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SCLERODERMA AND SCLERODERMA-LIKE DISORDERS

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SCLERODERMA AND SCLERODERMA-LIKE DISORDERS

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I. SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

A. Historical

Progressive systemic sclerosis (diffuse scleroderma) is a widespread disturbance of connective tissue which involves the skin (scleroderma) and various organs of the body including the heart, lungs, kidneys and gastrointestinal tract. According to Rodnan and Benedek (1), the first convincing description of the disease was published in a monograph by Carlo Curzio in 1753 (2). In 1754 this was translated by Robert Watson (3) as follows:

> *A Young woman, seventeen years old, call'd Patrizia Galiera, the daughter of a citizen of Naples, was brought to the royal hospital the twenty-second of June, 1752 and was placed in one of the wards assigned to the care of Dr. Crusio; who visiting her in her bed, and asking her the necessary questions to form a right notion of her disease, was inform'd by her, that her complaint was an excessive tension and hardness of her skin over all her body, by which she found herself so bound and straiten'd, that she could hardly move her limbs. Upon examining her, he found her skin hard to the touch, like wood, or a dry hide; however, he observ'd some difference in the degrees of the hardness: For in some places it was greater; as in the neck, forehead, and particularly in the eye-lids; insomuch that she could neither raise nor entirely shut them. It was also very great in the lips, tongue, and on each side of her body; but the muscles under the skin seem'd not to be affected, because the joints could be bent; and if in any place there was any difficulty in moving the limbs, this arose not from any defect in the muscles, but from the hardness and tension of the skin and cellular membrane, which did not yield to their contraction and relaxation. For example; she could scarce open her mouth; which happen's not from any fault in the digastric, or other muscles, but from the hardness of the skin, that cover'd the lips and cheeks, and that would not permit her to draw down the lower jaw. In the same manner was she incapable of bending her neck, or turning her head: Neither did this happen from any defect in the muscles destin'd to that office, but from the firmness of the skin and membrane, which in no wise yielded to their contraction. This was the case in the other parts of the body; the muscles being, as it were, tied down and compressed by a dry, hard, and unpliable covering.*
>
> *As to other particulars; her skin had lost its natural warmth, but was sensible, when it was press'd upon the nails, or a pin; the patient then saying, that she felt a pain, as if skin were tearing. Her pulse was perceiv'd to be deep, and obscure; but equal, and regular. Her respiration was free, and uninterrupted; her digestion was good, and she found no inconvenience after eating, except a greater streightness, and an*

uneasy constriction round the belly. As to the natural excretions, the alvine were easy and proper; but the urinary sometimes exceeded the quantity of what she drank, and appear'd loaded with salts; both which circumstances, perhaps, proceeded from the sensible and insensible perspiration being intirely wanting.

Treatment included warm milk and vapor baths, bleeding from the foot (accomplished with difficulty because of hardness of the skin), and small doses of quicksilver (1).

It is of interest that Capusan (15) in 1972 questioned the conclusion that Curzio's case was a description of scleroderma. Instead, Capusan believed that it was in fact, a case of scleredema. His arguments included:

1. *The disease developed at first at the level of the neck, extending to the face, arms, and trunk, causing an extreme tautness of the skin because of the "wooden" hardness of the cutaneous and subcutaneous tissues; the muscle strength, however, being preserved.*

2. *Raynaud's phenomenon was absent not only at the onset but also throughout the course of the disease.*

3. *The disease regressed completely after 11 months of a treatment that can be considered as anodyne in view of present knowledge: warm steam baths, low doses of metallic mercury, blood lettings, and so on.*

4. *Diagnostic considerations eliminate the possibilities not only of a progressive systemic scleroderma but also of other diseases of the same group.*

5. *The clinical features of Curzio's case fit well with the description of scleredema by Buschke in his original article quoted also by Rodnan and Benedek.*

By 1837 there were 8 known cases of scleroderma and the condition was designated as sclerodermie. A comprehensive review on the subject was written in 1865 by Horteloup (1, 4). By 1895 over 500 cases had been reported (1, 5).

The first description of localized scleroderma (morphea) is attributed to Addison (6) although his term for the lesion was *true keloid*. His description is as follows:

Like the keloid of Alibert, it has its original seat in the subcutaneous areolar tissue, and is first indicated by a white patch or opacity of the integument, of a roundish or oval shape, and varying in size from that of a silver penny to that of a crown piece, very slightly or not at all elevated above the level of the surrounding skin, and probably unattended, in the beginning, with pain or any other local uneasiness or inconvenience, although a more or less vivid zone of redness surrounding

the whole patch, or a certain amount of venous congestion in its immediate vicinity, sufficiently attests the vascular activity or inflammatory process going on in the parts beneath. . . . The slow and insidious change taking place in the areolar tissue either stops and the spot disappears, or it proceeds, and at length begins to declare itself by a feeling of itching pain, tightness, or constriction in the affected part, and frequently by a certain amount of subcutaneous hardness and rigidity. . . . At length the part originally affected becomes more or less hidebound; and a similar change taking place around the more superficial fasciae and tendons, the latter become so tightened, fixed, and rigid as to be no longer capable of performing their proper functions, and to such an extent, that the whole of a limb, but especially the fingers, may be permanently contracted, bent, and rendered almost as hard and immovable as a piece of wood. . . .

According to Rodnan and Benedek (1), the coexistence of scleroderma and cutaneous calcinosis was first recorded by H. Weber in 1878 (7). The patient was a 40 year old woman who had painful lentil-sized swellings on her fingers. She was originally believed to have gout, but chemical analysis revealed that these concretions consisted of calcium carbonate. Thibierge and Weissenbach (8) later "rediscovered" this association and their names have been attached to this entity as the Thibierge-Weissenbach Syndrome.

The association of scleroderma with peripheral vasoconstriction of the hands was first described by Raynaud in a personal communication in Horteloup's monograph (4). The patient was a 30 year old farmer who had numbness of the arm during the winter and noted the gradual development of hardness of his hands and darkening of the skin. Although Raynaud did not actually discuss the association of Raynaud's phenomenon with scleroderma, he noted that the skin of one patient was "white and hard, like parchment".

The development of acral changes in patients with Raynaud's phenomenon was first emphasized by Ball in 1871 (9). He described a woman who had marked sclerosis and atrophy of the fingers and painful ulcerations of the tips and later introduced the term sclerodactylie (10).

It is of interest that although many patients were known to die soon after onset of changes in the skin, the systemic nature of the disease was not appreciated until the present century. For example, in 1892 Wolters (11) noted that "scleroderma does not appear to be a disease that threatens life directly. . . . Exitus usually results from the greatest variety of disease which are not directly related to the process, such as: Heart failure, pulmonary phthisis, emphysema, anemia, diarrhea, gastroenteritis, pleuritis, Bright's disease."

In 1892 Osler wrote that scleroderma was "one of the most terrible of all human ills. Like Tithonus to 'wither slowly', and like him to be 'beaten down and marred and wasted' until one

is literally a nummy, encased in an ever-shrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern" (12).

According to Rodnan and Benedek (1), the existence of visceral involvement in scleroderma was first emphasized by Matsui in 1924 (13). He described sclerosis of the lungs, gastrointestinal tract and kidneys of 5 patients. By 1945 it was realized that scleroderma was but the cutaneous manifestation of a systemic disease and Goetz proposed that the term scleroderma be replaced by progressive systemic sclerosis (14).

> *Obviously the term 'scleroderma' should be abandoned. It is quite evident to-day that we are dealing with a systemic disease neither solely nor primarily involving the skin. 'Scleroderma' is only the obvious and striking symptom of a generalized disease and the most serious symptoms actually arise in the viscera.*
>
> *Now that the visceral changes are being more widely recognized as an integral part of the disease, the systemic implications will receive much more consideration than the dermatological aspect. . . . It appears therefore . . . that now is not an inopportune time to abandon the term 'scleroderma' which for so long has obstructed investigation into the cause of that disease and to replace it by one more descriptive of the true state of affairs. The term 'sclerosis' already being in use, it appears that 'progressive systemic sclerosis' would describe the condition adequately until such time as the etiology has been established. Scleroderma is then only one of the symptoms or signs of progressive systemic sclerosis.*

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B. Epidemiology

Since no large population survey of scleroderma has been reported the true incidence is unknown.

As shown in Table 1 the ratio of women to men with systemic scleroderma is about 3:1 with a range of 1.5:1 to 5.7:1.

Table 1

RATIO OF WOMEN TO MEN WITH SYSTEMIC SCLERODERMA

Reference	Year of publication	Number of cases	Ratio of women to men
Gonzalez[1]	1959	67	5.7:1
Tuffanelli and Winkelmann[2]	1961	727	2.9:1
Rodnan[3]	1963	101	1.6:1
Richardson[4]	1963	74	3.6:1
Sackner[5]	1966	65	1.5:1
Barnett and Coventry[6]	1969	61	3.1:1
Medsger and Masi[7]	1971	86	3.2:1

Modified from (8)

The age of onset of scleroderma is shown in Table 2.

Table 2

AGE OF ONSET OF SCLERODERMA

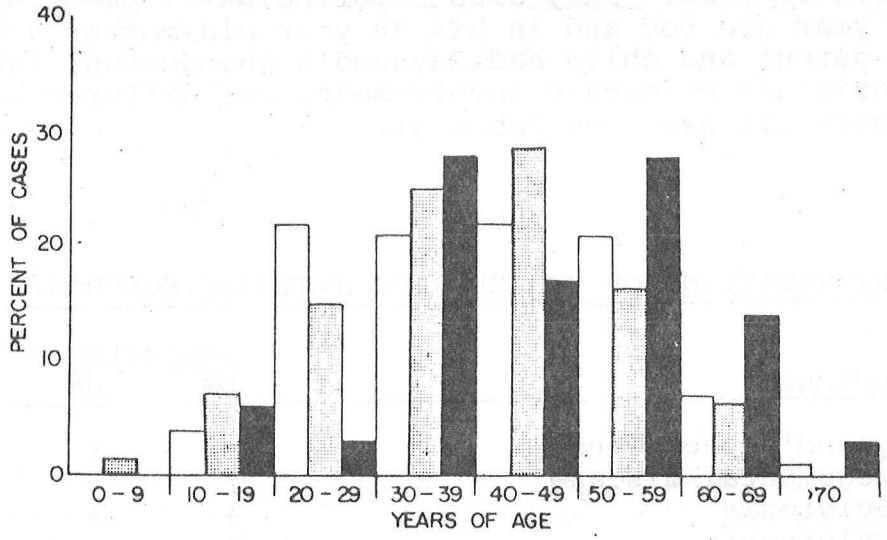
Age of onset	Reference	Year of publication	% of patients
Under 20 years of age	Tuffanelli and Winkelmann[2]	1961	8.7
	Barnett and Coventry[6]	1969	3.3
	Medsger and Masi[7]	1971	8.1
Over 60 years	Tuffanelli and Winkelmann[2]	1961	6.2
	Rodnan[3]	1963	10.0
	Medsger and Masi[7]	1971	12.8

Modified from (8)

Although the peak age of onset of initial symptoms is between 30 and 50 years, the incidence by age at diagnosis steadily increases, reaching a peak in the oldest age group (3). The median age of onset of systemic scleroderma has been estimated to be 40 years (2), with a range from 4 to 86 years (8). Systemic scleroderma in children is rare, constituting not more than 1.5 percent of 727 cases (2). The age of onset is shown in Figure 1.

Figure 1

AGE OF ONSET OF SCLERODERMA



From ref. (5)

Clear rectangles = 67 cases of Gonzalez (1)
Stippled rectangles = 727 cases from the Mayo Clinic (2)
Solid rectangles = 65 cases from Sackner (5)

In a fairly large scale epidemiologic study of 86 patients between 1947 and 1968, Medsger and Masi (7) estimated the annual incidence at 2.7 new patients per million population, with rates 3 times higher in females than males for both whites and blacks. No significant racial differences in incidence were observed. There were few childhood cases compared with adult cases and no male scleroderma patients under age 25 were identified. The incidence increased with age, peaking in the oldest age group studied (over 65 years). No socioeconomic variables affecting incidence were identified, nor was there any epidemiologic evidence of an infectious agent. The data suggested a sex and age influenced vascular abnormality involved in this disease. The authors concluded that the age, race and sex pattern of occurrence of scleroderma resembled that of adult rheumatoid arthritis.

The natural course of scleroderma is variable, from a rapidly fatal one to survival for many years. On the one hand, a majority (59%) of 727 patients of the Mayo Clinic were still alive after 10 years (2). However, in the same series only 17% of patients with diffuse scleroderma lived beyond 5 years. The wide variation depends primarily on whether the patient has only acroscleroderma or diffuse scleroderma. The most frequent causes of death in the latter group are cardiovascular, pulmonary and renal complications. The poorest prognosis is in those with renal involvement (10). Survival was not related to severity or extent of the cutaneous changes.

Gray and Altman (11) recently reviewed the familial occurrence of scleroderma. They also reported development of scleroderma in a 6 year old boy and in his 38 year old mother 9 years later. Both parent and child had Raynaud's phenomenon, integumental sclerosis and pulmonary involvement, but differed in other aspects of their disease (see Table 3).

Table 3

MANIFESTATIONS OF PROGRESSIVE SYSTEMIC SCLEROSIS

Findings	Subjects DM	NM
Raynaud's phenomenon	+	+
Integumental disease		
Sclerosis	+	+
Calcinosis	+	-
Telangiectasia	-	+
Gastrointestinal disease		
Esophageal hypoperistalsis	+	-
Small bowel hypomotility, colonic sacculations	-	-
Pulmonary disease		
Interstitial fibrosis (roentgenogram)	+	-
Restrictive lung disease (pulmonary function studies)	?	+
Arthralgias, arthritis	-	+
Renal disease	-	+

From ref. (11)

Their review of familial scleroderma is shown in Table 4.

Table 4

REPORTED CASES OF FAMILIAL SCLERODERMA

Authors	Subject Relationship and Age	Clinical Features	Comments
Orabona & Albano (1958)	Sister, 50	Raynaud's phenomenon, facial and acrosclerosis. Death from renal failure. *Postmortem*: pulmonary fibrosis, submucosal fibrosis of the esophagus, and renal changes consistent with PSS	PSS
	Sister, 57	Raynaud's phenomenon, acrosclerosis, inflammatory muscle infiltrates	Further details not reported
McAndrew & Barnes (1965)	Brother, 45	20-year history of Raynaud's phenomenon and flexion contractures of fingers; scleroderma of face and hands, steatorrhea, 5-year history of progressive pulmonary fibrosis leading to death. *Postmortem*: pulmonary fibrosis, submucosal fibrosis of the esophagus, and pancreatic fibrosis	PSS
	Brother, 54	20-year Raynaud's phenomenon and flexion contractures of fingers, telangiectasia, muscle atrophy, ulcers over interphalangeal joints and hands. Sudden death and no postmortem examination	PSS not documented
Blanchard & Speed (1965)	Brother, 36	Raynaud's phenomenon, scleroderma of face, trunk, and extremities, widened periodontal membranes, seizure disorder	Probable PSS
	Brother, 38	Scleroderma of face, trunk, and extremities; widened periodontal membranes; esophageal hypomotility	Probable PSS
Schimke *et al* (1967)	Sister, 56	CRST syndrome	Sister died with "typical scleroderma" but details not reported
Burge *et al* (1969)	Sister, 16	Linear progressing to generalized scleroderma, multiple peripheral joint contractures without synovitis, indolent pedal ulcers, subcutaneous calcinosis. Death at age 16 from inanition and bronchopneumonia. *Postmortem*: submucosal fibrosis of esophagus	Visceral disease not established until postmortem
	Sister, 12	Scleroderma of upper extremities and flexion contracture of hands; normal gastrointestinal roentgenograms; elevated immunoglobulins and sedimentation rate	Visceral disease not detected
Camus *et al* (1970)	Mother, 73	Raynaud's phenomenon, scleroderma, interphalangeal polyarthritis, parotid enlargement; esophageal hyperperistalsis	PSS
	Daughter, 46	Raynaud's phenomenon, sicca syndrome	PSS not established
	Daughter, 48	Raynaud's phenomenon, interphalangeal arthralgias; esophageal hypoperistalsis	11 of 23 family members, over 4 generations, with Raynaud's phenomenon
	Daughter, 44	Raynaud's phenomenon, interphalangeal arthralgias; esophageal hypoperistalsis	
	Daughter, 40	Raynaud's phenomenon	
Randall & McKenzie (1974)	Sister, 64	23-year history of Raynaud's phenomenon and mucocutaneous telangiectasia; scleroderma (biopsy) of neck only	Probable PSS
	Sister, 53	20-year history of Raynaud's phenomenon, sclerodactyly of fingers and toes, scleroderma of face and trunk, telangiectasia; esophageal hypoperistalsis. Death from anuria and congestive heart failure. *Postmortem*: myocardial fibrosis, fibrosing endarteritis kidneys; GI tract not examined	PSS

Table 4 (Cont'd)

REPORTED CASES OF FAMILIAL SCLERODERMA

	Sister, 74	24-year history of Raynaud's phenomenon, ulcers of toes without skin sclerosis	Studies to exclude visceral disease not reported
Greger (1975)	Father, 74	Raynaud's phenomenon, sclerodactyly; esophageal hypoperistalsis, bilateral interstitial pulmonary fibrosis	Inbred Brandywine isolate
	Son, 39	Raynaud's phenomenon, sclerodactyly, calcinosis cutis, facial sclerosis; skin biopsy of typical scleroderma; pleural thickening, esophageal aperistalsis, colonic sacculations	
	Fourth cousin, 56	Facial sclerosis, interphalangeal flexion contractures of hands, congestive heart failure; esophageal aperistalsis. Death from pneumonia. *Postmortem*: submucosal fibrosis of esophagus, stomach, small and large intestines, myocardial fibrosis, focal glomerulosclerosis with perivascular fibrosis, mild pulmonary interstitial fibrosis, and typical skin histologic changes of scleroderma	

Several possibilities exist regarding the familial occurrence of scleroderma. Genetic susceptibility may be important since chromosomal abnormalities are more common in scleroderma patients than in the general population and have been observed in afflicted members of some "familial" cases (20) but have been lacking in others (14). Serum antinuclear antibodies have been detected in 58% of first degree relatives of patients with scleroderma (21). Recently, histocompatibility antigens HL-A8 and HL-A9 were noted in higher frequency in scleroderma patients than in normal controls (22). In addition, HL-A27 was higher in the CRST variant.

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C. Pathology

The pathologic features of scleroderma consist primarily of fibrosis, atrophy, inflammation and a distinctive change in the vasculature (1). The fibrosis may be patchy or diffuse. Atrophy appears to represent an end-stage process. A perivascular mononuclear inflammatory infiltrate is commonly seen early in the disease in the synovium, muscle and subcutis associated with interstitial mucinous edema (2, 3). Although inflammation, fibrosis and atrophy all contribute to the clinical picture, the vascular lesion appears to be the primary determinant in the patient's survival (4-6).

The small artery (150-500μ in diameter) is the vessel which is primarily involved in this disease. In these vessels the intima concentrically enlarges with proliferation and swelling of the endothelial cells (1). The internal elastic lamina is intact and the media is either normal or slightly thin (1). The adventitia, however, possesses a characteristic fibrous cuff around the artery, which frequently obliterates the periarterial capillaries and lymphatics (7). Mononuclear cells may be present in the periarterial cuff but they do not infiltrate the arterial wall (1).

The smaller arteries (50-150μ in diameter) and arterioles may undergo intimal sclerosis, fibrinoid change and necrosis, especially in the kidney (1).

It is important to note that malignant hypertension appears to complicate renal scleroderma rather than cause the arterial changes (1). In fact, most patients with systemic sclerosis and distinctive small artery changes do not have malignant hypertension (7).

Capillaries are also affected. Maricq and LeRoy found marked dilatation of nailfold and skin capillaries and a decrease in capillary density in these areas (8). In electron microscopic studies of normal skeletal muscle in scleroderma patients, thickening and reduplication of capillary basement membranes were observed (9). In addition, swelling of endothelial cells and a marked decrease in number of capillaries were noted.

Glomeruli may have thickening of the basement membrane and increased lobulation in capillary tufts (1). However, this is a nonspecific finding.

The mucinous edema in the intima and interstitium is apparently due to increased glycoprotein, mucopolysaccharides and collagen (7, 10). The collagen in scleroderma skin and subcutaneous tissue has a narrow fibril diameter, and an immature banding with beaded filaments similar to that of embryonic skin (1). This collagen is apparently synthesized by the interstitial fibroblasts (11). Collagen from active scleroderma skin lesions has a high proportion of reducible cross-links (1), which is similar to children's normal skin. On the other hand, inactive sclerodermatous collagen changes to mainly nonreducible cross-links and resembles normal adult skin (1). Collagen freshly produced by fibroblasts has many reducible cross-links, but as it matures, most of the cross-links become nonreducible. An increase in collagen-bound hexosamine (12) and increased concentrations of glycosaminoglycans (chondroitin-4-6-sulfate and dermatan sulfate) (13, 14) have been reported in scleroderma skin.

In 58 autopsy cases of systemic sclerosis, the extent, frequency and type of involvement in various organs were compared with 58 matched controls (15).

The organs found to be frequently and significantly involved by the disease were the skin, gastrointestinal tract, lungs, kidneys, skeletal muscle and pericardium. Myocardial and pleural involvement was difficult to separate from similar lesions seen in matched controls. Involvement of the brain, anterior pituitary, cardiac valves, liver, spleen, gallbladder, urinary bladder, pancreas and peritoneum were not demonstrated.

The types of pulmonary involvement are shown in Table 5. Interstitial fibrosis and/or arterial thickening were the most common lesions.

Table 5

PULMONARY INVOLVEMENT IN SCLERODERMA

Lesions	Patients with Scleroderma (%)	Controls (%)
Interstitial fibrosis	74	21
Arteriolar thickening	29	2
Interstitial fibrosis and/or arterial thickening	81	22
Pneumonitis	57	33
Emphysema	45	29
Bronchiectasis	14	10
Edema or chronic passive congestion	60	57
Infarction	16	14
Atelectasis	15	33

From ref. (6)

As shown in Table 6, the mitral valve was the most commonly involved in scleroderma patients.

Table 6

VALVULAR HEART LESIONS IN SYSTEMIC SCLEROSIS

Lesions	Prevalence in Patients with Scleroderma		Prevalence in Controls		Corrected Control Prevalence After Subtraction of Known Rheumatic Heart Disease Patients	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Mitral valve	22/58	38	27/58	47	22/53	42
Aortic valve	7/58	12	11/58	19	8/53	15
Tricuspid valve	9/58	15	10/58	17	6/53	11
Known rheumatic heart	0/58	0	5/58	9	0/53	0

From ref. (6)

Some degree of myocardial fibrosis was observed in 81% of patients with scleroderma as compared with 55% of the controls ($p<.01$) (See Table 7).

Table 7

MYOCARDIAL INVOLVEMENT IN SCLERODERMA

Data	Patients with Scleroderma		Controls	
	No.	Per Cent	No.	Per Cent
Number with myocardial fibrosis by decade of age (yr.)				
10-19	0/1	0	0/1	0
20-29	1/1	100	0/1	0
30-39	8/13	62	2/13	15
40-49	13/17	76	10/17	59
50-59	12/13	92	9/13	69
60-69	7/7	100	5/7	71
70-79	6/6	100	6/6	100
Totals	47/58	81	32/58	55
Coronary arteriosclerosis	28/58	48	25/58	43
Arteriolar lesions	10/58	17	1/58	2

From ref. (6)

Involvement of the serous membranes is shown in Table 8. It is apparent that pericardial involvement is the most significant.

Table 8

INVOLVEMENT OF SEROUS MEMBRANES IN SCLERODERMA

Site and Lesions	Patients with Scleroderma		Controls		Corrected Controls	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Pericardium						
Fibrinous pericarditis	20/58	35	3/58	5	3/57*	5
Fibrous pericarditis	14/58	24	4/58	7	3/57*	5
Pericardial adhesions	16/58	28	5/58	9	4/57*	7
Any of above	31/58	53	8/58	14	7/57*	12
Pericardial effusion	20/58	35	18/58	31	18/57*	32
Pleura						
Fibrinous pleuritis	9/58	16	8/58	14	5/42†	12
Fibrous pleuritis	16/58	28	7/58	12	3/42†	7
Pleural adhesions	38/58	66	28/58	48	16/42†	38
Any of above	47/58	81	36/58	62	22/42†	52
Peritoneum						
Peritonitis	5/57‡	7	5/58	9	4/47‡	9
Peritoneal adhesions	13/57‡	23	17/58	34	13/47‡	28

* After subtraction of one control subject with tuberculosis and granulomatous pericarditis.

† After subtraction of sixteen control subjects with carcinoma and pleural metastases, tuberculosis or rheumatic heart disease.

‡ After subtraction of eleven control subjects and one patient with carcinoma and intraabdominal metastases.

From ref. (6)

As shown in Table 9, esophageal atrophy and fibrosis occurred only in the scleroderma patients.

Table 9

GASTROINTESTINAL INVOLVEMENT IN SCLERODERMA

TABLE VI
GASTROINTESTINAL INVOLVEMENT IN SCLERODERMA

Site and Lesions	Patients with Scleroderma		Controls	
	No.	Per Cent	No.	Per Cent
Esophagus				
Muscle atrophy and/or fibrosis	39/53	74	0/58	0
Esophagitis, ulcerations and other lesions	21/53	40	11/58	19
Small intestine				
Muscle atrophy and/or fibrosis	25/52	48	1/58	2
Peptic ulcers*	8/57	14	6/58	10
Other lesions	4/52	8	15/58	26
Large intestine				
Muscle atrophy and/or fibrosis	21/54	39	0/57	0
Carcinoma, polyps and other lesions	12/54	22	15/57	26
Diverticulosis*	9/57	16	6/58	10

* Determined by gross pathologic examination.

From ref. (6)

Significant renal changes included fibrinoid necrosis in the afferent arteriole or glomerulus, hyperplasia of the interlobular arteries and thickening of the basement membrane (Table 10).

Table 10

RENAL INVOLVEMENT IN SYSTEMIC SCLEROSIS

Lesions	Patients with Scleroderma		Controls	
	No.	Per Cent	No.	Per Cent
Fibrinoid necrosis in afferent arteriole or glomerulus	20/57	35	0/56	0
Hyperplasia of interlobular arteries	19/57	33	2/56	4
Thickening of basement membrane or wire-looping	18/57	32	4/56	7
Any of the above	33/57	58	5/56	9
Arteriolosclerosis	11/58	19	12/56	21
Renal arterial stenosis	8/57	14	3/58	5
Pyelonephritis	3/58	5	10/56	18

From ref. (6)

Involvement of other organs is shown in Table 11. Atrophy of the adrenals was more common in scleroderma ($p<0.01$). This may have been due to the use of steroids in these patients. Skeletal muscle atrophy was also more common in the scleroderma group.

Table 11

INVOLVEMENT OF OTHER ORGANS IN SCLERODERMA

Site and Lesions	Patients with Scleroderma		Controls	
	No.	Per Cent	No.	Per Cent
Liver				
Hepatomegaly (over 1,500 gm.)	24/49	49	36/57	63
Cirrhosis	5/57	9	11/58	19
Chronic passive congestion	38/57	67	36/58	62
Spleen				
Lymphoid hyperplasia	3/55	6	3/58	5
Infarct	8/58	14	7/58	12
Pancreas				
Fibrosis	10/58	17	11/58	19
Adrenals				
Atrophy	15/57	26	2/56	4
Skeletal muscle				
Atrophy	20/49	41	0/41	0
Round cell infiltration	4/48	8	0/41	0
Brain				
Lesions	10/34	29	16/44	36
Lymph nodes				
Hyperplasia	7/55	13	6/54	11
Fibrosis	7/56	12	0/54	0
Tuberculosis	4/54	7	5/53	9
Thyroid				
Fibrosis	10/41	24	3/42	7
Hashimoto's thyroiditis	0/41	0	1/42	2
Cancer	1/58	2	17/58	29
Arteries (lesions in two or more organs)				
Noninflammatory intimal proliferation	13/58	24	0/58	0
Inflammatory polyarteritis	5/58	9	0/58	0

From ref. (6)

Twelve of the 58 (21%) patients had some manifestations of an "overlap" syndrome.

Table 12
OVERLAP SYNDROMES

Data	Number	Per Cent
Patients with one or more manifestations of other connective tissue disease	12/58	21
Manifestation		
Myositis	5/58	9
Arteritis	5/58	9
Systemic lupus erythematosus	1/58	2
Rheumatoid arthritis	1/58	2
Manifestations of diffuse connective tissue disease in control subjects	0/58	0

From ref. (6)

The summary of organs principally involved is shown in Table 13. The skin, of course, was involved in 98% of cases. In addition, the esophagus, lungs, kidneys and small intestine were quite commonly involved.

Table 13

SUMMARY OF ORGANS PRINCIPALLY INVOLVED IN SYSTEMIC SCLEROSIS

Site	Prevalence in Systemic Sclerosis (%)	Excess Prevalence Over Controls (%)
Skin	98	98
Esophagus	74	74
Lungs	81	59
Kidney	58	49
Small intestine	48	46
Pericardium, any lesion	53	41*
Muscles	41	41
Large intestine	39	39
Pleura, any lesion	81	29*
Myocardium	81	26

*"Corrected controls"

From ref. (6)

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D. Pathogenesis

Campbell and LeRoy (1) have suggested that the pathogenesis of systemic sclerosis results from the following sequence of events: an unknown agent initiates a mononuclear inflammatory response around small arteries and in the interstitium of tissues. The fibroblastic proliferative phase of this response is markedly increased and prolonged and eventually leads to severe sclerosis of the intima of the small arteries and the interstitium. The resulting tissue induration and vascular insufficiency are responsible for the signs and symptoms of systemic sclerosis.

The appearance of mononuclear inflammatory cells in the interstitium and around arteries in the early stages of the disease and the increased production of normal products of the fibroblast are consistent with this idea (1).

Cultured scleroderma fibroblasts have an increased population doubling time over control fibroblasts (2). It has also been demonstrated that the scleroderma fibroblast produces more soluble collagen, synthesizes collagen more rapidly and four times more of its protein synthetic activity is directed to collagen production than in the normal skin fibroblast (3). More recently, however, other workers have been unable to demonstrate an increase in collagen synthesis by fibroblasts isolated from sclerodermatous skin or adjacent clinically noninvolved skin (4). This group has suggested that there is a possible defect in the *in vitro* maturation of collagen synthesized by scleroderma fibroblasts as compared with normal fibroblasts (5). Other studies have demonstrated a significant increase of 3-OH proline and a slight increase in 4-OH proline and OH-lysine in scleroderma collagen (6) and diminished growth of epidermal epithelial cells from involved areas of skin in systemic sclerosis patients (7). Analysis of the total dermis from scleroderma revealed a normal concentration of hydroxyproline while hexosamines were increased in a significant number of cases (8).

In one unique study (15), glycosaminoglycans obtained from the urine of patients with systemic scleroderma were injected intraperitoneally into mice. Following such daily injections for 12-13 days, a fibrotic process similar to the initial changes of human scleroderma was frequently observed, especially in the skin and esophagus.

1.) Possible Role of Cellular Immunity

One of the most potentially important observations regarding the pathogenesis of scleroderma is that of Johnson and Ziff (9). In this study, lymphokine-rich supernates from normal human peripheral blood mononuclear cells, stimulated by the mitogen, phytohemagglutinin, were shown to cause enhanced collagen accumulation by human embryonic lung fibroblasts. This nondialyzable factor was the first described lymphoid cell-derived activity capable of enhancing collagen accumulation. Another indication of the participation of abnormal cellular

immunity in scleroderma patients is the observation that lymphocytes from scleroderma patients with myositis produced cytopathic alterations in fibroblast cultures (27).

Thus Ziff's "Graveyard Hypothesis" of scleroderma suggests the following: an unknown agent is present in the skin of scleroderma patients. The body responds with an inflammatory mononuclear cell response. Such an infiltrate contains T-lymphocytes as mediators of cellular immunity by elaborating various lymphokines, including a fibroblast stimulating factor. The new collagen which is produced then crowds out normal tissue with resulting atrophy and death of normal structures. Vascular abnormalities may similarly result from lymphokines released from perivascular infiltrates, causing injury to vascular endothelial cells. This latter idea is supported by recent studies by Fleischmajer and coworkers (10) in which skin biopsy specimens were obtained from involved and noninvolved areas in a patient with early diffuse systemic scleroderma and were processed for histology, electron microscopy and *in vitro* autoradiography with tritiated thymidine. The affected area revealed cellular infiltrates around the eccrine sweat glands, consisting of plasma cells and lymphocytes. The capillaries showed thickening of the basement lamina, damage of endothelial cells, and obstruction of their lumens. Autoradiography with tritiated thymidine showed a marked increase in endothelial and periendothelial cell labeling (see Tables 14 and 15).

Table 14

TRITIATED THYMIDINE LABELING OF BASAL CELL LAYER AND DERMAL CELLS

	Basal Cell Layer			Dermis
	No. of Cells Counted	Labeled Cells	Labeling Index	Labeled Cells*
Scleroderma				
Involved	2,636	261	9.89	39.45
Noninvolved, adjacent to involved area	3,054	183	5.99	19.31
Noninvolved	3,674	190	5.17	5.98
Controls				
I	1,262	82	6.64	5.54
II	1,647	94	5.70	2.42
III	2,188	137	6.26	3.19

*Vascular and extravascular dermal labeled cells for a distance corresponding to 1,000 basal cells.

From ref. (10)

Table 15

TRITIATED THYMIDINE LABELING INDEX OF ENDOTHELIAL CELLS

	No. of Cells Counted	No. of Vessels Studied	Labeled Cells	Labeling Index
Scleroderma				
Involved	268	46	25	9.32
Noninvolved, adjacent to involved area	313	60	11	3.52
Noninvolved	213	46	2	0.94
Controls				
I	251	42	1	0.39
II	102	20	0	0.00
III	163	33	0	0.00

From ref. (10)

A new lymphokine that is chemotactic for human dermal fibroblasts has recently been described (11). The same workers have also demonstrated cellular immunity to collagen in patients with scleroderma (12). They demonstrated that leukocytes from scleroderma patients produced a factor chemotactic for human monocytes when cultured with collagen preparations. In addition, lymphocytes from some of the patients were found to transform when cultured with the collagen preparations. These responses were significantly different from the response of leukocytes from normal control subjects.

In similar studies (13) lymphocytes of patients with diffuse scleroderma responded to extracts of both normal and sclerodermatous skin in a macrophage migration inhibition assay. In the same study it was also demonstrated that T-lymphocytes made up the majority of lymphocytes in the infiltrates in scleroderma skin. These findings suggested that lymphocytes sensitized to skin extracts are present in patients with diffuse scleroderma. The authors concluded that the cell-mediated immune reaction to skin antigens may be a factor in the pathogenesis of diffuse scleroderma.

Somewhat similar to Johnson and Ziff's studies is the observation by Sisson and coworkers (14) that stimulation of the production of glycosaminoglycan occurred when retrobulbar fibroblasts were exposed to lymphocyte lysates.

(a) Scleroderma-like Changes in Chronic Graft vs. Host Disease

Further support for the concept that cellular immunity is of major importance in the pathogenesis of scleroderma is gained by recent observations in patients with chronic graft vs. host disease (16, 17, 26). This disease

has resulted from the increased usage of bone marrow transplantations. It occurs in approximately 70% of patients after successful bone marrow engraftment despite the use of marrow from siblings matched at the major histocompatibility loci (17).

It occurs when histoincompatible, immunologically competent donor lymphocytes are introduced into a recipient or host not capable of rejecting them. The immunologically compromised host does not recognize these cells as foreign and does not destroy them by usual defense mechanisms. Donor lymphocytes survive and become aggressive, affecting various host tissues, leading to the syndrome of graft vs. host disease (17-19). The dominant effector cell is the T-lymphocyte (17).

In animals, as well as in man, graft vs. host disease can occasionally produce sclerodermatous-like skin changes (20). In the homologous disease in the rat, active lesions showed dermal infiltration while chronic skin lesions showed atrophy of the epidermis and collagenization of the dermis with disappearance of the skin appendages, features similar to those seen in scleroderma.

2.) Possible Role of Genetics

A higher frequency of HL-A9 and HL-A8 transplantation antigens has been found in patients with progressive systemic sclerosis (21).

Chromosome aberrations such as gaps and breaks of one or both chromatids, acentric fragments, dicentrics, ring chromosomes and other abnormal chromosomes are observed in lymphocyte and fibroblast cultures as well as in direct bone marrow preparations from patients with systemic sclerosis as well as in family members (22-24). It has been shown that the serum of patients contains a chromosome-breaking agent which can be transferred into the lymphocyte cultures of healthy donors (24, 25). The aberration rate induced by this factor can be reduced to near normal if L-cysteine is added to the culture medium over the entire incubation period.

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E. Clinical Features

The clinical features in 261 patients with scleroderma are shown in Table 16.

Table 16

Systemic Involvement in Systemic Sclerosis
Survey of 261 Patients

Skin	90%
Raynaud's phenomenon	78%
Esophagus	52%
Lung	43%
Heart	40%
Kidney	35%
Anemia	27%
Articular	25%
Hypertension	21%
Muscle	20%
Small and large bowel	15%
Pericardium	11%

Modified from (1)

The initial manifestations which may be seen are shown in Table 17.

Table 17

INITIAL MANIFESTATIONS OF SCLERODERMA

1. Weakness, weight loss, easy fatigability, neurasthenia
2. Vague musculoskeletal aching
3. Arthritis (rheumatoid)
4. Raynaud's phenomenon
5. Stiffness of hands
6. Altered pigmentation
7. Unexplained edema (local or general)
8. Thickening of skin (local or general)
9. Telangiectases
10. Loss of body hair
11. Dysphagia, heartburn
12. Dyspnea on exertion
13. FUO
14. Renal insufficiency, hypertension (malignant)
15. Cardiac failure (cor pulmonale)
16. Pleuritis, pericarditis

From ref. (2)

In a study of 271 patients at the Mayo Clinic by Farmer et al (3), the initial symptoms were as shown in Table 18.

Table 18

INITIAL SYMPTOMS IN 271 PATIENTS WITH SCLERODERMA

Symptom	Number	Per Cent
Scleroderma of hands	132	48.7
Raynaud's phenomenon	88	32.5
Scleroderma of the extremities or face, but not of the hands	19	7.0
Generalized stiffness of the joints	14	5.2
Scleroderma of trunk	7	2.6
Trophic changes of the fingers (ulceration, fissuring, chronic paronychias)	5	1.8
Pigmentation	3	1.1
Dysphagia	2	0.7
Dyspnea	1	0.4

Many patients with scleroderma describe the initial changes in their hands as a swelling of the hands.

From ref. (3)

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1.) Cutaneous

Some authors (1) classify progressive systemic sclerosis into four categories as shown in Table 19.

Table 19

Systemic Forms of Scleroderma

Diffuse Progressive Scleroderma
Acrosclerosis
Thibierge-Weissenbach Syndrome (calcinosis cutis)
CRST Syndrome

From Ref. (1)

The latter two categories will be discussed later. In the diffuse progressive type of scleroderma the major skin lesions are limited to the trunk, upper arms and thighs. The hands and face are usually spared and Raynaud's phenomenon is usually absent. This form is unusual, occurring in only 5% of the 727 patients reported by the Mayo Clinic (2) and 8% of the 65 patients reported by Sackner (1).

In the acrosclerotic form, skin lesions are found mainly over hands, forearms, face and upper chest (1). The legs show little involvement. Raynaud's phenomenon and arthralgias are usually present.

In both of the above types, three distinct stages of the cutaneous involvement can be seen: 1.) edematous; 2.) indurative; and 3.) atrophic (3).

In the initial edematous stage, the skin appears tense and cannot be folded. The edema is non-pitting. The face has a mask-like appearance (1). During this stage periorbital edema may be seen (4). In the indurative stage, the skin becomes hard and stiff, especially over the fingers, dorsa of the hands and forearms. The fingers cannot be fully extended, and superficially, may mimic rheumatoid arthritis of the hands. In the indurative stage, hyperpigmented and depigmented spots may occur over the forearms, upper chest and scalp with alopecia.

In the atrophic stage, the tips of the fingers become small and pointed. The fingers become fixed in a flexed position, resulting in a claw-like appearance (1). Ulcerations may develop at the finger tips or over bony prominences of the hands. The aperture of the mouth becomes small and smiling is difficult. Telangiectasias may be present on the face. Two of Sackner's 65 patients (1) developed severe ulcers of the upper or lower extremities.

As mentioned previously (see Pathology and Pathogenesis) cellular infiltrates are commonly seen in scleroderma skin. In one study, infiltrates, perivascular or diffuse, were noted in 49% of systemic sclerosis and 84% of localized scleroderma patients and consisted of lymphocytes, plasma cells and macrophages (5). The frequency and localization of the cellular infiltrates are shown in Table 20.

TABLE 20

Frequency and Localization of Skin Cellular Infiltrates

		Location of Cellular Infiltrates		
Cellular Infiltrates	No. of Patients	Dermis	Subcutaneous Tissue	Dermis and Subcutaneous Tissue
Systemic scleroderma (65)*				
Diffuse	15 (23%)	2	9	4
Perivascular	17 (26%)	13	2	2
Absent	33 (50%)	0	0	0
Localized scleroderma (43)*				
Diffuse	31 (72%)	4	9	18
Perivascular	5 (12%)	3	0	2
Absent	7 (15%)	0	0	0

*Number of patients studied.

From ref. (5)

In a very interesting study by Fries and coworkers (6), full-thickness skin grafts were exchanged between involved forearm skin and uninvolved abdominal skin in patients with systemic sclerosis. After 7 to 9 months the grafts and adjacent skin were examined histologically. The results showed that when clinically normal skin is placed in a sclerodermatous bed, it becomes sclerodermatous. If sclerodermatous skin is placed in a normal bed, it remains sclerodermatous. The authors concluded that skin involvement in systemic sclerosis is irreversible, in contrast to morphea, in which the disorder is localized and reversible (7). In the morphea experiments (7), normal skin grafted into a morphea lesion became abnormal, while the diseased skin grafted into a normal region became normal.

In a recent study using widefield microscopy to observe skin and nailfold capillary abnormalities, a distinctive microvascular pattern was noted in scleroderma patients (8) as well as in patients with dermatomyositis and Raynaud's phenomenon. This abnormality consisted of dilated and distorted capillary loops alternating with avascular areas. A positive correlation was found between the degree and extent of abnormal microvascular patterns and multisystem involvement.

A number of unusual nail abnormalities have been reported in scleroderma patients. These include vesiculation of the periungual area, pterygium unguis, absence of the lunula, "wath glass" nail, development of deep longitudinal sulci, hapalonychia, onychorrhexis, onycholysis and onychogryphosis (9, 10). In the most recent report (11), over an 18-month period, four patients with scleroderma were found to have nail changes of pterygium inversum unguis, a condition which is characterized by adherence of the distal portion of the nail bed to the ventral surface of the nail plate, thereby obliterating the normal distal separation of these structures.

Various methods of assessing scleroderma skin involvement are available (12-14). A Schiotz tonometer has been modified to allow its application to the volar surface of the finger and thumb pads, halfway between the distal volar crease and end of the digit (15). The device is not intended to be used diagnostically but to follow improvement or worsening of the skin in scleroderma.

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2.) Cardiovascular

The various types of cardiovascular involvement in scleroderma are shown in Table 21.

TABLE 21

CARDIOVASCULAR SYSTEM INVOLVEMENT IN SCLERODERMA

	Clinical signs and symptoms	Pathological findings	Rosentgenographic findings
Cardiac	Arrhythmias Cardiac murmurs EKG abnomalities Chronic cor pulmonale Myocardial failure	Focal muscle necrosis Focal or diffuse fibrosis Valvularheart disease Pericarditis	Cardiomegaly Left ventricular hypertrophy Pericardial effusion
Vascular	Raynayd's phenomenon Large artery disease (ex: panaortitis, internal carotid) Arteriolar lesions	Subintimal proliferation of connective tissue Subendothelial fibrin deposits Basement membrane tickening Fragmentation of elastic tissue	

From ref. (1)

The causes of the heart failure are shown in Table 22.

Table 22

Causes of Heart Failure in Scleroderma

1.) Cor pulmonale (fibrosis, pulmonary arterial changes)
2.) Hypertension 2° to renal scleroderma
3.) Degenerative vascular changes
4.) Scleroderma myocarditis (Conduction defects)
5.) Pericarditis

From Ref. (2)

Dyspnea, especially with exertion, is the most common cardiorespiratory symptom found in scleroderma (3). In a study of 65 patients, Sackner and coworkers (3) concluded that scleroderma heart disease is an uncommon clinicopathologic entity. In spite of this, however, abnormalities of cardiac function are fairly common because myocardial function is affected by: 1.) pulmonary hypertension, 2.) systemic hypertension associated with "scleroderma kidney":, 3.) pericarditis and pericardial effusion and 4.) hypoxia associated with restrictive pulmonary disease. The associations of dyspnea are shown in Table 23.

TABLE 23

ASSOCIATIONS OF DYSPNEA IN SCLERODERMA

	Cases No.	(%)
Pulmonary fibrosis &/or pulmonary hypertension	27	(52%)
Scleroderma kidney	7	(13%)
Scleroderma heart with pulmonary hypertension or scleroderma kidney	3	(6%)
Coronary artery disease	3	(6%)
Acute pericarditis	2	(4%)
Mitral valvular disease	2	(4%)
Pulmonary tuberculosis	1	(2%)
Cause undetermined (necropsy in 4 cases)	5	(10%)
Cardiac enlargement, cause undetermined	2	(4%)

From ref. (3)

The incidence of pericardial disease is shown in Table 24.

TABLE 24

PERICARDIAL DISEASE IN SCLERODERMA

		Cases	
		No.	(%)
Acute fibrinous pericarditis		5	(20%)
Uremia	4		
Chronic pericarditis	1		
Chronic adhesive pericarditis		9	(36%)
Pericardial effusion		4	(16%)
No pericardial disease		7	(28%)
Total cases		25	(100%)

From ref. (3)

The electrocardiographic findings in 60 patients are shown in Table 25. It is apparent that evidence of right ventricular hypertrophy was the most common finding.

TABLE 25

ELECTROCARDIOGRAPHIC FINDINGS IN 60 CASES OF SCLERODERMA

	Cases	
	No.	(%)
RVH	16	(27%)
LVH	9	(15%)
RVH & LVH	3	(5%)
P pulmonale	9	(15%)
Notched P, standard leads	7	(12%)
Low voltage	3	(5%)
Right bundle branch block	3	(5%)
Left bundle branch block	1	(2%)
Pericarditis	2	(3%)
Myocardial infarction	4	(7%)
1° heart block	9	(15%)
2° heart block	1	(2%)
Atrial fibrillation	5	(8%)
Paroxysmal atrial tachycardia	5	(8%)
Atrial extrasystoles	5	(8%)
Ventricular extrasystoles	4	(7%)

From ref. (3)

Phonocardiographic findings are shown in Table 26.

TABLE 26

PHONOCARDIOGRAPHIC FINDINGS IN SCLERODERMA

Group	Hypertrophy No RV	Hypertrophy RV	Right Sided Failure	Scleroderma Kidney
Cases	13	9	8	5
Accentuation of pulmonic component of second heart sound	1	8	8	0
Presystolic gallop*	7 (3)	5 (4)	8 (8)	4 (4)
Protodiastolic gallop*	1 (1)	1 (1)	0 (0)	1 (1)
Apical systolic murmur	2	2	2	1
Basilar systolic murmur	1	0	0	2
Pericardial friction rub	1	0	2	0

*Numbers in parentheses represent cases in which gallop was heard upon clinical auscultation.
RV = right ventricular.

From ref. (3)

In more recent studies (4), the records of 210 patients with scleroderma seen between 1952 and 1972 revealed two clinical patterns of pericardial disease in 15 patients: 1.) Chronic pericardial effusion (11 patients), occurred in association with dyspnea, Raynaud's phenomenon, cardiomegaly, congestive heart failure and pleural effusion in the absence of renal failure. In 3 patients hemodynamic signs of pulsus paradoxus, Kussmaul's sign or pulsus alternans developed. In 6 patients with chronic effusion, renal failure developed within 6 months, an incidence higher than expected in the scleroderma population ar large. 2.) Acute pericarditis (4 patients) was associated with dyspnea, chest pain, pericardial friction rub, fever, cardiomegaly and elevated latex fixation titers (in 2 or 4 patients). (See Tables 27, 28 and 29).

TABLE 27

Summary of Clinical Data on Patients with Pericardial Disease

Data	Chronic Effusion	Acute Pericarditis
Age (yr.), mean (range)	53 (39-76)	50 (32-79)
Sex (male/female)	4/7	0/4
Race		
White	7/11	0/4
Black	3/11	4/4
Hispanic	1/11	0/4
Raynaud's syndrome	10/11	1/4
Dyspnea	10/11	4/4
Chest pain	4/11	3/4
Pericardial friction rub	0/11	4/4
Fever (>100°F)	4/11	3/4
Hypertension (diastolic >100 mm Hg)	2/11	0/4
Chest roentgenogram		
Cardiomegaly	11/11	4/4
Increased pulmonary markings	6/11	3/4
Pleural effusion	6/11	0/4
Electrocardiogram		
Low voltage	7/11	1/4
Loss of voltage	1/11	2/4
T wave abnormalities	8/11	3/4
Leukocytosis (>10,000/mm^3)	4/11	2/4
Erythrocyte sedimentation rate (>25)	7/11	4/4
Rapid renal failure within 6 months	6/11	0/4

From ref. (4)

TABLE 28

HEMODYNAMIC SIGNS

Signs	Chronic Effusion	Acute Pericarditis
Congestive failure		
1. Pedal edema	10/11	0/4
2. Distended neck veins	8/11	1/4
3. Hepatomegaly	7/11	0/4
4. Tachycardia without fever	3/11	0/4
Either 1, 2, 3 or 4	11/11	1/4
Pericardial signs		
5. Pulsus paradoxus	1/11	0/4
6. Kussmaul's sign	2/11	0/4
7. Pulsus alternans	2/11	0/4
Either 5, 6 or 7	3/11	0/4

From ref. (4)

Table 29
SUMMARY OF DATA ON 34 POSTMORTEM PATIENTS

Clinical Data		Total Series
Age (yr), mean (range)		53 (39–76)
Sex (male/female)		7/27
Race		
White		21/34 (62%)
Black		11/34 (32%)
Hispanic		2/34 (6%)
Postmortem Data	**Without Azotemia***	
Heart		
Pericardium		
Pericardial disease (total) at postmortem		19/34 (56%)
Adjusted incidence of pericardial disease (total)†	12/22 (55%)	21/34 (62%)
Pericardial effusion without pericarditis	7/22 (32%)	12/34 (35%)
Pericarditis without effusion	4/22 (18%)	8/34 (24%)
Pericarditis with effusion	1/22 (5%)	1/34 (3%)
Myocardium		
Fibrosis, diffuse		4/34 (12%)
Fibrosis, focal, severe		6/34 (18%)
Fibrosis, focal, mild		7/34 (21%)
Increased heart weight		20/32 (63%)‡
Left ventricular hypertrophy		15/32 (47%)‡
Right ventricular hypertrophy		9/32 (28%)‡
Biventricular hypertrophy		8/32 (25%)‡
Lung		
Fibrosis		22/34 (65%)
Pleural effusion (>100 cc)		20/34 (59%)
Gastrointestinal		21/34 (62%)
Skeletal muscle		7/34 (21%)
Vascular		26/34 (76%)

* Adjusted for two patients (L.G. and T.C., Table I) who had documented pericardial effusion when their blood urea nitrogen level was normal.
† Addition of two patients (A.D. and R.L., Table I) who had documented pericardial effusion prior to death during period of normal blood urea nitrogen.
‡ This determination was not made in two postmortem examinations.

From ref. (4)

Autopsy results from this group of patients are shown in Table 30.

Table 30

DATA ON PATIENTS WITH PERICARDIAL DISEASE AT POSTMORTEM

Patient	Age (yr), Sex, Race	Blood Urea Nitrogen (mg/100 ml)	Pericardium		Autopsy Organ Involvement*						
						Lung					
			Pericarditis	Effusion	Heart	Pleural Effusion	Fibrosis	Kidney	Vascular	Gastro-intestinal	Muscle
T.J.	44,M,W	104	Acute fibrinous	−	−	−	+	+	+	−	−
Z.D.	55,F,W	163	Acute fibrinous	−	−	+	+	+	−	+	−
K.G.	64,F,W	29	Acute fibrinous	−	−	+	+	−	−	−	−
M.M.	42,F,B	60	Fibrous—with inflammation	−	MFF	+	+	+	+	+	−
R.A.	66,F,W	15	Fibrous	−	MC MFF	+	+	+	+	+	+
A.Mc.	40,F,B	19	Fibrous	−	SFF	−	+	−	+	+	+
D.T.	32,F,B	11	Fibrous	−	DF	+	−	−	+	−	+
C.Th.	60,F,B	117	Fibrous	−	−	+	−	+	+	+	−
T.C.	52,F,H	60	Acute fibrinous	+	−	+	+	+	+	+	+
H.M.	63,F,W	110	−	+	SFF	+	−	+	+	−	−
M.E.	42,F,W	116	−	+	−	+	−	+	+	−	−
B.O.	76,F,W	14	−	+	MFF	+	+	−	−	−	−
M.R.	41,F,B	20	−	+	DF	+	+	−	+	+	−
E.R.	40,F,H	27‡	−	+	MFF	−	+	+	+	+	−
B.M.	67,F,B	49	−	+	DF	+	+	+	+	+	−
S.F.	43,F,W	12	−	+	−	−	+	+	+	−	+
F.D.	54,F,W	57	−	+	SFF	−	+	+	+	+	−
M.A.	40,F,W	46	−	+	MFF	+	+	+	+	+	−
L.G.	52,F,W	74	−	+	MC SFF	+	+	+	+	+	−

NOTE: W = white; B = black; H = hispanic; + = present; − = absent.

* See methods for criterial of organ involvement. MFF = mild focal fibrosis; SFF = severe focal fibrosis; DF = diffuse fibrosis; MC = myocarditis.

‡ Nonprotein nitrogen (normal = 15–35 mg/100 ml).

From ref. (4)

It is of interest that left ventricular hypertrophy at postmortem examination could not be correlated with hypertension and/or uremia prior to death; similarly, right ventricular hypertrophy could not be correlated with pulmonary fibrosis (4). Thus, this study did not support the findings of Sackner and coworkers (5, 6). McWhorter and LeRoy (4) concluded that pericardial disease is a recognizable clinical entity in scleroderma and should be considered in all patients with cardiomegaly, congestive heart failure or chest pain. In their studies, the incidence of pericardial involvement (62%) exceeded the incidence of significant myocardial fibrosis (30%).

Very few studies have been performed on the pericardial fluid of scleroderma patients (7-9). The findings from the study of Gladman and coworkers (9) are shown in Table 31.

Table 31

Comparison of the Properties of Serum and Pericardial Fluid from Scleroderma in Our Patient

Determinations	Serum	Pericardial Fluid
White cell count (mm^3)	7,800	400
Glucose (mg/100 ml)	122	108
Electrophoresis (g/100 ml)		
Total protein	7.2	5.8
Albumin	3.14	2.64
$Alpha_2$ globulin	1.23	0.85
Gamma globulin	1.33	1.09
Immunoglobulin levels		
IgG (normal 1,137 ± 200 mg/100 ml)	1,450	1,080
IgA (normal 231 ± 73 mg/100 ml)	220	170
IgM (normal 103 ± 36 mg/100 ml)	56	43
Latex test	Negative	Negative
Antinuclear factor	Negative	Negative
Lupus erythematosus test	Negative	Negative
C_3 (normal 100 to 140 mg/100 ml)	195	155
CH_{50} (normal 160 to 220 Units)	210	170
Cryoglobulins	Negative	Negative
Free DNA	Negative	Negative
Antinative DNA	Negative	Negative
Antisingle-stranded DNA	Positive	Negative
Soluble immune complexes		
Analytical ultracentrifugation	NA*	Negative
Histamine releasing activity	NA*	Negative

*NA = not ascertained.

From ref. (9)

A comparison of pericardial fluid properties from the 3 different studies is shown in Table 32.

TABLE 32

Properties of Pericardial Fluid from Patients with Scleroderma

Source	Meltzer	Meltzer	Bedford	Gladman (present report)
Volume (cc)	550	175	800	175
Appearance	Straw	Straw	Straw	Blood-tinged
Total protein (g/100 ml)	5.9	6.8	NA*	5.8
White cell count (mm^3)	37	4	NA*	400
Culture	Negative	Negative	Negative	Negative

*NA = not ascertained.

From ref. (9)

A comparison of the properties of pericardial fluid in rheumatoid arthritis, systemic lupus erythematosus and scleroderma patients is given in Table 33.

Table 33

Comparison of the Properties of Pericardial Fluid in Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis (SS)

Determinations	RA	SLE	SS
Number of cases	8	4	1
Source	19-21	22-24	Gladman (present report)
Appearance	Serous	Yellow-bloody	Blood-tinged
White cell count (mm^3)	950-88,100	1,280-30,800	400
Glucose (mg/100 ml)	14-65	61-90	108
Total protein (g/100 ml)	4.5-9.7	3.4-7.6	5.8
Immunoelectrophoresis	Increased gamma globulin	NA*	Normal
Latex test	Positive	Negative	Negative
Antinuclear factor	Negative	Positive	Negative
Lupus erythematosus	Negative	Positive	Negative
C_3	Normal or low	Low	Normal
CH_{50}	Low	Low	Normal
Cryoglobulins	NA*	NA*	Negative
Free DNA and DNA antibodies	NA*	NA*	Negative
Soluble immune complexes	Positive	NA*	Negative

*NA = not ascertained.

From ref. (9)

In a recent study (10) the focal replacement fibrosis characteristic of progressive systemic sclerosis heart disease was shown to evolve from foci of contraction band necrosis. Since the intramyocardial vessels were normal, it was suggested that the focal contraction band necrosis was caused by an intermittent spasm (Raynaud's phenomenon) of the supplying vessels. Thus it was concluded that such myocardial involvement was a relatively frequent occurrence (see Table 34) which may lead to arrhythmias, congestive heart failure, angina pectoris with normal coronary arteries and sudden death.

Table 34

Frequency of the Myocardial Lesion in 47 Patients*

Myocardial Lesion	Severe (3-4+)	Mild (1-2+)	Absent (0)
Number of patients	13	10	24
Contraction band necrosis (%)	10 (77)	4 (40)	2 (8)

*Five patients excluded because of coexisting severe epicardial coronary artery disease.

From ref. (10)

In a somewhat similar study by the same authors (11), it was concluded that despite the greater frequency of EKG abnormalities in patients with progressive systemic sclerosis heart disease, conduction system disease per se was rarely the cause. They believed that the conduction disturbances most commonly were a consequence of damaged myocardium rather than a specific damage to the proximal portion of the specialized conduction tissue. On the other hand, the conduction system may be replaced by fibroelastic tissue (12).

While the studies by Bulkley and coworkers (10, 11) suggested that the coronary arteries were normal in most cases, small vessels may be involved, particularly with intimal thickening (3, 13-15).

Echocardiography has recently been utilized for following progression of the disease process (16). Two patients with sclerodermatous cardiac disease were studied. In one patient the pattern was that of a congestive cardiomyopathy with ventricular dilatation and reduced wall motion. In the second patient the pattern was that of an infiltrative cardiomyopathy with thickened walls and reduced wall motion in the absence of ventricular dilatation.

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3.) Pulmonary

The lungs are frequently involved in scleroderma. Usually, pulmonary symptoms follow the cutaneous involvement but may occasionally occur before any skin changes (1). The most common symptom is dyspnea; cough and sputum production are also quite common. Hemoptysis, pleuritic chest pain and recurrent fever are infrequent symptoms (2). (See Table 35).

Moist basilar rales are present in 50% of those with pulmonary involvement (3).

As shown in Table 35, interstitial fibrosis and thickening of the alveolar septa are the most common pathological changes.

TABLE 35

Pulmonary System Involvement in Scleroderma

	Clinical signs and symptoms	Pathological findings	Roentgenographic findings
LUNGS	Dyspnea Cough (nonproductive mucopurulent) Hemoptysis Pleuritic pain Chest pain Basilar rales Decrease breath sounds Clubbing of nails Secondary emphysematous changes Spontaneous pneumothorax	Pleural adhesions, thickening, fibrosis Interstitial fibrosis, thickening of alveolar septa Vascular lesions preivascular fibrosis medial hypertrophy intimal proliferation Subpleural cysts	Symmetroc fibrosis with increased density toward bases; apices usually spared Nodular type of fibrosis less frequent Cystic lesions, honeycomb lung Disseminated pulmonary calcification Pleural fibrosis

From ref. (2)

Abnormal pulmonary function studies can often be detected before clinical and x-ray evidence of the disease are apparent.

The initial physiologic event is a restrictive defect manifested by a reduced vital capacity and total lung capacity. The restrictive defect is attributed to sclerosis of the chest wall, involvement of the diaphragm and fibrosis and contraction of the pleura. With the development of peribronchial fibrosis, an obstructive pattern develops which is manifested by diminished maximal breathing capacity and increased residual volume (2, 4).

As high as 70% of scleroderma patients will have abnormal pulmonary function tests.

In a recent study of 45 patients with scleroderma (5), various pulmonary function tests were performed (see Table 36).

Table 36

Clinical and Pulmonary Function Parameters of the Three Groups

	Restrictive Disease	Obstructive Disease	Small Airway Disease
Number of patients	13	12	19
Mean years of disease	4.54	3.91	4.36
Smokers*†	3/12 (25%)	2/11 (48%)	9/18 (50%)
Dyspnea*	12 (92%)	7 (58%)	6 (32%)
Abnormal chest film*	13 (100%)	7 (58%)	6 (32%)
Dyspnea and abnormal chest film*	12 (92%)	5 (41%)	1 (5%)
Vital capacity‡	57.6±6.2	78.8±19.3	81.7±19.6
Total lung capacity‡	57.7±8.2	101.5±13.4	103.3±16.0
Residual volume‡	109.9±29.6	151.7±36.2	165.7±30.8
RV/TLC X 100§	40.8±7.3	44.9±11.2	42.5±8.9
FEV_1/FVC X 100§	82±5	68±7	86±5
MMFR‡	54±17	43±17	95±28
D_L(ml/min/mmHg)§	9.8±4.8	13.3±7.0	15.9±4.2
Abnormal D_L*	11 (85%)	8 (67%)	8 (42%)

RV/TLC = residual volume/total lung capacity: FEV_1/FVC = forced 1-second expiratory volume/forced vital capacity: MMFR = maximal midexpiratory flow rate: D_L = diffusing capacity for carbon monoxide.

*Number of patients and percentage of group total.

†Denominator represents number questioned about smoking.

‡Mean percentage of predicted ± standard deviation.

§Mean ± standard deviation.

From ref. (5)

Of the 45 patients, 13 (29%) had restrictive disease, 12 patients (27%) had obstructive disease and 19 patients (42%) had small airways disease (SAD). A low diffusing capacity was most common in patients with restrictive disease and rarely the only abnormality in pulmonary function. SAD was usually found in patients who had normal chest radiographs and no pulmonary symptoms and was often the only abnormality. The authors concluded that SAD was an early and sensitive indicator of pulmonary involvement in scleroderma (5).

Pulmonary fibrosis may lead to cor pulmonale. Changes in the pulmonary arterial system may cause progressive pulmonary hypertension and right heart failure (6). The lung fibrosis may induce pulmonary hypertension by replacement and mechanical compression of the pulmonary vascular bed and by periadventitial fibrosis and hyalinization (2). Fibrosis may also cause hypoxia through thickening of the alveolar septa and by arteriovenous shunting in the lungs. The hypoxia also may contribute to pulmonary hypertension.

In a study of 41 cases, the frequency of roentgenographic pulmonary arterial hypertension (PAH) was determined (7). The primary criteria employed included enlargement of the main pulmonary artery segment or pulmonary outflow tract and unequivocal enlargement of both right and left main pulmonary arteries.

Secondary criteria included rapid peripheral tapering of pulmonary arterial branches and signs of right ventricular enlargement. Finally, the medical records were surveyed for clinical evidence of PAH (i.e. increased pulmonic component of the second heart sound, a widely split or fixed split second heart sound, right ventricular heave, EKG evidence of right ventricular hypertrophy). Results showed that 12% of cases showed definite roentgenographic evidence of PAH. A total of 37% had suggestive evidence of PAH. The degree of PAH was out of proportion to the severity of interstitial pulmonary disease attributable to scleroderma. No correlation between PAH and presence of Raynaud's phenomenon was found.

Three basic processes in the lungs may be identified: 1.) predominantly lung fibrosis; 2.) both pulmonary parenchymatous and vascular lesions; and 3.) predominantly involvement of the pulmonary arteries (8).

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4.) Oral

Involvement of the oral mucous membranes occurs commonly in systemic scleroderma. The lips are thinned (microcheilia) and the mucous membranes are tense (1). Telangiectases may be present around the lips, tongue and mucous membranes. The mouth is distinctly narrowed (microstomia). The tongue is stiff and immobile which is due to thickening and shortening of the insertion of the base of the tongue (1).

One of the most common findings is that of widening of the periodontal ligament, which affects the posterior more than the anterior teeth (2). Other features which have been reported include induration and atrophy of the musculature of the tongue, lips and soft palate, resorption of alveolar bone, pseudoankylosis of the temporomandibular joint and the occurrence of scleroderma-tous patches in the gingival tissues (3). Involvement of the lips and temporomandibular joint can lead to trismus. With progressive atrophy of the tongue papillae, taste perception may be impaired (4, 6).

The teeth may also be affected. Transparency (as shown by transillumination) of the enamel may be greatly increased in comparison with normal (4). In addition, there may be crescent-shaped areas of severe enamel and dentine dissolution and minute enamel fractures.

In a very recent study (5) thickening of the periodontal membrane was found in 30% of patients with systemic sclerosis (see Table 37).

Table 37

INCIDENCE OF SYSTEMIC INVOLVEMENT IN 30 PATIENTS WITH SYSTEMIC SCLEROSIS

Systemic involvement	%
Calcinosis	23
Pulmonary involvement	23
Widening of periodontal membrane (grades 2 & 3)	30
Cardiac involvement	33
Renal involvement	40
Oesophageal involvement	47

From ref. (5)

As shown in Table 38, no direct relationship was found between widening of the periodontal membrane and other systemic changes and prognosis.

Table 38

Incidence of widening of the periodontal membrane in relation to the presence or absence of calcinosis, involvement of oesophagus, lungs, heart or kidney, and antinuclear factor

	Present	Absent	*P*
Calcinosis	4/7 (57)*	17/23(74)	N.S.
Oesophageal involvement (radiological)	8/14(57)	13/16(81)	< 0·3
Pulmonary involvement (radiological)	4/7(57)	17/23(74)	N.S.
Cardiac involvement (E.C.G.)	8/10(80)	13/20(65)	< 0·7
Renal involvement (creatinine clearance)	9/12(75)	11/18(61)	< 0·7
Antinuclear antibody	5/14(35)	7/12(58)	< 0·5

* Percentage in parentheses

From ref. (5)

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5.) Gastrointestinal

A summary of gastrointestinal tract involvement in scleroderma is given in Table 39.

Table 39

Gastrointestinal Tract Involvement in Scleroderma

	Clinical signs and symptoms	*Pathological findings*	*Roentgenographic findings*
Esophagus	Dysphagia	Submucosal thickening Atrophy of smooth muscle layers Adventitial sclerosis	Altered esophageal motility Dilated, smooth walled. Tapering of terminal end secondary to fibrosis from reflux esophagitis Hiatal hernia
Stomach	Dyspepsia	Submucosal thickening, sclerosis Fibrosis of muscularis Smooth muscle atrophy Serosal thickening	Dilatation Decreased peristalsis Delayed gastric emptying
Small bowel	Constipation Diarrhea Ileus Malabsorption	Increase in fibrous connective tissue Muscular atrophy	Dilatation Pseudosaculation Prolonged transit time Hypomotility
Colon	Ulceration Bleeding Perforation Obstruction	Atrophy, fibrosis of muscularis	Dilatation Atony Succulations of transverse and descending colon
Liver	Primary Biliary Cirrhosis hepatosplenomegaly jaundice steatorrhea xanthomas pruritus	Inflammation of portal spaces Fibrosis Absence of cholangioles	Hepatomegaly

From Ref. (1)

Approximately 10% of patients may have gastrointestinal symptoms prior to the appearance of cutaneous manifestations (1). Dysphagia is the most commonly reported sign of gastrointestinal involvement (2). Other possible presenting problems include malabsorption and steatorrhea, chronic and intermittent diarrhea or apparent intestinal obstruction or infarction of the bowel.

a.) Esophagus

The esophagus is involved in up to 80% of patients with scleroderma but only half of these have dysphagia (3).

Atrophy of the smooth muscle layers takes place and it is replaced by collagenous tissue. There also may be adventitial sclerosis and proliferation of periarteriolar connective tissue. These changes lead to decreased peristalsis and dilatation of the esophagus with loss of the intraluminal longitudinal folds (4).

Involvement of the cardioesophageal junction leads to gastric reflux with eventual esophagitis and stricture formation. In a recent study of 53 patients, the most common esophageal symptoms were heartburn and dysphagia (Table 40).

Table 40

Esophageal Symptoms of Scleroderma (53 Patients)

Symptom	No. of Patients	Percent
Heartburn with postural aggravation	36	68
Substernal dysphagia	27	51
Regurgitation	26	49
Delayed emptying	24	45
Reflux to throat	23	43
Cervical dysphagia	17	32
Chest pain	13	25
Nocturnal aspiration	11	21
Cough with swallowing	6	11

From ref. (5)

Abnormal motility was seen radiologically in 43 patients and gastroesophageal reflux in only 9 (Table 41).

Table 41

Barium Swallow Findings in Scleroderma (53 Patients)

Abnormality	No. of Patients	Percent
Diminished primary peristalsis	43	81
Dilatation	26	49
Hiatal hernia	17	32
Stricture	13	25
Delayed emptying	10	19
Gastroesophageal reflux	9	17

From ref. (5)

The results of the esophageal function tests are shown in Table 42.

Table 42

Results of Esophageal Function Tests in Scleroderma (53 Patients)

Test	Finding	No. of Patients	Percent
Manometry			
Characteristics of HPZ (mean ± SD)			
Mean pressure (mm Hg)	3.02 ± 2.69		
Peak pressure (mm Hg)	8.34 ± 4.65		
Length (cm)	1.83 ± 1.65		
No HPZ		18	34
Motility disorder			
None		2	4
Mild		10	19
Moderate		24	45
Severe		17	32
Acid-reflux test			
Negative		11	21
Minimal (1+)		4	8
Moderate (2+)		4	8
Severe (3+)		34	64
Acid-clearance test			
Abnormal		50	94
Normal		3	6
Acid-perfusion test			
Positive		16	30
Negative		37	70

From ref. (5)

Esophageal function tests demonstrated: 1.) abnormal motility in 51 patients and lack of a distal esophageal high-pressure zone (HPZ) in 18; 2.) moderate to severe gastroesophageal reflux in 38; and 3.) abnormal acid-clearing ability in 50. It was concluded that gastroesophageal reflux rather than impaired motility is the major cause of esophageal symptoms in scleroderma.

In a recent study of 12 patients with scleroderma, no relationship was noted between the extent of motility abnormality and the duration or severity of Raynaud's phenomenon (6). This study demonstrated that it is not possible to predict the degree of esophageal motility dysfunction in scleroderma based on Raynaud's phenomenon alone. Two different pathogenetic components were recognized. One component is closely linked to Raynaud's phenomenon and involves impairment of neuromuscular electrical transmission. The other component, which is independent of Raynaud's phenomenon, involves progressive loss of muscle strength in the distal esophagus and in the lower esophageal sphincter. This study is in disagreement with an earlier study in which it was concluded that the esophageal dysfunction correlated closely with Raynaud's phenomenon suggesting that a common neurogenic abnormality may cause both disorders (7).

Cohen and coworkers (8) tested the lower esophageal sphincter (LES) with: 1) methacholine acting directly at the cholinergic receptor on the muscle; b) edrophonium, a cholinesterase inhibitor, enhancing the effect of released acetylcholine; and c) gastrin I, acting through the release of acetylcholine. The data indicated that in patients with scleroderma and Raynaud's disease, the LES response to direct muscle stimulation by methacholine was intact while the response to gastrin I and edrophonium was diminished. The data implied that a defect in neural function may be responsible for some portion of the esophageal manifestations.

Martinez (9) has suggested that air in the esophagus is strongly suggestive of scleroderma. In his experience, in the lateral chest films of patients with sclerodrema, frequently there is air in the esophagus without an air-fluid level and without dilatation of the esophageal lumen. The air in the esophagus may be localized to one segment, or may extend throughout the entire esophagus. Gas in the gastric fundus is also a consistent finding. In the normal individual the empty esophagus is a collapsed cavity, thus the lateral chest film does not show air in the esophagus.

Air within the esophagus with an associated air-fluid level and significant distention is more suggestive of tumor, stricture or achalasia. In addition, in these conditions, no air is present in the gastric fundus (9).

b.) Stomach

Involvement of the stomach occurs in less than 10% of patients with scleroderma (1). By x-ray there is dilatation and decreased peristalsis. Delayed gastric emptying results from atony (10). Histologically, submucosal thickening and sclerosis, fibrosis of the muscularis with smooth muscle atrophy are present (1).

c.) Small Bowel

The involvement histologically consists of muscular atrophy and thickening with increase in fibrous connective tissue. The duodenum is involved in about one-third of patients, especially the second and third parts (1). Dilatation and lack of peristalsis are seen.

Collagenous encapsulation (periglandular sclerosis) of Brunner's glands, with or without pathological changes in the muscularis mucosae, was found in peroral duodenal biopsies from 6 of 8 patients with progressive systemic sclerosis (11). It was recommended by these authors that peroral duodenal biopsies showing Brunner's glands be obtained in patients suspected of scleroderma or in those with known scleroderma in whom evidence of small bowel involvement is sought.

Roentgenographic changes of the jejunum and ileum occur in 10% of patients and consist of dilated loops of bowel with impairment of peristalsis (12).

A characteristic mucosal fold pattern has been described and labeled as the "hide-bound" small bowel of scleroderma (27). In this condition the valvulae conniventes tend to remain abnormally packed together despite bowel dilatation. These workers concluded that such a strikingly narrowed intervalvular distance was disproportionate for the degree of dilatation and distinctive of scleroderma of the small bowel. It occured in over 60% of the 42 cases studied. In addition, 17% of the cases had transient, nonobstructive intussusceptions. Symptoms may include constipation, diarrhea, ileus and steatorrhea. Bacterial colonization is commonly accepted as a cause of the steatorrhea. Responsiveness of the malabsorption syndrome to treatment with antibiotics (especially tetracycline) is well documented (13-15). Wide, hypomotile loops of small bowel provide good sites for bacterial colonization (16, 17). An unusual complication of small bowel scleroderma is that of pneumatosis cystoides intestinalis and pneumoperitoneum resulting from rupture of the cysts (18, 19).

d.) Colon

In the colon early histologic lesions consist of patchy involvement with replacement of smooth muscle by fibrosis. Because of increased intracolonic pressure, sacculations develop in 50-70% of cases in atrophic areas (1). As the disease progresses, atrophy and fibrosis of the muscularis becomes more widespread. The colon becomes dilated and atrophic and the sacculations disappear (4). The wide-mouthed sacculations are very typical of this disease (20, 21). However, loss of colonic haustration is also common (22). Various complications may occur and include ulceration and perforation (23), obstruction secondary to fecal impaction (24), megacolon (25) and volvulus of the transverse colon (26).

3.) Liver, Gallbladder and Pancreas

The major type of liver involvement in scleroderma patients is primary biliary cirrhosis (28-32).

Involvement of the gallbladder by the sclerotic process has been described (29).

In a study of pancreatic secretion in 31 patients, pancreatic deficiency was noted in 12 of the 31 patients; hypersecretion was present in 7 additional cases (33). Thus, only 12 patients had normal pancreatic secretion. Pancreatic insufficiency was often associated with depressed gastric secretion and/or abnormal gallbladder function.

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6.) Renal

A summary of the types of kidney involvement is shown in Table 43.

Table 43

Kidney Involvement in Scleroderma

Clinical signs and symptoms	*Pathological findings*	*Roentgenographic findings*
Proteinuria Azotemia Renal failure Hypertension Malignant hypertension	Intimal proliferation of interlobular arteries Increased lobulation of glomerular tuft with mesangial hypercellularity Basement membrane thickening Cortical ischemia and necrosis	Irregular arterial narrowing Tortuosity of interlobular arteries Persistence of arterial phase with prolonged transit time Absence of a nephrogram Greater reduction of blood flow in outer renal cortex

From ref. (1)

A very extensive study of 210 scleroderma patients was carried out over a 20-year period (2). Clinical markers of renal involvement included proteinuria, azotemia and hypertension. A 45% incidence of renal involvement was found using these criteria. Proteinuria occurred in 36%, hypertension in 25%, azotemia in 20% and malignant hypertension in 7%. Sixty percent of the patients with renal involvement died during the 20 year period while only 10% of those without the above criteria died over the same period of time. Azotemia was the worst prognostic indicator. It is of interest that two-thirds of all deaths and 76% of deaths from renal involvement by scleroderma occurred in fall and winter. The mean time from onset of a clinical marker to death in this group was: hypertension 13 months, proteinuria, 7 months, malignant hypertension and azotemia, 1 month.

On histologic examination, the scleroderma kidney shows intimal proliferation of interlobular arteries and fibrinoid deposition in the intima or media of more distal interlobular arteries and afferent arterioles (3). Thickening of the glomerular basement membrane resulting in wire loops may occasionally be seen. In advanced stages, granular, eosinophilic masses may develop in the lumen of glomerular capillaries and fibrinoid material is deposited in the walls (1, 3). The renal lesions are similar to those seen in patients with malignant hypertension. In addition to the above findings, the studies by Cannon and coworkers (2) demonstrated histologic features different from those seen in hypertensives. These changes included: 1.) adventitial fibrosis around interlobar, arcuate and interlobular arteries; 2.) the interlobular arteries were the site of the most advanced vascular changes rather than the smaller arteries and arterioles as seen in hypertension; 3.) mesangial hypercellularity; 4.) more marked cortical ischemia and focal cortical necrosis than that seen in malignant hypertension.

A very recent report (4) has summarized the experience with 84 patients with diffuse scleroderma who were seen between January, 1973 and December, 1975 at the Columbia Presbyterian Medical Center (CPMC). (See Table 44).

Table 44

SCLERODERMA AT CPMC, 1973-1975

	Number	%
Population	84	100
Females	68	81
Males	16	19
White	63	75
Black	21	25
Patients with proteinuria	22	26
Associated with hypertension	18	
Associated with azotemia	16	
Isolated	1	
Fatalities	14	
Patients with hypertension	44	52
Associated with proteinuria	18	
Associated with azotemia	17	
Isolated	24	
Fatalities	15	
Patients with azotemia	23	27
Acute renal failure with 'malignant' hypertension	11	
Acute renal failure with moderate hypertension	2	
Normotensive acute renal failure	2	
Fatalities	16	
Patients with no renal involvement	34	40
Fatalities	0	

From ref. (4)

Of this group, 52% had hypertension, 27% were azotemic with 16 fatalities (70%). About 40% had no renal involvement and none of the patients in this group died. In the azotemic patients with hypertensive or normotensive renal failure, death usually occurred within 1-3 months after the BUN became elevated. Death also occurred soon after development of "malignant" hypertension (see Table 45).

Table 45

Hypertension in scleroderma, n = 44

	n	%	Blood pressure mean ± SE mm Hg	Months from onset disease to hypertension mean ± SE	Mortality		Months from onset hypertension to death mean ± SE
					n	%	
'Malignant' hypertension	11	25	185 ± 8/115 ± 6	34 ± 9	9	82	2 ± 1
Hypertension presenting without renal failure	33	75	159 ± 3/100 ± 1	72 ± 13	5	15	44 ± 20

From ref. (4)

Renal arteriograms were obtained in 17 patients. Seven were distinctly abnormal. The main renal and interlobar arteries were normal or showed spasm and "standing pressure waves" indicative of increased resistance to blood flow. The arteriovenous transit time of contrast material was increased. The arcuate and interlobular arteries were markedly narrowed or obliterated, the corticomedullary junction was indistinct and contrast material did not penetrate to the margin of the cortex. The cortical nephrogram was mottled and suggested focal areas of necrosis (4).

Elevated renin activity and juxtaglomerular hyperplasia have been reported in scleroderma patients (2, 5, 6). Support for the role of the renin-angiotensin system in the hypertension of scleroderma patients has been given by reports that propranolol reduced the hypertension of 2 patients (7) and by restoration of normal blood pressure following nephrectomy (2, 5). In the CPMC study (4), 7 patients underwent bilateral nephrectomy (see Table 46) for obliguric renal failure and severe hypertension.

Table 46

Bilateral nephrectomy in oliguric renal failure with hypertension in scleroderma

Case No.	Blood pressure, mm Hg		Outcome
	before nephrectomy	after nephrectomy	
1	170/120	97/60	expired within 1 month, cardiac arrest
2	180/105	120/80	expired within 1 month, cardiac arrest
3[1]	220/120	180/86	renal transplant 5 months later; expired 2 weeks after of hyperacute rejection
4	190/120	180/100	expired within 1 month, cardiac arrest
5[1]	240/150	90/60	renal transplant 2 months later; 3 years later developed chronic rejection; alive
6[2]	210/140	140/60	alive 1 year after
7[1]	230/110	110/80	expired of cerebral vascular accident 1 month later

[1] Patients previously reported [1].

[2] We acknowledge Dr. *J. VanGender* for the follow-up of this case.

From ref. (4)

Normal blood pressure was fully restored in all 7 patients. Two of them were alive 1 and 5 years after the procedure. Another successful transplantation with graft survival of 14 months has been reported (12). However, no prospective controlled studies have been done.

Two instances of recurrence of scleroderma in the grafted kidneys have recently been reported (8, 11). (See Table 47, cases 5 and 6).

Table 47

Summary of Data for PSS Patients Who Received a Kidney Transplant

Patient No.	Sex/Age (yr)	Time from PSS Onset to Transplantation	Hypertension* (mm Hg)	Source of Graft	Function of Graft	Histology of Graft	Reported by
1	M/40	15 yr	200/120	Cadaver	Excellent at 18 mo	No biopsy	Richardson (5)
2	F/23	3 yr	240/150	Mother	Very poor at 3 yr	Chronic rejection	Cannon et al (2)
3	F/40	5 yr	185/105	Mother	Excellent at 14 mo	No biopsy	Hayes (9)
4	M/31	2 yr	190/110	Sister	Excellent at 14 mo	No biopsy	Anderson (10)
5	F/24	10 mo	230/130	Mother	Removed at 2 mo	Recurrent scleroderma	Woodhall et al (11)
6	F/41	4 mo	210/130	Cadaver	Removed at 3 mo	Recurrent scleroderma	Merino et al (8)

*Highest measurement reported.

From ref. (8)

The two cases of scleroderma recurrence in the kidney grafts appeared to have more aggressive disease (8).

Immunologic studies on scleroderma kidneys have shown vascular localization of IgM, Clq, C4 and C3 in all cases studied (13). Fibrinogen and antiglobulin were also present in several specimens. Eluates of the glomeruli contained antiglobulin and antinuclear antibodies (13, 14). Such Ig and C components have also been seen in a transplanted kidney with scleroderma recurrence (13). The authors suggested that rheumatoid factor containing immune complexes may play a pathogenetic role in production of renal vascular lesions in scleroderma.

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7.) Raynaud's Phenomenon

Raynaud's phenomenon is the most common clinical expression of vascular disease in scleroderma (1). Excerpts from some of the original descriptions by Raynaud (2) are summarized as follows:

Under the influence of a very moderate cold, and even at the height of summer, she [Case I] sees her fingers become ex-sanguine, completely insensible, and of a whitish yellow colour. This phenomenon happens often without reason, lasts a variable time, and terminates by a period of very painful reaction, during which the circulation is re-established little by little and recurs to the normal state.

On the 8th April, Easter Day, being at chapel, she [Case V] was taken without assignable cause with pains in the hands sufficiently severe to make her cry; in the back she felt as though violently compressed by a vice. I found her in the middle of an attack of cyanosis which had lasted for two hours; the pulse was quite perceptible; the skin of the hands was very cold, and of a violet tint.

The attacks recur now in the feet and in the hands five or six times a day without any periodicity.

Her [Case VI] cheeks and chin were of indigo colour; her hands were as cold as marble.

It was at the extremities of the fingers that the cyanosis and the cold persisted longest. Finally at the end of a quarter or half an hour the whole hand was of a vermilion red; the pulse had regained its force, the warmth of skin was perfectly developed, and a slight sweat had moistened the cutaneous surface. All these phenomena were reproduced each time that Rose was exposed to cool air, whether in the evening, morning, or at the middle of the day.

By degrees the second and first phalanges of the fingers had presented successively the same phenomena, that is to say, sensation of habitual cold, tinglings, slaty tint, incomplete anaesthesia at the moment of the attack, return of sensibility during the intervals, and then acute pains in the region of the punctures which had been made. Soon we saw bullae appear at the extremities of the ungual phalanges; they passed from one to the other, and preceded the fall of all the nails, which came to pass in six weeks' time.

Extreme pallor. The lines of the countenance are flaccid, and expressive of sadness.

So soon as she allows her hands to be exposed to a rather low temperature the fingers become pale, oedematous, half flexed; they are attacked with painful sensations, numbness, and torpor; shortly afterwards they become blue, then black, in their whole extent.

. . . the epidermis is raised by pus, so as to imitate a bulla, which develops, breaks, and leaves the derma naked. Eight days afterwards a cicatrix is formed, and this morbid process is repeated elsewhere.

In scleroderma roentgenographic changes are commonly seen early in the course of the disease (3). Abnormal findings were noted in 33 (63%) of 52 patients with scleroderma. (see Table 48).

Table 48

Roentgenographic Changes of Fingertips in Scleroderma

Bone Changes
Erosion of the distal ungual tufts
Erosion of the margin of the distal interphalangeal joint
Soft Tissue Changes
Calcifications limited to the pulp of the fingertips or associated with interphalangeal joint capsule calcifications.
Atrophy of the fingertip soft tissue

From Ref. (3)

Soft tissue atrophy of the fingertips was usually associated with neurovascular manifestations (Raynaud's phenomenon). Calcifications of the pulp of the fingertip and bone erosion are commonly seen in scleroderma and are not necessarily associated with the presence or absence of Raynaud's phenomenon (3). Severe resorption of the terminal phalanges may occur (4).

Total (plethysmography) and capillary (radioisotope disappearance rate) fingertip flows were measured in 24 patients with Raynaud's phenomenon and compared to 10 normal subjects in a warm room and during reflex sympathetic nerve stimulation by body cooling (5). Patients with Raynaud's phenomenon had a significantly smaller capillary flow in both warm and cool rooms than normal subjects. With body cooling, total and arteriovenous shunt flow, but not capillary flow, decreased significantly in normal controls, whereas all three decreased in Raynaud's phenomenon.

During oral reserpine treatment, 11 patients with Raynaud's phenomenon showed a significantly larger capillary flow during warming and cooling (5). Thus this study demonstrated that patients with Raynaud's phenomenon have a smaller finger nutritional (capillary) flow than normal subjects, and this flow decreased significantly during sympathetic stimulation. In these patients reserpine produced increased finger nutritional flow.

Plethysmography correlated with arteriography findings in 50% of cases (6). Where agreement was not good, the plethysmograph underestimated the anatomic extent of disease.

Unilateral Raynaud's phenomenon caused by cervical or first rib anomalies has been reported (7). The Raynaud's phenomenon resulted from subclavian artery thrombosis and distal arm thromboemboli in the digits.

Treatment of Raynaud's phenomenon has included oral (see above and ref. 5) reserpine intra-arterial reserpine (7-11), alpha methyldopa (12), griseofulvin (13, 14), phenformin plus ethylestrenol (15), low molecular weight dextran infusions (16) and hypnotic and operant (biofeedback) techniques (17). The dextran was not successful but the others have been successful although results with intra-arterial reserpine have been somewhat controversial.

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8.) Musculoskeletal

A summary of the musculoskeletal findings in scleroderma is shown in Table 49 (1).

Table 49

Musculoskeletal System Involvement in Scleroderma

	Clinical signs and symptoms	*Pathological findings*	*Roentgenographic findings*
Bones and joints	Polyarthralgia, stiffness (especially of hands, feet, knees) Swelling Limitation of movement Contractures Joint effusions	Hyperemia of synovium Increased fibrosis, synovium being replaced by collagenous connective tissue	Absorption of tufts of terminal phalanges of fingers Osteopoikilosis Calcinosis circumscripta Narrowing of cartilage space Juxta-articular osteoporosis Thickening of the periarticular soft tissue
Tendons	Rubs with audible cracking	Thickening of the tendon sheath	
Skeletal muscle	Wasting, weakness of proximal muscle groups	Interstitial fibrosis Atrophy Necrosis Eosinophilic floccular degeneration	

From ref. (1)

Rheumatic symptoms may be a primary manifestation of scleroderma (2). In a series of 150 cases of scleroderma, Rodnan and Medsger (3) found 61 patients (41%) in whom polyarthralgia or arthritis was the initial symptom or developed within 1 year after the onset of Raynaud's phenomenon and/or cutaneous changes (4). The patients commonly complain of symmetric polyarthralgia and stiffness, affecting chiefly the fingers, wrists, knees and ankles (5). Morning stiffness similar to that seen with rheumatoid arthritis may be a prominent symptom. Although objective findings are usually minimal, frank inflammation indicated by tenderness, redness and warmth may be present, with joint effusions that contain large numbers of polymorphonuclear leukocytes. The latex agglutination test is positive in 30% of cases (3). Histologically the synovium may be very similar to those seen in rheumatoid arthritis, except that in scleroderma there tends to be a strikingly thick deposition of fibrin on the surface and within the substance of the synovium (3). Later in the course of the disease there is dense fibrosis of the synovium. Similar inflammatory and fibrotic lesions may be present in the tendon sheaths and the skeletal muscles (11). This is presumably responsible for the noises and leathery crepitus, grating sensations and rubs and audible creaking which may be seen in certain tendinous areas; especially the distal portions of the forearms and the legs (6).

While some patients may have muscle atrophy, profound weakness, easy fatiguability and muscle pain, the majority have few complaints referable to muscle (3). Diplopia due to an ocular myositis has been reported (12). Absorption of the tufts of the terminal phalanges of the fingers is the most common abnormality by x-ray (7). Calcinosis may also be associated. Complete dissolution of the terminal phalanx may occur (8). Most joint abnormalities are limited to the fingers and wrists and include narrowing of the joint space, bone erosions, juxta-articular osteoporosis, alteration of the ulnar styloid process, subluxations, ankylosis of the wrist and thickening of the periarticular soft tissue (1, 13). Only rarely is there subchondral bone destruction (9). In one unusual case, a classic pencil-in-cup (Mortar and pestle) deformity was seen in the distal interphalangeal joints of the fifth digits of both hands (10). This deformity is most commonly seen in psoriatic arthritis and less frequently in rheumatoid arthritis.

Five of 16 patients with scleroderma had bone resorption at the angle of the mandible (14). This finding is apparently related to the tightness of the skin of the face, atrophy of the masseter and pterygoid muscles, small size of the oral orifice or bone ischemia secondary to vasospasm (14, 15). There is a significantly high frequency in blacks (14). Bone resorption of the ribs and cervical spine have also been reported (16, 17).

A more recent study of scleroderma synovial membrane and fluid has been done by Schumacher (18). The synovial membrane was characterized by superficial deposition of fibrin, mild chronic inflammation with very little proliferation of lining cells, prominence of immature connective tissue and obliterative microvascular disease. Leucocyte counts were usually less than 1000 cells per cu mm, predominantly mononuclear cells (see Table 50).

Table 50

Progressive Systemic Sclerosis, Synovial Fluids

Patient's Age (Years), Sex	Disease Duration, Years	Synovial Fluid Volume ml.	Total Nucleated Cell Count	Differential			
				Polymorphonuclear Leukocytes	Lymphocytes	Large Mononuclear Cells	Viscosity
Patient 1 46, M							
1	1	1	700	6	76	18	
2	1.5	1	250	28	50	22	↓
Patient 2 57, M							
1	1	5	150	3	36	62	↓
2	2	.5	500	4	12	84	↓
Patient 3 67, M	.75		800	39	37	24	
Patient 4 66, F	.25	2	2400	15	40	45	↓

From ref. (18)

In one patient with scleroderma and calcification of the suprapatellar pouch, chalky white synovial fluid resulted from apatite crystals being shed into the fluid from the heavily calcified synovium (19).

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9.) Neurologic

The nervous system is rarely involved in scleroderma. In a study of 130 patients, 24 were found to have a total of 28 neurologic manisfestations (1). However, none were definitely related to the primary pathological process of scleroderma. This may be due to the lack of collagen in the brain.

Involvement of the peripheral nervous system is also rare, but mild peripheral neuropathy results in paresthesias and sensory lesions. Trigeminal sensory and other neuropathies (2-6) and subacute combined degeneration following vitamin B_{12} deficiency caused by sclerodermal involvement of the small intestine (7) have also been reported.

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10) Laboratory

There are no specific laboratory abnormalities associated with the disease scleroderma. A number of hematologic and immunologic abnormalities may be present, however.

(a) Hematologic

Hematologic evaluation of 164 patients with scleroderma showed the frequency of anemia to be 29% (1). Marrow aplasia associated with severe intestinal malabsorption of fat, iron and vitamin B_{12}, was observed in 6% of the anemic patients. Iron deficiency was considered the cause or contributed to the cause of anemia in 50% of the anemic patients. Pancytopenia has been reported (2). Microangiopathic hemolytic anemia was found in 7 of 20 patients with systemic scleroderma (3). All 7 patients had renal arterial fibrin deposits. The authors suggested that erythrocyte fragmentation results from contact with intravascular fibrin. Only 4 patients had severe hypertension. Thrombocytopenia (2, 4) and Coombs-positive hemolytic anemia (4, 5) may also occur.

(b) Immunologic

Sera from 47 patients with scleroderma were studied for the presence of antinuclear antibodies (6). Antinuclear antibodies (ANA) were present in 60% of the sera. The ANA pattern was usually speckled (6, 7) but was sometimes nucleolar (8). Both IgG and IgM antibodies were present. The prevalance of high titers of ANA's was greater in patients with hypergammaglobulinemia than in those with normal levels of gammaglobulin. The ANA's are complement fixing (9). Rheumatoid factor is present in 33% of sera (6). It has recently been shown that antibodies to RNA that are found in scleroderma (10) are directed to uracil and thus specific to single-stranded RNA, whereas RNA antibodies found in SLE sera are heterogeneous and directed to either the base, to the site of union of the base and sugar moiety to the ribose backbone, or to the helical structure of double-stranded RNA (11-13).

Immunofluorescent studies of the skin have shown immunoglobulin (Ig) and complement (C') deposition at the basement membrane or within blood vessel walls (14). Foci of intercollagenous staining for connective tissue antigens in the reticular layer of the dermis have also been described (15).

Immunohistological studies of scleroderma kidneys have shown deposition of Ig, C' and fibrin in diseased renal arteries and arterioles (16, 17).

The numbers of T-lymphocytes are reduced in scleroderma and the degree of reduction correlates with the extent of visceral involvement by the disease (18, 19).

A significantly decreased lymphocyte response to concanavalin A (con A) and pokeweed mitogen (PWM) (20, 21) and increased leucocyte migration inhibition (22) have been demonstrated in scleroderma lymphocytes.

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F. Associated Conditions

Some of the conditions (or complications of scleroderma) which have been reported in association with scleroderma are listed in Table 51. In some instances these represent individual case reports only.

Table 51

Conditions Reported in Association with Scleroderma

Sjögren's Syndrome (1, 2)
Primary Biliary Cirrhosis (3-5)
Cryoglobulinemia (6)
Carcinoma of the Lung (7, 8)
Urticaria Pigmentosa (9)
Hyperthyroidism (10, 11)
Fatal Heat Stroke (12)
Carcinoid (13)
Phenylketonuria (14, 15)
Malignant Atrophic Papulosis (16)
Regional Enteritis (17)
Thymona (18)
Myasthenia Gravis (19)
Arterial Thrombosis (20)
Lymphangiectasis (21)
Pneumatosis Cystoides Intestinalis and Pneumoperitoneum (22, 23)
Syndrome of Polyneuropathy and Anasarca (24)

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G. CREST Syndrome

The association between scleroderma and calcinosis is well known. In 1911, Thibierge and Weissenback (1) published the first series of such patients and included 3 cases in which only sclerodactylia was accompanied by calcinosis. Since then the combination of scleroderma and calcinosis has been referred to as the Thibierge-Weissenback syndrome.

In 1964, Winterbauer (2) described 7 patients with what he termed the CRST syndrome, i.e. calcinosis (C), Raynaud's phenomenon (R), sclerodactyly (S), and telangiectasia (T).

These same features occur in the classic form of progressive systemic sclerosis, which is marked by more diffuse scleroderma; but in the CRST syndrome the calcinosis is often much more extensive, the Raynaud's phenomenon more frequently complicated by digital ulcerations and gangrene, and the telangiectasia more profuse (3). It has been claimed by some that the CRST syndrome is more benign than classic scleroderma (4-6). However, Salerni and coworkers (3) point out that although the CRST syndrome tends to pursue a very slowly progressive course, it is frequently associated with serious problems, especially that of esophageal (E) dysfunction (7) which is similar to that seen in progressive systemic sclerosis but may be more severe. Thus, these workers believe the syndrome should be called the CREST syndrome (see Table 52).

Table 52

Components of the CREST Syndrome

(C)alcinosis
(R)aynaud's phenomenon
(E)sophageal dysfunction
(S)clerodactylia
(T)elangiectasias

In addition to the esophageal dysfunction, pulmonary hypertension also may occur (3-5). Histologically, the small and medium-sized pulmonary arteries and arterioles showed intimal proliferation or thickening with narrowing of the vessel lumen leading at times to nearly complete obliteration (3). IgG and the Clq component of complement were found in the pulmonary vessels. It was concluded that the relatively high frequency of severe pulmonay hypertension in the CREST syndrome is related to prolonged survival of the individuals compared with patients with the classic form of progressive systemic sclerosis. Death occurred in several patients and resulted from the pulmonary hypertension and pulmonary fibrosis.

Occasionally the telangiectasias seen in the CREST syndrome may be confused with those seen in hereditary hemorragic telangiectasia. A comparison of the features of both conditions is shown in Table 53.

Table 53

A Comparison of the Clinical Features of the Telangiectasia in HHT and the CRST Syndrome

Clinical features	Hereditary haemorrhagic telangiectasia	The CRST syndrome
Age of onset	10-40 (usually 30-40) yrs	20-70 (often 40+) yrs
Sex	M1 : F1	Predominantly females
Family history	Positive (autosomal dominant inheritance)	Negative
Distribution of lesions	Face, oral mucosa, trunk and upper limbs. Widespread internal and visceral involvement	Predominantly face, oral mucosa and upper extremities. Visceral lesions uncommon
Haemorrhagic diathesis		
(*a*) Epistaxis	Common (75%). Often severe and may precede appearance of telangiectases	Less common (40%) Never severe
(*b*) Melaena and haematuria	Common	Uncommon
(*c*) Oral and cutaneous bleeding	Common	Not reported

From Ref. (6)

Both epistaxis and bleeding from the skin and oral cavity are less frequent and much less severe in the CREST syndrome than in hereditary hemorrhagic telangiectasia (2, 8). The same is true for gastrointestinal bleeding although it may rarely occur in the CREST syndrome (2, 9).

The types of calcinosis are shown in Table 54. Calcinosis circumscripta is the type frequently seen in scleroderma.

Table 54

Classification of Calcinosis (10)

(1) Calcinosis circunscripta: Small nodules seen at the fingertips and long extensor joint aspects in systemic sclerosis, and dermatomyositis.

(2) Calcinosis universalis: A progressive and often fatal calcification involving fascia, bone and tendon.

(3) Calcinosis tumoralis: Massive cystic lesions seen around the buttocks and sometimes elbows in natives of Africa and possibly related to their sleeping on hard ground.

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H. Scleroderma and Pregnancy

A number of authors have emphasized the high maternal mortality rate and excessive fetal wastage in patients with scleroderma who become pregnant (1-4).

Karlen and Cook (4) have summarized the reports of patients with coexisting scleroderma and pregnancy (Table 55).

Table 55

SUMMARY OF CASE REPORTS OF PATIENTS WITH COEXISTING SCLERODERMA AND PREGNANCY

Author	*Maternal age*	*Scleroderma pre-pregnancy*	*Change in scleroderma during preg.*	*Verified sclerodermal renal disease*	*Toxemia*	*Prematurity*	*Perinatal death*	*Maternal death*
Eno (1937)	31	cutaneous	worse				yes	
Eno (1937)	33	cutaneous	unchanged		yes			
Guttmacher (1934)	30	systemic	unchanged			yes		
Etterich (1955)	29	systemic	worse	possible	yes	yes		yes
Tischler (1957)	25	cutaneous	unchanged					
Hoffman (1961)	35	systemic	unchanged					
Hayes (1962)	24	systemic	unchanged		yes		yes	
Winkelman (1962)	36	systemic	unchanged					
Spellacy (1964)	20	systemic	unchanged			yes	yes	
DeCarle (1964)	27	systemic	worse					
DeCarle (1964)	29	systemic	unchanged			yes		
DeCarle (1964)	36	systemic	worse					
Gunther (1964)	21	systemic	improved					
Gunther (1964)	22	systemic	improved					
Gunther (1964)	24	systemic	worse		yes			
Fear (1968)	26	systemic	worse	yes	yes	yes	yes	yes
Sood (1970)	25	cutaneous	worse	yes	yes		yes	yes
Karlen (1973) (present study)	26	cutaneous	worse	yes	yes	yes		yes

From Ref. (4)

These authors concluded that so grave is the prognosis for mother and fetus in sclerodermal renal disease, that it seems reasonable to recommend the immediate termination of a pregnancy associated with scleroderma when the first sign of pre-eclampsia with any evidence of diminishing renal function occurs (4).

In a very recent case (5), a patient with scleroderma developed malignant hypertension with rapidly progressive renal failure after a successful delivery. The blood pressure was refractory to all therapy, including hemodialysis. The patient then underwent bilateral nephrectomy, following which the blood pressure returned to normal, and she survived on hemodialysis for 17 months. She then died of recurrent severe hypertension with a CVA.

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I. Treatment

Many different types of drug therapy have been used for treatment of systemic and localized scleroderma. These include penicillin (for morphea), procaine (for vasomotor disturbances), vitamin E (inhibition of collagen synthesis), vegetable oils e.g. Piascledine, EDTA-ethylenediamine-tetraacetic acid (improvement in Raynaud's and joint mobility), EACA-epsilon-amino-caproic acid (softening of skin), low molecular weight dextran (Raynaud's), penicillamine (softening of skin, lessening of stiffness, improvement in pulmonary function), B-aminopropionitrile (increase in urinary hydroxyproline and acid-extractable dermal collagen), madecassol (suppresses biosynthesis of ground substance and collagen fibers of the connective tissue), hyaluronidase (by injection),

PABA-para-aminobenzoic acid (possibly inhibits fibrosis), relaxing estrogen and progesterone, indocin (for arthralgias), anti-malarial drugs, colchicine, corticosteroids (may be contraindicated in renal disease with hypertension) and immunosuppressive agents (1).

Phenoxybenzamine, reserpine, and alpha-methyldopa have been used for treatment of Raynaud's phenomenon. Dimethyl sulfoxide (DMSO) has been used for topical treatment of skin lesions. Finally, tetracycline is used for treatment of malabsorption in scleroderma.

The agents which have been most recently under consideration are colchicine, penicillamine and immunosuppressive agents. However, at this time, there does not appear to be any effective or specific treatment for localized or systemic scleroderma although some drugs can produce temporary improvement, depending on the form of the disease and its advancement.

REFERENCE (Treatment)

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II. Localized Scleroderma (Morphea)

Localized scleroderma (or morphea) is either confined to the skin and subcutaneous tissue, or also involves (secondarily) the muscle and skeletal system. Initially the lesions present as porcelain-white indurations and later as atrophy of skin and subcutaneous tissue with depigmentation or hyperpigmentation. The onset of the disease is insidious and usually goes unnoticed by the patient, although in some cases it is related to trauma (2). The internal organs are usually not involved. The types of morphea are shown in Tables 56 and 57, differing with regard to depth of the lesions and degree of deformity (1).

Table 56

Varieties of Localized Scleroderma

Morphea en plaques (plaque-like morphea)
Linear Scleroderma (incl. Coup de Sabre)
Guttate morphea

From Ref. (1)

Table 57

ATYPICAL VARIETIES OF LOCALIZED SCLERODERMA

Bullous
Vesicular
Subcutaneous
Keloid or Nodular
Generalized

From Ref. (1)

Plaque-like morphea is characterized by lesions which are extensive and deep, with a violaceous border, called the lilac ring (1). Linear scleroderma consists of band-like lesions with a linear distribution resulting in deep atrophy not only of skin and subcutaneous tissue, but also of muscles and bones. Severe cosmetic disfiguration such as facial hemiatrophy, en coup de sabre lesions and crippling deformities may result. Guttate morphea is less frequent. The distinctive feature is absence of keratotic plugging, and changes in the mucous membranes and skin of the genital region (1).

The bullous form is characterized by periodically appearing bullae (5). Vesicular scleroderma is a variety of morphea with small lymphangiectatic vesicles formed as a result of new formation and proliferation of lymphatic vessels (6). In the subcutaneous variety the indurations are indistinctly outlined, the lilac ring is absent, and the lesions lack the ivory or porcelain color characteristic of morphea (1). In the keloid or nodular form, the lesions are deep, confluent, or isolated nodules, sometimes with processes characteristic of keloid (7). In the generalized variety, a combination of morphea and linear scleroderma lesions may be so extensive as to involve the entire skin (1).

Histochemical studies reveal an increase of positive PAS material, diastase resistant, in the areas of homogenized collagen (8). An increase in hexoses and hexosamines was also noted.

In an interesting bacteriologic study (9), acid-fast, gram-positive, pleomorphic organisms were cultured from skin from seven patients with scleroderma or morphea.

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III. Mixed Connective Tissue Disease and Overlap Syndromes

Patients with connective tissue diseases may frequently have "overlap" syndromes, e.g., scleroderma and systemic lupus erythematosus, lupus with myositis, scleroderma with myositis, lupus with rheumatoid arthritis-like features etc.

In 1972 Sharp and coworkers (1) described the clinical and serologic findings in 25 patients with what they believed to be a distinct rheumatic disease syndrome. All of these patients had hemagglutinating antibody to an extractable nuclear antigen (ENA) which consisted mainly of protein and ribonucleic acid (RNA), i.e. ribonucleoprotein (RNP). (See Table 58). The marked sensitivity of the antigen to ribonuclease, indicated that the specificity of the antibody to ENA was different from that of antibody to ENA which occurred in about 50% of patients with systemic lupus erythematosus. Serum from patients with mixed connective tissue disease (MCTD) also contained high titers of speckled pattern fluorescent antinuclear antibody which showed the same response of tissue antigens to enzyme digestion. There was no detectable Sm antibody. Antibody to native deoxyribonucleic acid (DNA) was infrequent and of low titer, and serum complement levels were normal or elevated.

Table 58

Serologic Characteristics of Twenty-Five Patients with Mixed Connective Tissue Disease

	Per Cent
High titer ENA antibody by hemagglutination	100
High titer speckled fluorescent antinuclear antibody	100
Precipitating antibody to Sm soluble nuclear antigen	0
Free circulating DNA by immunodiffusion	40*
Positive lupus erythematosus cell test	20†
Antibody to heat denatured DNA by hemagglutination	16†
Antibody to native DNA by hemagglutination	12†
Elevated or normal serum complement	100‡

* Eight of twenty patients tested had at least one positive result on multiple analyses of many different serum specimens.

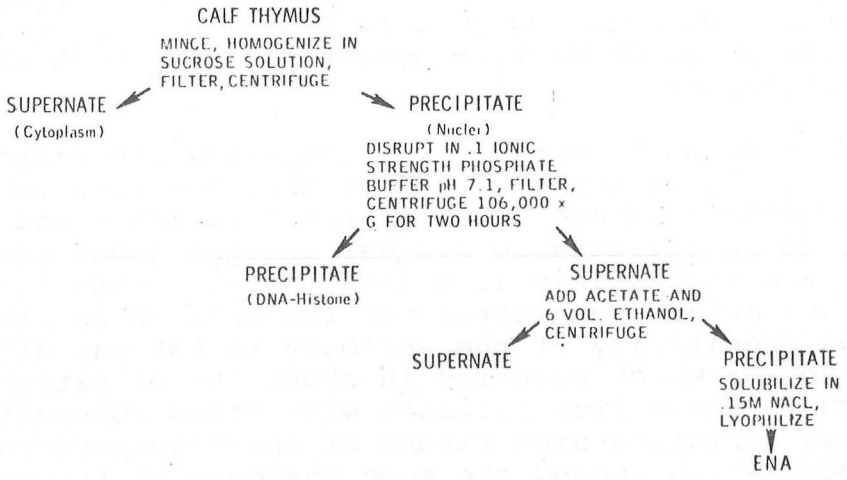
† Incidence of positive results on initial testing of all twenty-five patients (during time of active disease).

‡ Analyses of forty-four different serum specimens from eleven patients.

From Ref. (1)

The preparation of extractable nuclear antigen for these studies is shown in Figure 2.

Figure 2



Preparation of extractable nuclear antigen (ENA) from calf thymus

From Ref. (1)

The clinical characteristics of these patients are shown in Table 59.

Table 59

Clinical Characteristics of Twenty-Five Patients with Mixed Connective Tissue Disease

Characteristic	Per Cent
Arthritis/arthralgias	96
Swollen hands	88
Raynaud's phenomenon	84
Abnormal esophageal motility	77
Myositis	72
Lymphadenopathy	68
Fever	32
Hepatomegaly	28
Serositis	24
Splenomegaly	21
Renal disease	0*
Anemia	48
Leukopenia	52
Hypergammaglobulinemia	80

* At the time this manuscript was being completed renal disease developed in one patient; the nature of the disease had not been elucidated.

From Ref. (1)

These characteristics included a combination of features similar to those of systemic lupus erythematosus (SLE), scleroderma and polymyositis. The incidence of renal disease was very low. Most of these abnormalities were responsive to corticosteroid therapy (see Table 60).

Table 60

Response to Therapy and Clinical Course of Patients with Mixed Connective Tissue Disease

	No. of Patients	No. of Courses of High Dose Steroids	Clinical Status			Mean Follow-Up (mo)
			Remission	Improved	Active	
	15	1	8	7	0	28
	3	2	2	0	1	40
	3	3	1	1	1	72
Total	21		11	8	2	

From ref. (1)

The anti-ENA antibodies tended to be much higher in the MCTD group than in the SLE group. In addition, treatment with RNAase appeared to selectively decrease or abolish the anti-ENA titers only in the MCTD group.

Control groups showed less than a 0.5% incidence of antibody to ENA.

The anti-ENA antibody which is present in SLE sera has been termed anti-Sm antibody (1, 2). This antigen is not sensitive to RNase digestion and is, therefore, not an anti-RNP antibody.

Sharp (3) has recently reviewed his experience since the initial report in 1972 (1). (See Table 61).

Table 61

Distinguishing clinical and laboratory characteristics of patients with antibodies to RNase-sensitive and RNase-resistant ENA

Clinical and laboratory characteristics	Antibodies to: RNase-sensitive ENA (RNP alone) n = 100 %	RNase-resistant ENA (Sm or Sm + RNP) n = 27 %
Swollen hands	66	15
Scleroderma changes	33	7
Raynaud's phenomenon	85	26
Myositis	63	26
CNS disease	10	33
Renal disease	5	37
Antibodies to DNA	12	41
Low serum complement	4	75
Positive LE cell test	14	52

From Ref. (3)

It is apparent that the MCTD group (as characterized by presence of anti-RNP antibodies) tended to have swollen hands with sclerodermatous changes, Raynaud's phenomenon and myositis while the Sm antibody positive group (SLE) tended to have a higher incidence of CNS and renal disease, elevated anti-DNA antibodies, positive LE preps and low serum complement levels.

The incidence of rheumatic disease syndromes in patients with antibodies to RNase-sensitive and RNase-resistant ENA is shown in Table 62.

Table 62

Incidence of rheumatic disease syndromes in patients with antibodies to RNase-sensitive and RNase-resistant ENA

Clinical syndrome	Antibodies to RNase-sensitive ENA (RNP alone) n = 100 %	Antibodies to RNase-resistant ENA (Sm or Sm + RNP) n = 27 %
MCTD	74	7
SLE[a]	12	85
Scleroderma	8	4
Mild CTD[b]	6	0
Dermatomyositis	0	4

[a] Fulfilled ARA preliminary criteria (Cohen et al. 1971).
[b] Mild undifferentiated connective tissue disease.

From Ref. (3)

A recent multicenter study of 127 patients (4) has confirmed the initial observations. It was concluded that antibodies to nuclear ribonucleoprotein and Sm are of diagnostic use; if the serum contains only ribonucleoprotein antibody in high titer it is likely that the patient has MCTD.

Table 63

Comparison of Clinical Features of MCTD Patients in Different Studies

	Chubick & Gilliam (PMH+) (12,13)	Sharp's Multi-center study (4)	Prystowsky & Tuffanelli (UCSF) (11)	Farber & Bole (U. Mich) (5)
	(N=25)	(N=100)	(N=44)	(N=13)
Arthralgia/arthritis	100%	95%	91%	85%
Raynauds	80%	85%	81%	85%
Swollen Hands	72%	66%	45%	62%
Myalgia	68%	70%	57%	54%
Lymphadenopathy	64%	40%	30%	15%
Cutaneous LE (or "skin rash")	55%	38%	51%	46%
Alopecia	48%	—	43%	31%
Fever	36%	33%	—	31%
Serositis	32%	27%	32%	38%
Sjogrens	8%	7%	19%	23%
Vascular Headaches	—	—	30%	—
Neurological Lesions	4%	10%	6%	8%
Nephritis	10%	10%	21%	15%

Table 64

Comparison of Laboratory Findings in MCTD Patients in Different Studies

	Chubick & Gilliam (12,13) (PMH)	Sharp et. al. (4)	Prystowsky & Tuffanelli (11)	Farber & Bole (5) (Mich.)
	(N=25)	(N=109)	(N=47)	(N=13)
FANA	100%	100%	98%	100%
Hypergammaglobulinemia	83%	80%	72%	91%
Anemia	58%	41%	20%	69%
Leukopenia	36%	35%	18%	69%
LE Cells	32%	14%	46%	33%
Pos. Rheumatoid Factor	20%	55%	48%	69%
Esophageal Dysfunction	33%	73%	58%	46%
Anti-nDNA Antibodies	19%	12%	24%	31%
Low Serum Complement	30%	4%	39%	38%
Lupus Band Test	33%	—	34%	—

Decreased esophageal motility and decreased pulmonary diffusing capacity have been added to the list of clinical features although the incidence is not much higher than the SLE group. Thus, the major differentiating features clinically include Raynaud's phenomenon, swollen hands, sclerodermatous changes and myositis (all higher in MCTD than in SLE). The pulmonary involvement in MCTD and SLE is roentgenographically indistinguishable. Differentiating laboratory features included (in the MCTD group) higher titers of anti-RNP antibodies, lower titers of anti-DNA antibodies, lower incidence of positive LE prep, and normal complement levels.

These conclusions have generally been supported by other laboratories (5, 6). Chubick and Gilliam (12, 13) have recently reviewed patients with MCTD at Parkland Hospital, and have compared clinical and laboratory features in the Parkland group with those of three other series. These results are shown in Tables 63 and 64. In several patients, it has been observed that a reduction of anti-RNP accompanied the appearance of anti-DNA and the subsequent development of renal disease (1, 7).

Gilliam and Prystowsky (8) have described the cutaneous manifestations of a group of MCTD patients (see Table 65).

Table 65

Cutaneous Manifestations in Patients With Serum Antibody to RNase-Sensitive ENA* (RNP)†

Manifestation	No. of Patients	No. Positive	% Positive
Alopecia	15	10	67
Dyspigmentation	15	10	67
Swollen hands and sclerodactyly	15	7	47
Chronic cutaneous LE‡	15	5	33
Subacute LE	15	2	13
Acute LE (malar eruption or "butterfly rash")	15	1	7
Scleroderma	15	1	7

*ENA indicates extractable nuclear antigen.
†RNP indicates ribonucleoprotein.
‡LE indicates lupus erythematosus.

From Ref. (8)

Direct immunofluorescence of normal, unexposed skin revealed a particulate ("speckled") epidermal nuclear staining pattern in all of 15 patients and subepidermal immunoglobulin deposits in 5. This type of epidermal nuclear staining was associated with high titers of RNP antibodies.

Non-MCTD overlap syndromes also occur (9). Maas and Schubothe (10) described 25 patients with an SLE-like syndrome who showed only antimitochondrial antibodies without evidence of liver disease, antinuclear factor, or LE cells. Their major manifestation was chronic recurrent attacks of pyrexia. In addition, there were varying combinations of polyarthritis, muscle aching, pericarditis and myocarditis, pleuritis, pleural effusions and pulmonary infiltrates. Dubois (9) has also observed several similar cases whose sera on immunofluorescence showed high titers or cytoplasmic fluorescence with absent nuclear fluorescence. They had no LE cells and negative spot tests for nucleoprotein and DNA antibodies.

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IV. Eosinophilic Fasciitis

In 1974 Shulman (1) reported two men with a scleroderma-like disease of the extremities in which biopsies showed striking inflammation and thickening of the facia between the subcutis and muscle. These patients also were noted to have eosinophilia and hypergammaglobulinemia. By 1975 he had two more cases. In Table 66 the pertinent features are summarized.

TABLE 66

DIFFUSE FASCIITIS WITH EOSINOPHILIA

1. Four patients with a "new" connective tissue disease:
   a. Firm, "puckered" skin tightly bound to underlying structures;
   b. Involves legs, arms (and trunk, in some);
   c. Contractures (elbows, shoulders, knees, ankles).
2. Laboratory abnormalities:
   a. Eosinophilia; blood, marrow;
   b. Erythrocyte sedimentation rate elevated;
   c. Hypergammaglobulinemia (IgG);
   d. Plasmacytosis; marrow.
3. Pathology:
   a. Striking thickening of deep fascia between fat and muscle;
   b. Collagenous hypertrophy;
   c. Infiltrate with plasma cells, lymphocytes; lymphoid follicles, perivascular or scattered.
4. Response to prednisone favorable, but gradual:
   a. Natural history unknown.
5. Pathogenesis:
   a. Unusual response to undue physical exertion;
   b. Host factors.

From Ref. (1)

Subsequently Rodnan and Coworkers (2) and others (3-5) have reported several other cases. The disease is characterized by transient eosinophilia, which is commonly preceded by physical exertion. The primary pathological alterations consist of intense inflammation and thickening with or without eosinophils in the fascia rather then the skin. Staining for IgG and C3 in deep fascia and muscle septa has been observed (2). Many patients respond well to treatment with steroids.

The syndrome probably represents an interesting, but relatively benign variant of diffuse scleroderma (5).

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V. Scleredema Adultorum of Buschke

In 1900 Buschke (1a) described the case of a 44-year old carriage painter who, following influenza, developed "a peculiar stiffness" of the neck which gradually spread to involve the skin of the face, chest and upper extremities (2). In 1920 (16) he summarized his experience and characterized the disease as follows:

> . . . hardening (Versteifung) of the deeper layers of the cutis, the subcutaneous tissue, and most likely, to some degree the fascia and musculature. The disease apparently begins acutely, in most cases, on the neck spreading on to the face, the upper arms and the trunk to the abdomen. The lower extremities may be involved but seldom are. At the beginning the patients may be affected with weakness and prostration or may feel perfectly well. It has most frequently followed influenza-like affections, scarlet fever and parotitis but it cannot be denied that the former may have been a part of the disease itself. There is no pain, only a feeling of tenseness and rigidity. The movements of the body and breathing may be more or less interfered with by the latter. The skin usually looks pale or infrequently may be slightly cyanosed and the upper layers have a velvet-like feel. . . . The full development of the disease may take place rather acutely in weeks or it may take months. It may last months or years but either regresses slowly to complete recovery or apparently some of the induration may remain indefinitely. . . . Histologically the disease shows no inflammatory reaction but is a deposit of a homogeneous exudate which presses apart the connective tissue without involving the elastic tissue, the upper layer of the cutis, or the epidermis. There is no atrophy or disturbance of pigmentation. Nothing is definitely known as to the nature of the exudate . . .

Buschke believed the disease was distinct from scleroderma. In 1946 Vallee reported 4 additional cases and described the occurrence of pleural and pericardial effusions and hydrarthrosis (3). In 1951, Leinwand (4) reported the findings on the postmortem examination of a case.

As pointed out previously (Scleroderma - A. Historical) Capusan (5) believes that the case reported by Rodnan and Benedek (2) to be the first reported case of scleroderma (by Curzio in 1753) was, in fact, a case of scleredema. The major argument in his favor is the fact that the disease regressed completely after 11 months when the patient's skin had become "perfectly soft, and flexible, being capable of being moved, raised, extended, and of performing all its natural functions" (2, 5).

In 1950 Dr. Leonard Madison (6) reported a case from the Dallas Veterans Administration Hospital and reviewed the literature. The comparison of scleredema with scleroderma made by him is shown in Table 67.

Table 67

DIFFERENTIAL DIAGNOSIS

	Scleredema	Scleroderma (Edematous Phase)
Clinical		
Preceding infection	Almost always; usually streptococcal; followed by latent period 1-6 wk.	Rare; no constant relationship
Prodromal period	Infrequent; malaise, myalgia, low grade fever	Common; athralgia with pain, swelling and stiffness of joints; vasomotor symptoms in extremities in ¾ of the cases
Edema	Rapidly progressive, maximum involvement within 2 wk.	Slow progressive involvement
	Hands and feet never involved	Hands and fingers (sclerodactylia) involved at onset or early in the disease
	Involved areas pale but not dead white	Dead white or ivory colored; sheen or waxy hue present
Sequelae	None; no pigmentation, atrophy, or telangectasia	Atrophy, pigmentation, telangectasia, hidebinding frequent
Course	Spontaneous recovery within months to years; usually within 18 mo.	Relentless, progressive atrophy and hidebinding common; spontaneous remission rare; 10% mortality; 75% protracted course
Pathology		
Epidermis	Uninvolved, no atrophy	Involved; increased pigmentation; atrophy
Cutis	Round cell perivascular infiltration collagen fibers markedly enlarged and separated by clear spaces giving a fenestrated appearance	Edema, homogenization fibrosis and sclerosis of collagen; proliferation of connective tissue with sclerosis and atrophy
Blood vessels	No endarteritis	Sclerosis and obliteration of blood vessels, some vessels thrombotic
Muscles	Normal	Edema and loss of cross striations early, degenerative changes later

From ref. (6)

By the time of his review, i.e., 1950 (50 years after Buschke's case), a total of 107 cases had been reported. By 1965, 215 cases had been reported (7). These authors pointed out that 25% of the cases showed either no improvement or only partial improvement two or more years after the onset of the disease. Unlike

scleroderma, scleredema frequently involved the tongue but not the esophagus, rarely the hands, and never the feet (7).

In a classical description of scleredema an episode of infection, often streptococcal, is followed in one to six weeks by the appearance of cutaneous induration which appears first on the posterior and lateral neck and, within the next few days or weeks, spreads to the face, shoulders, anterior neck, arms, upper back and chest (7-9). Occasionally the induration involves the hands, abdomen, and lower extremities (9). The skin is hard, taut and board-like, is difficult to pick up in folds and shows no pitting on pressure (9). The process usually resolves spontaneously within a period of several months (8, 10). Acid mucopolysaccharides may be demonstrable histologically in the dermis of involved sites.

As Curtis and Shulak (7) have pointed out, however, the disease is not as benign or self-limited as previously believed. The induration has failed to resolve in many of the patients (25% - see above). Internal abnormalities have been more frequent than initially thought and have included serosal effusion (3, 11), skeletal muscle involvement (10, 12-14), electrocardiographic abnormalities (3, 12), tongue involvement (7, 10, 12), ocular disease (15), hepatomegaly (12), osteosclerosis (14), parotid gland enlargement (6), severe neuromuscular involvement (18) and pericarditis (16). The carditis may be due to concomitant rheumatic fever (17). One case terminated in death (4). It has also been pointed out that the name Scleredema Adultorum is a misnomer since children also may be involved (11-13, 17, 19). It has also become apparent that acid mucopolysaccharides have not been demonstrated in affected skin from a number of patients (7, 20).

Histochemical and biochemical studies of the skin in scleredema reveals, besides the increase in acid mucopolysaccharides, which probably represent hyaluronic acid, no increase in neutral polysaccharides, collagen content or noncollagenous proteins (21). Thus sclerosis is not a feature of scleredema. One case showed an increase in mast cells scattered throughout the entire dermis (21). In an electron-microscopic study of the skin of a patient with scleredema and diabetes mellitus, the unmyelinated nerve fibers showed accumulations of glycogen (22).

In skin specimens stained with H & E the histologic features of scleredema are suggestive but not completely diagnostic (20, 23). The dermis is usually thickened and there are often large, swollen collagen bundles that are separated by wide, clear spaces (9). Mast cells may be increased in numbers (7, 14, 21). When present, most of the acid mucopolysaccharide appears to be in the clear spaces between collagen bundles (21).

The classification (Table 68), differential clinical manifestations (Table 69) and differential histologic and laboratory features between scleredema and scleroderma have more recently been summarized (Table 70).

Table 68

SCLEREDEMA

A. Two classes
   1. Scleredema adultorum of Buschke
      a. any age
      b. 2-6 weeks after URI
      c. spontaneous resolution 6-24 months
   2. Scleredema diutinum
      a. not associated with URI
      b. often associated with diabetes
      c. duration = years to life time
      d. onset 3rd-4th decade

B. Clinical Manifestations
   1. Non-pitting induration
   2. Symmetrical
   3. Sharply or poorly demarcated
   4. No atrophy, pigmentary changes, hair loss, loss of sweating, loss of sensation, or evidence of inflammation
   5. May have dysphagia (secondary to tongue and pharynx involvement), pleural effusions, pericardial effusions, hydrarthrosis, EKG abnormalities, parotid gland enlargement, osteosclerosis and ocular involvement.

Table 69

CLINICAL MANIFESTATIONS

	Scleredema	Scleroderma
Dysphagia	often	often (secondary to esophageal motility; lower 1/3)
Tongue	involved 40-70%	never
Nipple	yes if surrounding skin involved	no if surrounding skin involved
Atrophy	no	often
Hands and feet	unusual	often
Inflammation	no	often
Pigmentary abn.	no	often
Raynauds	no	often
Obesity	often	no
Sex	increase, females	increase, females

Table 70

HISTOPATHOLOGY AND LABORATORY

	Scleredema	Scleroderma
epidermis	normal	may have atrophy and loss of rete ridges
interfascicular spaces	widened	decreased
subcutaneous fat	normal or replaced by connective tissue	atrophied or replaced by abnormal connective tissue
sweat glands	normal (may appear bound down)	atrophic, decreased in number, bound down
inflammatory infiltrate	+ —	+++ in early morphea
pilosebaceous apparatus	normal	usually atrophic or absent
collagen bundles	thickened	thickened
elastic tissue	normal	broken up or destroyed
muscle bundles	normal	may show degeneration
glycosaminoglycans	increased hyaluronic acid, normal dermatan sulfate	normal hyaluronic acid, marked increased dermatan sulfate
sedimentation rate	normal	60-80% show increase
ANA	normal	90% +
Electronmicroscopy	dermis and subcutaneous = fibers clumped by interfibrillary material, thinner, and show splitting.	elastic fiber degeneration, thickened basal lamina at dermal epidermal junction, 3 types of collagen fibrils: 1) uniform, 700 Ang, round; 2) clusters of thin and thick fibrils 200A-900A; 3) bundles of 1000A fibrils with polygonal cut surface, acid glycosaminoglycans between collagen fibrils and elastic fibers

From ref. (24)

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VI. Scleromyxedema (Lichen myxedematosus, papular mucinosis)

This condition is a cutaneous myxedematous state characterized by numerous lichenoid papules, which by aggregation form generalized lichenoid plaques, causing extensive thickening and hardening of the skin (1). The term scleromyxedema emphasizes the clinical similarity to scleroderma, mostly the mask-like facies and sclerodactyly. However, in this condition the skin is folded and pendulous and appears too loose, as opposed to true scleroderma, in which the sclerotic and atrophic skin seems to be too tight and bound close to the underlying tissues (1).

Histologic examination reveals mucinous deposits in the middle and deeper layers of the corium, which partly push the collagen fibers apart, and partly destroy them, but which do not involve the papillae (1). The mucinous substance is a heterogeneous mixture of acid mucopolysaccharides (stained positively with alcian blue and toluidine blue). The main component is probably hyaluronic acid (2), although chondroitin-sulfuric acid type B predominates in some lesions (1). Large, stellate, elongated fibroblasts may be present (2).

Paraproteinemia may be present in this disease. In the majority of cases the paraprotein was a basic monoclonal IgG globulin with light chains exclusively of the lambda type (1). In a few cases the protein was IgM (3). Proliferation of plasma cells in the bone marrow may take place but without characteristic myeloma bone lesions.

The disease has been fatal in a few instances due to serious vascular disorders (2, 4).

Both corticosteroids (5) and melphalan (3,5) may produce dramatic improvement.

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VII. Werner's Syndrome

Oppenheimer and Kugel (1) first introduced this syndrome in the literature under the name Werner's Syndrome although Werner had described the coexistence of scleroderma with cataract 30 years earlier, in 1904 (2).

The clinical characteristics as summarized by Jablonska (3) are shown below:

CLINICAL CHARACTERISTICS OF WERNER'S SYNDROME

Typical habitus of the patient:

1. Short stature.
2. Disproportionately thin distal parts of limbs (hands, forearms, feet, and lower legs) compared with moderately developed proximal parts and trunk.
3. Bird-like facies.

Premature senility:

1. Graying and loss of hair, which in conjunction with the atrophic skin changes causes senile appearance.
2. Early atherosclerosis.
3. Early signs of senile debility.

Endocrine disturbances:

1. Sexual underdevelopment (hypogonadism), secondary sex characters retarded or absent, amenorrhea or early menopause, frequently sterility, sexual potency and libido greatly diminished or absent, underdevelopment of sex organs.
2. Proneness to diabetes.
3. Occasionally hypopituitarism, which may be associated with hypogenitalism, falsetto voice, and generalized loss of body, axillary and pubic hair.
4. Occasionally hyperthyroidism or hypothyrodism.
5. Occasionally parathyroid hyperfunction with decalcification of bones and deposition of calcium salts in the soft tissues and vascular walls.
6. Occassionally disordered adrenal cortex function with impairment in the metabolism of glucocorticoids, which may be secondary to hypopituitarism.

Osteoporosis

Osteoporosis is an almost invariable feature, presenting as characterisitic joint and bone deformities, more distinct in the feet, and occasionally demonstrable only by radiography.

Ocular changes

Bilateral juvenile-type cataract is a cardinal feature of Werner's syndrome; it differs from cataract associated with aging. Several other ocular abnormalities have also been described, e.g., glaucoma and corneal lesions.

Voice

The voice is very characteristic - high-pitched and thin, and at the same time hoarse, owing to inflammatory changes in the vocal cords.

Progression of the disease

Late development of the usually simultaneous ocular and cutaneous changes is a characteristic feature. The lesions appear usually after puberty, and cataract most commonly begins in the third decade, differing in this respect from cataract in Rothmund's syndrome, which begins in early childhood. Occasionally, the symptoms become manifest before puberty or develop much later. The changes are usually slowly progressive, leading to severe disability.

Familial occurrence of the syndrome

Frequent occurrence of the disease in siblings or abortive manifestations in preceding generations indicate its genetic character. Inheritance is of the recessive type. Chromosome studies have not given convincing results.

In summary: Werner's syndrome is a distinct entity, in which the skin lesions have scleroderma-like character, but are not scleroderma. Endocrine disturbances seem to be of fundamental importance, although the hypothesis has also been proposed that a defect in the synthesis, repair, or both of some connective tissue elements is responsible for the disease.

Werner's syndrome does not seem to be very rare, particularly the incomplete and abortive forms, as well as intermediate forms between it and Rothmund's syndrome. Rothmund's syndrome differs from Werner's in the poikilodermatous character of the skin lesions (mostly telangiectases intermingled with atrophies), onset of cataract and cutaneous manifestations in early childhood, and less pronounced hormonal derangements. It bears no resemblance to scleroderma,

and consequently intermediate forms between it and Werner's syndrome raise no diagnostic problems

While sclerodactyly is a prominent feature in scleroderma, in Werner's syndrome the hands and feet are thinned, and the fingers atrophied and deformed. The cutaneous changes in Werner's syndrome are sclerodermalike, resembling atrophic forms of systemic scleroderma. However, their distribution, absence of vasomotor manifestations and visceral involvement characteristic of scleroderma, and on the other hand presence of hormonal disorders and other classic symptoms of the syndrome, are a sufficient basis for differentiation from scleroderma (3).

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VIII. Porphyria Cutanea Tarda

Scleroderma-like changes in porphyria cutanea tarda have been described by many authors. Lesions may resemble morphea, generalized morphea or diffuse scleroderma (1). Histologic examination usually shows dermal sclerosis very similar to that seen in scleroderma. Cases with advanced facial sclerosis, sclerosis on the hands and forearms with contractures of the fingers and sclerodactyly may be indistinguishable from diffuse scleroderma (1-3). The differential diagnosis with scleroderma is assisted by histologic finding of actinic elastosis, especially in the exposed skin (4, 5) and vascular changes in the papillary and subpapillary plexus (6).

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IX. Occupation-Induced Scleroderma-like Lesions

Vasospastic disease of the hands following certain types of occupational trauma is well recognized (1-3). Such a Raynaud's phenonmenon generally has a good prognosis and is not associated with ulceration, gangrene or other trophic changes (3). The type of occupational trauma is usually that of a vibrating tool, e.g., a pneumatic hammer producing "white fingers" and sclerodactylia (4-8). Christophers has argued, however, (2) that the vibration is not important etiologically, but rather that most of the patients reported were working outdoors in the cold. He believed that the patients had Raynaud's phenomenon which was precipitated by the cold and the gripping of the construction tools with the hands.

Polyvinyl chloride has also been incriminated in causation of acro-osteolysis. This disorder includes sclerodermatous skin changes, osteolysis, especially of terminal phalanges, Raynaud's phenomenon, thrombocytopenia, portal fibrosis and imparied hepatic and pulmonary function (9). Most of the affected workers cleaned autoclaves after the polymerization process in the manufacture of polyvinyl chloride (11). Other possible environmental occupational associations with scleroderma include welding and exposure to silicates (12, 13).

A patient with a lupus-scleroderma syndrome following ethosuximide therapy for convulsions (14) has been reported. The disease spontaneously regressed after discontinuance of the drug. Generalized scleroderma-like lesions have also been reported in subjects working for several years with pesticides (15).

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X. Miscellaneous Conditions

A number of other conditions may produce scleroderma-like lesions (1). These include progeria, acrogeria gottron, sclerema neonatorum and poikiloderma. Scleroderma-like changes may also be seen in Sheehan's syndrome, phenylketonuria, amyloidosis, shoulder-hand syndrome, scalenus anticus and cervical rib syndromes, acrodermatitis atrophicans, lichen sclerosis et atrophicus and atrophoderma of Pasini-Pierini.

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