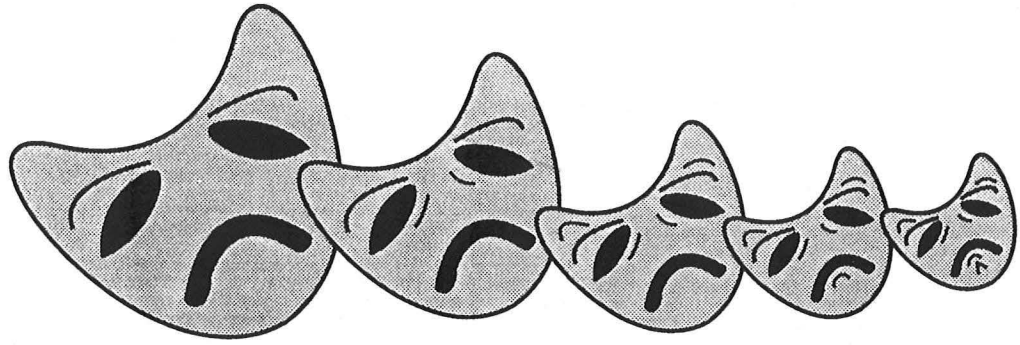


UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

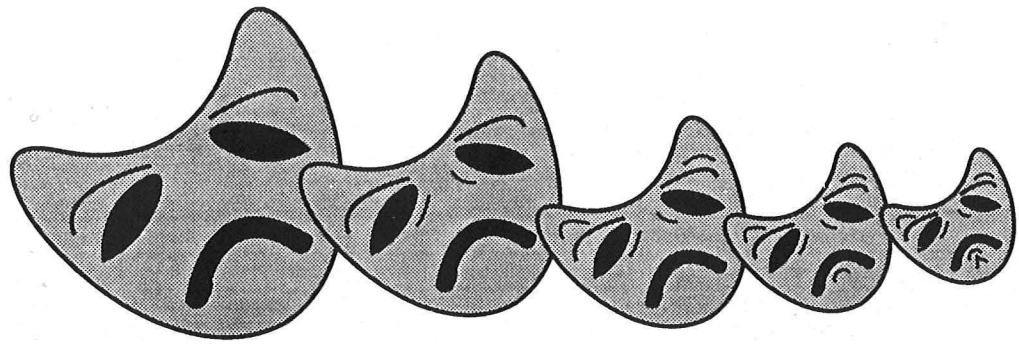
PARKLAND MEMORIAL HOSPITAL

MEDICAL GRAND ROUNDS

MAY 14, 1992

THE MANY FACES OF SCLERODERMA

J. DONALD SMILEY, MD



THE MANY FACES OF SCLERODERMA

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THE MANY FACES OF SCLERODERMA

"The cause of the consumption (tuberculosis) is well known. It derives from breathing miasma from a swamp." Theophilus Lobb, Lecture to the Royal Society of Medicine, London, 1778 (Ref 1).

When dealing with disease(s) of unknown cause, it is tempting to oversimplify from one's own narrow viewpoint like one of the five blind men describing an elephant. Each investigator explains the illness based on his own special interest area. Scleroderma, which probably represents several diseases with various etiologies affecting genetically unrelated patients in multiple organ systems is the proverbial elephant under discussion today. It gives us an opportunity to explore a wealth of new knowledge related to blood vessel function (endothelial relaxing factor, endothelins), inflamation of blood vessels and connective tissues (cytokines, integrins) and the fibrosis which follows anoxic injury of a variety of organ systems. It provides the opportunity to explore the experiments of Nature and medical science which simulate some of the features of idiopathic scleroderma (toxic oil ingestion, L-tryptophan, silicone breast implantation). And it permits speculation about important new directions for the therapy of these serious diseases. It is an ideal subject for an Internal Medicine Grand Rounds because virtually everyone in the audience can enjoy being one of the blind men (or women).

Table 1. CLASSIFICATION OF SCLERODERMA AND SCLERODERMA-LIKE CONDITIONS

Raynaud's disease and Raynaud's phenomenon
Diffuse systemic sclerosis (DSSc)
Limited cutaneous systemic sclerosis (SSSc, CREST)
Overlap syndromes (sclerodermatomyositis, mixed connective tissue disease)
Eosinophilic fasciitis/eosinophilia-myalgia syndrome (L-tryptophan)
Responses to other toxic substances (Toxic oil, silicone implants, etc)
*Morphea and linear scleroderma
*Other isolated fibrosing conditions (Ormond's, Peyronie's, etc)

(Adapted from Ref 2,3)
*These conditions will not to be discussed in this presentation.

Table 2. INCIDENCE OF RAYNAUD'S, DSSc, LSSc, AND OVERLAP SYNDROMES

Raynaud's Disease (no other identifiable connective tissue disease)	1-5% women 0.1% men
Raynaud's Phenomenon (associated with scleroderma or other CTD)	150/100,000 women rare men
DSSc (Diffuse systemic sclerosis)	7-45/100,000 women 1-6/100,000 men
LSSc (Limited cutaneous systemic sclerosis)	4-22/100,000 women rare men
Overlap Syndrome(MCTD,Sclerodermatomyositis)	0.4-3/100,000 women rare men

(Adapted from Ref 2-4)

Once permanent skin or internal organ changes begin to appear, several physical and laboratory differences separate SSc patients into useful subsets, each with a separate clinical presentation and often, very different long-term prognosis. The degree of skin involvement is one of the most useful predictors. Clements, et al (Ref 5,6) have devised an elaborate diagram to calculate a "Skin Score", and this will be very useful for research studies of scleroderma. From the point of view of the physician in practice, it is usually possible within the first one or two years of observation to determine whether involvement of the skin of the upper arms, face or trunk is occurring, suggesting DSSc. LSSc usually shows limited cutaneous involvement of fingers or hands only. Rarely, early in the course of the disease, no tightening of the skin is present at all in LSSc, but in 93% of LSSc patients rectangular telangiectases can be found on the fingers and palms (Ref 6). The "neck sign", elicited by having the patient raise the chin as high as possible and palpating the folds of the anterolateral neck for induration, is said to be positive in 90% of patients with DSSc at the time of initial examination (Ref 7).

When followup of the 264 patients in the multicenter Scleroderma Criteria Cooperative Study was made in 1990, several interesting observations resulted (Ref 8). On average, each patient went 3.8 years from the onset of symptoms until the diagnosis was made suggesting that most physicians have considerable difficulty diagnosing early disease. In all likelihood, the early symptoms were Raynaud's phenomenon or puffy swelling of hands and feet. This means that diagnostic laboratory tests which could sort early patients with primarily Raynaud's phenomenon into those likely to develop DSSc, LSSc or Overlap syndromes are needed.

Table 3. AUTOANTIBODIES USEFUL IN DIFFERENTIATING SCLERODERMA VARIANTS

Antinuclear Antibody (HEp-2, K-B cells)	% positive
Raynaud's phenomenon	25
DSSc (80% female)	58-70
LSSc (98% female)	98
Overlap syndromes (90% female)	98
Anti-Topoisomerase I (Scl-70 kd kinetochore)	
Raynaud's phenomenon	2
DSSc (White 17,Black 37, Latin 11)*	23-75
LSSc	2-18
Overlap syndromes	0
Anti-Centromere	
Raynaud's phenomenon	14
DSSc	0-1
LSSc	43-80
Overlap syndromes	0
Anti-nucleolar (PM-Scl,RNA polymerase I, U3 Ribonucleoprotein-fibrillarin), Anti-RNP	
Raynaud's phenomenon	6
DSSc	8
LSSc	14
Overlap syndromes	80

(Composite data derived from Ref 9-13). Variable % reflect different values reported in the literature.
*Illustrates racial variations in Houston (Ref 10).

This distribution of serological findings among the major scleroderma types which may be useful in the diagnosis and in providing prognosis in the three major variants of SSc (scleroderma) is illustrated in Figure 1 on the next page.

AUTOANTIBODIES DIFFERENTIATING SCLERODERMA VARIANTS

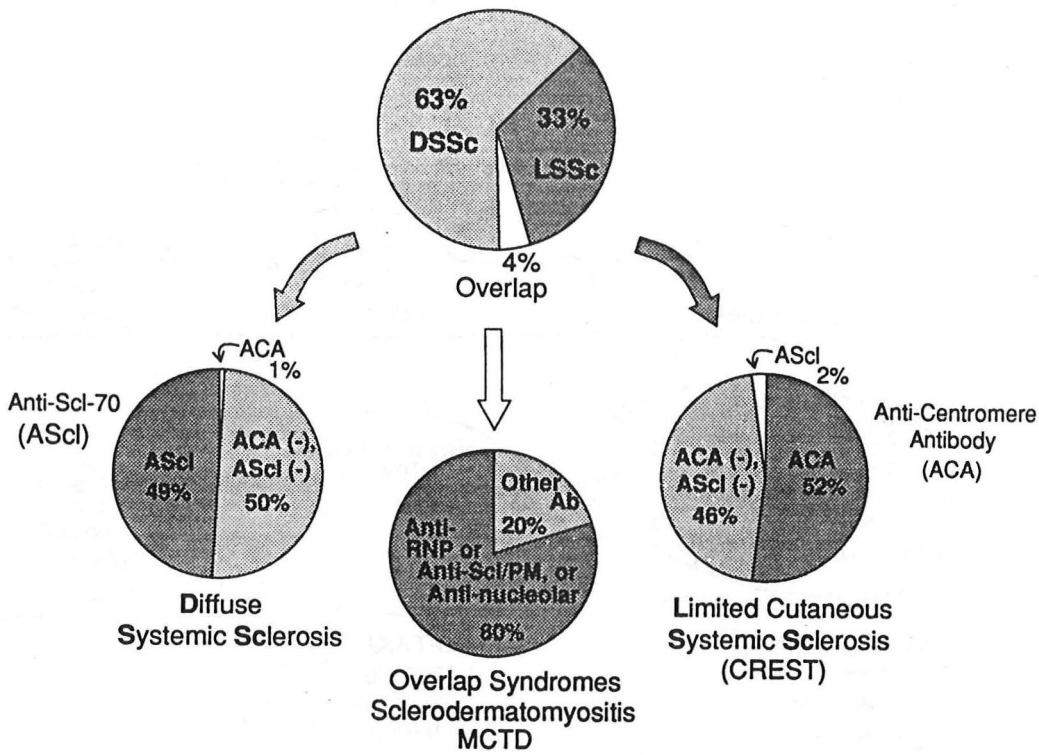
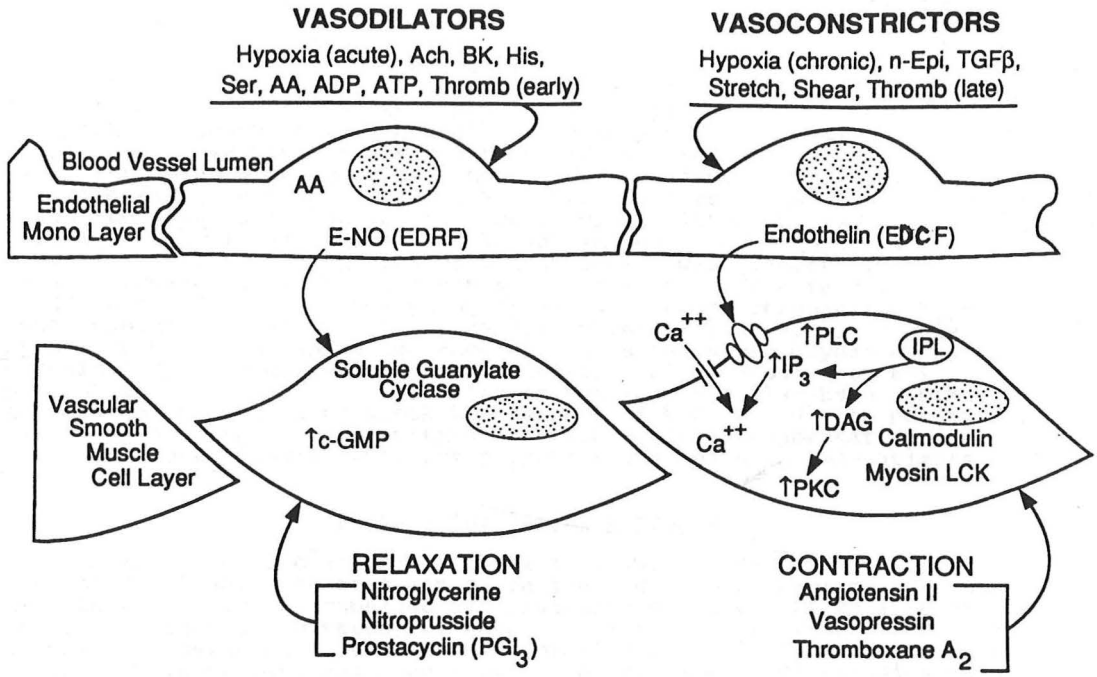


Figure 1. Distribution of autoantibodies which may be useful in the diagnosis and in providing prognosis in the three major variants of SSc.

Factors Regulating Vascular Tone

Most investigators of SSc believe that vasospasm which remains for prolonged periods causes anoxic injury that results in secondary fibrosis and scarring. Hundreds of publications, primarily in the cardiology literature during the last five years, have changed our view of the mediators of vascular tone in large and small blood vessels. Redundant, interacting systems which include neural mediators such as acetylcholine and norepinephrine, humoral mediators such as bradykinin, cell-membrane-derived mediators such as arachidonic acid derivatives, and various inflammatory mediators such as cytokines all impinge on vascular endothelial cells to modify their function. Other factors such as physical stress or trauma and hypoxia also change endothelial cell function and influence vascular tone. The new information which is most fascinating relates to the secreted products of the endothelial cells themselves (relaxing factors and constricting factors) which locally alter vascular smooth muscle tone (Ref 14). These complex interactions are illustrated in Figure 2.

ENDOTHELIAL CELL REGULATION OF VASCULAR TONE



Abbreviations

Vasodilators
Ach = acetylcholine
Bk = bradykinin
His = histamine
EDRF = endothelial relaxing factor
E-NO = nitric oxide from endothelium
Thromb(early) = early effect of local thrombin activation
AA = Amino acids arginine, lysine, ornithine
ADP,ATP = adenosine di-,triphosphate
Ser = serotonin

Vasoconstrictors
n-Epi = norepinephrine
TGFβ = Tissue growth factor beta
Stretch, shear = stress injuries
EDCF = endothelial constricting factor
Thromb(late) = delayed effect of local thrombin activation

Figure 2. Local endothelial cell regulation of vascular tone (Adapted from Ref 14).

The purification of endothelin (Ref 15) revealed the most potent vasoconstrictor known with effective vasoconstriction being produced at concentrations of only 4×10^{-14} M, which makes it 10 times more potent than angiotensin II or vasopressin on a molar basis. It is now believed that endothelin plays an important role in hemostasis after injury (Ref 16). It is increased in the serum after trauma (Ref 16), and in the serum of patients with advanced atherosclerosis (Ref 17).

A recent fascinating paper by Adnot, et al, (Ref 18) explored the role of chronic anoxia on the vascular tone in an isolated rat lung preparation. Rats were maintained in a simulated high altitude chamber (10-11% O_2) for 1 or 3 weeks, then the respective isolated lung preparations compared with normal rat lungs and with 3-week-hypoxic rat lungs removed 48 hours after the rats had been returned to room air (20% O_2). Perfusion with acetylcholine was used to induce EDRF (Endothelial relaxing factor = E-NO). Vasodilation was reduced in the 1-week-hypoxic lungs, totally abolished in the 3-week-hypoxic lungs and restored to the normal control level in the 3-week-hypoxic lungs returned for 48 hours to room air. Endothelin-induced vasoconstriction was greatest in the 3-week-hypoxic lungs, and was not potentiated by E-NO antagonists suggesting that no E-NO was being released by these chronically hypoxic lung endothelial cells. This provides an interesting model of pulmonary hypertension which can become accelerated as the serum oxygen drops to hypoxic levels by depleting the counter-balancing vasodilator EDRF (E-NO) present in normal endothelial cells in the lung and elsewhere. Other factors which deplete or block the release of E-NO could also potentiate pulmonary hypertension, resulting in stetch-induced augmentation of vascular smooth muscle tone, cor pulmonale and death in SSc patients.

Factors Initiating Fibrosis

Immunological, chemical or physical injury causes activation of fibroblasts leading to collagen secretion and tissue scarring. We now know that T-cells, macrophages and platelets migrate into an area of injury and become activated, release a variety of cytokines which cause tissue mast cells and fibroblasts to proliferate and differentiate (Ref 19-21). This process has been shown to accelerate in SSc leading to gene activation for the production of intracellular matrix components (collagen-I,-III,-VI, fibronectin, glycosaminoglycans), and resulting in dense scar formation which chokes out organ function in the skin and elsewhere (Ref 2,19-21).

Tissue mast cells in the skin and other tissues are throught to play a pivotal role in the fibrosis of scleroderma (Ref 22-26). Figure 3, taken from a recent publication of Dr. Henry Claman of the University of Colorado (Ref 22), summarizes this complex cascade showing the role of T-cells, macrophages, platelets, mast cells, fibroblasts, and endothelial cells, and the interacting cytokines and transforming cell growth factors in this phase of the pathogenesis of SSc.

A case report of the induction of a clinical remission in a patient with early scleroderma by ketotifen (Zaditen, Sandoz)(Ref 26), a mast cell inhibitor, emphasizes the need for further study of the central role of tissue mast cells in the pathogenesis of SSc.

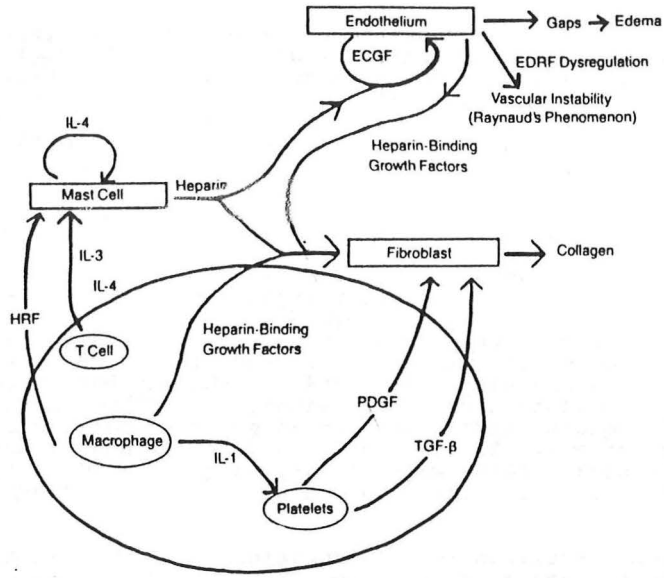


Figure 3. Endothelial cell, mast cell and fibroblast interactions in SSc (From Claman, HN, Ref 22).

Raynaud's Disease and Raynaud's Phenomenon

Patients who evenually show clinical features of DSSc, LSSc or Overlap syndromes with scleroderma often give a history of many years of gradually worsening Raynaud's phenomenon prior to an accelerated phase of systemic involvement (Ref 2,3). In the past, deciding which patient would progress to systemic involvement has been difficult. As will soon be discussed, new developments now make this task easier, but first I would like to share with you two examples of the induction of clinical Raynaud's phenomenon, both involving gastrointestinal illness. In 1964 Greisman, Hornick and Woodward (Ref 27) at the University of Maryland decided to study the role of gram-negative bacterial sepsis on cardiovascular function. They paid 9 healthy volunteers to be examined with nailfold capillary blood flow observations using a dissecting microscope, then infused norepinephrine by drip intravenously and counted the number of drops/minute necessary to cause sufficient vasoconstriction to obliterate nailbed blood flow. This was shown to be very reproducible in each normal subject. They then infected each subject with Salmonella typhosa, and while each was ill with typhoid fever, the investigators again repeated the nailbed blood flow experiment. The patient was then treated with chloramphenicol until fully recovered and 1-5 weeks later, the nailbed blood flow experiment again repeated. Both during the active typhoid fever illness, and for many days after convalescence, all 9 subjects remained two to ten times more sensitive to norepinephrine than before their infection. In other words, a temporary supersensitivity to a stimulus of vasoconstriction had been induced. The investigators (Ref 27) concluded that exposure to significant amounts of bacterial endotoxin over the several days of the typhoid illness had sensitized the vascular system to the effect of norepinephrine and that both systemic blood pressure and to an even greater degree, the microvascular circulation had been temporarily altered.

Years later, when the vogue of ileal-colonic by-pass surgery for massive obesity was at its height, it was observed that about one-third of operated patients developed rheumatic disease complaints.

In 1980 Utsinger (Ref 28) collected 85 symptomatic by-pass disease patients and found 82% to have an inflammatory arthritis, and 17% to have Raynaud's phenomenon! No such symptoms had been present prior to by-pass surgery, and the arthritis and Raynaud's phenomenon disappeared within 1-2 weeks after the bowel was restored to a normal flow path. Utsinger (Ref 28) was able to show elevated levels of immune complexes (cryoglobulins) containing E. coli and B. fragilis antigens in the serum of 78 of the 85 patients studied.

These two examples raise interesting questions about the role of bacterial endotoxin in the induction of Raynaud's phenomenon.

CASE I. This 37 WF was seen 8-9-91, with a three-year history of pain in her hands and feet after exercise, especially during cold weather. She is a biking enthusiast, usually bicycling 200 miles/week. The hand pain is accompanied by the classical Raynaud's triad of pallor, cyanosis, then red flush. She has no sclerodactaly, trophic ulcerations, fingernail or cuticle changes, and the ANA and Anti-Scl-70 are negative. Her ESR is 2mm/hour. The Raynaud's has progressed to such an extent that she has had to stop bicycling. She never has the problem except after vigorous exercise, usually requiring about 20 minutes of exercise before an attack. A trial of nifedipine (30 mg, slow-release form/day) caused intolerable hypotension. She is now evaluating capoten, 12.5 mg tid on a trial basis.

Comment: This patient is reminiscent of the occasional long-distance runner who develops cardiovascular collapse near the end of a 20K race. To explain this cardiovascular collapse, it has been postulated that the shift of blood flow from the GI tract to the leg muscles is so profound and prolonged that, near the end of the long distance race, ischemia of the bowel occurs. This impairs the bowel:blood barrier and allows absorption of bacterial endotoxins which precipitate vasodilation and shock. It is intriguing to speculate that a rare individual with a defect or partial depletion of EDRF (E-NO), would then experience rebound release of endothelin with resulting vasospasm (Raynaud's) after very vigorous, prolonged exercise. Methodology is now available to explore this possible sequence in this patient.

Early Detection of SSc-Spectrum Disorders in Raynaud's Patients

The presence of biphasic (pallor, cyanosis), or triphasic (pallor, cyanosis, red flush) Raynaud's phenomenon, a positive ANA and changes in the nailfold capillary bed with tortuous, dilated capillaries and/or areas of atrophy and scarring due to capillary loss are strongly correlated with the presence of a variant of SSc. Takehara, et al (Ref 29) thoroughly studied a group of 50 patients with severe Raynaud's phenomenon in 1990, and found 3 with visceral involvement compatible with early DSSc, 15 with a positive anti-centromere ANA compatible with LSSc, and 6 others with a positive anti-RNP compatible with early overlap syndrome (MCTD or sclerodermatomyositis).

Treatment of Raynaud's Disease and Phenomenon

Whether linked to scleroderma or not, patients with severe Raynaud's often require treatment (Ref 30). The role of emotional stress in modifying expression of vasospasm cannot be underestimated. Biofeedback requiring an enormous amount of time and considerable motivation on the part of the patient (must be a true believer) is said to improve 57% of patients (Ref 30). In practical terms, this is best viewed as a placebo effect, useful for patients with mild disease. This placebo effect, however, spills over into evaluation of any drug therapy of Raynaud's. For example, glowing reports of lasting benefit after intraarterial reserpine persist to this day. A sincere, dedicated, persuasive, driven, supersalesman physician can strongly influence the Raynaud patient.

When a randomized, double-blind, crossover study was done comparing intraarterial reserpine with intraarterial saline, identical subjective improvement was obtained in 48% of both groups (Ref 31)!

Perhaps rate of digital ulcer healing is one of the better endpoints to follow to assess efficacy of a given treatment. This has been used to claim benefit from prostaglandin E1, a vasodilator and potent inhibitor of platelet aggregation, given at 6-10 ng/kg/min via a central venous catheter by continuous drip over a 72-hour period in single-blind, cross over studies (Ref 32,33). The effect was persistent for several weeks and the treatment was well-tolerated with few side effects.

Why not modify prostaglandin production to help Raynaud's? Omega-3-fatty acids from cold water fish oil compete with arachidonic acid and result in increased production of prostacyclin (PGI_3) (cyclooxygenase pathway), and decreased production of thromboxane A_2 (5-lipoxygenase pathway) by forming the inert analogue thromboxane A_3. When fish oil was given in a dose of 6.5 g/day, and compared to the same amount of olive oil in a double-blind, controlled, prospective study (Ref 34), fish oil recipients with Raynaud's disease had impressive improvement. However, Raynaud's phenomenon due to SSc failed to show significant improvement.

Probably the best response in Raynaud' disease has been obtained with calcium channel blockers. Remember, these drugs block the action of endothelin (Ref 15). Two recent double-blind, crossover studies (Ref 35,36) decreased the frequency and severity of Raynaud's attacks in Raynaud's disease, but not in Raynaud's associated with SSc. On the other hand, prazosin, taken orally 0.1 mg three times daily, has been shown (Ref 37,38) to decrease the frequency and severity of Raynaud's attacks in patients with SSc. About half of the patients were able to tolerate the mild orthostatic hypotension and gain lasting benefit.

A serotonin receptor antagonist ketanserin, has also been reported to improve Raynaud's in 83% of patients with SSc as measured by serial digital strain gauge plethysmography during controlled cold challenge (Ref 39). Angiotensin converting enzyme inhibitors, such as capoten or enalpril, also have been recommended for patients with Raynaud's with SSc because of their additional advantage in improving renal blood flow (Ref 3,30). However, from my own clinical experience, many SSc patients with Raynaud's phenomenon do not respond well to any vasodilator agent (or combinations of agents).

Cold-induced "Raynaud's of the Lungs and Heart"

There has been considerable debate about whether or not pulmonary and/or cardiac vasospasm occurs simultaneously with cold-induced peripheral Raynaud's phenomenon in SSc. A carefully done study of mean pulmonary artery pressures obtained before, during and after cold exposure showed no change, suggesting that the pulmonary vasculature did not react to brief external cold exposure of the hands (Ref 40). On the other hand, the development of reversible myocardial perfusion defects seen with thallium myocardial scintigraphy during cold-water hand immersion in SSc patients with Raynaud's suggests that coronary vasospasms may occur (Ref 41).

Pregnancy in Patients with Raynaud's

Other workers have argued strongly that Raynaud's phenomenon can be generalized, causing vasospasm of internal organs including the placenta during pregnancy (Ref 42,43). In patients with both Raynaud's disease (having no other connective tissue disease), and in Raynaud's associated with SSc, there is an increased frequency of premature births and decreased fetal birth weight, but no increase in fetal wastage when compared to a matched control population. The authors conclude that an uneventful, healthy pregnancy is possible in women with Raynaud's with or without SSc, but advise against elective pregnancy in patients with rapidly progressive DSSc because of concern for renal crises and the shortened overall life expectancy (Ref 43).

Case II. This 33 WF was seen on referral from the Mayo Clinic in 1978 with a 3-month history of severe Raynaud's phenomenon followed by puffy swelling of her hands and forearms. She had been living in Wisconsin and moved to Dallas to escape the cold weather which had worsened her Raynaud's. Prior to three months before her visit she had been entirely well with two normal pregnancies within three years of onset of her illness. During the next three months after her initial visit, the skin involvement accelerated with hidebound scarring extending to her face and trunk. Work-up showed her to have B.P.=90/60, a positive ANA=1:320 speckled, ESR=50 mm/hr, and DLco=82% of predicted normal value. She refused cyclophosphamide therapy after hearing of its potential toxic side effects, and was unable to tolerate vasodilators because of induced orthostatic hypotension. Her hands became clawed with loss of finger range of motion and absorption of distal phalanges. She developed ulcerations over her proximal interphalangeal joints and elbows. Over a weekend she developed severe headaches and dyspnea, and when seen in the Baylor University Hospital Emergency Room was found to have B.P=240/140, and retinal hemorrhages, exudates and papilledema compatible with malignant hypertension. She then experienced complete renal shutdown. In spite of heroic effort (not including angiotensin converting enzyme inhibitors), she died seven days later. Total duration of illness--eight months...!

Comment: Factors identifying patients with a poor prognosis were reviewed in 1990 (Ref 8); 484 demographic, clinical and laboratory variables in 264 patients with definite SSc followed for more than five years are shown in Table 5.

Table 5. PREDICTORS OF A POOR PROGNOSIS IN SYSTEMIC SCLEROSIS

	Died<2yrs	Alive>2yrs	p-value
General Factors			
Older age--average in years	53 yrs	46 yrs	<0.001
Digital pitting	53%	43%	<0.001
Proximal muscle weakness	43%	15%	<0.001
Taking prednisone	31%	13%	<0.01
Renal			
Proteinuria	35%	10%	<0.001
Increased BUN, creatinine	25%	14%	<0.05
Microangiopathic erythrocytes	6%	0%	N.S.
Pulmonary			
Dyspnea	67%	36%	<0.001
DLco-% of predicted normal value	64% predic.	83% predic.	<0.001
Forced Vit. Capacity-% predic. normal	69% predic.	84% predic.	<0.001
Arterial pO_2-mm Hg	74.6 mm	87.2 mm	<0.001
Smoking tobacco	47%	22%	<0.01
Cardiovascular			
Heart rate-beats/minute	88/min	81/min	<0.001
Pedal edema	26%	4%	<0.001
Neck vein distension	19%	1%	<0.001
Abnormal EKG-PVCs,ST-T wave changes	34%	23%	<0.001
Left ventricular enlargement	26%	4%	<0.001
Laboratory Findings			
D-Xylose absorption-grams	3.1 gm	5.4 gm	<0.001
ESR mm/hour	42 mm	23 mm	<0.001
Anti-Topoisomerase I (Scl-70)	51%	21%	<0.001
Anti-Centromere	5%	19%	<0.001

If renal disease was present at the initial visit, 50% were dead within 3 months and 70% were dead within 5 years. The median survival for patients with significant cardiac involvement was 32 months with 60% dead at 5 years; pulmonary disease, 78 months with 60% dead at 5 years; gastrointestinal disease, 99 months with 42% dead at 5 years; none of the above, 108 months with 39% dead at 5 years (Ref 8).

Kidney Disease With and Without Hypertension

Case III. This 38 BM engineer had noted Raynaud's phenomenon and heartburn for 18 months before he finally consulted his family physician in January 1978. A thorough evaluation showed normal SMA-18 values, normal CBC with Hgb=16 gm/DL, and BP=100/60 with regular pulse and normal EKG findings. He had a positive ANA 1:640, speckled pattern (an anti-Scl-70 was unavailable at that time). He was noted to have extensive, puffy, non-pitting "edema" of his hands and feet, and some skin tightness over his upper chest. There was increased skin pigmentation in the areas of edema and tightening. He was given a thiazide diuretic and referred to a rheumatologist with a diagnosis of scleroderma. Five days later, when seen in the Arthritis Clinic, he was found to have BP=230/140, a rapid pulse 108/min, increased respirations 24/min, and a severe, throbbing headache which was worse when lying down. He was hospitalized where he was found to have retinal hemorrhages, and papilledema, compatible with malignant hypertension. Laboratory examination showed BUN=32, Creatine=2.1, WBC=18,000, 83% PMNs, Hgb=8.2 gm/DL, and blood smear showed burr cells, marked poikilocytosis and numerous fragmented erythrocytes (helmet cells) compatible with microangiopathic hemolytic anemia. Blood and urine cultures were consistently negative. Platelet count was 108,000/cu mm. A direct Coombs test was negative, and his reticulocyte count was 9%. A nephrology consultant was called and the patient begun on maximum doses of alpha-methyl dopa and hydralazine to control his rising blood pressure. His urine volume was 300-400 ml/24 hours, and showed 4+ proteinuria and 35-50 RBCs/HPF. Each day his creatinine climbed approximately 3 gm/DL suggesting essentially complete loss of renal function. On Aldomet and hydralazine, his blood pressure was poorly controlled, but when he was begun on renal dialysis, the blood pressure became manageable. He was scheduled for renal transplant when he was lost to follow-up.

Comment: This patient in the only one in whom I have had the opportunity to see at the exact onset of "scleroderma kidney", but he provides a very powerful example of the devastation possible in this disease in a matter of a few days. Three major points should be made about the course of his disease. First, those patients with rapid progression of skin involvement of the trunk are more likely to develop renal failure. Second, any process which results in abrupt changes in blood volume (either increases it or decreases it) may precipitate renal failure. In this patient, the administration of a diuretic for "edema" may have triggered the renal change. Precipitation of scleroderma kidney failure may follow administration of corticosteroids (perhaps modifying vascular tone or increasing blood volume), an association also noted in the multicenter Scleroderma Criteria Study (Ref 8) reviewed in Table 5 above. And third, this patient demonstrated a drop of 50% in his hemoglobin level within a five-day period with no evidence of bleeding, and with large numbers of fragmented erythrocytes seen on his admitting blood smear. Heptinstall and his colleagues (Ref 44) have noted this association of evidence of intravascular hemolysis in 7 of 20 patients dying of scleroderma and autopsied at Johns Hopkins Hospital. Six of the 7 were azotemic at the time the microangiopathic hemolytic anemia was noted, but only 4 were hypertensive (Ref 44).

Five of the 7 had pathology findings classical for scleroderma kidney with marked intimal proliferation of interlobular arteries and fibrinoid necrosis of the afferent arterioles. One of these patients had had normal diastolic blood pressure every time that she had been examined prior to death. Non-occlusive, intravascular fibrin deposits were noted throughout the kidney vasculature in all 7 patients with microangiopathic hemolytic anemia, but in none of the 13 other patients with scleroderma dying of other forms of organ failure. These authors interpret the red blood cell fragmentation to be related to the malignant hypertension due to shear forces from the abnormal blood pressure with occasional intravascular fibrin. They were at a loss to explain the 3 patients without severe hypertension.

A recent review of 131 patients with "scleroderma renal crisis" encountered in Pittsburgh over a 33-year period noted 11% (15 patients) who were normotensive (Ref 45), and 90% of these normotensive patients showed microangiopathic hemolytic anemia. These patients were also more likely to have had recent prior corticosteroid use, pulmonary hemorrhage and thrombocytopenia. I would like to suggest an alternate interpretation for the microangiopathic hemolytic anemia. If the degree of erythrocyte lysis were sufficiently large (as was the case in the patient described above in which about half of the blood lysed in less than 5 days), the capacity of the spleen and liver fixed macrophages to clear red cell ghosts would be overwhelmed and mechanical obstruction of the renal vasculature could occur suddenly, with resulting anoxia of the kidney, activation of the renin/angiotensin system and severe hypertension. This mechanism would explain the reversal of the renal failure and hypertension if angiotensin-converting-enzyme (ACE) inhibitors are given within the first few days of onset of the scleroderma renal crisis. Not only do ACE inhibitors block conversion of Angiotensin I into angiotensin II, but they may raise the level of bradykinin and lysylbradykinin by delaying the degradation of these potent vasodilators, thus relaxing the kidney vasculature sufficiently that erythrocyte and fibrin fragments could leave the kidney to be degraded elsewhere.

Heart Involvement in DSSc and LSSc

The acute induction by cold exposure of the hands of reversible myocardial perfusion defects in SSc patients has been noted above (Ref 8). However, about 15% of SSc patients have overt cardiac signs and symptoms characterized by pedal edema, distended neck veins, palpitations or syncopal attacks shown to be caused by ventricular tachycardia (Ref 2,3,8). Over 60% of the SSc patients with no cardiac symptoms also have objective evidence of cardiac abnormalities as determined by chest x-ray (enlarged heart size), Holter monitering of EKG and echocardiographic studies. The latter shows about 25% of SSc patients to have pericardial effusions (usually small or moderate and assymptomatic) (Ref 2). When exercise thallium studies were done in 22 patients with LSSc (CREST) and compared with thallium studies of 26 patients with DSSc (Ref 46), 64% of LSSc patients and 77% of DSSc patients had abnormal studies. However, LSSc patients had smaller defects more restricted to the right ventricle. Thallium reperfusion defects were not found in LSSc, but were noted in 38% of the DSSc patients who otherwise had no evidence of extramural coronary artery disease. The authors (Ref 46) concluded that cardiac manifestations in LSSc patients are distinct from those found in DSSc patients, and primarily involved right ventricular dysfunction related to accompanying pulmonary vascular disease in LSSc.

It should be stressed that in general digoxin should be avoided in managing congestive heart failure in SSc patients because of the risk of inducing fatal arrhythmias, and that loop diuretics should be used with great caution because they are believed to induce renal crises (Ref 3).

Pulmonary Disease in Systemic Sclerosis (Scleroderma)

Multiple organ system involvement is often seen in a given patient with SSc. However, now that ACE inhibitors are available to treat (and perhaps, to prevent) scleroderma renal crises, more SSc patients ultimately die of pulmonary involvement than from renal, cardiac or gastrointestinal dysfunction. The obliteration of the pulmonary capillary bed is associated with interstitial pulmonary fibrosis (IPF) and ultimately leads to the onset of pulmonary hypertension. This increased load on the right ventricle results in cor pulmonale and eventually sudden death due to cardiac arrhythmias. However, the initial problem starts with the pulmonary injury. There is debate whether or not patients with DSSc and LSSc have the same frequency and severity of IPF. Some observers found the same risk (Ref 47,48), while others (Ref 49,50) found features of DSSc (Anti-Scl-70 and digital pitting) to be associated with worse IPF, and features of LSSc (anti-centromere) to be less associated with serious abnormalities of pulmonary function. British patients tend to be more likely to be HLA-DR3 and have anti-Scl-70 antibody if they have severe pulmonary involvement (Ref 50), whereas Italian patients have no increase in HLA-DR3 and have similar frequency of IPF whether they are DSSc or LSSc in clinical presentation (Ref 48).

In the past, the DLco (total lung diffusing capacity measured by inspiring a single breath of carbon monoxide) has been the gold standard for assessing the presence and extent of IPF (Ref 47,51). It remains valuable if performed in a reliable laboratory since it is reasonably reproducible (+/-10%) and progressive decreases correspond fairly closely to the actual number of lung capillaries lost. Two new tests have become available which offer both diagnostic and prognostic data of great value. The high resolution computed tomographic (HRCT) scan evaluates 1 mm thick slices of lung in selected areas. It is impractical for whole lung scanning because of the excess radiation exposure. This technique showed characteristic changes of early IPF in 91% of 21 SSc patients (so-called subpleural lines in 74%, and honeycombing in 30%, with both in some patients) compared to the 39% of the 21 patients with definite abnormality on the routine chest x-ray (Ref 52). HRCT may be particularly valuable in separating IPF from other conditions which give an abnormal DLco such as sarcoidosis by directing the physician to patchy areas of involvement when planning a transbronchial or open lung biopsy. Harrison and his colleagues (Ref 53) evaluated 16 SSc patients (all of whom had a normal chest x-ray) by HRCT, bronchoalveolar lavage and ^{99m}Tc-DTPA clearance. ^{99m}Tc-DPTA is an aerosolized, radioactive tracer which is absorbed from the alveolus into the lung capillaries in a manner similar to carbon monoxide. They found 44% of the routine-X-ray-normal SSc patients to have abnormal HRCT findings. However, since 73% and 71%, respectively had abnormal bronchoalveolar lavage (BAL) and ^{99m}Tc-DPTA clearances, they concluded that even earlier, more subtle abnormalities could be detected by the latter two methods.

Use of (BAL) to Detect Early or Active Lung Disease in SSc

Bronchoalveolar lavage (BAL) involves passing a fiberoptic bronchoscope into a large bronchus, wedging it in place and instilling four successive 50-ml aliquots of isotonic saline into the lung beyond the obstruction point, allowing each to remain for 30 seconds, then aspirating the fluid through the bronchoscope. After four aspirations, the bronchoscope is then placed in another large bronchus and the procedure repeated. The fluid from each bronchus is pooled and analyzed for volume recovery, total cells and cell-type recovered, and for proteins of various types in the lavage fluid. Numerous interesting studies have appeared in the last five years comparing BAL to other pulmonary function tests in patients with DSSc and LSSc (Ref 54-65). The major findings of these studies are summarized in Table 6 adapted from Silver and his coworkers at University of South Carolina (Ref 51).

Table 6. EVIDENCE FOR FIBROSING ALVEOLITIS IN SYSTEMIC SCLEROSIS
BRONCHOALVEOLAR LAVAGE RESULTS IN PATIENTS AND CONTROLS

BAL data	SSc Pts(43)	Controls(14)
% of Instilled fluid recovered	56 *	72
Total WBC/ml x 10,000	17.2 *	7.8
Differential (%)		
Alveolar macrophages	90.7%	93.1%
Lymphocytes	4.1%	5.8%
Granulocytes	5.1%*	1.1%
Neutrophils	4.0%	0.7%
Eosinophils	1.1%	0.4%
IgG mg/ml	1.44*	0.51
Albumin mg/ml	3.34	1.99
Immune complexes (as µg/ml aggr.IgG)	32.7 *	8.9
Fibronectin (ng/million cells/day)	306. *	18.

(Adapted from Silver RM, et al, Ref 51)
* = p-value significantly different from control

As noted above, most patients have a dominance of granulocytes in their alveolar exudate. A few, particularly, those with associated Sjögren's syndrome, have a predominance of lymphocytes (Ref 54,62). Overall, the higher the neutrophil count in the BAL, the worse other parameters of pulmonary function, such as DLco, will be, and the more rapidly the IPF will progress (Ref 62). Overlap syndrome patients with a positive anti-RNP antibody are also more likely to show rapidly progressive IPF when compared to other SSc patients and to patients with SLE and rheumatoid arthritis who develop IPF (Ref 66-67).

Intersitial Pulmonary Fibrosis in SSc Sine Scleroderma

Male patients who develop scleroderma are more likely to show minimal skin involvement and to have other internal features, and serological changes compatible with DSSc. An interesting retrospective review of 10 such patients (all men) is presented in Ref 68. Eight of nine who were examined had esophageal dysmotility, seven of eight in whom it was measured had a positive ANA, six of eight measured had restrictive lung studies; six of six had abnormal nailfold capillaroscopy, and six of the ten developed classical scleroderma in 4 months to seven years of follow-up. Lung biopsies were obtained in six patients and all had changes of interstitial pneumonitis and pulmonary fibrosis (Ref 68). Meliconi, Facchini and their coworkers (Ref 69) recently described 16 patients with "cryptogenic fibrosing alveolitis", a term coined by Dr. Ron Crystal at the NIH for Hamman-Rich disease (idiopathic pulmonary fibrosis), and found six of the 16 to have high levels of autoantibodies against topoisomerase II (a close enzyme relative of the 70 kd topoisomerase I, Scl-70, which reacts with 25-50% of the sera from DSSc patients, depending upon the patient's ethnic origin. An extensive survey of other autoantibodies in 41 different patients with cryptogenic fibrosing alveolitis found no other significant serological associations with this possible variant of SSc (Ref 70).

Gastrointestinal Disease in SSc - Role of Malabsorption

Gastrointestinal motility disturbances develop in 50% of SSc patients, usually later in the course of the illness. The initial area usually affected is the lower esophagus, but smooth muscle from stomach to anus is affected to a variable degree (Ref 71). As motility drops, compensatory increase in the release of motilin, the initiator of the peristaltic migrating motor complex, occurs, and serum levels of motilin rise well above normal levels. In spite of this, migrating motor

complexes in the small intestine decrease to near zero in involved SSc patients. The result is a massive bacterial overgrowth of the small bowel resulting in a variety of symptoms and nutritional deficiencies. In particular, the bacteria in the small intestine eat ingested carbohydrates and, unique to bacterial metabolism, release hydrogen which is absorbed and can be detected in expired air within 15 minutes after a meal. This "Hydrogen Breath Test" provides an accurate means to quantitate bacterial overgrowth of the small intestine and to assess therapy designed to counteract it (Ref 72). Intermittant bloating, and pseudoobstruction/obstipation/constipation alternating with diarrhea often result from the motility disturbance and abnormal small intestinal bacterial overgrowth. The result is weight loss, nausea, malaise and inanition leading to death in some SSc patients.

A variety of attempts to stem this tide of events include elevation of the head of the bed, intermittant antibiotic administration, increased oral and parenteral vitamin administration, ingestion of short-chained fatty acids, and even intravenous hyperalimentation given over a long period in the home (Ref 73). Recently a study from the University of Michigan (Ref 72) evaluated five SSc patients who had been hospitalized for severe nutritional deprivation. Each had failed to respond to most of the treatments outlined above, and each had been shown to have evidence of small bowel bacterial overgrowth by the Hydrogen Breath test. After baseline evaluation of intestinal motility and serum motilin levels, each was fasted and Hydrogen Breath tests performed before and after a 50 g glucose challenge. Each patient was then given 50 ug of the long-acting somastatin analogue, octreotide, injected subcutaneously at bedtime for three weeks. The results were impressive. All patients had decreased bloating and constipation. By motility testing, they had return of previously totally absent small intestinal peristalsis, showed a sharp drop in serum motilin levels and had an 85% drop in bacterial overgrowth as assessed by the Hydrogen Breath test. An accompanying Editorial in the same issue of the New England Journal of Medicine (Ref 71) hailed the paper as, "hope for the treatment of intestinal scleroderma".

Other Treatment of DSSc, LSSc and Overlap Syndromes

We have already discussed the use of vasodilators in the treatment of Raynaud's phenomenon associated with SSc, and the dramatic benefit provided by ACE inhibitors when used in the early treatment of scleroderma kidney crises (Ref 2,3). Most investigators are unimpressed with any other long-term benefit of vasodilators on other aspects of scleroderma, including the general lack of efficacy for pulmonary hypertension (Ref 74). In contrast, the serotonin S_2-receptor antagonist, ketanserin, has been reported to benefit pulmonary hypertension in SSc (Ref 75).

D-Penicillamine, acting as a modifier of T-cell function, and perhaps in other ways, after more than 12 months of use in a dose of 750 mg/day, is said to decrease progression of skin and pulmonary changes in SSc (Ref 76,77). I am personally skeptical after having treated 13 patients with DSSc with 2.0 g of D-penicillamine/day for 6 months. The eight patients who could tolerate the drug for 6 months had no subjective or objective benefit (the latter assessed with DLco measurements at bimonthly intervals). For details, see Eric Hurd's excellent review of D-penicillamine actions and its use in scleroderma (Ref 2).

Immunosuppressive therapy in rapidly advancing DSSc has a rational basis because of documented increases in helper T-cells in involved tissues, elevated γ-globulin levels, elevated interleukin-2 receptors, elevated autoantibodies, and autoreactive lymphocytes in the blood which secrete lymphokines when exposed to autologous skin (Ref 2, 78). However, it is very difficult to do double-blinded or placebo-controlled studies of cyclophosphamide or similar immunosuppressive drugs because of the myriad of toxic side effects which they induce. Individual case

reports of remissions in DSSc induced by cyclophosphamide or chlorambucil exist, but a recent parallel, randomized, double-blind study of 65 SSc patients carried out over a three-year period with chlorambucil failed to show significant differences in disease-related parameters between the chlorambucil-treated and the placebo-treated groups (Ref 79). Nevertheless, most rheumatologists still resort to cyclophosphamide in a dose of 100-150 mg/day (given before noon with 8 glasses of water) to patients whose DLco drops below 50% of the predicted normal value, and in whom long-term prognosis is grim.

An interesting case report in 1990 of a substantial remission induced in a patient with SSc and digital ulcers requiring amputations, who experienced an acute myocardial infarction, and was treated with recombinant human tissue plasminogen activator (rt-PA) (Ref 80) warrants further evaluation of rt-PA treatment of other carefully selected patients with SSc.

Intimal Proliferation, Capillary Obliteration, and Fibrosis

The discussion of the pathogenesis of scleroderma will be limited to the DSSc variant where an array of findings, like pieces of a puzzle, have been accumulated, but have not yet been assembled into a meaningful picture. Let us review some of these. At any given time, the sera of 20-40% of patients with active DSSc will contain a cytotoxic factor for vascular endothelial cells and fibroblasts (Ref. 81,82). This factor is a protein (destroyed by proteases), has a molecular weight similar to human serum albumin (65,000 kd), and is not altered by lipid extraction (does not appear to be bacterial lipopolysaccharide). It causes cell death to cultures of human endothelial cells and foreskin fibroblasts, and inhibits the uptake of H-thymidine into dividing endothelial cells and fibroblasts (Ref 82). It may be some type of cytokine released in response to some other toxin, but it provides a means of altering endothelial cells to set in motion the type of abnormal vascular spasm discussed earlier.

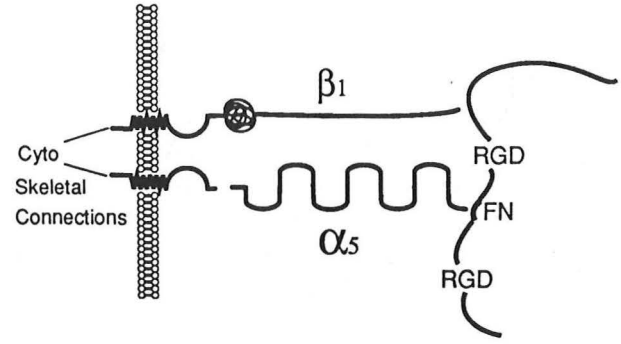
Bacterial lipopolysaccharide causes monocytes and macrophages to become activated and to release tumor necrosis factor-alpha which has the ability to modify endothelial cells to express a receptor for leukocytes (PMNs, monocytes, eosinophils, platelets) (Ref 83). Activated monocytes and macrophages also produce interleukin-1, tissue growth factor-beta, (TGF-b) and platelet derived growth factor (PDGF) (Ref 84) which can stimulate collagen, fibronectin and glycosaminoglycan synthesis by fibroblasts. The complex interactions of these cytokines in causing endothelial and fibroblast changes which are occurring in SSc has been reviewed recently by LeRoy (Ref 84).

Skin fibroblasts (Ref 85,86) and vascular endothelial cells from patients with recent onset of SSc express intracellular adhesion molecule-1 (ICAM-1) or endothelial leukocyte adhesion molecule-1 (ELAM-1) as well as beta-1 and beta-2 integrins (Ref 86). The expression of ICAM-1, ELAM-1 and beta-1 and beta-2 integrins are believed to reflect the activation described above which leads to the fibrosis characteristic of scleroderma.

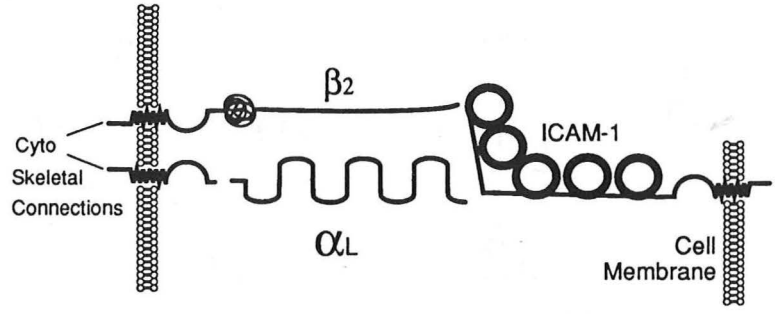
To help follow this relatively new field, I would like to briefly review what we now know about integrins and better pinpoint their important role in the pathogenesis of scleroderma. Integrins are a family of cell surface proteins that mediate cell adhesion, providing anchorage to basement membranes or connective tissue matrix. They also signal cell to cell adhesion allowing certain lymphocytes to end up in Peyer's patches in the intestine, for example. They also allow the homing of monocytes and granulocytes to areas of injury by allowing the local endothelial cells overlying the injury to express a signal molecule to which leukocytes can attach (ELAM-1). Each integrin is made up of an alpha and a beta chain which are non-covalently associated on the cell surface. This relationship is diagrammed in Figure 4 adapted from Rouslahti (Ref 87) shown on the next page.

Fig 4. INTEGRIN STRUCTURE, INTERACTIONS AND BINDING MODES

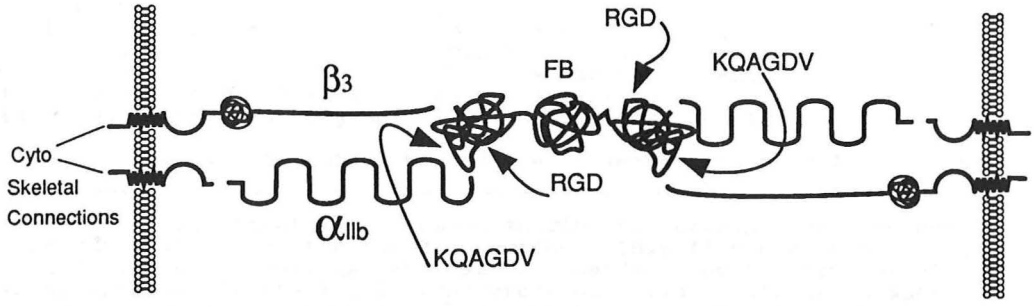
1.



2.



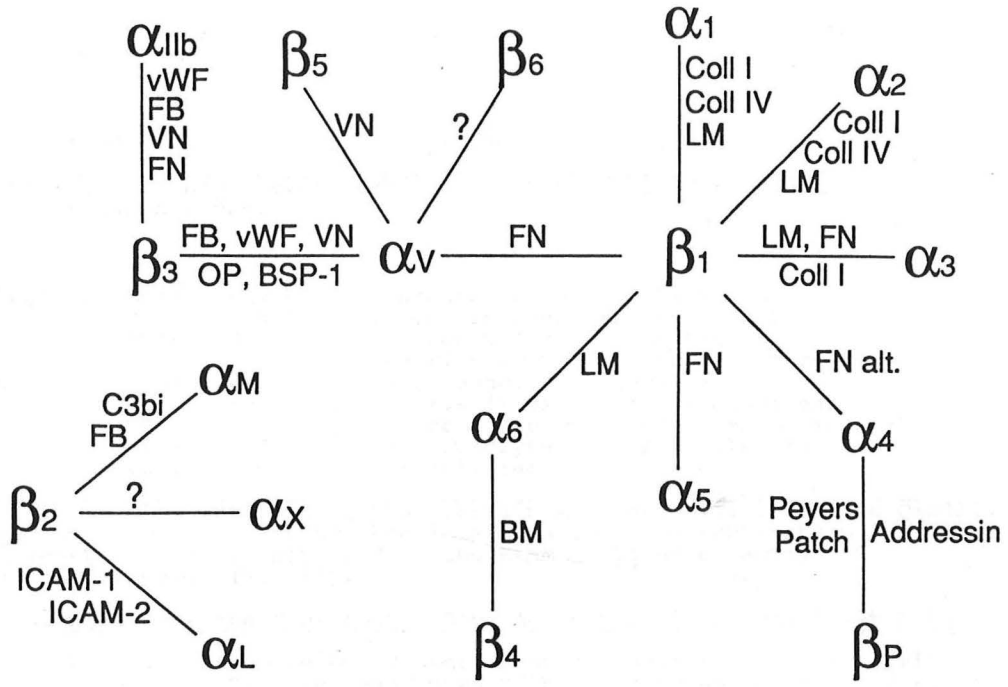
3.



RGD = Arg-Gly-Asp	FB = Fibrinogen
KQAGDV = FB peptide	FN = Fibronectin

Modified fron Ruoslahti, J. Clin. Invest. 1991

FAMILIES OF INTEGRINS AND THEIR LIGANDS



Abbreviations

vWF= von Willebrand's Factor
VN = Vibronectin
FN = Fibronectin
LM = Laminin
OP = Osteopontin
BSP-1 = Bone sialoprotein-1
C3bi = inactivated C3 fragment
ICAM-1 = Intracellular adhesion molecule-1
ICAM-2 = Intracellular adhesion molecule-2
Coll I = Collagen type I
Coll IV= Collagen type IV
BM = Basement membrane
FN alt = Fibronectin, alternatively spliced domain

Figure 5. Families of integrins and their ligands (adapted from Ref 87).

Figure 5 illustrates the common sharing of certain alpha and beta chains composing 16 of the known integrins. This figure also shows their cytospecificity and cellular and matrix ligands. Those integrins of special interest in the T-cell/monocyte/endothelial cell/fibroblast interactions in scleroderma are then presented in Table 7 on the next page.

Table 7. INTEGRINS AND THEIR LIGANDS OF INTEREST IN SSc PATIENTS

Cell-Integrin	(Synonyms)	Cell-ligand	Matrix-ligand
Lymphocyte-$\alpha L/\beta 2$ Monocyte-$\alpha M/\beta 2$ Polys-$\alpha X/\beta 2$	(LFA-1, Mac-1, CD11 /CD18)	*ICAM-1-Endothelial C3bi	Fibrinogen
Fibroblasts(activated)			Laminin, Collagen
Lymphocytes-$\alpha 5/\beta 1$	(VLA)	CD3-T-lymphocytes	Fibronectin
Leukocytes-$\alpha 4/\beta 1$	(VLA-4)	VCAM-1-Endothelial	Fibronectin
Platelets-$\alpha IIb/\beta 3$	(gpIIb/IIIa)	*ELAM-1-Endothelial	vWill Factor

*Expression on endothelial cells induced by IL-1, TNF, and bacterial lipopolysaccharides.

Abbreviations

Integrins
LFA-1 = Leukocyte function associated antigen-1
Mac-1 = C3bi complement fragment receptor on PMNs
CD11a/CD18 = ICAM-1 receptor on leukocytes
VLA = very late appearing VCAM-1 receptor on T-cells

Ligands
ICAM-1 = Intercellular adhesion molecule-1
C3bi = Inactivated large fragment of C3-complement
VCAM-1 = Endothelial cell V-protein adhesion molecule-1
ELAM-1 = Endothelial-leukocyte adhesion molecule-1
vWill = von Willebrand's factor

It is also interesting that certain microorganisms, such as Candida albicans, mimic the the surface integrins found on neutrophils, allowing the yeast to selectively bind to the ELAM-1 ligand on activated endothelial cells (Ref 88).

Collagen Gene and Fibronectin Gene Activation in Recent Onset DSSc

Fibroblasts from recently excised skin biopsies of patients with recent onset of DSSc have been shown to have increased gene activation for type I, III, and VI collagen (Ref 89) and fibronectin (Ref 90). A similar activation is seen in healing wounds, keloids, and neurofibromas, but not in fibroblasts from normal skin. This would suggest an attempt at healing (? from the anoxic injury) rather than an intrinsic defect in fibroblast function in DSSc.

Role for Neutrophils and Eosinophils in SSc

Riches, and his coworkers in Denver have shown that the interleukin-8 gene is activated in alveolar macrophages in patients with pulmonary fibrosis (Ref 91). IL-8 is a cytokine which is a potent chemotactic factor for neutrophils, and probably plays an important role in attracting neutrophils into the alveolar space contributing to the fibrosing alveolitis of IPF.

Even though only 7% of patients with DSSc and LSSc show peripheral blood eosinophilia (defined as >400 eosinophils/cu mm) (Ref 92), you may recall that eosinophils make up 25% of the granulocytes present in BAL fluid from SSc patients (Ref 51), and the eosinophil cationic protein is elevated 4-fold in patients with SSc when compared to the levels in the blood of normal healthy control subjects (Ref 93). SSc skin biopsy specimens and BAL fluid also contain significantly higher levels of eosinophil basic protein suggesting that eosinophils play a substantial role in the inflammatory process in scleroderma (Ref 93).

Genetic and Viral Factors in SSc

One rarely encounters scleroderma in two members of the same family. Maricq in her discussion of Ref 4 noted that only 4 reports of siblings both having scleroderma existed in the entire world literature in 1989! In over 30 years of practice, I have encountered only one such family. I interpret this to mean that there is essentially no genetic susceptibility factors of consequence in DSSc or LSSc, although expression of certain autoantibodies which are markers of various subsets of patients may be genetically linked. For example, there is an association of polar amino acids at position 26 of the HLA-DQB1 first domain with the anti-centromere antibody response in LSSc patients (Ref 94), and we have previously noted the association in English patients of HLA-DR3 and lung involvement (Ref 50).

Scleroderma may turn on non-specific B-lymphocyte activation leading to expression of viral antibodies not usually found in the general population. For example, antibodies to retroviral gag proteins such as anti-p24 gag of HIV-1 were detected in 26% of 58 patients with DSSc, in 7% of 57 patients with LSSc, and in only 0.7% of 135 control subjects (Ref 95). Alternative explanations for non-specific B-lymphocyte activation would be a cross-reactivity with one of the autoantibodies being produced in these diseases although the investigators could show no such correlation in the patients studied with anti-Scl-70 or anti-centromere antibodies (Ref 95).

Eosinophilic Fasciitis/Eosinophilia Myalgia Syndrome

Case IV : In 1974, I saw a 45WM accountant who had developed unwanted adipose tissue around his waist and atrophy of biceps and quadriceps compared to his prior status when younger. He installed a home spa, complete with a full range of exercise equipment, and proceeded to exercise 6-7 hours/day. After a relatively short time, he was dismayed to observe marked tightening of the skin of both arms with a peculiar sort of brawny edema which allowed the arm veins to be recessed slightly below the surface. The swelling did not extend to the top of his hands or fingers, and no Raynaud's phenomenon was present. His internist obtained numerous laboratory tests. All were normal except the CBC which showed WBC=14,000, 50% eosinophils. At UTSWMC-Dallas various other tests, including DLco were obtained, again all normal, but the eosinophilia persisted. The swelling also involved both lower legs, but to a much lesser degree than his arms. I diagnosed early acute scleroderma, and advised conservative (no medicine) treatment. However, he insisted that something had to be done, and elected to seek a second opinion. He went to Johns Hopkins Hospital where he consulted Dr. Lawrence Schulman, who, by the way, had just seen 4 other exercise enthusiasts with the same presentation. Thus was born : "Schulman's Disease", or eosinophilic fasciitis. The American Journal of Medicine article cited the LMD in Dallas who referred Patient 5, and who had misdiagnosed him as scleroderma.

I am sure that most of you are now familiar with the association of L-tryptophan with the eosinophilia-myalgia syndrome first reported from New Mexico in 1989. What none of us realized until about three years ago was that these two conditions may share a common etiology (and are probably the same disease expressed in different hosts). That common etiology is probably L-tryptophan in most patients (Ref 96-99). Retrospective questionaires to previous eosinophilic fasciitis patients, including one of my own, shows what a poor historian we all are. "Yes", they were taking "protein supplements" as part of their muscle building program and had bought them at the same health spa that sold or rented exercise equipment, and "yes" the protein supplement contained extra large amounts of added L-tryptophan, known to be an "essential" amino acid.

Dr. Sharad Lakhanpal (now practicing here in Dallas) along with his

Mayo Clinic colleagues, wrote an excellent review of eosinophilic fasciitis (Ref 96). He followed 52 patients and studied the clinical features, genetics, serology, and response to steroids (25 of 34 patients had a partial to complete response to 40-60 mg of prednisone/day, and nine patients had a poor response and were treated with hydroxychloroquin, colchicine or D-penicillamine with equivocal results. Time alone may contribute to the recovery of most patients. The finding of 20-fold increases above the normal range of plasma histamine levels in patients with eosinophilic fasciitis (Ref 100) led to clinical trials of cimetidine, an H2-histamine receptor antagonist. This has provided lasting benefit in a majority of patients and may be a way of avoiding side-effects of long-term steroid use (Ref 101).

Two other aspects of these unusual scleroderma-like conditions should be mentioned. Nerve entrapment (both ulnar and median nerve) may be fairly common and account for much of the discomfort experienced by some patients (Ref 102), and magnetic resonance imaging of the involved areas may be a good way to avoid a biopsy since there is thickening of the fascia and an increased signal density in the superficial muscle fibers correlating with inflammation (Ref 103). Winkleman and his colleagues at the Mayo Clinic (Ref 104) have recently seen five patients with biopsy findings characteristic of scleroderma who were taking L-tryptophan. Their scleroderma-like illness cleared when L-tryptophan was stopped and steroid therapy was administered. The reaction to L-tryptophan, or more likely, to an oxidized contaminant, is reminiscent of the response to aniline-adulterated rapeseed oil (heated to get rid of the aniline, thus causing toxic oxidation products) which produced hundreds of cases of scleroderma-like disease in Madrid (Ref 3).

Scleroderma-like Disease in Patients with Silicone Breast Implants

The recent extensive publicity in the media following the suspension, then sharp restriction by the Food and Drug Administration of the use of silicone breast implants has focused attention on a little known literature reaching back to 1964. At that time, Japanese plastic surgeons observed disastrous results from direct injection of liquid silicone into subcutaneous sites around the breast for cosmetic augmentation of breast size. When 36 patients, in whom well-documented illnesses had occurred following the procedure, were reviewed in 1984 (Ref 105), about one-third had developed scleroderma-like illness. Many of the other patients, who had developed much more common diseases such as rheumatoid arthritis, were considered to represent mere coincidental events, but scleroderma was so relatively rare that its frequency far exceeded the expected incidence in Japanese patients. Meanwhile, American plastic surgeons were busily implanting the presumably inert silicone rubber bags filled with the same liquid silicone gel on the assumption that rupture or leakage would be unlikely to occur. Hundreds of thousands of women had the implants, then increasingly frequent cases of scleroderma-like disease began to appear, raising the question of a delayed leakage with disemination of the liquid silicone to draining lymph nodes and elsewhere in the body. These reports are presented for your evaluation in Ref 105-114. They include several well-documented examples of scleroderma, and at least one patient (Ref 114) whose disease reversed after removal of her implants. None of the studies are controlled or prospective, and the small numbers reported suggest that this complication is infrequent and, possibly even completely coincidental. The present direction of the FDA, to mandate a prospective study of women implanted after mastectomy only, may be the most rational scientific approach to this difficult question. Meanwhile, it is recommended that excessive tenderness around an implant, lymphadenopathy in the axillae, and/or significant objective findings of scleroderma-like illness warrant (for medical legal purposes, if nothing else) removal of prior implants.

Future Directions for the Treatment of Scleroderma

Four interesting papers have appeared in the last two years which could have future impact on the treatment of DSSc. Vedder and his colleagues (Ref 115) studied the effect of injection of monoclonal anti-CD18 (the integrin on polymorphonuclear cells and monocytes which attaches to the induced ligand, ELAM-1, on the surface of vascular endothelium) in the rabbit-ear-reperfusion model. This blocked attachment of leukocytes to the anoxia-damaged endothelium, and prevented sloughing of the ear. The implications for the treatment of post-myocardial infarction patients after rt-PA therapy is more immediate than scleroderma, but post-vasospasm anoxic injury in scleroderma would also be a possible target for anti-CD18 monoclonal antibody, particularly if such an antibody could be designed to allow repeated, long-term use to avoid the risk of anaphylaxis.

Margulies, et al, (Ref 116) have studied the additive effect of ACE inhibitors and SQ 28,603 (an inhibitor of kidney neutral endopeptidase) which can enhance renal blood flow, and would be of potential value in treating scleroderma renal crises.

Vogelmeier, et al, (Ref 117) have studied a human recombinant neutrophil elastase inhibitor which can effectively be delivered without denaturation to the lung as an aerosol, and may be of great value in treating fibrosing alveolitis in interstitial pulmonary fibrosis in SSc.

And finally, Hoaglum, et al, (Ref 118) have found that high levels of d-alpha-tocopherol suppress collagen gene activation, providing a potential new tool to suppress fibrosis.

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