderma kidney" leading to a rapid demise.

These two clinical presentations may be explained by the fact that vascular lesions may be present in the kidneys of normotensive PSS patients dying with normal renal function (73,74). In addition, recent evidence suggests that vasopasm leading to cortical renal ischemia plays a precipitating or synergistic role in the subsequent development of cortical necrosis. Functional vasospasm has been demonstrated by a reduction of renal cortical blood flow during induced RP, by increased flow after intrarenal administration of vasodilators, by arteriographic abnormalities suggesting vasoconstriction, and by the observation that the great majority of deaths caused by renal involvement occur in the fall and winter months (72).

From the physiological point of view, renal ischemia is strongly suggested by the elevated levels of plasma renin activity (PRA) in PSS patients without clinically apparent renal disease, and by the markedly elevated values found in normotensive or hypertensive patients with oliguric renal failure (73). The PRA levels correlate with the degree of vascular renal involvement seen in the biopsies of normotensive patients with normal renal function (74). Moreover, in patients with prominent vascular lesions, a marked elevation of PRA has been observed during cold pressor tests (72,74,75).



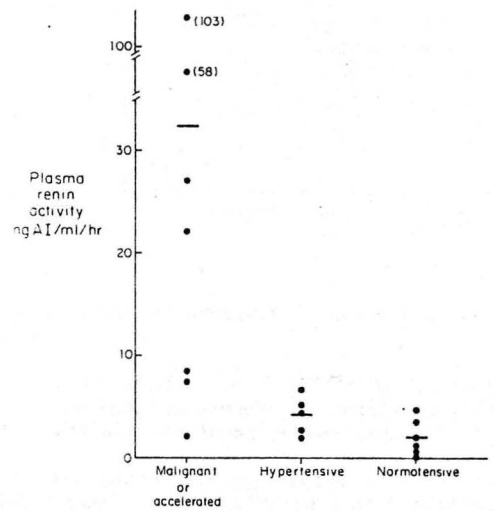
Plasma renin activity values in PSS patients (74).

Several recent reports have shown that aggressive antihypertensive treatment can control scleroderma renal crisis without nephrectomy and can preserve renal function. In 1978 Mitnick and Feig (76) reported one patient treated successfully with a combination of diazoxide, hydralazine and propanolol. The patient later recovered renal function after six months of maintenance hemodialysis. Wasner et al (77) described three additional cases of scleroderma kidney crisis in which administration of multiple antihypertensive agents resulted in blood pressure control and preservation of renal function.

Following the reports that PRA is elevated in normotensive as well as hypertensive PSS patients, it became apparent that a logical approach to treatment of scleroderma renal disease, and perhaps prophylaxis may lie in

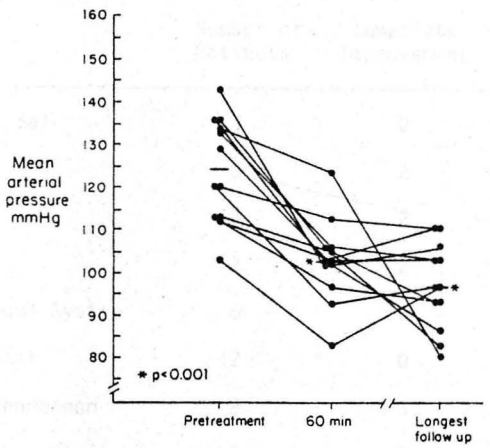
the pharmacological manipulations of the renin-angiotensin system with captopril, an angiotensin converting enzyme inhibitor. Lopez-Ovejero et al. (78) first reported the use of captopril in two patients with renal crisis, with dramatic results.

Very recently, Whitman et al (66) published a careful study of 12 patients with scleroderma and hypertension. Seven had renal crisis and had not responded to conventional anti-hypertensive therapy. Five had hypertension without malignant features.



Plasma renin activity in 12 scleroderma patients (66).

PRA was elevated in 6 of the 7 patients with renal crisis. Captopril, 10 to 50 miligrams, was first given to these patients while seated or slightly reclined with the head of the bed elevated. The drug was continued for a period of one year. The first dose lowered mean pressure in all patients by an average of 21.3 mm Hg. Blood pressure was controlled in all patients.



Response of mean arterial pressure to captopril in scleroderma patients over time (66).

Encephalopathy present in 6 patients was relieved. Two of the seven with renal crisis had improvement of renal function. Despite good pressure control, renal failure developed in the remaining five patients.

As mentioned above, an unexpected positive result was that there was immediate improvement in severe RP in 3 of 8 patients; long term benefit was achieved in five. Skin improvement occurred within 1 week in 2 patients. An additional three patients sustained improvement over a six-month period. In one, there was a 50% decrease in tissue weight of serially obtained punch skin biopsies.

Table 16

EFFECTS OF ADMINISTRATION OF CAPTOPRIL IN HYPERTENSIVE SCLERODERMA PATIENTS

	Number of Patients	Immediate Improvement	Long-Term Improvement	Progression
Gastrointestinal	8	0	0	1
Pulmonary	9	2	1	0
Cardiac	8	2	1	1
Renal	7	2	2	5
Central Nervous System	6	6	6	0
Musculoskeletal	12	0	2	1
Raynaud's phenomenon	8	3	5	0
Cutaneous ulcerations	9	3	6	0

From Whitman et al (66).

Despite successful control of blood pressure, five of the twelve patients died while under study, four were in the group presenting with renal crisis. Three of the five deaths occurred after captopril was discontinued. These patients were normotensive and their demise was due to complications of scleroderma and renal failure. The authors conclude that early therapy with captopril holds promise in preventing malignant hypertension and renal insufficiency.

It is, however, painfully obvious that in spite of the significant advances in our understanding of the pathogenic mechanisms and clinical modalities discussed today, scleroderma still presents a therapeutic challenge to the clinician.

REFERENCES

1. Wilson, R.H., McCormick, W.E., Tatum, C.F., et al. Occupational acroosteolysis. Report of 31 cases. JAMA 201:577, 1967.

2. Harris, D.K., Adams, W.G.F. Acroosteolysis occurring in men engaged in the polymerization of vinyl chloride. Brit Med J 3:712, 1967.

3. Suciu, I., Drejman, L., Valaskai, M. Contributii Studiul imolnavirilor produse de clorura de vinil. Med Intern 15:967, 1963.

4. Cordier, J.M., Fievez, C., Lefevre, M.J., et al. Acroosteolyse et lesions cutanées associées chez deux ouvriers affectés au nettoyage d'autoclaves. Cah Med Travail 4:3, 1966.

5. Selikoff, I.J., Hammond, E.D., editors. Toxicity of vinyl chloride-polyvinyl-chloride. Ann NY Acad Sci 246:1-337, 1975.

6. Jayson, M.I.V., Bailey, A.J., Black, C., et al. Collagen studies in acro-osteolysis. Proc Royal Soc Med 69:295, 1976.

7. Maricq, M.R., Johnson, M.N., Whetstone, C.L., et al. Capillary abnormalities in polyvinyl chloride production workers. JAMA 236:1368, 1976.

8. Saihan, E.M., Burton, J.L., Heaton, K.W. A new syndrome with pigmentation, scleroderma, gynecomastia, Raynaud's phenomenon and peripheral neuropathy. Brit J Dermatol 99:437, 1978.

9. Jablonska, S. Scleroderma and pseudoscleroderma. Polish Medical Publishers, Warsaw, 1976.

10. Cohen, I., Mosher, M., O'Keefe, E., et al. Cutaneous toxicity of bleomycin therapy. Arch Dermatol. 107:553, 1972.

11. Finch, W.R., Rodnan, G.P., Buckingham, R.B., et al. Bleomycin-induced scleroderma. J Rheumatol 7:651, 1980.

12. Vogelzang, N.J., Bose, G.J., Johnson, K., et al. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. Ann Int Med 95:288, 1981.

13. Teutsch, C., Lipton, A., Harvey, H.A. Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. Cancer Treat Rep 61:925, 1977.

14. Schlicher, J.E., Zuehkle, R.L., Lynch, P.J. Local changes at the site of pentazocine injection. Arch Dermatol 104:90, 1971.

15. Palestine, R.F., Millns, J.L., Spigel, G.T., et al. Skin manifestations of pentazocine abuse. J Am Acad Dermatol 2:47, 1980.

16. Noriega, A.R., Gómez-Reino, J., Lopez-Encuentra A., et al. Toxic epidemic syndrome, Spain, 1981. Lancet II:697, 1982.

17. Shulman, L.E. Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: A new syndrome. J Rheumatol 1:46, 1974 (Suppl).

18. Moore, T.L., Zuckner, J. Eosinophilic fasciitis. Seminars in Arthritis Rheum 9:228, 1980.

19. Hoffman, R., Dainiak, N., Sibrack, L., et al. Antibody mediated aplastic anemia and diffuse fasciitis. N Engl J Med 300:718, 1979.

20. Shulman, L.E., Hoffman, R., Dainiak, N., et al. Antibody-mediated aplastic anemia and thrombocytopenic purpura in diffuse eosinophilic fasciitis. Clin Res 27:514A, 1979.

21. Weltz, M., Salvado, A., Rosse, W., et al. Humoral suppression of hematopoiesis in eosinophilic fasciitis. Blood 52:218, 1978 (Suppl).

22. Littlejohn, G.O., Keystone, E.C. Eosinophilic fasciitis and aplastic anemia. J Rheumatol 7:730, 1980.

23. Winterbauer, R.H. Multiple telangectasia, Raynaud's phenomenon, sclerodactily, and subcutaneous calcinosis: a syndrome mimicking hereditary hemorrhagic telangectasia. Bull Johns Hopkins Hosp 14:361, 1964.

24. Rodnan, G.P., Medsger, T.A., Buckingham, R.B. Progressive systemic sclerosis - CREST syndrome: observations on natural history and late complications in 90 patients. Arth Rheum 18:423, 1975.

25. O'Leary, P.A., Waisman, M. Acrosclerosis. Arch Derm Syphilol. 47:382, 1943.

26. Farmer, R.G., Gifford, R.W., Hines, E.A., Jr. Prognostic significance of Raynaud's phenomenon and other clinical characteristics of systemic scleroderma. A study of 271 cases. Circulation 21:1088, 1960.

27. Salerni, R., Rodnan, G.P., Leon, D.F., et al. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Int Med 80:394, 1977.

28. Reynolds, T.B., Denison, E.K., Frankl, H.D., et al. Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon, and teleangectasia. New Syndrome. Am J Med 50:302, 1971.

29. Cipoletti, J.F., Buckingham, R.B., Barnes, E.L., et al. Sjögren's syndrome in progressive systemic sclerosis (scleroderma). Ann Int Med 87:535, 1977.

30. Osial, T., Whiteside, T.L., Buckingham, R.B., et al. Presented at the 1982 Southeastern Regional Meeting of the ARA, Birmingham.

31. Rodnan, G.P., Lipinsky, E., Luksick, J. Skin collagen content in progressive systemic sclerosis (scleroderma) and localized scleroderma. Arth Rheum 22:130, 1979.

32. LeRoy, E.C. Increased collagen synthesis by scleroderma skin fibroblasts in vitro. A possible defect in the regulation or activation of the scleroderma fibroblast. J Clin Invest 54:880, 1974.

33. Buckingham, R.B., Prince, R.K., Rodnan, G.P., et al. Increased collagen accumulation in dermal fibroblast cultures from patients with progressive systemic sclerosis (scleroderma). J Lab Clin Med 92:5, 1978.

34. Brady, A.H. Collagenase in scleroderma. J Clin Invest 56:1175, 1975.

35. Norton, W.L., Hurd, E.R., Lewis, D.C., et al. Evidence of microvascular injury in scleroderma and systemic lupus erythematosus. Quantitative study of the microvascular bed. J Lab Clin Med 71:919, 1968.

36. Norton, W.L., Nardo, J.M. Vascular disease in progressive systemic sclerosis (scleroderma). Ann Int Med 73:317, 1970.

37. Rodnan, G.P. Myerowitz, R.L., Justh, G.O. Morphologic changes in the digital arteries of patients with progressive systemic sclerosis (scleroderma) and Raynaud's phenomenon. Medicine 59:393, 1980.

38. Rodnan, G.P. Progressive systemic sclerosis: clinical features and pathogenesis of cutaneous involvement (scleroderma). Clinics in Rheum Dis 5:49, 1979.

39. Maricq, H.R., LeRoy, E.C. Progressive systemic sclerosis: disorders of the microcirculation. Clinics in Rheum Dis 5:81, 1979.

40. Kahaleh, M.B., Sherer, G.K., LeRoy, E.C. Endothelial injury in scleroderma. J Exp Med 149:1326, 1979.

41. Kahaleh, M.B., Delustro, F., Osborn, I., et al. Scleroderma mononuclear cells inhibit endothelial cells and stimulate fibroblasts through soluble mediator(s). Clin Res 29:166A, 1981.

42. Stastny, P., Stembridge, V.A., Ziff, M. Homologous disease in the adult rat, a model for auto-immune disease. I. General features and cutaneous lesions. J Exp Med 118:635, 1963.

43. Hood, A., Soter, N., Rappeport, J., et al. Graft-vs-host reaction: cutaneous manifestations following bone marrow transplantation. Archs Derm 113:1087, 1977.

44. Furst, D.E., Clements, P.J., Graze, P., et al. A syndrome resembling progressive systemic sclerosis after bone marrow transplantation. Arthritis Rheum 22:904, 1979.

45. Fleischmajer, R., Perlish, J.S., Reeves, J.R.T. Cellular infiltrates in scleroderma. Arthritis Rheum 20:975, 1977.

46. Kondo, H., Rabin, B.S., Rodnan, G.P. Cutaneous antigen-stimulating lymphokine production by lymphocytes of patients with progressive systemic sclerosis (scleroderma). J Clin Invest 58:1388, 1976.

47. Johnson, R.L., Ziff, M. Lymphokine stimulation of collagen accumulation. J Clin Invest 58:240, 1976.

48. Stuart, J.M., Postlethwaite, A.E., Kang, A.H. Evidence for cell-mediated immunity to collagen in progressive systemic sclerosis. J Lab Clin Med 88:601, 1976.

49. Fennell, R.H., Rodnan, G.P., Vazquez, J.J. Variability of tissue-localizing properties of serum from patients with different disease states. Lab Invest 11:24, 1962.

50. Tan, E.M. Rodnan, G.P., Garcia, I., et al. Diversity of antinuclear antibodies in progressive systemic sclerosis. Anti-centromere antibody and its relationship to CREST syndrome. Arthritis Rheum 23:617, 1980.

51. Tan, E.M. Autoantibodies to nuclear antigens (ANA): their immunobiology and medicine. Adv Immunol 33:167, 1982.

52. Bernstein, R.M., Steigerwald, J.C., Tan, E.M. Association of antinuclear and antinucleolar antibodies in progressive systemic sclerosis. Clin Exp Immunol 48:43, 1982.

53. Moroi, Y., Peebles, C., Fritzler, M., et al. Autoantibody to centromere (kinetochore) in scleroderma sera. Proc Natl Acad Sci USA 77:1627, 1980.

54. Fritzler, M.J., Kinsella, T.D., Garbutt, E. The CREST syndrome: a distinct serologic entity with anticentromere antibodies. Am J Med 69:520, 1980.

55. Müller, O. Die Kapillaren der menschlichen Kórperoberfläche in gesunden und kranken Tagen. (Enke, Stuttgart, 1922).

56. Brown, G., O'Leary, R. Skin capillaries in scleroderma. Arch Int Med 36:73, 1926.

57. Maricq, H.R. The microcirculation in scleroderma and allied diseases. Adv Microcirc 10:17, 1982.

58. Maricq, H.R., LeRoy, E.C. Patterns of finger capillary abnormalities in connective tissue disease by "wide-field" microscopy. Arthritis Rheum 16:619, 1973.

59. Kenik, J.G., Maricq, H.R., Bole, G.G. Blind evaluation of the diagnostic specificity of nailfold capillary microscopy in the connective tissue diseases. Arthritis Rheum 24:885, 1981.

60. Maricq, H.R., Harper, F.E., LeRoy, E.C. Nailfold capillary abnormalities in scleroderma-spectrum redefined. Clin Res 29:167A, 1981.

61. Masi, A.T., Rodnan, G.P., Medsger, T.A., et al. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 23:581, 1980.

62. Rösch, J., Porter, J.M., Gralino, J. Cryodynamic hand angiography in the diagnosis and management of Raynaud's syndrome. Circulation 55:807, 1977.

63. Dabich, L., Bookstein, J.J., Zweifler, A., et al. Digital arteries in patients with scleroderma. Arch Int Med 130:708, 1972.

64. Blunt, R.J., Porter, J.M. Raynaud syndrome. Seminars in Arthritis Rheum 10:282, 1981.

65. Farmer, R.G., Gifford, R.L., Hines, E.A. Raynaud's disease with sclerodactily. Circulation 23:13, 1961.

66. Whitman, H.H., Case, D.B., Laragh, J.H., et al. Variable response to oral angiotensin-converting-enzyme blockade in hypertensive scleroderma patients. Arthritis Rheum 25:241, 1982.

67. Miyazaki, S., Miura, K., Kasai, Y., et al. Relief from digital vasospasm by treatment with captopril and its complete inhibition by serine proteinase inhibitors in Raynaud's phenomenon. Brit Med J 284:310, 1982.

68. Medsger, T.A., Masi, A.T. Epidemiology of progressive systemic sclerosis. Clinics in Rheum Dis 5:15, 1979.

69. Medsger, T.A., Masi, A.T. Epidemiology of systemic sclerosis (scleroderma). Ann Int Med 74:714, 1971.

70. Farmer, F.G., Gifford, R.W., Hines, E.A. Prognostic significance of Raynaud's phenomenon and other clinical characteristics of systemic scleroderma. Circulation 21:1088, 1960.

71. Medsger, T.A., Masi, A.T. Survival with scleroderma-II. A life-table analysis of clinical and demographic factors in 358 male U.S. veteran patients. J. Chronic Dis 26:647, 1973.

72. Cannon, P.J., Hassar, M., Case, D.B., et al. The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. Medicine 53:1, 1974.

73. D'Angelo, W.A., Fries, J.F., Masi, A.T., et al. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. Ann J Med 46:428, 1969.

74. Kovalchik, M.T., Guggenheim, S.J., Silverman, M.H., et al. The kidney in progressive systemic sclerosis. A prospective study. Ann Int Med 89:881, 1978.

75. Kahaleh, M.B., LeRoy, E.C. Progressive systemic sclerosis: kidney involvement. Clinics Rheum Dis 5:167, 1979.

76. Mitnick, P.D., Feig, P.U. Control of hypertension and reversal of renal failure in scleroderma. N Engl J Med 299:871, 1978.

77. Wasner, C., Cooke, R., Fries, J.F. Successful medical treatment of scleroderma renal crisis. N Eng J Med 299:873, 1978.

78. López-Ovejero, J.A., Saal, S.D., D'Angelo, W.A., et al. Reversal of vascular and renal crisis of scleroderma by oral angiotensin-converting enzyme blockade. N Engl J Med 25:1417, 1979.

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