NEW DEVEOPMENTS IN THE THERAPY OF SYSTEMIC SCLEROSIS

Thomas D. Geppert, M.D.

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DEFINITION

Systemic sclerosis is a generalized disorder of small arteries, microvasculature and connective tissue, characterized by scarring (fibrosis) and vascular obliteration in the skin, gastrointestinal tract, lungs, heart, and kidneys. Hidebound skin is the clinical hallmark of systemic sclerosis, and organ compromise the prognostic keystone. The term scleroderma (Gr. *skleros* hard + *derma* skin) is a term which describes the clinical appearance of the skin in systemic sclerosis a number of disorders otherwise minimally related to systemic sclerosis. Localized scleroderma is a term used to describe a variety of conditions, including linear scleroderma and morphea, with skin manifestations similar to those of systemic sclerosis, but in which the internal organ and vascular features are lacking.

EPIDEMIOLOGY

Incidence: 20 per million population per year. Estimated to be 50,000 cases of systemic sclerosis in the United States.

Sex ratio: 4:1, females:males

Race: Possible slight increase in blacks

Age: Disease onset is highest between ages 30 and 50.

INITIAL APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF PATIENTS WITH SCLERODERMA

An approach to the differential diagnosis of patients with sclerodermatous skin changes is illustrated in Figure 1. The initial approach to a patient with scleroderma involves determining whether the patient has been exposed to solvents, talwin, bleomycin, vinblastine, penicillamine or vinyl chloride or has had a silicone breast implant. These agents have been reported to cause a clinical picture that is nearly indistinguishable from systemic sclerosis, but is usually reversible on withdrawal of the offending agent. Once it has been established that the patient has not been exposed

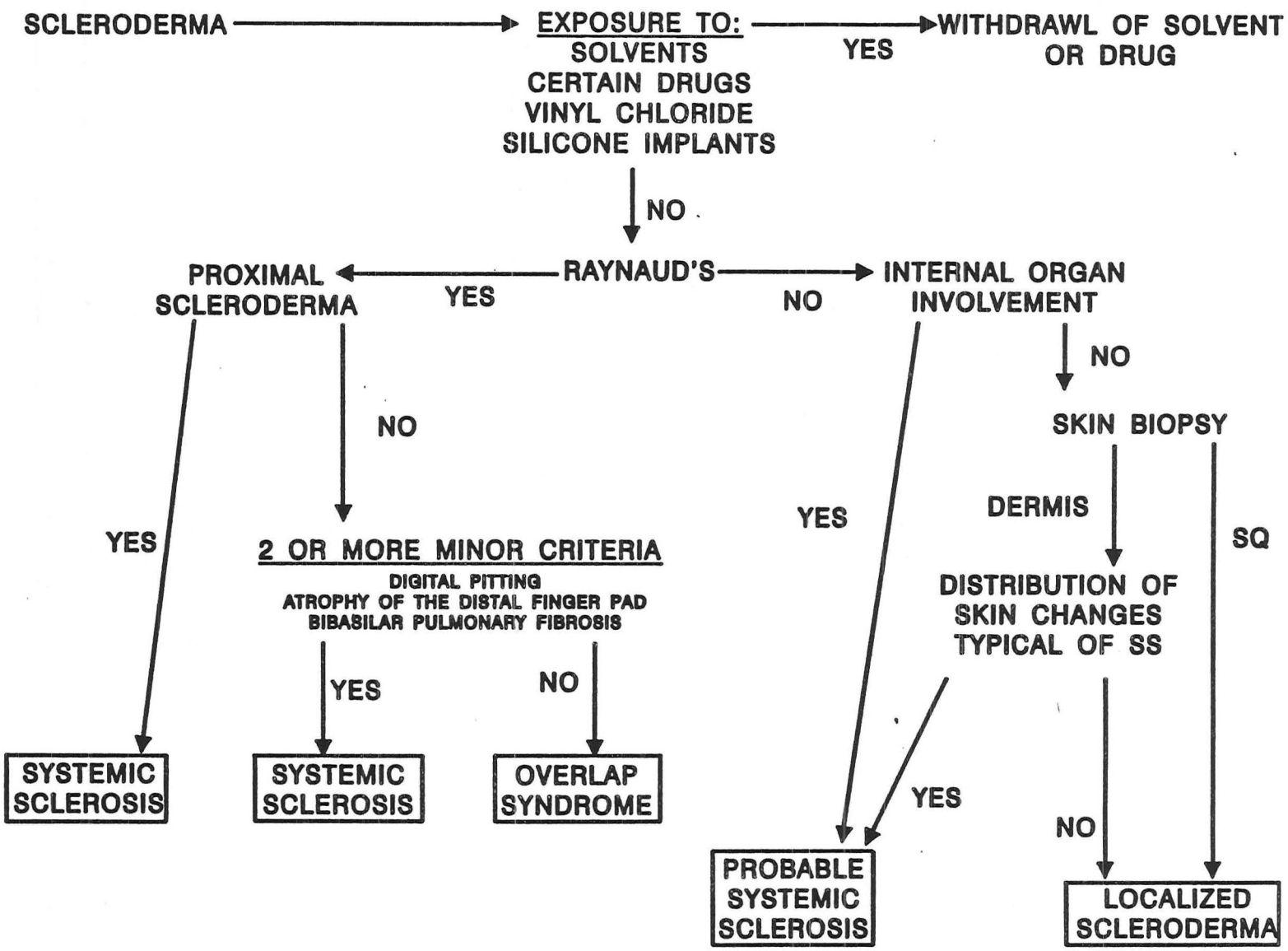

SCLERODERMA
EXPOSURE TO:
SOLVENTS
CERTAIN DRUGS
VINYL CHLORIDE
SILICONE IMPLANTS
YES
WITHDRAWL OF SOLVENT OR DRUG
NO
RAYNAUD'S
PROXIMAL SCLERODERMA
YES
NO
INTERNAL ORGAN INVOLVEMENT
NO
SKIN BIOPSY
DERMIS
SQ
YES
NO
2 OR MORE MINOR CRITERIA
DIGITAL PITTING
ATROPHY OF THE DISTAL FINGER PAD
BIBASILAR PULMONARY FIBROSIS
YES
NO
DISTRIBUTION OF SKIN CHANGES TYPICAL OF SS
YES
NO
SYSTEMIC SCLEROSIS
SYSTEMIC SCLEROSIS
OVERLAP SYNDROME
PROBABLE SYSTEMIC SCLEROSIS
LOCALIZED SCLERODERMA

Figure 1

to these drugs or solvents, it is important to attempt to elicit a history of Raynaud's phenomenon as the presence of Raynaud's phenomenon makes a diagnosis of localized scleroderma unlikely.

Systemic sclerosis can be distinguished from other rheumatic disorders that might cause Raynaud's phenomenon and skin changes by the criteria established by the Subcommittee for Scleroderma Criteria of the Arthritis and Rheumatism Association Diagnostic and Therapeutics Criteria Committee. The data obtained by that committee are illustrated in Table I.

Table I

NUMBERS OF PATIENTS WHO SATISFIED EITHER MAJOR OR MINOR CRITERIA FOR SYSTEMIC SCLEROSIS GROUPED ACCORDING TO THEIR DIAGNOSIS

	Systemic sclerosis		Comparison Patients		
	Definite N=264	Probable N=35	SLE N=172	PM/DM N=120	Raynaud's N=121
Major Criterion					
Proximal Scleroderma	239	18	1	0	0
Minor criterion	(N=25)	(N=17)	(N=171)	(N=120)	(N=121)
Sclerodactyly	19	8	1	4	11
Digital pitting scars	15	7	15	8	18
Bibasilar pulmonary fibrosis	8	1	11	22	3
Two or more criteria	17	4	0	3	6
Criteria satisfied	256 (97%)	22 (63%)	1 (1%)	3 (3%)	6 (5%)

These investigators compared a group of patients with a definite, probable or early stage systemic sclerosis with those that carried a diagnosis of systemic lupus erythematosus, polymyositis (PM),

dermatomyositis (DM), or Raynaud's phenomenon. Only one patient out of 413 patients fulfilling the criteria for SLE, Raynaud's phenomenon, polymyositis or dermatomyositis had scleroderma proximal of the metacarpophalangeal joints. In the absence of proximal scleroderma a diagnosis of systemic sclerosis can be made if 2 or more of the minor criteria, sclerodactyly, digital pitting, or bilateral basilar pulmonary fibrosis, are present. As can be seen, only 9 patients without systemic sclerosis had 2 or more of these criteria.

Although Raynaud's phenomenon occurs in approximately 90% percent of patients with systemic sclerosis, a small group of patients with systemic sclerosis do not have Raynaud's phenomenon. In the absence of Raynaud's phenomenon, the differential diagnosis of sclerodermatous skin changes includes localized scleroderma. Since internal organ involvement is a common feature of systemic sclerosis and not a feature of localized scleroderma, it can be used to differentiated these two possibilities. In the absence of visceral involvement, systemic sclerosis and localized scleroderma can be best differentiated based on a full thickness skin biopsy. Lymphocytic or eosinophilic infiltration and/or fibrosis of the subcutaneous tissue strongly supports a diagnosis of localized scleroderma whereas involvement limited to the dermis is more characteristic of systemic sclerosis. Those patients with dermal involvement are likely to have systemic sclerosis, particularly if the distribution of scleroderma is typical of systemic sclerosis. Those with atypical distribution probably have localized scleroderma.

SUBSET OF SYSTEMIC SCLEROSIS

Systemic sclerosis has been further subdivided into 2 groups of roughly equal size based on the clinical findings. One group of patients has sclerodermatous skin changes limited to the hands, forearms and face. The other group of patients has diffuse cutaneous involvement. The clinical features of patients with limited cutaneous involvement are listed in Table II. Patient with limited cutaneous involvement have a more insideous onset of their illness, usually presenting with a history of Raynauds phenomenon and swelling of the digits for years. Thus, these patients are older at presentation, and have a longer duration of symtoms. Patients with limited cutaneous involvement have a more benign course as evidenced by the increased percentage of patients surviving 10 years. The improved survival appears to be due to a lower incidence of renal involvement and restrictive

pulmonary disease. These patients were initially called CREST patients because of the slightly higher incidence of calcinosis, telangiectasia and esophageal dysmotility in this subgroup. It now appears that calcinosis, telangiectasia and esophageal dysmotility do not correlate as well as the extent of cutaneous involvement with the subsequent prognosis. Therefore, the term, limited is now used by many investigators to describe these patients.

Patients with diffuse cutaneous involvement ususally present soon after symptoms develop. These patients often present with arthritis or scleroderma rather than Raynaud's phenomenon. The skin thickening advances rapidly to involve the upper arms and trunk. These patients have a higher incidence of renal disease. Of interest is the finding that tendon fricition rubs occur almost exclusively in patients with diffuse cutaneous involvement. Many investigators now include the presence of a tendon friction rub in the criteria of diffuse systemic sclerosis (Table III). The incidence of visceral involvement characteristic of each subgroup will be discussed in detail separately under each organ.

Table II

COMPARISON OF DEMOGRAPHIC AND CLINICAL FEATURES FOUND AT ANY TIME DURING THE COURSE OF SYSTEMIC SCLEROSIS

	Diffuse Scleroderma	Limited Scleroderma
	(Percentage of patients)	
Demographic		
Age (<40 at onset)	30	14
Race (nonwhite)	10	5
Sex (Female)	76	84
Duration of symptoms	3	11
Organ system involvement		
Skin (Total skin score)*	39	8.6
Telangiectasias	64	91
Calcinosis	17	42
Raynaud's	92	98
Arthralgias or arthritis	72	56
Tendon friction rubs	62	9
Joint contractures	89	62
Esophageal hypomotility	73	79
Pulmonary hypertension	<1	7
Pulmonary fibrosis	38	38
Restrictive pulmonary disease	55	24
"Renal Crisis"	20	1
Cumulative Survival (10 years from first diagnosis)	55	71

*As described by Steen
Modified from Medsger, TA 1988

Table III
CLASSIFICATION CRITERIA FOR PATIENTS WITH SYSTEMIC SCLEROSIS

Diffuse scleroderma: sclerodactyly plus any of the following:

Scleroderma of the trunk; or

Scleroderma proximal to the elbow; or

Palpable tendon friction rubs.

Limited scleroderma: sclerodactyly and both of the following:

Scleroderma limited to hands and arms distal to the elbow and/or face; and

Absence of palpable friction rubs

LeRoy, 1988

Table IV

AUTOANTIBODY STATUS OF SYSTEMIC SCLEROSIS PATIENTS

ACCORDING TO DISEASE SUBTYPE CLASSIFICATION

Authors	Autoantibody		Disease subtype	
	α-ACA	α-Topo I	Limited (n=191)	Diffuse (n=206)
			% of patients	
Steen et al. (n=397)	-	-	39	66
	+	-	43	3
	-	+	18	33
	+	+	0	0
Chorzelski et al. (n=114)	-	-	75	100
	+	-	25	0
	-	+	44	77
	+	+	0	0
Wiener et al.* (n=355)	-	-	44	46
	+	-	55	26
	-	+	11	28
	+	+	2	0

* Use CREST rather than limited systemic sclerosis to separate patients.

Patients with systemic sclerosis can also be subdivided based on their production or autoantibodies, specifically antibodies against the centromere and topoisomerase I (anti-Scl-70). The relationship between the production of these autoantibodies, and limited and diffuse systemic sclerosis is shown in Table IV. Patients without both autoantibodies can fall into either group. Patients that are anti-centromere antibody (ACA) positive generally have limited disease. Although found in patients with limited disease, antibodies to topoisomerase I occur in a slightly higher frequency in patients with diffuse disease. The most interesting feature of these antibodies is that they are mutually exclusive. Thus, in well over 1,000 patients thus far described, only 4 patients have been reported to have both antibodies. This has led some investigators to conclude that limited and diffuse systemic sclerosis are different disorders with different etiologies.

The other interesting feature of these autoantibodies (Table V) is that they are relatively specific for systemic sclerosis. Thus, few if any normal controls, or patients with other connective tissue diseases produce these autoantibodies.

Table V

CLINICAL ASSOCIATION OF ANTICENTROMERE ANTIBODIES AND ANTIBODIES TO TOPOISOMERASE I

Diagnostic group	Number of patients	% ACA positive	% α-topo I positive
Controls	34	0	3
Connective tissue disease controls			
SLE	25	0	0
RA	31	0	0
Sicca syndrome	2	0	0
Primary and secondary Raynaud's	154	19	4
CREST	54	55	11
Proximal systemic sclerosis	89	26	28

From Weiner et al.

CLINICAL FEATURES

Raynaud's phenomenon: Raynaud's phenomenon is a vascular disorder characterized by reversible vasospasm of the arteries. Symptomatically, this may result in biphasic, triphasic or occasionally uniphasic color changes primarily on the hands, feet and nose on exposure to cold or stress. Typically the hands turn white on exposure to cold reflecting vasospasm followed by a blue color that is caused by the stagnation of blood flow as the capillaries and venules dilate. These color changes are then followed by a red color as reactive vasodilation occurs. The incidence of Raynaud' phenomenon in systemic sclerosis is 80-97%. Raynaud's is slightly more common in limited systemic sclerosis.

The relationship between Raynaud's phenomenon and systemic sclerosis is reasonably clear. Cold sensitivity that results in colors changes and causes the patient to seek medical attention occurs

in 1-2% of the population. The vast majority of these patients have primary Raynaud's and will never develop a connective tissue disease, but a small percentage (<4%) of these patients will eventually develop a connective tissue disease. Most of these patients will develop either systemic sclerosis or an undifferentiated connective tissue disease.

Several studies have attempted to determine if clinical or laboratory finding will predict which patients will develop systemic sclerosis. These studies have employed patients seeking medical attention for their Raynaud's and, therefore, have a higher percentage of patients that eventually develop a connective tissue disease than expected if all patients with Raynaud's phenomenon were followed. Antinuclear antibodies are found in from 8-16% of these patients, but the presence of these antibodies do not necessarily indicate that the patient will develop systemic sclerosis. For example, in one study, 91 patients with primary Raynaud's phenomenon were followed for a mean of 8.8 years. 23 of the patients had antinuclear antibodies at the initiation of the study. Only 2 of these ANA positive patients developed systemic sclerosis. Moreover, 2 other ANA negative patients developed an undifferentiated connective tissue disease. In another study of 58 patients with primary Raynaud's phenomenon followed prospectively for an average of 2.7 years, 17 patients were ANA positive at the initiation of the study. 7 ANA negative patients developed limited systemic sclerosis and 4 ANA positive patients developed undifferentiated connective tissue disease. The adjusted odds ratio associated with a positive ANA was determined to be only 1.52.

It has been claimed that capillary microscopy more accurately predicts which patients are going to develop a connective tissue disorder. Capillary microscopy is a technique in which the nailfold capillaries are directly examined using a widefield microscope. Patients with systemic sclerosis have been observed to have a decrease in the absolute number of capillary loops, with dilation and distortion of the remaining loops. The evidence supporting the claim that capillary microscopy predict the patients going on to develop systemic sclerosis is illustrated in Tables VI and VII.

Table VI

EVOLUTION OF PRIMARY RAYNAUD'S PHENOMENON TO CONNECTIVE TISSUE DISEASE

	Developed collagen vascular disease	
Nailfold capillaroscopy	No	Yes
	Number of Patients	
Normal	87	4
Abnormal	15	13
Total	102	17

From Maricq, 1982; Harper, 1982; and Fitzgerald, 1988

The data in Table VI were obtained from 3 studies in which nailfold capillary microscopy was performed on patients with primary Raynaud's phenomenon and the patients were followed prospectively to determine whether they would develop a connective tissue disease. Capillary microscopy was normal in only 4 patients that eventually developed a connective tissue disease. The specificity of the test was less impressive as it was abnormal in 15 patients who never developed systemic sclerosis. The adjusted odds ratio for abnormal capillary microscopy, positive antinuclear antibodies, abnormal pulmonary function tests, and esophageal dysmotility are depicted in Table VII.

Table VII

EVOLUTION OF RAYNAUD'S PHENOMENON

Features at entry	Diagnosis at followup			Adjusted Odds ratio
	Nil	Limited SSc	Diffuse SSc	
All patients	58	8	3	
Abnormal nailfold capillaroscopy	11	2	4	22.68
Antinuclear antibody	17	2	2	1.52
Abnormal pulmonary function tests*	7	2	2	4.78
Abnormal esophageal motility	7	1	1	1.99

*Decreased Total Lung Capacity or decreased DLCO.

From Fitzgerald

The adjusted odds ratio for abnormal nailfold capillary microscopy is 22.68. Thus, it appears that capillary microscopy is a useful test in predicting which patients with primary Raynaud's phenomenon need to be followed closely for the development of other signs of a connective tissue disease and those that can be reassured that none will develop. An abnormally low total lung capacity or DLCO correlated with the development of systemic sclerosis with an adjusted odds ratio of 4.7, whereas, esophageal dysmotility and a positive ANA correlated poorly.

Although cold induced vasospasm initiates Raynaud's phenomenon, Raynaud's phenomenon need not be caused by abnormally intense vasospasm. Thus, the normal physiologic response to cold exposure can elicit vascular insufficiency when the blood vessels are abnormally narrow. It is clear that the digital arteries in patients with systemic sclerosis are narrowed due to intimal fibrosis. The results of one study of 25 digital arteries obtained at postmortem examination from 16 patients with systemic sclerosis and Raynaud's phenomenon of 2-22 years duration are depicted in Table VIII.

Table VIII

HISTOLOGIC FINDINGS IN DIGITAL ARTERIES OF PATIENTS

Table VIII

HISTOLOGIC FINDINGS IN DIGITAL ARTERIES OF PATIENTS WITH SYSTEMIC SCLEROSIS AND RAYNAUD'S PHENOMENON

Finding	Percent of patients
Intimal fibrosis	100
Adventitial fibrosis	40
Severe narrowing (>75%)	79
Evidence of thrombosis	24

From Rodnan, 1980

Intimal fibrosis was found in 100% of the specimens, and significant narrowing of the lumen (>75%) was found in 79% of the specimens. Similar findings were observed in angiographic studies. Although structural features dominate consideration of the mechanism of Raynaud's phenomenon in systemic sclerosis, other factors may play a role. Thus, for example, platelet activation occurs in vivo in systemic sclerosis and platelets release substances that exert powerful local effects on vascular tone such as thromboxane A_2 and serotonin. The observation that ketanserin, a serotonin antagonist, improves digital artery perfusion across a broad range of temperatures in patients with systemic sclerosis suggests that serotonin may be playing a role in enhancing vascular tone in this disease.

Skin. The skin thickening of systemic sclerosis generally begins on the fingers and hands. The skin initially appears shiny and edematous with a loss of superficial landmarks such as skin creases. The skin of the face is usually involved next, leading to immobile facies. Extension to the forearms and then trunk follows in some cases. In those cases developing generalized scleroderma, the thickening progresses over 3 months to 3 years. Ulcers often develop over bony prominences. Hyper and hypopigmentation may develop.

Skin biopsies from early disease reveal an increase in compact hyalinized collagen fibers in the lower dermis and upper subcutaneum in association with perivascular and interstitial lymphocytic and histiocytic infiltrates. The proportion of type I and III collagen is the same as normal skin. Skin biopsies taken later in the course of the disease reveal only dermal fibrosis.

Pulmonary. The frequency of lung involvement in systemic sclerosis varies from 40-90% depending on the definition of lung involvement and the patient population studied. In Table IX, several clinical and radiographic features of a large series of nonsmoking patients with systemic sclerosis (n=165) are correlated with pulmonary function studies.

Table IX

PULMONARY FUNCTION ABNORMALITIES IN 165 NONSMOKING SYSTEMIC SCLEROSIS PATIENTS

	Normal	Restrictive	Obstructive	DLCO
Percent of patients	32.7	27.8	12.1	22.4
FVC (% predicted)	105.0	65.0	98.0	97.0
FEV_1/FVC (% predicted)	82.0	83.5	55.0	79.0
DLCO (% predicted)	100.0	70.0	77.0	66.5
Fibrosis on X-ray	14.0	48.0	-	23.0
Dyspnea	26.0	67.0	-	40.0
Bibasilar rales	8.0	44.0	-	14.0

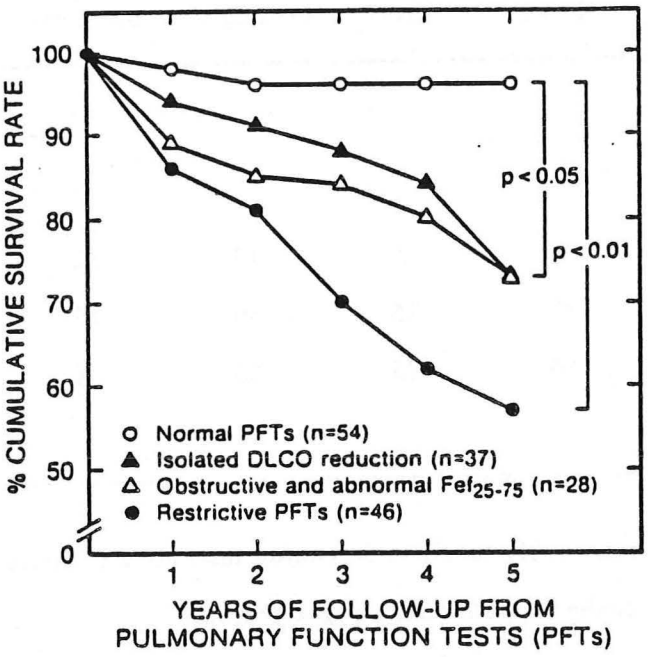
Modified from Steen et al. Arth. Rheum. 28:759.

Thirty percent of patients had normal pulmonary function tests, even though 26 % of these patients had dyspnea on exertion and 14 % had bibasilar fibrosis. The lack of correlation between symptoms, physical findings, and chest radiographs has been noted by several investigators. A restrictive defect was the most common abnormality on pulmonary function tests, and an abnormal

DLCO was the second most common abnormality. The obstructive defects noted in these patients were felt to be secondary to systemic sclerosis since no other cause could be found. Several studies have examined the rate at which pulmonary function abnormalities progress in systemic sclerosis. These studies found great individual variability and were unable to demonstrate that the pulmonary function tests deteriorate at rates that are significantly greater than control populations.

Gallium scans have been used in the evaluation of patients with interstitial lung disease and have been found to be positive in many patients with systemic sclerosis, but their clinical usefulness has not been established. Similarly, the value of bronchoalveolar lavage which frequently reveals an increase in the proportion of lymphocytes has not been established. Neither gallium scanning nor lavage appear to correlate with pulmonary function testing, although it remains possible that they predict future changes in pulmonary function testing.

Figure 2; from Steen et al., 1985



The effect of pulmonary involvement on mortality is illustrated in Figure 2. Patients with restrictive PFTs have significantly shortened life expectancy compared with systemic sclerosis patients without these changes. An isolated abnormality in DLCO and obstructive abnormalities on PFTs were also associated with a decreased cumulative survival, although to a lesser extent.

Pulmonary hypertension is a serious complication of systemic sclerosis. Clinically apparent pulmonary hypertension with dyspnea and evidence of right sided heart failure occurs in 5-10% of patients. Once pulmonary hypertension is clinically evident, the patients rarely survive longer the one year. One study, however, has suggested that clinically inapparent pulmonary hypertension occurs

in many patients with systemic sclerosis and that the actual frequency of pulmonary hypertension is closer to 33%. In that study, hemodynamic studies were performed on 49 patients with systemic sclerosis. They found 8 cases of definite pulmonary hypertension and 8 cases of borderline pulmonary hypertension. The capacity of noninvasive studies to detect pulmonary hypertension in these patients can be seen in Table X.

Table X

CAPACITY OF NONINVASIVE TESTS TO DIAGNOSE PULMONARY HYPERTENSION IN PATIENTS WITH SYSTEMIC SCLEROSIS

		Percent of screening test suggestive of PAH				
Pulmonary artery pressure	Range	Physical Exam	Chest X-ray	EKG	Echo-cardiogram	DLCO < 43% predicted
	(mmHg)					
Normal (n=33)	7-19	12	0	9	12	12
Borderline (n=8)	14-20	37	0	25	50	12
Definite (n=8)	22-55	62	50	75	50	88

From Ungerer et al. 1983

Although the DLCO below 43% of predicted is a reasonably sensitive screening test, none of these nonivasive tests is an effective screening test for moderate pulmonary hypertension.

Pathologically the arterial changes in pulmonary hypertension resemble those in the digital arteries with intimal fibrosis and narrowing of the lumen. The relationship between the pulmonary manifestation of systemic sclerosis and the disease subsets as defined by clinical parameters or autoantibodies are listed in Tables XI and Table XII, respectively.

Table XI

CORRELATION OF LUNG INVOLVEMENT WITH DISEASE CLASSIFICATION AND AUTOANTIBODY PRODUCTION IN PROGRESSIVE SYSTEMIC SCLEROSIS

	Limited Scleroderma (n=191)		Diffuse Scleroderma (n=206)	
	ACA +	ACA -	α-Scl-70 +	α-Scl-70 -
	Percentage of patients with lung involvement			
Interstitial fibrosis[1]	22	42	48	29
Restrictive Disease[2]	13	33	70	48
Isolated Pulmonary Htn[3]	14	14	0	0

[1]Bibasilar fibrosis on chest radiograph

[2]FVC<80% predicted

[3]Right sided CHF with clinical evidence of pulmonary hypertension or increased PA pressures.

Modified from Steen et al. Arth Rheum 31:196

Although many of the patients from both disease subgroups have bibasilar fibrosis, restrictive disease is more common in patients with diffuse disease, and less common in those patients that are anti-centromere antibody positive. Pulmonary hypertension, however, is more common in the patients with limited disease regardless of the presence of the anticentromere antibody.

Table XII

ORGAN INVOLVEMENT IN PSS ACCORDING TO AUTOANTIBODY PRODUCTION

	ACA + α-Scl-70-	ACA - α-Scl-70 -	ACA - α-Scl-70 +
	Percentage of PSS patients		
GI	78	64	83
Lung	34	42	57
Interstitial Fibrosis[1]	22	31	53
Restrictive Lung Disease[2]	13	39	68
Heart	6	13	16
Kidney	0	10	6

[1] Bibasilar fibrosis on chest X-ray.

[2] FVC<80% predicted.

Modified from Steen et al. Arth Rheum 31:196

Myocardial involvement. Myocardial involvement in systemic sclerosis is common, but rarely clinically significant. For example, 35% of patients with systemic sclerosis have pericardial effusions at autopsy or when examined with echocardiography whereas clinical pericarditis occurs in approximately 10-15% of patients. Typically, pericarditis in systemic sclerosis is chronic and may be associated with chest pain or dyspnea. Whether pericarditis causes chest pain in patients with systemic sclerosis is not clear as these symptoms are common in patients without evidence of pericarditis. Pericardial effusions have rarely been reported to cause tamponade.

Myocardial fibrosis is observed in 30-50% of patients. The fibrosis is patchy and randomly distributed throughout the myocardium. It differs from atherosclerotic disease in its lack of left ventricle predominance, lack of relationship to coronary vessels, lack of hemosiderin deposition, and the distinctive involvement of the immediate subendocardium. Of interest is the finding of myocardial contraction band necrosis in 30% of patients with systemic sclerosis. Contraction band necrosis is a pathologic finding usually seen in patients who have died within 30 days of cardiac surgery and is thought to be due to transient intraoperative cessation of flow. It occurs only in the distribution of patent bypass grafts. Moreover, it can be produced by temporary coronary artery occlusion in the dog. The lesion is thought to represent a response of the myocardium to ischemia with reperfusion. The observation that contraction band fibrosis is found in patients with systemic sclerosis has suggested that myocardial fibrosis may be secondary to repeated ischemic episodes with reperfusion. This hypothesis has been supported by a study examining maximal exercise and redistribution thallium scans in 26 patients with systemic sclerosis. Although only 6 of the patients had clinical cardiac involvement, 20 of the patients had abnormal thallium scans including 10 with reversible exercise induced defects and 18 with fixed defects. 7 of the 10 patients with a reversible thallium defects underwent cardiac catheterization and were found to have normal coronary arteries. Another study examined the effects of exposing the skin to cold on myocardial perfusion and function in 13 patients. 10 patients were found to have reversible, cold induced, transient segmental left ventricular wall hypokinesis. These defects anatomically correlated with perfusion defects. Thus, the data demonstrate that in patients with systemic sclerosis, transient episodes of cardiac hypoperfusion are induced by cold exposure or exercise. The data support the conclusion that myocardial fibrosis in systemic sclerosis is secondary to repeated episodes of transient ischemia caused by recurrent vasospasm with or without fixed vascular lesions.

Extramural coronary arteries are usually normal. Involvement of intramural coronaries is controversial. Several case reports and small series have claimed extensive intramural coronary artery intimal fibrosis and narrowing. Larger autopsy series, however, have found only minimal disease.

The prevalence of electrocardiographic findings in systemic sclerosis is depicted in Table XIII.

Table XIII

ESTIMATED PREVALENCE OF ELECTROCARDIOGRAPHIC FINDINGS IN SYSTEMIC SCLEROSIS BASED ON 436 CASES

Normal EKG	56 %
PR prolongation	5 %
Right bundle-branch block	2 %
Left bundle branch block	1 %
Left anterior fascicular block	5 %
Nonspecific conduction abnormality	4 %
Second or third degree heart block	1 %
Left ventricular hypertrophy	7 %
Right ventricular hypertrophy	7 %
Low voltage QRS	5 %
Nonspecific T wave abnormality	7 %
Atrial ectopy	7 %
Ventricular ectopy	5 %
Q waves in V_1 and V_2	10 %*

*Based on only 100 patients

Modified from Follansbee et al.

Many of these abnormalities such as left and right ventricular hypertrophy are likely to be secondary to extracardiac disease such as pulmonary hypertension, and systemic hypertension. It is felt that many of the conduction system disturbances are related to myocardial fibrosis. This is supported by the finding that the presence of fixed thallium defects in the septum correlated with the presence of conduction disturbances. Though, the clinical significance of these defects is not completely clear, several findings suggest that they be clinically relevant. For example, episodes of ventricular tachycardia, which occur in as many as 10 percent of patients, and the number of PVC's and PVC

pairs in 24 hours correlate with a decreased survival and with other clinical and laboratory evidence of pulmonary and cardiac disease. In summary, cardiac involvement in systemic sclerosis occurs commonly and adversely effects survival.

Cardiac involvement in limited systemic sclerosis may be less frequent and less severe than that observed in diffuse systemic sclerosis. The relationship between cardiac disease and the clinical subtype of systemic sclerosis is depicted in Table XIV.

Table XIV

CARDIOVASCULAR SYMPTOMS OF 102 PATIENTS WITH SYSTEMIC SCLEROSIS

Clinical feature	Diffuse systemic sclerosis	Limited systemic sclerosis
	% of patients	
Raynaud's phenomenon	88	91
Dyspnea	56	47
Palpitations	23	29
Angina pectoris	6	4
Systemic hypertension	13	20
Clinical cardiac systemic sclerosis		
Congestive heart failure	9	2
Pericardial disease	2	10
Arrhythmias*	11	6

*Requiring therapy

Modified from Follansbee et al.

Cardiac involvement was defined in this study as any of the following: symptomatic pericarditis, congestive heart failure, or arrythmia requiring therapy. Cardiac involvement was found to be slightly more common in diffuse disease. Other investigators have found that, although patients with

limited systemic sclerosis had a similar number of fixed thallium defects, the defects were smaller in size. Moreover, the left ventricular ejection fraction of patients with fixed thallium defects and limited systemic sclerosis was entirely normal, whereas several patients with fixed thallium defects and diffuse systemic sclerosis had markedly depressed ejection fractions. In addition, fewer patients with limited systemic sclerosis had congestive heart failure and arrhythmias requiring therapy than patients with diffuse systemic sclerosis. Patients with diffuse systemic sclerosis also were found to have more exercise induced ventricular arrhythmias. Finally, 38% of patients with diffuse systemic sclerosis had exercise-induced thallium defects with normal coronaries whereas this abnormality was not detected in any of 22 patients with limited systemic sclerosis. Interestingly, pericardial disease is apparently more common in patients with limited disease.

Gastrointestinal: The gastrointestinal abnormalities observed in patients with systemic sclerosis are listed in Table XV.

Table XV

GASTROINTESTINAL MANIFESTATION OF SYSTEMIC SCLEROSIS

Abnormality	Clinical manifestation
Esophageal hypomotility	Dysphagia
Decreased lower esophageal pressure	Reflux esophagitis
Upper and lower gastrointestinal telangiectasias	Gastrointestinal bleeding (Rare)
Gastric atony (rare)	Nausea and vomiting
Small intestinal hypomotility	Small bowel obstruction
Small bowel bacterial overgrowth	Diarrhea and Malabsorption
Small bowel dilation	Volvulus
Pneumatosis intestinalis	Benign Pneumoperitoneum
Colonic hypomotility	Constipation and/or diarrhea
	Chronic intestinal pseudoobstruction
Colonic wide mouth diverticula	Rare perforation
	Rare obstruction secondary to impaction
Primary biliary cirrhosis	Pruritus and jaundice

Esophageal hypomotility is present in at least 75% of patients with systemic sclerosis. The extent of the hypomotility varies from occasional weak or uncoordinated contractions to complete paralysis. The prevalence of these abnormalities in a group of 103 patients with systemic sclerosis is depicted in Table XVI.

Table XVI

ESOPHAGEAL MOTILITY FINDINGS

OF 103 PATIENTS WITH SYSTEMIC SCLEROSIS

Esophageal Manometry	Percent of patients
Normal	13
Diffuse spasm	5
Variability in contraction strength	19
Weak and uncoordinated contractions	26
Complete paralysis	36

From Garrett et al. 1971

Although abnormalities could be detected with manometry in 87% of the cases, only 60% had dysphagia and 35% had heart burn. Thus, esophageal abnormalities may be detected in asymptomatic patients. The absolute pressures generated by contractions in the upper and lower esophagus and lower esophageal sphincter are provided in Table XVII.

Table XVII

ESOPHAGEAL MANOMETRY FINDINGS IN PATIENTS WITH SYSTEMIC SCLEROSIS

	Normal (n=20)	Systemic Sclerosis (n=42)	
Upper esophageal sphincter pressure	125.7 ± 11.6	108.5 ± 7.9	NS
Wave amplitude of the proximal third	85.3 ± 4.9	60.0 ± 6.2	(P < .0025)
Wave amplitude of distal two thirds	84.7 ± 6.1	6.3 ± 4.7	(P < .0005)
Lower esophageal sphincter pressure	32.4 ± 1.8	15.2 ± 2.2	(P < .0005)

From Weihrauch and Korting, 1982

It can be seen that pressures in the upper esophagus are not significantly different from controls. Rarely patients with systemic sclerosis may develop defective skeletal muscle contractility in the esophagus. In contrast to upper esophageal pressures, lower esophageal pressure are dramatically less

than the same measurements in control patients. This leads to esophageal reflux in a large percentage of the patients. For example, in one study 33 of 55 patients with systemic sclerosis had heartburn, and reflux identified by 12 hour esophageal pH-monitoring in 66%. The presence of reflux was found to correlate loosely with evidence of esophageal hypomotility on manometry.

As a result of esophageal reflux, patients with systemic sclerosis may develop Barrett's metaplasia. In a retrospective analysis of 75 patients with systemic sclerosis, 24 patients had symptoms leading to endoscopy and 9 of these had Barrett's metaplasia (Table XVIII).

Table XVIII

CLINICAL FEATURES OF 24 PATIENTS WITH SYSTEMIC SCLEROSIS UNDERGOING ENDOSCOPY

	Patients with Barrett's Metaplasia (n=9)	Patients without Barrett's Metaplasia (n=15)
Heartburn duration (mos)	94 ± 40	52 ± 22
Dysphagia (mos)	39 ± 22	7 ± 3
CREST (%)	66	7
LES pressure		
End-expiratory	2.0 ± 2.6	4.5 ± 1.5
Mid-respiratory	9.3 ± 2.3	14.7 ± 2.0

From Katzka et al 1987

Barrett's metaplasia was found significantly more frequently in the patients with CREST. Other smaller series have failed to identify Barrett's metaplasia in patients with systemic sclerosis.

The presence of chronic reflux and the finding of Barrett's metaplasia by at least some observers, suggests the possibility that patients with systemic sclerosis may predispose to carcinoma of the esophagus. To evaluate this possibility, Segel et al. reviewed 680 case of systemic sclerosis patients in a retrospective analysis and found only one cases of adenocarcinoma. One case in 680 was found to be within the expected range for adenocarcinoma of the esophagus in control populations. The authors concluded that the incidence of adenocarcinoma of the esophagus is not increased in

systemic sclerosis and that screening procedures were not indicated.

Involvement of the stomach is unusual, but has been reported. In one series of 727 patients, 5 had dilated atonic stomachs, although these investigators did not specifically examine each patient for stomach involvement.

Small bowel hypomotility has been reported to occur in 40 percent of cases of systemic sclerosis. Duodenal myoelectic studies depicted in Table XIX have demonstrated that the frequency of slow waves and the velocity of their propagation is normal in patients with systemic sclerosis.

Table XIX

DUODENAL MYOELECTRICAL ACTIVITY IN NORMAL CONTROLS AND PATIENTS WITH SYSTEMIC SCLEROSIS

Activity	Controls	Scleroderma
Slow wave frequency (cycles/min)	11.4 ± 0.3	11.5 0.3
Slow-wave propagation velocity (cm/sec)	4.5 ± 0.6	4.3 ± 0.8
% of slow waves eliciting action potentials		
Resting	15.8 ± 7.1	12.2 ± 8.6
Duodenal instillation of water	95.7 ± 4.8	20.1 ± 2.8
Secretin	98.4 ± 1.6	53.0 ± 4.5

From DiMarino et al. 1973

Moreover, the number of slow waves eliciting action potentials and subsequent contractions was normal. When the bowel was stimulated by the instillation of saline, however, the percentage of action potentials elicited by the slow waves was dramatically increased in controls, but only minimally increased in patients with systemic sclerosis. These data suggest that patients with systemic sclerosis have a defect in the neurogenic reflex responsible for increasing small bowel contractility

in response to a fluid load. In early disease, this defect could be corrected by adding pentagastrin, but later in the disease course, the colon became completely unresponsive. This observation has suggested that the intestinal smooth muscle loses the ability to contract as the disease progresses despite retaining the capacity to generate slow waves.

Patients with systemic sclerosis frequently experience steatorrhea that is thought to be due to bacterial overgrowth. Support for this hypothesis is the demonstration that serum unconjugated bile acids are increased in patients with systemic sclerosis. Moreover, patients with systemic sclerosis and diarrhea have markedly increased serum levels of unconjugated bile acids compared to patients with systemic sclerosis that do not have diarrhea (Table XX). Finally, there are numerous reports of improvement in the diarrhea following antibiotic treatment.

Table XX

CORRELATION BETWEEN SERUM UNCONJUGATED BILE ACIDS AND DIARRHEA IN SYSTEMIC SCLEROSIS

	Number	Unconjugated bile acid (μmol/L)
Controls	16	.39
Systemic sclerosis		
without diarrhea	26	.51
with diarrhea	10	1.68

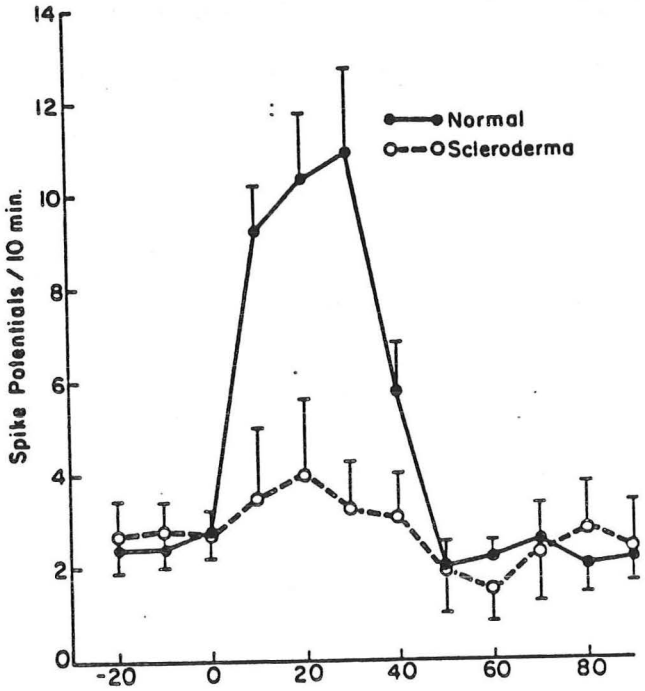
From Stellaard et al. 1987

The incidence of colonic involvement on barium enema varies from 10% to 50%. Wide mouthed diverticula are the characteristic finding. These diverticula can rarely perforate. In addition, there are reports of impaction of diverticula leading to intestinal obstruction.

Colonic hypomotility has also been reported in systemic sclerosis. Figure 3 depicts the number of spike potentials per 10 minutes for normal controls, or for patients with systemic sclerosis.

In the basal state, patients with systemic sclerosis and normal controls had comparable frequency of spike potentials. After eating, however, the number of spike potentials observed in normal small bowel increased

Figure 3; Battle, 1981



dramatically, whereas the frequency of spike potentials in patients with systemic sclerosis remained stable. Thus, like small bowel activity in systemic sclerosis, the colon is unable to respond to stimuli that would normally increase its contractile activity. Bowel hypomotility can occasionally be so severe that patient develop recurrent symptoms of obstruction called, chronic intestinal pseudoobstruction.

Patients with systemic sclerosis have telangiectasia throughout the gastrointestinal tract. Upper and lower gastrointestinal bleeding occasionally occurs from these lesions.

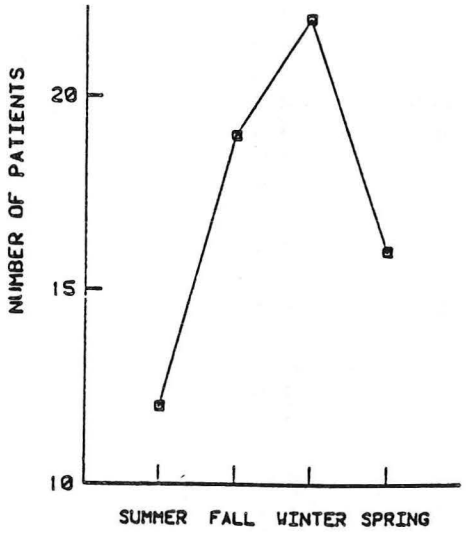
Histologically, the changes throughout the gastrointestinal tract include thinning of the mucosa, increased collagen content in the submucosa and lamina propria, and atrophy of the muscularis. The walls of the small arteries and arterioles are thickened and often surrounded by periadventitial fibrosis. The serosa overlying the colon and small bowel are thickened with fibrosis.

The co-existence of primary biliary cirrhosis and limited systemic sclerosis was first described in 1971. The incidence of this association is not known, but one study reviewed 83 cases

of primary biliary cirrhosis and found sclerodactyly in 13. 4 of these patients had esophageal dysmotility. 8 had a positive ANA. Several had "reduced gas transfer". None had diffuse scleroderma. In another study, antimitochondrial antibodies were sought in 250 patients with systemic sclerosis. 141 of the patients had limited disease whereas 101 had diffuse disease. 11 of the limited patients had a positive antimitochondrial antibody. 3 of these patients had primary biliary cirrhosis and 1 had an elevated alkaline phosphatase. Only 3 patients with diffuse scleroderma had an anti-mitochondrial antibody, and none of these had primary biliary cirrhosis.

Renal. Renal involvement occurs in as many as 20 percent of patients with diffuse systemic sclerosis, but occurs only rarely in patients with limited systemic sclerosis. Renal involvement in systemic sclerosis, termed scleroderma renal crisis, is characterized by the sudden development of hypertension, elevated plasma renin levels, hypertensive retinopathy, and rapid deterioration of renal function. Other more chronic forms of renal failure have been described, but the causal relationship to systemic sclerosis has not been determined. Not surprisingly, the onset of renal crisis is often in the winter months (Figure 4).

Figure 4; from Traub et al., 1983



Renal crisis occurs more commonly in black patients with systemic sclerosis than in white patients. Patients present acutely with severe headache, blurred vision, congestive heart failure and seizures. The outcome of the illness prior to 1980 was almost uniformly fatal. Thus, in a series of 824 patients with systemic sclerosis prior to 1981, 61 developed renal crisis and 57 died. Most of these patients died as a direct result of scleroderma renal crisis with renal failure, hypertensive encephalopathy, or acute congestive heart failure, although cerebral vascular accidents, gastrointestinal bleeding, bronchopneumonia and complications of dialysis also caused deaths in this group of patients.

Evidence of chronic renal dysfunction in the absence of renal crisis also adversely effects prognosis although to a lesser extent. Whether chronic renal disease in these patients is secondary to systemic sclerosis has not been determined.

Pathologic examination of the kidney reveals vascular changes similar to those discussed for digital arteries. Thus, intimal proliferative changes in the interlobular and smaller arteries are the major pathologic change. Changes in the interlobular arteries tend to distinguish these patients from those with hypertension in the absence of systemic sclerosis, but these changes can occasionally be seen in nonsclerodermatous malignant nephrosclerosis or hypertension. Cortical infarcts can also be observed in these patients.

Inducing cutaneous Raynaud's phenomenon by cooling the skin has been shown to decrease renal perfusion similar to its effect on cardiac perfusion noted earlier.

Table XXI

HEMATOLOGIC MANIFESTATIONS OF 164 PATIENTS WITH SYSTEMIC SCLEROSIS

Abnormality	Cause	% of patients
Anemia	**Total**	**27 %**
	Uremia	6 %
	GI bleeding	4 %
	Microangiopathic Hemolytic Anemia	4 %
	Iron deficiency 2° Malabsorption	5 %
	Malignancy	1 %
	Unknown	2 %
Leukocytosis	**Total**	**14 %**
	Unknown	14 %
	Associated with overlap syndrome	8 %
Leukopenia	**Total**	**6 %**
	Overlap syndrome	3 %
	Unknown	3 %
Thrombocytopenia	**Total**	**5 %**
	Microangiopathic hemolytic anemia	2.5 %
	Overlap syndrome	1.5 %
	Unknown	1 %

From Frayha et al. 1980

Hematologic abnormalities. Hematologic abnormalities listed in Table XXI are not uncommon in systemic sclerosis, but are rarely clinically significant problems. Anemia is seen in 27% of patients and is usually secondary to renal disease, microangiopathic hemolytic anemia or bleeding from gastrointestinal telangiectasias. Microangiopathic hemolytic anemia is occurs commonly in association with renal crisis. Leukocytosis and leukopenia are rarely observed and are usually secondary to an overlap syndrome when a cause can be identified. Thrombocytopenia can be observed in patients with a "SLE like" overlap syndrome or in patients with microangiopathic hemolytic anemia.

Table XXII

RADIOGRAPHIC FINDINGS IN THE HANDS OF PATIENTS WITH SYSTEMIC SCLEROSIS

	Diffuse systemic sclerosis (n=33)		Limited systemic sclerosis (n=7)	
	Initial	Final*	Initial	Final
Changes consistent with inflammatory arthropathy				
Juxtaarticular osteoporosis	3	9	0	14
Joint space narrowing	15	24	0	14
Marginal erosions	9	27	0	14
Dorsal erosions	6	15	14	14
Ankylosis	3	3	0	0
Changes generally regarded as typical for systemic sclerosis				
Soft tissue atrophy	79	93	71	71
Subcutaneous calcinosis	52	67	58	58
Digital resorption	55	67	43	43
Flexion contractures	85	88	71	71
Diffuse osteopenia	39	54	58	58

*Mean followup of 29 months
Blocka et al. 1981

Joints Arthritis has been reported to be the initial symptom in as many as two thirds of patients with diffuse systemic sclerosis. Arthritis has been described in nearly every articulation, but arthritis of the fingers is the most common site of involvement. Physical examination frequently reveals swelling,

warmth, tenderness, and loss of range of motion consistent with an inflammatory arthritis. Many patients initially receive a diagnosis of rheumatoid arthritis before the cutaneous changes of systemic sclerosis are evident. The radiographic changes noted in 33 patients with diffuse systemic sclerosis and 7 patients with limited systemic sclerosis at the initiation of the study and at followup (mean of 29 months later) are provided in Table XXII. It can be seen that although symptoms of arthritis are present in 60% of patients, radiographic changes associated with inflammatory arthritis are less frequent. Joint space narrowing and marginal erosions similar to those seen in rheumatoid arthritis were found in 15 and 9 percent of the patients at presentation, respectively, and each was found in one quarter of the patients at followup. An unusual bony resorption of the dorsal heads of selected metacarpal or proximal phalangeal heads was found in 6 percent of the patients on initial examination and in 15 percent on followup. Thus, a significant number of patients with systemic sclerosis develop an erosive inflammatory arthritis.

Salivary glands Salivary gland histology and clinical evidence of Sjögren's syndrome in patients with systemic sclerosis have been evaluated by several studies. One such study in depicted in Table XXIII.

Table XXIII

SJÖGREN'S SYNDROME IN PATIENTS WITH PROGRESSIVE SYSTEMIC SCLEROSIS

	Salivary gland biopsy result		
	Sjögren's syndrome (n=6)	Fibrosis (n=17)	Normal (n=12)
	% of patients		
CREST	66	35	58
Renal or GI* involvement	0	25	0
Mortality	0	30	0
2 or more clinical markers of SS	83	12	33

*Esophageal involvement was not considered GI involvement
From Cipoletti et al. 1977

As can be seen, Sjögren's syndrome occurs in approximately 17% (6/35) of patients and may be more common in the patients with limited systemic sclerosis. In addition to Sjögren's syndrome, many patients with systemic sclerosis have salivary gland fibrosis without inflammation. This histologic picture occurred more often in the group with diffuse systemic sclerosis and visceral involvement. Patients with salivary gland fibrosis without inflammation did not generally have symptoms of dry eyes or mouth. Moreover, this group of patients appeared to have a significant mortality during the study period in two separate studies.

Muscle Skeletal muscle involvement is common in systemic sclerosis. Selected clinical, laboratory and pathologic features of muscle involvement in 2 series of patients with systemic sclerosis is provided in Table XXIV.

Table XXIV

MYOSITIS IN PATIENTS WITH SYSTEMIC SCLEROSIS

	Author of publication	
	Medsger* (n=53)	Clements (n=24)
	% of patients	
Proximal muscle weakness	60	84
Severe proximal muscle weakness	20	30
Elevated CPK	6	44
Marked elevated CPK (> 2 fold)	0	24
Elevated aldolase	57	48
Polyphasic motor unit potentials	ND	96
Fibrillation, Insertional irritability	ND	0
Interstitial fibrosis	24	ND
Perivascular inflammatory infiltrate	6	16

* Excluded patients with overlap syndrome including overlap with dermatomyositis.

The series by Clements et al. did not exclude patients with features of overlap syndrome and, therefore, includes several patients with polymyositis/systemic sclerosis overlap syndrome. These patients were excluded from the Medsger series. Weakness was common in both series. Mild elevations of CPK were not uncommon, but marked elevations of CPK were found only in those patients that had inflammatory changes on subsequent biopsy and fit into the polymyositis/systemic sclerosis overlap syndrome diagnostic group. Elevations in the serum aldolase were more common. EMG revealed polyphasic motor unit potentials consistent with myopathy, but insertional irritability and fibrillation, more characteristic of inflammatory myopathy, were detected only in those patients with an overlap syndrome. With the exception of patients with an polymyositis/systemic sclerosis overlap syndrome, the muscle involvement was left untreated and in general did not progress. Interstitial fibrosis was the most common pathologic finding when one was observed. Many patients with systemic sclerosis, therefore, experience a chronic stable form of myopathy characterized by mild weakness, minimal elevations in CPK, elevations in aldolase, polyphasic motor unit potentials on electromyography without insertional irritability and interstitial fibrosis on biopsy. These patients probably do not require therapy. In contrast, a smaller subgroup of patients develop inflammatory myositis requiring treatment. The presence of inflammatory myositis has been reported to correlate with the production of the PM-Scl-70 autoantibody. Moreover, these patients have been reported to develop an inflammatory myocarditis.

Neurologic manifestations. Neurologic involvement is uncommon in systemic sclerosis. Carpal tunnel syndrome has been reported to occur in 3 percent of patients. Trigeminal neuralgia has been reported to occur in as many as 4 percent of patients. Many of these patients, however, appeared to have an overlap syndrome with other connective tissue disorders. Patients with secondary Sjögren's may develop a systemic vasculitis that may involve the neurologic system.

PATHOGENESIS

The pathogenesis of progressive systemic sclerosis is not known. Any hypothesis regarding the pathogenesis of systemic sclerosis must explain the vascular features, including endothelial injury and vasospasm, fibrosis of the skin and viscera, and immunologic abnormalities.

Immunologic Hypothesis. Most theories of the pathogenesis of systemic sclerosis portray the immune system playing a central role. Support for this hypothesis is depicted in Table XXV.

Table XXV

EVIDENCE SUPPORTING IMMUNE DYSREGULATION IN THE PATHOGENESIS OF PSS

I.	Overlap conditions in which patients with systemic sclerosis also have features of rheumatoid arthritis, polymyositis, systemic lupus erythematosus, or mixed connective tissue disease.
II.	Immune complexes observed in 25-75% of patients.
III.	Increased concentration of interleukin 2 and gamma interferon in the serum of patients with systemic sclerosis.
IV.	Increase T4/T8 cell ratio due to a decrease in the number of T8 cells.
V.	Activated monocyte phenotype with diminished in vitro interleukin 1 production.
VI.	Depressed NK cell function.
VII.	Mononuclear cell infiltrate consisting predominantly of activated T4 cells in the dermis in 50% of patients with systemic sclerosis.
VIII.	Seen in both murine and human graft versus host disease.
IX.	In vitro evidence of abnormalities in lymphocyte function.
X.	Autoantibodies present in nearly all patients.

The serum concentration of at least two lymphokines, interleukin 2 and gamma interferon, are increased in patients with systemic sclerosis. Moreover, activated T lymphocytes can be found in the skin in 25-50% of skin biopsies of patients with systemic sclerosis, and the products of activated T cells including gamma interferon and interleukin 2 have found in the serum of systemic sclerosis patients at levels higher than control serum. These findings suggest that T cells are activated in

systemic sclerosis and that they are present at the site of the pathology in many cases. There is also evidence that the peripheral blood monocytes of patients with systemic sclerosis express an activated phenotype. Whereas T helper cells and monocytes appear to be activated, others are either deficient in number, such as T8 cells, or deficient in function, such as NK cells. These findings suggest that the regulation of the immune response may be abnormal in patients with systemic sclerosis. Finally, autoantibodies to a variety of nuclear antigens are detected in almost all patients and immune complexes are detected in many patients. These findings confirm the hypothesis that the immune response is abnormally regulated and suggest the possibility that autoimmunity plays a role in the pathogenesis of systemic sclerosis.

The possibility that the immune system might be playing a role in systemic sclerosis is further supported by the finding that several features of systemic sclerosis are found in both human and murine graft-versus-host disease. Thickening of the dermis has been described as a feature of chronic murine GVH. It is interesting to note that in studies by Charlie et al., widespread cutaneous sclerosis occurred in murine GVH even when the donor marrow was treated prior to transplantation to eliminate the precursors of cytotoxic T lymphocytes. These studies suggest that the systemic sclerosis like disorder associated with murine GVH is mediated by helper lymphocytes and not cytotoxic cells. These data suggest that many of the manifestation of systemic sclerosis may be mediated by helper T lymphocytes.

As many as 30% of patients surviving long term human bone marrow transplantation have skin changes that resemble those seen in patients with systemic sclerosis. Moreover, many of these patients develop visceral fibrosis in the lungs, gastrointestinal tract, joints, and muscles. Raynaud's phenomenon and vascular changes, such as fibrotic intimal proliferation of the renal artery, have also been observed. Finally, antinuclear antibodies have been observed in as many as 80% of the patients. Several features of systemic sclerosis and human graft-versus-host are different, however. Thus, although many GVH patients develop antinuclear antibodies, few develop anti-centromere or anti-topoisomerse I antibodies. Moreover, the incidence of vascular changes and visceral involvement is less in GVH (Table XXVI).

Table XXVI

COMPARISON OF THE FEATURES OF CHRONIC HUMAN GRAFT-VERSUS-HOST DISEASE WITH SKIN INVOLVEMENT AND SYSTEMIC SCLEROSIS

	GVH	Systemic Sclerosis
	% of patients	
Sicca syndrome (% of patients)	67	55
Raynaud's phenomenon (% of patients)	33	94
Gastrointestinal tract		
Esophagus (% of patients)	33	41
Small bowel (% of patients)	0	69
Large bowel (% of patients)	0	31
Lungs		
Fibrosis (% of patients)	67	47
DLCO (% of normal)	58	54
Total lung capacity (% of normal)	76	85
Cardiac (% of patients)	16	63
Renal (% of patients)	16	55

From Furst et al. 1979

Finally, the inflammation and fibrosis in GVH starts just below the epidermis and proceeds toward the subcutaneous tissue whereas it begins in the lower dermis in systemic sclerosis and proceeds toward the epidermis. Regardless of these differences, however, GVH disease serves as a useful model for examining the mechanisms involved in immune mediated cutaneous fibrosis, many of which are likely to play a role in systemic sclerosis.

Further support for the hypothesis that an aberrant immune response is involved in the

pathogenesis of systemic sclerosis is the observation that overlap syndromes exist in which the patients have several features of autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and mixed connective tissue disease in addition to features of systemic sclerosis. Thus, the pathogenesis of systemic sclerosis may be similar to the pathogenesis of these disorders in which autoimmunity is more a firmly established pathogenic mechanism.

Mechanisms leading to Fibrosis. It is clear from both morphological and biochemical studies that the fibrosis of the skin and viscera is the result of the overproduction of collagen. Thus, the weight and hydroxyproline content of the skin are greater than controls. Moreover, the serum of systemic sclerosis patients with active progressive disease contains elevated levels of a product, aminopropeptide of procollagen, formed when procollagen is converted into collagen. Finally, fibroblasts isolated from most patients with systemic sclerosis transcribe increase levels of mRNA for procollagen type I and III and synthesize increased amounts of hyaluronic acid and collagen. Surprisingly, this difference between systemic sclerosis and normal fibroblasts persists for several passages. It is also possible that decreased collagen breakdown contributes to the excessive accumulation of collagen in systemic sclerosis, although, fibroblasts from patients with systemic sclerosis do not appear to produce less collagenase than control fibroblasts. In order to construct a model of the pathogenic mechanisms involved in systemic sclerosis, therefore, it is important to understand both the factors that regulate fibroblast collagen synthesis normally and what is known about fibroblast collagen production in patients with systemic sclerosis.

The regulation of fibroblast collagen production is summarized in Table XXVII.

Table XXVII

EFFECT OF VARIOUS CYTOKINES ON FIBROBLAST PROLIFERATION AND COLLAGEN PRODUCTION

Cytokine	Proliferation	Collagen synthesis	Collagenase synthesis
Platelet derived growth factor	Increases	No effect	Increases
Transforming growth factor β	Increases or decreases depending on the presence of other growth factors	Increases	Decreases
Epidermal growth factor	Increases	No effect	Increases
Interleukin 1	Increases	Controversial	Increases
Tumor necrosis factor α	Increases	Controversial	Increases
Interleukin 6	Inhibits	Unknown	Unknown
Gamma interferon	Inhibits	Inhibits	Unknown
Prostaglandin E_2	Inhibits	Unknown	Unknown

Collagen can accumulate at a site by increasing the number of fibroblasts producing collagen, increasing the synthesis of collagen by each fibroblast, or by decreasing the breakdown of collagen. Although it appears that increased collagen production is important in the pathogenesis of systemic sclerosis, the role of decreased breakdown is not clear. Fibroblast growth can be enhanced by platelet derived growth factor (PDGF), produced by platelets, interleukin 1, secreted by monocytes, and epidermal growth factor (EGF), produced by a variety of cell types including cells of the salivary and submandibular glands, liver, and kidney. Moreover, in the presence of these other growth factors, transforming growth factor β (TGFβ), produced by a variety of cells including aggregated platelets, activated T cells and activated monocytes, can increase fibroblast proliferation. Fibroblast

growth can be inhibited by gamma interferon, prostaglandin E_2 and interleukin 6. Fibroblast collagen production can be upregulated by TGFβ and inhibited by gamma interferon. Although it remains somewhat controversial, it appears that TGFβ may be the only one of these factor that downregulates fibroblast collagenase production. The importance of the role of TGFβ in inducing fibrosis was recently demonstrated in in vivo studies. In these studies, it was demonstrated that injecting TGFβ subcutaneously into newborn mice stimulated both angiogenesis and fibrosis. Injecting EGF or PDGF did not have a similar effect. Whereas it has not been demonstrated that TGFβ levels are increased in the skin or serum of patients with systemic sclerosis, it has been demonstrated that factors in the serum from patients with early systemic sclerosis and more extensive skin involvement stimulate normal fibroblasts to produce more collagen and proliferate. It is likely, therefore, that TGFβ or other similar factors play an important role in the pathogenesis of the cutaneous and visceral fibrosis characteristic of systemic sclerosis. Moreover, developing agents which interfere with the ability of TGFβ to induce fibrosis is an attractive approach to developing new therapeutic modalities in this disorder.

A variety of studies support the hypothesis that the fibrosis which is consistently observed in systemic sclerosis is regulated by products released by inflammatory cells. For example, activated T lymphocytes can be found in the skin in the early phases of the disease and T cell lymphokines are present in the serum of systemic sclerosis patients at higher than levels than controls. In addition, monocytes appear to be activated in patients with systemic sclerosis. Moreover, serum from patients with systemic sclerosis stimulates normal fibroblasts to produce more collagen than when they are cultured with normal serum. Finally, mitogen stimulated peripheral blood mononuclear cells from normal individuals produce factors that enhance fibroblast growth, and glycosaminoglycan and collagen production. Under the influence of these mononuclear cell derived supernatants, normal fibroblasts produce as much collagen and glycosaminoglycan as systemic sclerosis fibroblasts. Several investigators have suggested that these cytokines promote the expansion of a subset of fibroblasts that produce more collagen rather than upregulate collagen production by each fibroblast. This view is supported by the finding that fibroblasts obtained from patients with systemic sclerosis produce more collagen even after weeks of in vitro culture. Moreover, normal fibroblasts stimulated to synthesize

increased amounts of collagen and glycosaminoglycan by cytokines or systemic sclerosis serum continue to synthesize increased amounts for weeks after the removal of the stimulus. Finally, Botstein et al. examined the capacity of cloned normal fibroblast cell lines to produce collagen and to proliferate in response to systemic sclerosis serum. They found great heterogeneity between clones in their baseline capacity to produce collagen. A weak, but statistically significant direct correlation between the capacity of the clones to produce collagen and the proliferative response to systemic sclerosis serum was found. The data support the hypothesis that a factor in systemic sclerosis serum enhances the growth of a subset of fibroblasts with an enhanced capacity to synthesize collagen.

It is possible that the regulation of proliferation and collagen production by fibroblasts obtained from patients with systemic sclerosis is defective. One mechanism whereby fibroblast collagen production is controlled is the feedback inhibition provided by aminopropeptide, the product formed when procollagen is converted to collagen. It has been observed in one study that the normal feedback inhibition provided by aminopropeptide of procollagen type I is defective. Whether this finding will be reproduced in other laboratories and whether this is a primary defect in fibroblasts from patients with systemic sclerosis that is responsible for the fibrosis characteristic of systemic sclerosis is not yet known.

Several investigators have suggested that mast cells may play a role in stimulating cutaneous fibrosis in systemic sclerosis. The evidence supporting this claim is that the number of mast cells is increased in the dermis of patients with systemic sclerosis and in mice undergoing chronic graft versus host disease. Moreover, it appears that mast cell degranulation occurs during the progression of murine graft versus host disease. Whether the products released during mast cell degranulation lead to fibrosis in systemic sclerosis is not yet known, but the lack of cutaneous fibrosis in systemic mastocytosis makes it unlikely that mast cell degranulation is the only factor involved in stimulating the fibrosis.

Vascular hypothesis. One nearly constant finding in systemic sclerosis is pathologic evidence of vascular disease. Thus, as discussed earlier, intimal fibrosis is evident in 100% of the digital arteries of patients with systemic sclerosis and adventitial fibrosis is present in the vast majority of cases.

Several findings have suggested that the vascular disease characteristic of patients with systemic sclerosis is due to endothelial cell injury. Thus, plasma von Willebrands factor, β-thromboglobulin, factor VIII/von Willebrands antigen and tissue plasminogen activator are increased in systemic sclerosis patients. The serum levels of von Willebrands factor and factor VIII/von Willebrands factor antigen ratio in patients with systemic sclerosis are depicted in Table XXVIII. The percent circulating platelet aggregates and β-thromboglobulin are depicted in figures 5 and 6. In addition, decreased platelet serotonin levels and increase serotonin induced platelet aggregation have been reported. These changes presumably reflect endothelial injury and repair.

Table XXVIII

CIRCULATING PLASMA LEVELS OF VON WILLEBRAND FACTOR AND FACTOR VIII/VON WILLEBRAND FACTOR ANTIGEN IN PATIENTS WITH RAYNAUD'S PHENOMENON AND SYSTEMIC SCLEROSIS

	Control (n=8)	Systemic sclerosis (n=17)	Raynaud's Phenomenon (n=9)
von Willebrand factor			
Percent of patients with increased level	0	88	77
Mean ± SD (percent of control)	102 ± 6	374 ± 40	502 ± 104
Factor VIII/von Willebrand factor Ag			
Percent of patients with increased ratio	0	88	77
Mean ± SD (percent of control)	97 ± 3.7	255 ± 24	271 ± 46

From Kahaleh et al. 1981

Figure 5; Kahaleh, 1982

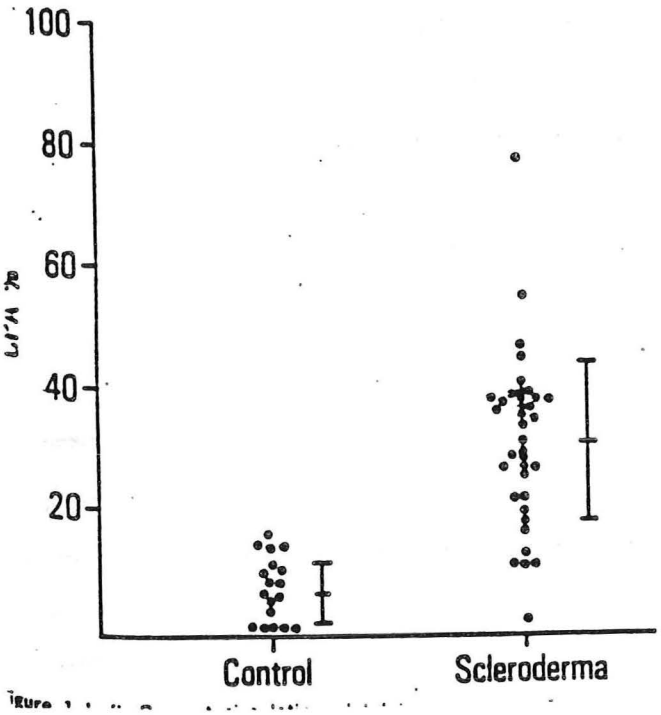
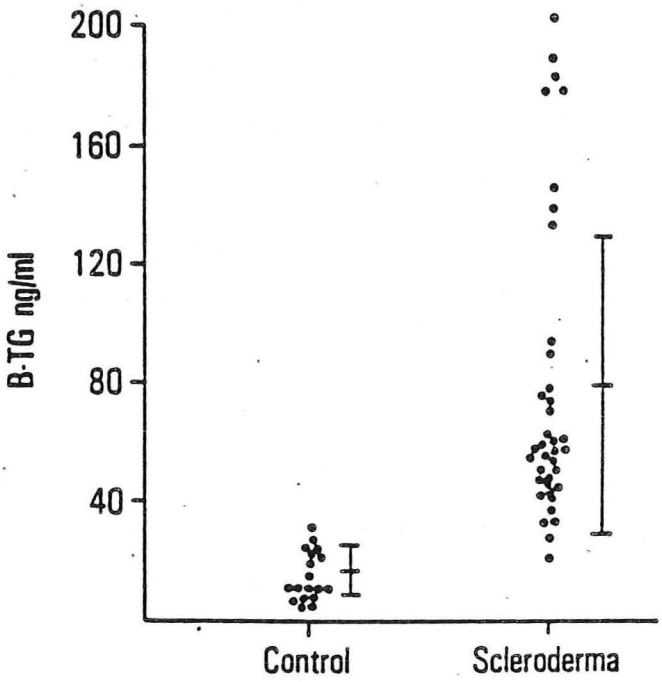


Figure 6; Kahaleh, 1982



The mechanism responsible for endothelial cell injury is not well understood. Immune complexes have been identified in the renal capillaries, but not in the peripheral capillaries. Moreover, no evidence of complement consumption has been reported. Antibodies to endothelial cells have been observed in some, but not all patients with systemic sclerosis. A factor, present in the serum of patients with systemic sclerosis, that is toxic for endothelial cells, has been reported by some, but not all investigators.

The finding that in the vast majority of patients cutaneous thickening is preceded by Raynaud's phenomenon has suggested that endothelial injury and the subsequent vascular insufficiency may lead to cutaneous fibrosis. Thus it is possible that chronic vascular insufficiency leads to tissue injury and that fibrosis is part of the repair process. Alternatively, it is possible that endothelial injury leads to platelet aggregation and the release of TGFβ which leads to fibrosis. Support for this vascular hypothesis for the pathogenesis of systemic sclerosis is depicted in Table XXIX.

Table XXIX

SUPPORT FOR THE VASCULAR HYPOTHESIS

1.	Raynaud's phenomenon usually precedes skin thickening.
2.	Increased von Willebrand antigen and factor VIII levels in the serum of PSS patients.
3.	Evidence of coagulopathy in PSS.
	a. Increased β_2 thromboglobulin levels
	b. Evidence of microangiopathic hemolytic anemia.
	c. Increased fibrinogen turnover.
	d. Increased platelet aggregation.
4.	Finding that platelets are one of the most abundant sources of TGFβ.

Inciting Agent. Little is known about the factor or agent that initiates the series of pathologic processes leading to systemic sclerosis. Recently, Maul and Jimenez suggested the possibility that retroviruses might play a role in the pathogenesis of systemic sclerosis. These investigators compared the amino acid sequence of the region of topoisomerase I recognized by autoantibodies produced by

patients with systemic sclerosis with the sequence of retroviral proteins. They observed that an 11 amino acid sequence of topoisomerase I, that was recognized by serum from patients with systemic sclerosis, contained a 6 amino acid sequence identical to the group specific antigen ($p30^{gag}$) of three mammalian retroviruses. The homology between topoisomerase I and the gag polyprotein of the feline sarcoma virus is illustrated in Table XXX.

Table XXX

AMINO ACID SEQUENCE HOMOLOGY BETWEEN THE REGION OF TOPOISOMERASE I RECOGNIZED BY AUTOANTIBODIES AND A MAMMALIAN RETROVIRUS.

Topoisomerase I	K	K	W	G	V	P	I	E	K	I	Y	N	K	T	Q	R	E	K	F
								|	|	|	|	|	|					
Feline sarcoma virus	S	D	L	L	K	E	A	E	K	I	Y	N	K	R	E	T	P	E	E

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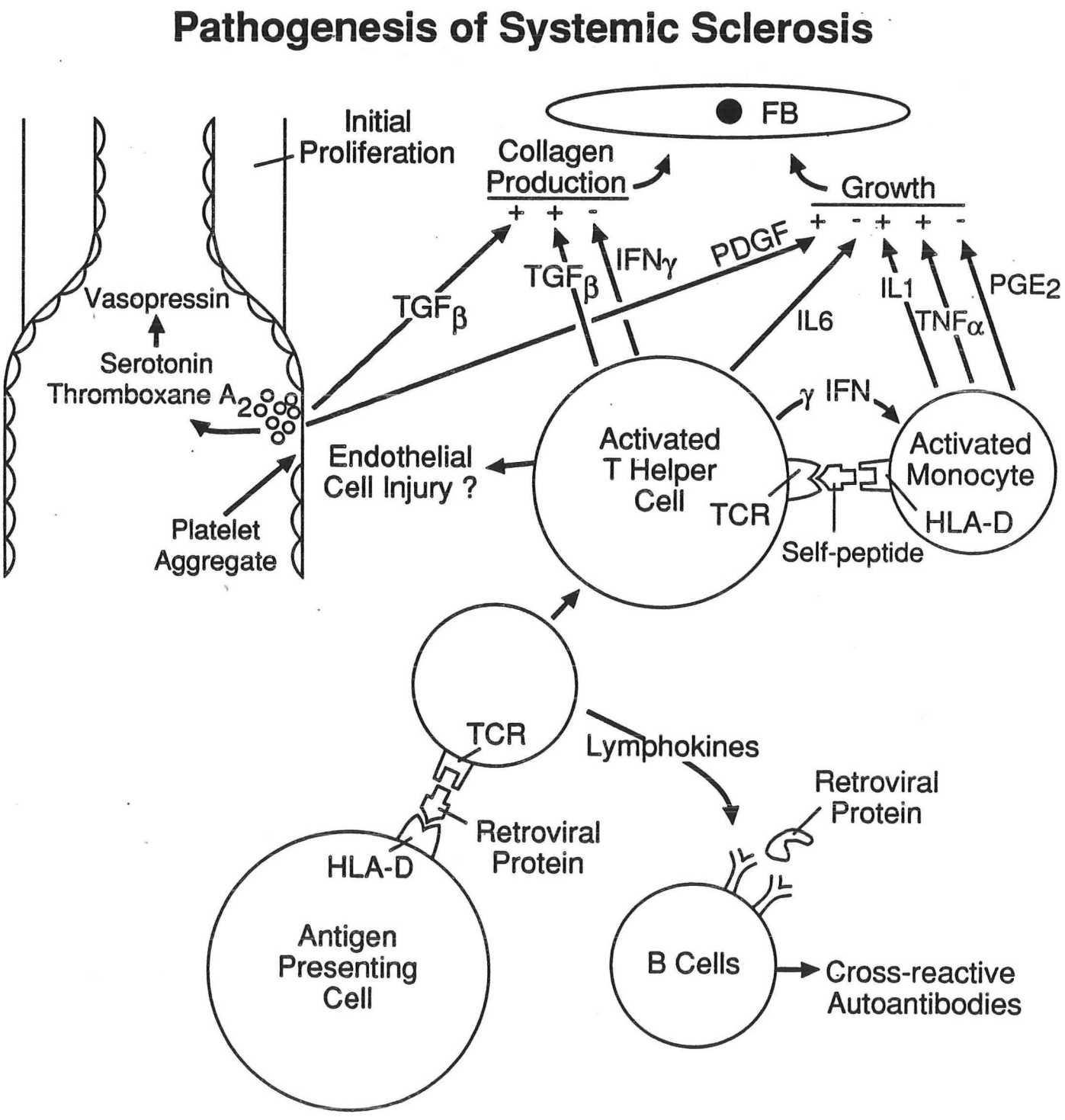
The chances that this homology would occur by chance in a single instance is extremely unlikely, but the chance that it would occur with three separate retroviruses is greater than one in 10^8. These data suggest the possibility that autoantibody production in systemic sclerosis is really cross-reactivity between self components and retroviral gene products. Whether T lymphocytes recognize similar retroviral products that cross-react with self and initiate T cell autoimmunity is not yet known.

The possibility that environmental factors or agents such as retroviruses contribute to the pathogenesis of systemic sclerosis is also supported by the finding that both genetically related and unrelated family members of patients with systemic sclerosis have a higher incidence of antinuclear autoantibodies than controls. Thus, an infectious agent may infect a variety of individuals leading to asymptomatic autoantibody production. This state may predispose these individuals to developing systemic sclerosis, but other unknown environmental or genetic factors are required for the individuals to develop systemic sclerosis.

It is possible to create a hypothesis based on these findings (Figure 7). A patient is infected with an unknown retrovirus. The immune response to the retrovirus cross-reacts with self components found in the skin and viscera. The inflammatory response may lead to endothelial cell injury either by direct antigen specific cytotoxicity or by the release of a toxic lymphokine. Endothelial injury induces platelet aggregation leading to serotonin and thromboxane A_2 release that

induce vasospasm. TGFβ and platelet derived growth factor released by the platelets combines with lymphokines produced by the T cells and monokines produced by the monocytes to stimulate fibroblast growth and collagen production.

Figure 7



PROGNOSIS

The 7 year cumulative survival rate of a prospective study of 223 patients published in 1971 was 35%. A similar study reported in 1988 reported the cumulative 10 year survival to be 60%. The survival curves in patients with systemic sclerosis according to type of visceral involvement at presentation are provided for 1971 and 1986 in figures 8 and 9, respectively. The data from the 1971 report are compared with the data from the same series in 1986. As you can see mortality was highest in those patients with heart and kidney involvement. Mortality in patients with pulmonary disease is also higher than patients without visceral involvement, but is not as high as in those patients with cardiac and kidney disease. As will be discussed later the management of renal crisis has dramatically changed the mortality in patients with renal disease since 1971 and it is likely that this curve will continue to improve, leaving patients with cardiac disease with the highest mortality rate. The percent survival as a function of skin involvement is also provided (Figure 10). Patients with skin involvement which was limited to sclerodactyly (type 1) had the highest percent survival. Patient with forearm involvement (type 2) had an intermediate survival rate and those with diffuse disease had the lowest percent survival (type 3).

Figure 8

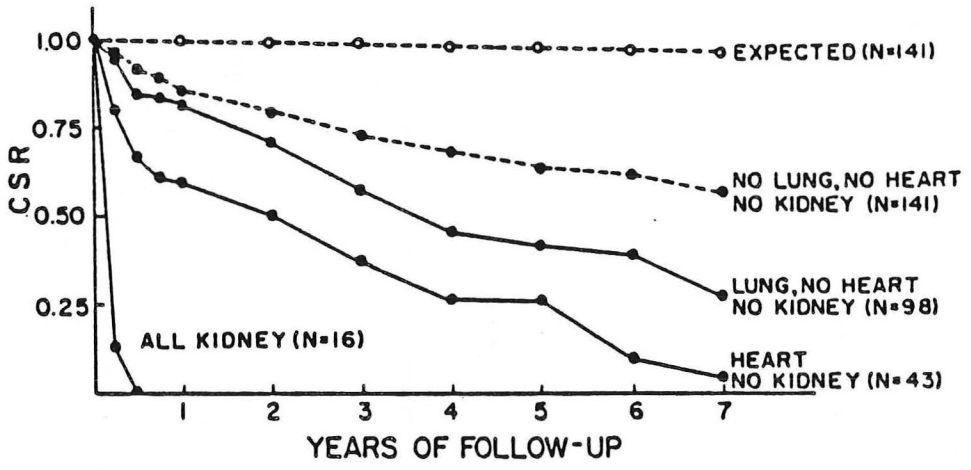


Figure 9

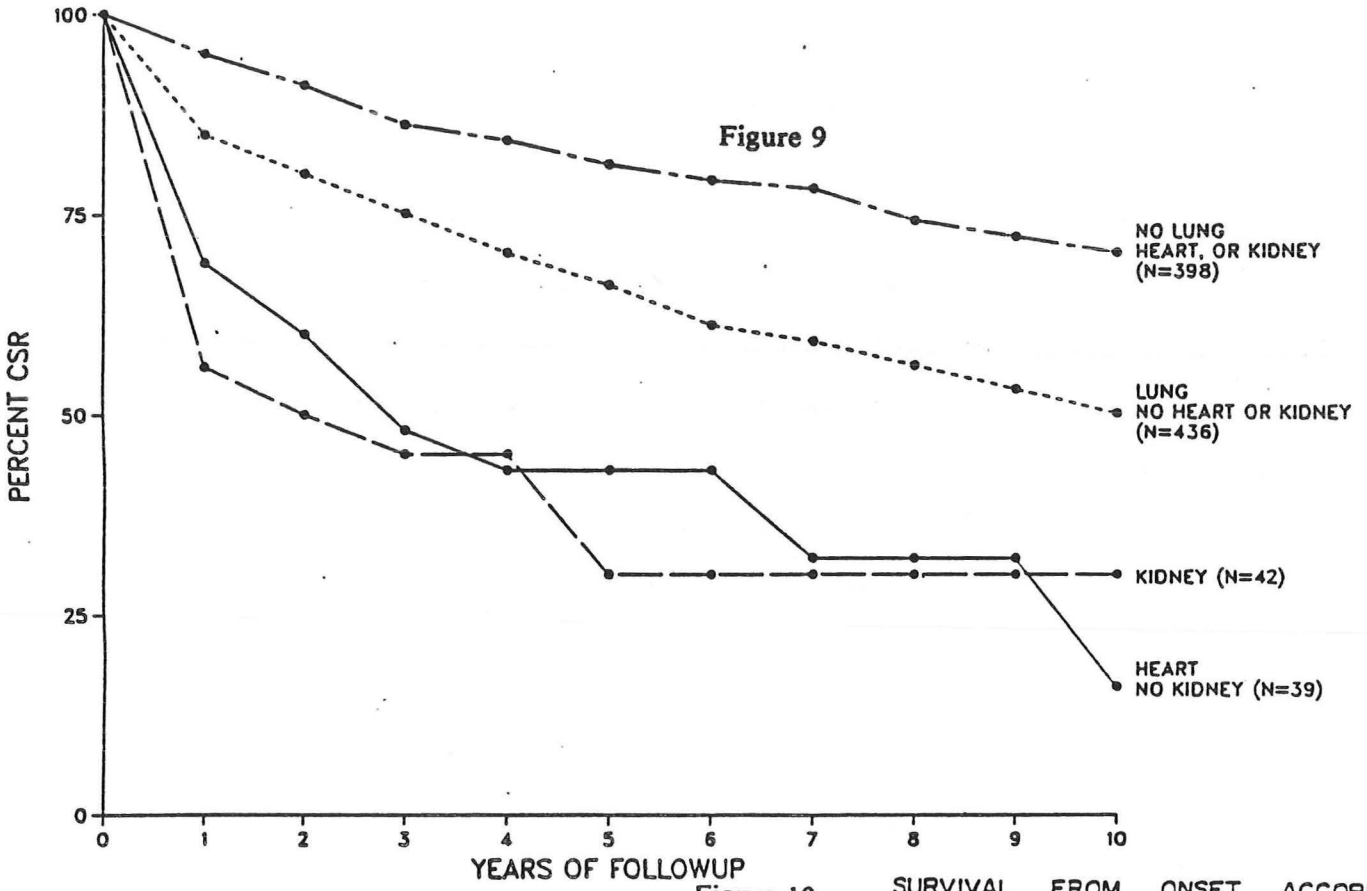
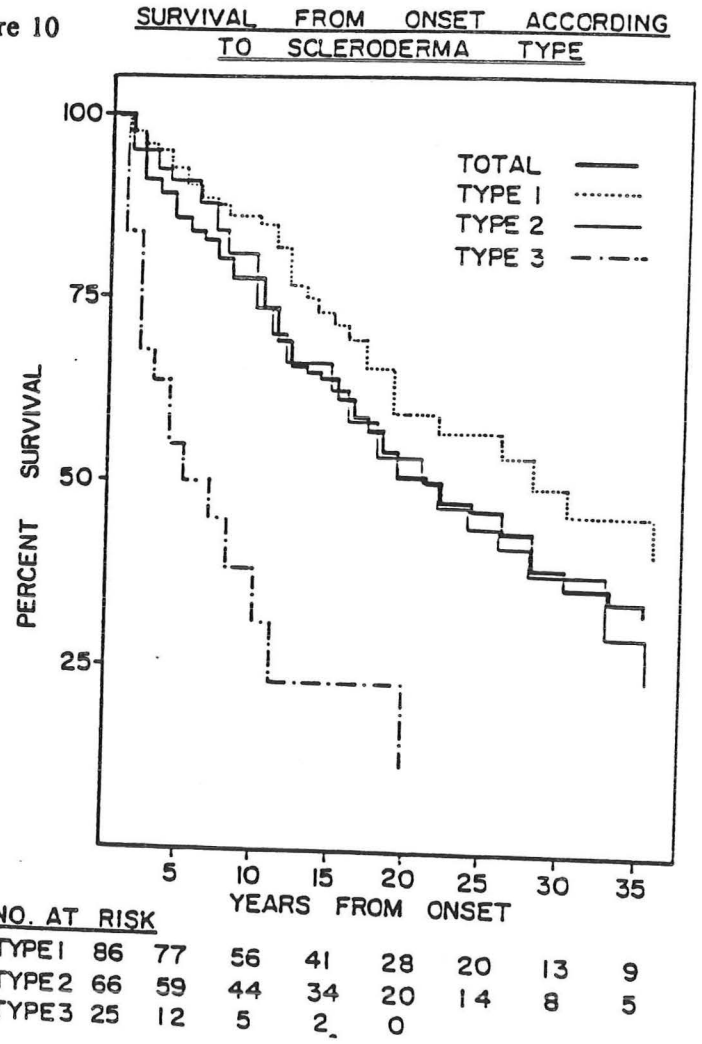


Figure 10



TREATMENT

Therapeutic trials in systemic sclerosis are difficult to conduct and design. Since systemic sclerosis is variable in both the rate of progression and severity, trials must be of sufficient length to reach the required skin, visceral and survival endpoints. In addition, because systemic sclerosis occasionally will regress spontaneously, control groups are essential. The results of controlled and uncontrolled trials of a variety of drugs used in the treatment of systemic sclerosis are given in Table XXXI.

Table XXXI

THE RESULTS OF VARIOUS THERAPEUTIC TRIALS IN SYSTEMIC SCLEROSIS

		Efficacy in:	
		Uncontrolled	Controlled
Drug	Rationale	Trials	Trials
N-acetylcysteine	Reduces sulfhydyl bonds	-	No
Colchicine	Inhibition of collagen production	No	?
Penicillamine	Inhibition of collagen production	Yes	?
Chlorambucil	Immunosuppressive	Yes	No
5-fluorouracil	Immunosuppressive	Yes	?
Azathioprine	Immunosuppressive	Maybe	?
Cyclophosphamide + prednisone + Plasmapheresis	Immunosuppressive	Yes	?
Cyclosporine	Immunosuppressive	Yes	?
Dipyridamole and ASA	Platelet-inhibiting	-	No
Antihypertensive therapy	Reduce microvascular injury	-	No

The most carefully studied therapy of systemic sclerosis is D-penicillamine. D-penicillamine was originally chosen as a therapy for systemic sclerosis because of its in vitro effect on collagen

synthesis. There are no controlled blinded studies comparing penicillamine with placebo. The strongest evidence suggesting penicillamine beneficial effect in systemic sclerosis comes from a retrospective analysis of 118 patients with diffuse systemic sclerosis of less than three years duration at time of entry into the study. 73 of these patients had been treated with penicillamine and 43 had not. 20 patients were treated with colchicine (18 in the penicillamine group and 2 in the control group) and 23 were treated with immunosuppressive agents (18 in the control group and 5 in the penicillamine group). The demographic and clinical characteristics of the two groups were reasonably similar. The authors found that patients treated with penicillamine had a greater improvement in their skin score, lower incidence of developing new renal involvement and improved survival. The time between initiating therapy and the time at which a beneficial effect was observed was greater than 18 months. More recent studies have focused on the effect of penicillamine on pulmonary disease. 2 retrospective studies found that patients treated with penicillamine had higher DLCO values, but found no effect of penicillamine on the forced vital capacity. This differential effect of penicillamine on forced vital capacity and DLCO has led some investigators to suggest that penicillamine reduces endothelial damage occurring in the lung, but has no effect on the fibrosis. The effect of penicillamine in each of these studies is rather modest. From these studies it can be concluded that penicillamine may have a nominal effect on the long term course of systemic sclerosis. To balance this modest beneficial effect, however, it must be remembered that penicillamine has a causes severe side effects in a high percentage of patients. Thus, one third of patients must discontinue penicillamine due to side effects, including nausea, skin rash, leukopenia, thrombocytopenia and proteinuria.

Colchicine was also chosen as a therapeutic agent in systemic sclerosis because of its ability to inhibit collagen production. One long-term (mean followup of 39 months) open trial showed improvements in skin thickening (Table XXXII). This effect was particularly pronounced in those who could tolerate 2 or more tablets of colchicine per day for the entire period of the study. Other shorter term studies have not found a beneficial effect of colchicine.

Table XXXII

COLCHICINE TREATMENT OF PATIENTS WITH SYSTEMIC SCLEROSIS

Parameters	Better	Same	Worse
	Number of patients (n=19)		
Grip strength	8	9	2
Finger palm distance	2	15	2
Mouth opening	7	7	6
Skin elasticity	16	1	2
Raynaud's phenomenon	5	14	0
Pulmonary function test	1	9	3
Skin biopsy	5	8	4

Modified from Alarcon-Segovia et al. 1979

Immunosuppressive drugs have been promoted for the management of systemic sclerosis because of evidence suggesting that immune mechanisms play a role in the pathogenesis of the disease. Several uncontrolled studies have suggested that azathioprine, prednisone in combination with cyclophosphamide, 5-fluorouracil, and anti-thymocyte globulin might be effective in treatment of patients with systemic sclerosis. In one trial of 5-fluorouracil, 12 patients were treated as indicated in Table XXXIII.

Table XXXIII

5-FLUOROURACIL THERAPY IN 12 PATIENTS WITH SYSTEMIC SCLEROSIS

Dosage	
Induction	12.5 mg/kg/day IV for 5 days followed by 8 mg/kg IV QOD for 4 doses
Maintenance	10-20 mg/kg IV Weekly

Table XXXIV

5-FLUOROURACIL IN THE TREATMENT OF SYSTEMIC SCLEROSIS

Parameter	Baseline	Followup	% patients improved
Skin score	36.5	22.0	100
Esophageal	1.6	0.8	50
Pulmonary	1.8	1.2	42
Functional index	12.4	6.5	100

From Casas et al. 1987

The results are depicted in Table XXXIV. 100 percent of patients had improved total skin scores and a index of function capabilities over the length of the study which ranged from 1.5 to 20 months. Some isolated improvement in visceral involvement was also noted. Unfortunately, it is unclear from this study how the visceral involvement was assessed and scored, and the validity of the functional index as method of assessing extent of disease in systemic sclerosis was not established. Further controlled studies are needed to determine whether this therapy is effective in systemic sclerosis. Moreover, although the authors claimed minimal toxicity, the therapy does have potentially serious

toxicity which would limit its use in this condition which often is not life threatening.

The effect of azathioprine on systemic sclerosis was assessed in an uncontrolled study of 21 patients with systemic sclerosis. Most of these patients appeared to have limited disease. 8 of the patients were judged to be improved, 7 unchanged and 2 progressed. The method of assessing response in these patients was largely subjective.

The combination of cyclophosphamide, prednisone and plasmapheresis was recently tried in an uncontrolled study of 15 patients. 5 of these patients had limited systemic sclerosis, one had linear scleroderma and 9 had diffuse systemic sclerosis. Improvement in skin thickening and resolution of digital ulcers was noted in 14/15 patients. Visceral manifestations also appeared to benefit from therapy. 2 patients, however, died from complications of their systemic sclerosis in spite of the therapy.

A patient with systemic sclerosis and aplastic anemia at the VA hospital in Dallas was recently treated with anti-thymocyte globulin for the aplastic anemia. The aplastic anemia responded to therapy. Surprisingly, all manifestations of systemic sclerosis also disappeared. To determine whether anti-thymocyte globulin might be an effective therapy in the treatment of systemic sclerosis 2 patients with systemic sclerosis were recently treated with anti-thymocyte globulin at Parkland Memorial Hospital. Both patients had improved skin scores. One patient had improvement in dysphagia and the size of his esophageal sphincter and another had resolution of her dyspnea and improvement in her forced vital capacity and DLCO. Several additional patients with systemic sclerosis have been treated in Germany with anti-thymocyte globulin. These investigators have noted improvements in skin ulcers, skin scores and pulmonary function. These studies suggest that anti-thymocyte globulin may be effective therapy for systemic sclerosis.

Finally, there are several case reports of dramatic responses of patients to cyclosporine. Unfortunately, this therapy may be too toxic to be given chronically to patients with systemic sclerosis.

Agents designed to prevent platelet aggregation and subsequent release of platelet derived growth factor and TGFβ have not been successful, despite their ability to normalize plasma thromboglobulin levels and the number of circulating platelet aggregates.

In summary, therefore, there is no therapy that has been found in a controlled study to be effective in treating systemic sclerosis, although there are several uncontrolled reports of drugs that are effective in this disease. Many of these latter therapies have significant toxicities. Their use, therefore, should be restricted to patients with life threatening, rapidly progressive disease with informed consent of the patient. Until a therapy is found that can be demonstrated to be effective therapy in controlled trials, therapy in the average patient should be directed toward treating organ-specific manifestations.

Raynaud's phenomenon. Patients should be instructed to avoid undue exposure to cold, dress warmly, and abstain from tobacco. Whether preventing vasospasm and Raynaud's phenomenon with these measures affects other manifestations of systemic sclerosis is not yet known. The observation that exposing the hands to cold induces vasospasm in the heart and kidney, indicates that cold exposure does lead to transient hypoperfusion in these organs. The data suggest the possibility that preventing cold exposure may minimize disease progression by preventing episodes of visceral ischemia.

A variety of drugs have been used to treat Raynaud's phenomenon. Many of these drugs including methyldopa, reserpine, alcohol, and niacin have been found effective in uncontrolled studies, but have a variety of side effects that make them less appealing. Recently, several drugs have been developed with fewer side effects. The efficacy of several of these have been evaluated by controlled studies. The results of these trials and one uncontrolled trial are depicted in Table XXXV.

Table XXXV

EVIDENCE SUPPORTING THE EFFICACY OF DRUG THERAPY IN THE MANAGEMENT OF RAYNAUD'S SYNDROME

Drug	% Reduction in the frequency of attacks	% of patients responding	Reduction in the size of digital ulcers	Improved digital blood flow
Nifedipine	28	55	ND	No
Diltiazem	No effect	No effect	ND	ND
Nitroglycerin	ND	76	Yes	ND
Prazosin[1]	50	ND	ND	ND
Prazosin[2]	No improvement	-	ND	ND
PGE_1 lipospheres	No improvement	-	Yes	ND
Carbaprostacyclin[3]	No improvement	-	Yes	Yes
Ketanserin[4]	50	88	Yes	Yes

[1] Surwit et al.

[2] Russell et al.

[3] Uncontrolled

[4] Preliminary

The calcium channel blocker nifedipine has been shown to decrease the frequency of attacks in approximately 70% of patients. The magnitude of the effect is, however, relatively modest (28 percent reduction in the frequency of attacks). Moreover, it has not been possible to demonstrate long-term increased digital blood flow in patients treated with nifedipine. Calcium channel blockers have the potential disadvantage of worsening the patients esophageal reflux and dysphagia due to their effect on esophageal smooth muscle tone. In this regard, it has recently been reported that

diltiazem had a lower tendency to lower LES pressure in patients with systemic sclerosis than nifedipine. These investigators suggested that diltiazem may be a better drug than nifedipine for managing the Raynaud's phenomenon in these patients. Unfortunately, the only controlled studies examining the ability of diltiazem to prevent or ameliorate Raynaud's phenomenon in patients with systemic sclerosis found it to be ineffective. Studies directly comparing the effectiveness of these two calcium channel blocking agents in managing Raynaud's phenomenon in patients with systemic sclerosis have not been reported.

Topical nitroglycerin has also been promoted as an effective therapy in patients with secondary Raynaud's phenomenon. In one study, the effect of nitroglycerin was compared with a group of patients using placebo and the contralateral hand of both groups. Nitroglycerin reduced the frequency of attacks and increased the rate of healing of digital ulcers. Like nifedipine, however, only a subset of patients responded, and the response was not complete in the responding patients.

The effectiveness of prazosin in the treatment of Raynaud's phenomenon has been examined in two prospective double blind single crossover studies. In one study, prazosin reduced the frequency of attacks by 50% compared with placebo. In the other smaller study, prazosin had an effect in only one patient, and the overall effect of prazosin was not significantly different from that of the placebo.

Ketanserin is a specific serotonin antagonist. It has been suggested that serotonin might be involved in the pathogenesis of the vasospasm. The effectiveness of ketanserin in the management of Raynaud's phenomenon has been evaluated in several studies. In one controlled trial, an intravenous ketanserin was shown to increase digital blood flow immediately following the injection in patients with Raynaud's phenomenon. The only study evaluating the long term effect of oral ketanserin on Raynaud's phenomenon is the uncontrolled trial depicted in Table XXXV. Ketanserin decreased the frequency of attacks compared with the pretreatment period by 50%, with 88% of the patients experiencing some benefit. Improvement in ulcer healing and improved digital blood flow were also noted.

Prostacyclin has vasodilatory properties. Intravenous carbaprostacyclin therapy is currently under investigation in a large multi-center placebo controlled trial. Preliminary results suggest that

ulcer healing improves with drug therapy. Moreover, digital plethysmography revealed improved cold tolerance and digital temperature recovery with therapy. The frequency Raynaud's phenomenon as judged by patient diaries did not improve. The authors ascribed the lack of apparent effect of the drug on the frequency of Raynaud's phenomenon to several weeks of unusually warm whether that improved the placebo treated group.

Prostaglandin E2 has been reported to inhibit platelet aggregation and have vasodilatory properties. PGE_1 lipospheres were evaluated in a multicenter double blind controlled trial. Although there was no difference in the frequency of Raynaud's phenomenon, the frequency of ulcer healing was improved in the PGE_1 treated group.

Dysphagia and symptoms of esophageal reflux Metoclopramide and cisapride are known to augment esophageal tone in normal individuals. The ability of these drugs to ameliorate the dysphagia and heartburn in patients with systemic sclerosis has been evaluated in a variety of controlled and uncontrolled studies. In one uncontrolled study of 12 patients with systemic sclerosis, an intravenous infusion of metoclopramide increased lower esophageal sphincter pressure, solid phase gastric emptying (Figures 11). Moreover, the number of episodes of reflux in a 24 hours time period as assessed by esophageal pH monitoring was decreased by the oral administration of metoclopramide (Figure 12). In addition metoclopramide improved esophageal transit time in 5/12 of the patients. Although this study reported that metoclopramide did not induce peristalsis in patients whose esophagus was aperistaltic prior to therapy, another study reported that metoclopramide induced peristalsis in 9/9 patients whose esophagus was aperistaltic

Figure 11; from Johnson et al., 1987

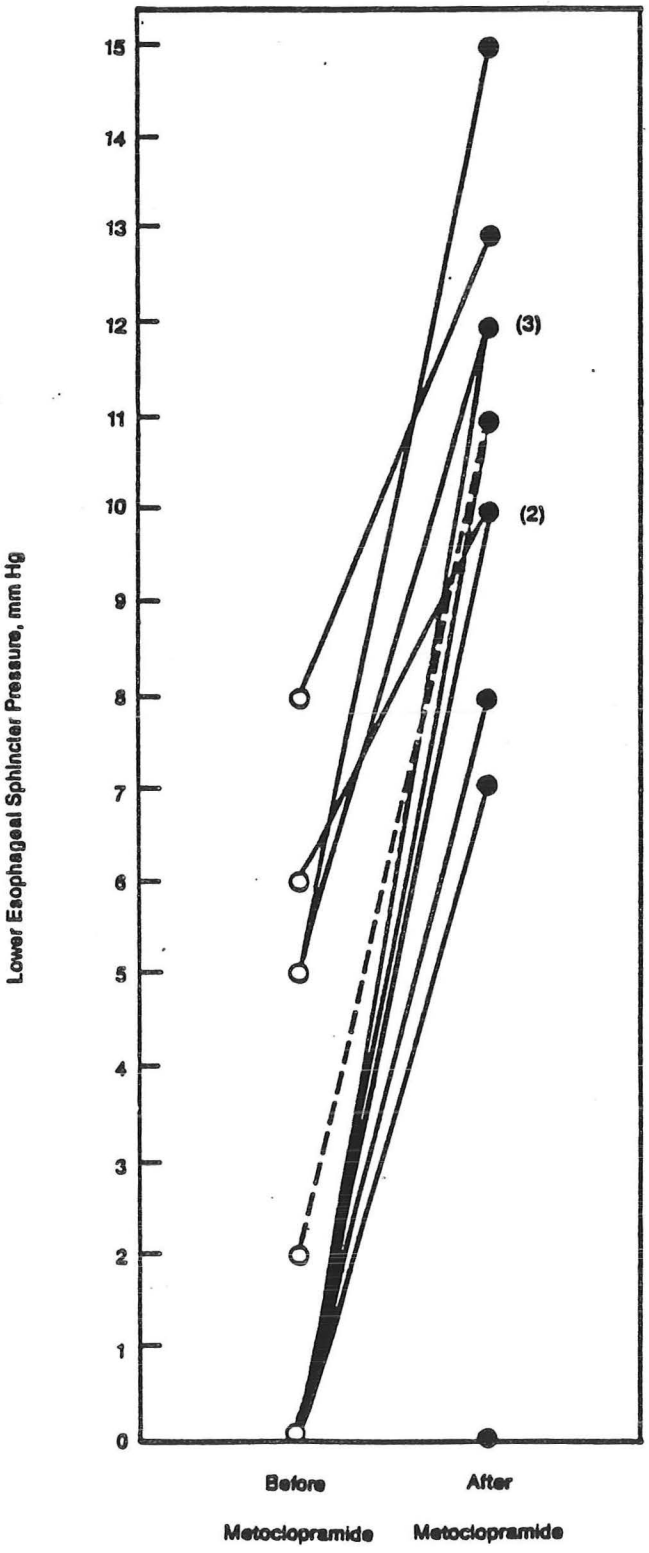
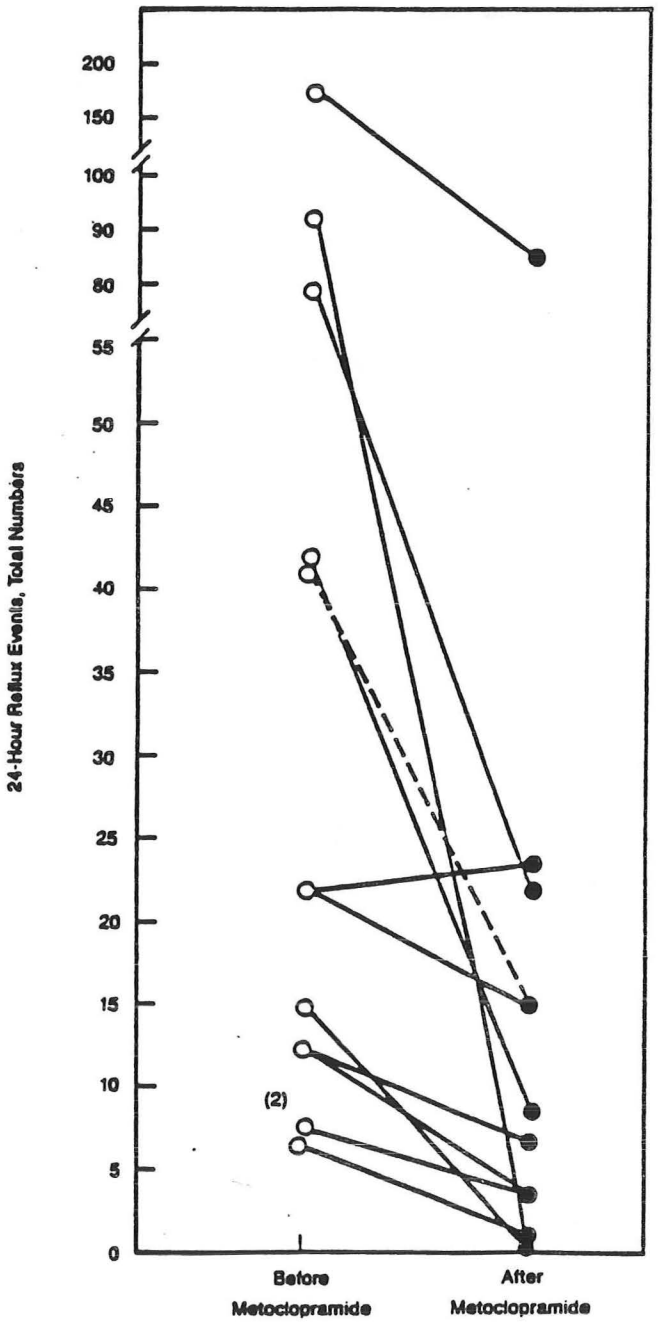


Figure 12; from Johnson et al., 1987



prior to therapy. Whereas these studies suggest that chronic administration of metoclopramide may ameliorate the symptoms of esophageal reflux and dysphagia, they do not directly address this possibility. Moreover, since metoclopramide has significant central nervous system toxicity related to its anti-dopaminergic properties, it is likely that a significant proportion of patients would not tolerate the drug if taken chronically. Cisapride is newly developed drug that stimulates gastrointestinal motility, but does not have anti-dopaminergic properties. The effects of cisapride on gastric and esophageal emptying was recently evaluated in a double blind placebo controlled study of 20 patients with systemic sclerosis. Patients were given an initial bolus of intravenous cisapride or placebo and gastric and esophageal manometry performed. A significant increase in lower esophageal sphincter pressure was observed. The patients were then treated with oral cisapride for one month and assessed using clinical criteria, esophageal manometry, and 24 hour pH monitoring. Chronic treatment with cisapride significantly improved the scores for dysphagia, heartburn and regurgitation. The results of esophageal manometry, and 24 hour pH monitoring are provided in Table XXXVI.

Table XXXVI

CISAPRIDE IN THE TREATMENT OF ESOPHAGEAL ABNORMALITIES IN SYSTEMIC SCLEROSIS

	Placebo	Cisapride	
Lower esophageal sphincter pressure	8.9 ± 2.1	11.8 ± 2.0	($p < 0.05$)
Percent of time pH < 4 (upright)	8.0 ± 1.5	4.3 ± 0.9	($p < 0.01$)
Reflux number (upright)	33 ± 10	18 ± 3	($p < 0.05$)

From Kahan et al. 1989

No side effects were reported in the one month study. The data suggest that cisapride may be effective in relieving the upper gastrointestinal symptoms of patients with systemic sclerosis.

Another approach to relieving symptoms of esophageal reflux in patients with systemic sclerosis is by reducing acid secretion. The ability of cimetidine and antacids to relieve the symptoms of heartburn in 15 patients with systemic sclerosis was recently compared in a double blind single crossover study. From the results in Figure 13 it can be seen that cimetidine was dramatically more effective at relieving daytime heartburn than the antacid therapy. Similar effects were observed when nighttime heartburn was assessed in experiments not shown. The patients also underwent endoscopy at the initiation of treatment and after 8 weeks of therapy. The endoscopy score of esophageal erosion was significantly lower in the patients treated with cimetidine. Stricture size and lower esophageal sphincter pressure were not effected by cimetidine therapy.

The management of upper gastrointestinal symptoms in patients with systemic sclerosis is

summarized in Table XXXVII.

Figure 13; from Petrokubi et al., 1979

Table XXXVII

MANAGEMENT OF UPPER GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH SYSTEMIC SCLEROSIS

Symptom	Treatment
Reflux	Elevate the head of the bed
	Reduce gastric acid
	Histamine receptor blockade
	Antacids
	Increase LES pressure
	Metoclopramide?
	Cisapride
	Avoid Nifedipine
Dysphagia	Improve esophageal motility
	Metoclopramide
	Cisapride
Gastric retention	Improve gastric emptying
	Metoclopramide
	Cisapride

Steatorrhea and malabsorption. There are numerous case reports of tetracycline improving the steatorrhea in patients with systemic sclerosis. This therapy is often insufficient, however, and many

patients with this complication require parenteral alimentation.

Pulmonary fibrosis and hypertension. The possibility that penicillamine may improve the DLCO in patients with pulmonary fibrosis is discussed above. Steroids are recommended by some investigators for those patients who have an inflammatory alveolitis documented by finding neutrophils in the bronchoalveolar lavage fluid. No uncontrolled or controlled trials support this approach. If steroids are to be used they should be used only in the patients with significant pulmonary disease. Moreover, the response of the patient should be monitored with objective tests of pulmonary function and discontinued as soon as it is clear that the therapy is unsuccessful.

There are also no accepted therapies for patients with pulmonary hypertension. This complication often becomes clinically evident at the terminal stage. Verapamil has been reported in one case report to lower pulmonary pressure and relieve symptoms over a one year period. This finding has not yet been confirmed.

One study investigated the effect of various vasodilators on pulmonary artery pressures and resistance (Table XXXVIII).

Table XXXVIII

TREATMENT OF PULMONARY HYPERTENSION IN 14 PATIENTS WITH SYSTEMIC SCLEROSIS

Agent	Number of Patients	Mean PAP (mm Hg) Before	Mean PAP (mm Hg) After	Calculated PVR (dynes/sec/cm^{-5}) Before	Calculated PVR (dynes/sec/cm^{-5}) After
Nifedipine	6	46 ± 16	45 ± 17	697 ± 416	619 ± 388
Captopril	5	50 ± 12	49 ± 14	725 ± 288	680 ± 368
Isosorbide Dinitrate	4	48 ± 13	48 ± 10	713 ± 356	705 ± 342
Ketanserin	14	46 ± 13	42 ± 15	846 ± 410	684 ± 221*

*Difference in PVR between control and ketanserin treatment is significant ($p < 0.02$)

Modified from Seibold et al. 1986

In this study, 14 patients with systemic sclerosis and pulmonary hypertension underwent right heart catheterization and intravenous ketanserin infusion. Following a 2 hour washout, some of the patients were treated with sublingual nifedipine or isosorbide dinitrate or oral captopril. Captopril, isosorbide dinitrate, and nifedipine did not decreased pulmonary artery pressure or resistance. Ketanserin, in contrast, decrease pulmonary resistance modestly. Whether chronic administration with a serotonin antagonist will eventually be effective in pulmonary hypertension is not yet know. The data do suggest, however, that serotonin plays a role in the pathogenesis of pulmonary hypertension in systemic sclerosis.

Cardiac. The chest pain associated with pericarditis usually resolves spontaneously and can be treated with nonsteroidal anti-inflammatory agents or, in some resistant cases, steroids. Systemic sclerosis patients rarely develop cardiac tamponade. This complication seems to occur more often in patients who have chronic, largely asymptomatic, pericardial effusions. No treatment has been shown to prevent this complication. No treatment is available for the left ventricular dysfunction caused by myocardial fibrosis. It has, however, been demonstrated that the number of myocardial perfusion

defects observed on thallium scan can be decreased acutely by nifedipine therapy. Whether chronic treatment with nifedipine would reduce the incidence of subsequent left ventricular dysfunction is not known.

Cardiac arrhythmias are generally managed with anti-arrhythmic agents. Whether they respond to therapy with anti-arrhythmic therapy any differently than other patient groups is unclear.

Renal. Recent evidence has suggested that the outcome of scleroderma renal crisis has changed as a result of dialysis antihypertensive therapy. Thus, in one group of 68 patients with scleroderma renal crisis, 26 patients could be identified that were treated conservatively before 1971. This group had a one hundred percent mortality with a average survival of 23 days. Since severe hyperreninemia is present in patients with renal crisis, several investigator have tried inhibitors of angiotensin converting enzyme as treatment of these patients. The compilation of 5 reports involving 21 patients are shown in Table XXXIX. It is clear that captopril controls blood pressure in these patients. Only 2 patients of 21 had persistently elevated blood pressures on captopril. These patients were eventually controlled on minoxidil in one case or methyldopa in the other. More impressively, death did not occur in any of these 21 patients. The patient renal function following therapy was quite variable. There was a loose correlation between the creatinine at admission and following therapy, but several patient were reported who presented with moderately severe renal disease and progressed despite control of their blood pressure. Moreover, several were reported who presented with severe renal dysfunction and had near normal renal function after treatment. Survival of renal crisis has also been described with other antihypertensive agents including alpha methyl dopa, minoxidil, and propranolol. No controlled trials compare various antihypertensive therapies in the management of renal crisis in patients with have been reported. The data indicate that the combination of dialysis and aggressive treatment of hypertension prolongs survival in renal crisis and aggressive control of blood pressure may preserve renal function.

Table XXXIX

TREATMENT OF RENAL CRISIS IN SYSTEMIC SCLEROSIS WITH CAPTOPRIL

	Percentage of patients
Control of blood pressure	90
Creatinine < 1.5	28
Creatinine 1.5-3	19
Creatinine 3-9	19
Dialysis	33
Death	0

There are several reports of improvement in visceral and cutaneous manifestation of systemic sclerosis following survival of renal crisis. This improvement was noted in as many as 50% of the patients in some series, but did not occur in others.

From these studies, it is clear that there are several potentially exciting new therapies for patients with systemic sclerosis, but each of these awaits a controlled trial. Moreover, a variety of approaches now exist for ameliorating some of the symptoms of patients with systemic sclerosis. Finally, there are several new insights into the pathogenesis of systemic sclerosis that should help us develop more effective therapies in the future directed at the etiologic agent.

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