MEDICAL GRAND ROUNDS

Parkland Memorial Hospital
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J. Donald Smiley, M.D.

SCLERODERMA

"Scleroderma is one of the most terrible of all human ills. Like Tithonus to 'wither slowly,' and like him to be 'beaten down and marred and wasted' until one is literally a mummy, encased in an ever-shrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern."

Sir William Osler, 1898.

"Scleroderma is only the obvious and striking symptom of a generalized disease, and the most serious symptoms actually arise in the viscera. . . . Scleroderma is then only one of the symptoms or signs of progressive systemic sclerosis."

Goetz, 1945.

I. The Natural History of Scleroderma (Progressive Systemic Sclerosis)

Case #1: [redacted] This 57 CF [redacted] was admitted for her 7th and final [redacted] admission on [redacted]-63 after two episodes of sudden rt. ant. pleuritic pain each lasting about 3 days. She had been in excellent health until mid-1958 when mild DOE and occasional small hemoptyses began, and she noted her fingers to turn blue-grey without pain when she hung out wet clothes. Shortly afterward, persistent nausea and frequent regurgitation of food brought her to [redacted] ([redacted]-59) for evaluation. Admitted at that time, tightness of the skin of the fingers with telangectases on both palms, and spotty vitiligo of the skin of the face and neck without tightness were noted. Old hyperpigmented scars on the lower legs were assigned to healed varicose ulcers. B.P. 120/90, a loud P_2, a presystolic apical rumble and a normal left atrium by cardiac fluoroscopy were present. Barium swallow x-rays revealed a dilated esophagus with a contracted outlet into the stomach, and decreased motility of esophagus and stomach was noted on fluoroscopy. Biventricular cardiac enlargement was seen by x-ray, and cardiac catheterization showed markedly diminished cardiac output; pulmonary hypertension, 64/30, decreasing to 51/28 on 100% O_2; arterial O_2 saturation 94.1% on room air, 100% on 100% O_2. Pulmonary function studies showed TVC 54% of predicted with FEV 0.5 sec. of 52 to 71% of the total, and no alveolar-capillary block was detected. EKG: rt. ventricular hypertrophy and occasional PVC's. LE prep, latex fixation, SSCA, all negative; protein electrophoresis, diffuse hyper-gamma-globulinemia of 36%. ESR was 52 (Westergren).

In spite of a skin biopsy (neck) showing "degeneration of fibrocollageneous tissue without cellular infiltration with normal skin appendages, blood vessels and muscle. . . not consistent with the diagnosis of scleroderma," it was concluded that she had early scleroderma with visceral involvement. Her subsequent course over the next 4 years proved this diagnosis to be eminently correct. Insidious progression of tautness of the skin of the upper arms and face, development of typical Raynaud's phenomenon with small ulcerations of some of her fingertips, progressive pulmonary hypertension with cor pulmonale, increasing dysphagia, recurrent

varicose ulcers of her legs, and weight loss of 51 lbs. produced a slow downhill course.

Two series of injections with Versene (disodium ethylenediamine tetraacetate) failed to produce objective evidence of improvement although the patient felt subjectively better after the first course.

At the time of the last admission, thepatient showed no unusual distress, but died suddenly, presumably of a pulmonary embolus or cardiac arrhythmia, 3½ hours after admission. Autopsy permission was not granted.

Initial Symptoms of 271 Patients with Scleroderma (Farmer, et al)

Symptom	No.	Percent
Scleroderma of hands*	132	48.7
Raynaud's phenomenon	88	32.5
Scleroderma of extremities or face, but not of hands	19	7.0
Generalized stiffness of the joints	14	5.2
Scleroderma of trunk	7	2.6
Trophic changes of fingers (ulceration, fissuring, chronic paronychias)	5	1.8
Pigmentation	3	1.1
Dysphagia	2	0.7
Dyspnea	1	0.4

*Many patients described this as "swelling" of the hands.

Involvement and Complications at Time of Diagnosis of Scleroderma (Farmer, et al)

Involvement or Complication		Percent
Cutaneous:		
Hyperpigmentation		45.0
Trophic changes		39.9
Calcinosis cutis		10.0
Amputation of digit		1.5
Visceral:		
Esophagus		64.5
Lungs		21.0
Heart		8.9
Kidneys		1.5
Other Gastrointestinal	approx.	2.0
Miscellaneous:		
Periodontal membrane		36.0
Hypertension		3.7

Prognosis in Scleroderma (Follow-up of 705 patients)
(Tuffanelli and Winkelmann)

Group	No. of Pts.	% Alive
Diagnosis known 5 to 10 yrs.	491	56
Diagnosis known more than 10 yrs.	214	59

Causes of Death in 42 Patients with Scleroderma (Rodnan)

Cause of Death		
Renal involvement	21	(14)
Cardiac failure	9	(7)
Intestinal disease	2	(2)
Other (esophageal perforation and mediastinitis, aspiration pneumonia, myocardial infarction, miliary tuberculosis, pulmonary infarction)	5	(4)
Unknown (patients died out of hospital)	5	
Total	42	(27)

( ) Number of cases having postmortem examination.

Poor prognostic indicators in any given patient

1. Heart involvement
2. Renal involvement (elevated BUN or HBP)
3. Anemia
4. Elevated ESR (Westergren) of more than 50 mm/hr.

Ratio of females to males with the disease is approximately 3 to 1.
Only one patient in 40 with scleroderma is under the age of 20.
Peak age of onset is between age 40 and 50.
Complete remission of generalized scleroderma is very rare.

II. Differential Diagnosis of Scleroderma

Case #2: [redacted] (Pt. of Dr. Leonard Madison at [redacted] This 41 [redacted] was admitted [redacted]-49, 3 weeks after onset of pain in the ankles, knees, and fingers. No preceding febrile illness was recalled. Seven days after the onset, when arthralgias involved the low back, shoulders and wrists, the pt. was bedridden. Three days following this he became asymptomatic and remained symptom-free until 3 weeks after the onset of the initial joint symptoms when he noted that the skin over his neck was thickened and tight. Within a few days this process spread to his face, shoulders, chest, back and abdomen. There was no noticeable progression or regression of this edema after the initial spread and his general health was otherwise excellent. Bilateral parotid swelling was also observed simultaneously with the onset of the edema.

P.E. revealed a well developed, rather obese male with a puffy "moon face" and striking bilateral parotid enlargement. A hard, brawny, non-tender, non-pitting edema of the skin was noted in the areas mentioned. The hands and feet were free and the joints were normal. P.E. was otherwise normal.

Examination of the blood and urine revealed no morphologic or chemical abnormalities. The ESR varied from 26 to 8 mm/hr (Wintrobe). The Wasserman was negative. X-ray of the chest revealed a density outside the cardiac border that was more radiolucent than the remainder of the cardiac silhouette and extended from the diaphragm to the aortic arch. The exact nature of this density was not known, but it was interpreted as being an unusual fat pad. Skin biopsy disclosed the classic findings of scleredema adultorum except that the perivascular infiltration consisted of polys instead of round cells. Cresyl violet stain for the mucin-like substance in the cutis was negative. Later skin biopsy showed a transition of perivascular cell type to round cells.

Shortly after subcutaneous epinephrine treatments were begun, the patient began to show resolution of the edema, and within 3 weeks, the face and neck were edema free and there was diminution of edema of the chest wall. Several months later, follow-up showed persistence of some of the chest edema, but no recurrence otherwise.

Comparison of Scleroderma with Scleredema (From Madison)

	Scleroderma (edematous phase)	Scleredema
Clinical		
Preceding infection	Rare	Usual, with 1-6 week latent period before edema. Often streptococcal pharyngitis.
Prodromal period	Common: Arthralgias arthritis; Raynaud-like symptoms.	Unusual, occasional malaise, low grade fever.
Edema	Slow progressive involvement, often very white with waxy sheen.	Pale, but not dead white.
Sequelae	Atrophy, pigmentation, telangectasia hidebinding freq.	None
Course	Relentless, progressive systemic sclerosis.	Recovery in months to years (usually about 18 months).
Pathology		
Epidermis	Loss hair follicles, sweat glands, atrophy, pigmentation.	Uninvolved
Cutis	Edema, increase in collagen content, "homogenization" of collagen fiber (late).	Round cell perivascular infiltration. Collagen bundles separated by (?) mucopolysaccharide.
Blood vessels	Intimal thickening occasional thrombosis.	No endarteritis.
Muscles	Edema, loss of cross-striations early, atrophy, later.	Normal

Raynaud's Disease	-versus-	Raynaud's Phenomenon
1. Exacerbated by cold or emotion		1. Exacerbated by exposure to cold
2. Bilaterally symmetrical		2. May or may not be symmetrical
3. No gangrene or minimal atrophic fingertip changes		3. Gangrene may occur in about 2% of patients, ulceration in about 40%
4. Present at least 2 years		4. Etiology
5. Etiology unknown and no associated primary disease present		A. Traumatic: Occupational or after nerve injury
6. Reported to have elevated peripheral venous blood concentrations of epinephrine and norepinephrine, 10 of 11 pts. (Peacock, 1959)		B. Other neurogenic: Cervical rib, diencephalic or psychomotor seizures
(Modified from a Saturday morning resident's conference given by Dr. Charles Jarrett)		C. Occlusive arterial diseases: Arteriosclerosis, Berger's, arterial embolism
		D. Poisons: Heavy metals, ergot
		E. Abnormalities of blood or serum: Cryoglobulins, macroglobulins, multiple myeloma, cold agglutinins in high titer, sickle cell C disease, polycythemia or leukemia (advanced)
		F. Rheumatic diseases: Scleroderma, SLE, dermatomyositis, rheumatoid arthritis

Other Conditions which Present Features of Generalized Scleroderma

A. Dermatomyositis vs. edematous phase of scleroderma
Usually shows muscle weakness of shoulder girdle muscles and more erythematous rash than scleroderma. SGOT is usually elevated. Rarely the two conditions are indistinguishable. Calcinosis of skin and subcutaneous tissues occasionally is a late feature of both. Leukocytosis and fever are often present in the acute phase of dermatomyositis.

B. Localized fibrosing conditions of unknown relationship to generalized scleroderma
Sclerodactyly of Raynaud's disease or phenomenon
Linear scleroderma (morphea)
Dupuytren's contracture
Peyronie's disease
Reidel's struma
Sclerosing mediastinitis
Idiopathic retroperitoneal fibrosis (Ormand's syndrome)
Ainhum

III. Pathological Changes in Scleroderma (Skin changes during the stage of early edema already reviewed under Scleredema vs. Scleroderma, p. 5)

Post-Mortem Studies or Organ Involvement, 31 patients (Piper and Helwig)

Skin	100%
Heart and Lungs	90
Kidneys	74
G.I. tract	64

Visceral changes in 27 cases of circumscribed scleroderma (morphea)--None.

General Pathological Changes of Involved Organs in Scleroderma

1. Primarily a general thickening and increase of normal collagen bundles in involved organs without much cellular infiltrate. No demonstrated mucopolysaccharide or enzyme defects detected by histochemical or other techniques thus far.
2. No localization of gamma globulin in involved tissues by fluorescent staining techniques. or other
3. Late atrophy of associated glandular/structures in involved organs (such as sweat glands and hair follicles of skin, smooth muscle cells of G.I. tract).
4. Occasional calcification of involved structures.
5. "Mucoid" and fibrinoid infiltration with thickening and cellular proliferation of intima of proximal interlobular arteries of kidney sometimes producing ischemic atrophy of renal cortex late in the disease. Occasionally, distal interlobular arteries and afferent arterioles show dissection-like fibrinoid changes between the thickened intima and the internal elastic membrane (unique for scleroderma), or more commonly, smudging of the afferent arteriole by fibrinoid change similar to that seen in malignant nephrosclerosis.

IV. Therapeutic Measures of Value in Scleroderma

A. Physical Therapy most useful measure presently available.
B. Avoidance of exposure to cold.
C. Lubriderm and toilet lanolin to dry skin areas.
D. Sympathectomy for excessively symptomatic Raynaud's phenomenon.
E. Use of antacids and elevation of head of bed in patients with esophageal involvement.
F. Use of aspirin, steroids, Relaxin, Potaba, Endrate all of doubtful value.

V. Speculation on the Mechanism of Pathogenesis of Scleroderma

Case #3: [redacted] [redacted] This 18 CM [redacted] was admitted [redacted]-63 complaining of cough productive of occasional flecks of blood with marked x-ray changes "compatible with sarcoidosis, disseminated Tbc and/or scleroderma of the lung." Past history included pertussis age 6 mo., several episodes of pneumonia as a child, and an extensive burn of the left lower leg at age 5 when his clothing caught fire. This burn required multiple grafting because of infection and sloughs. Excessive granulation led his physicians to x-irradiate (2400 R) the lower leg which produced radiation ulcers requiring excision to promote healing only complete 3 years later.

At age 14 he began to notice easy fatigability and a tightening of the skin of the left leg and right arm with loss of range of motion of the right elbow. No changes in the skin of his hands or Raynaud's symptoms were observed at that time. Age 15, after injury of his left ankle, he developed a large ulcer over the old burn site which required hospitalization on [redacted]-58 for grafting.

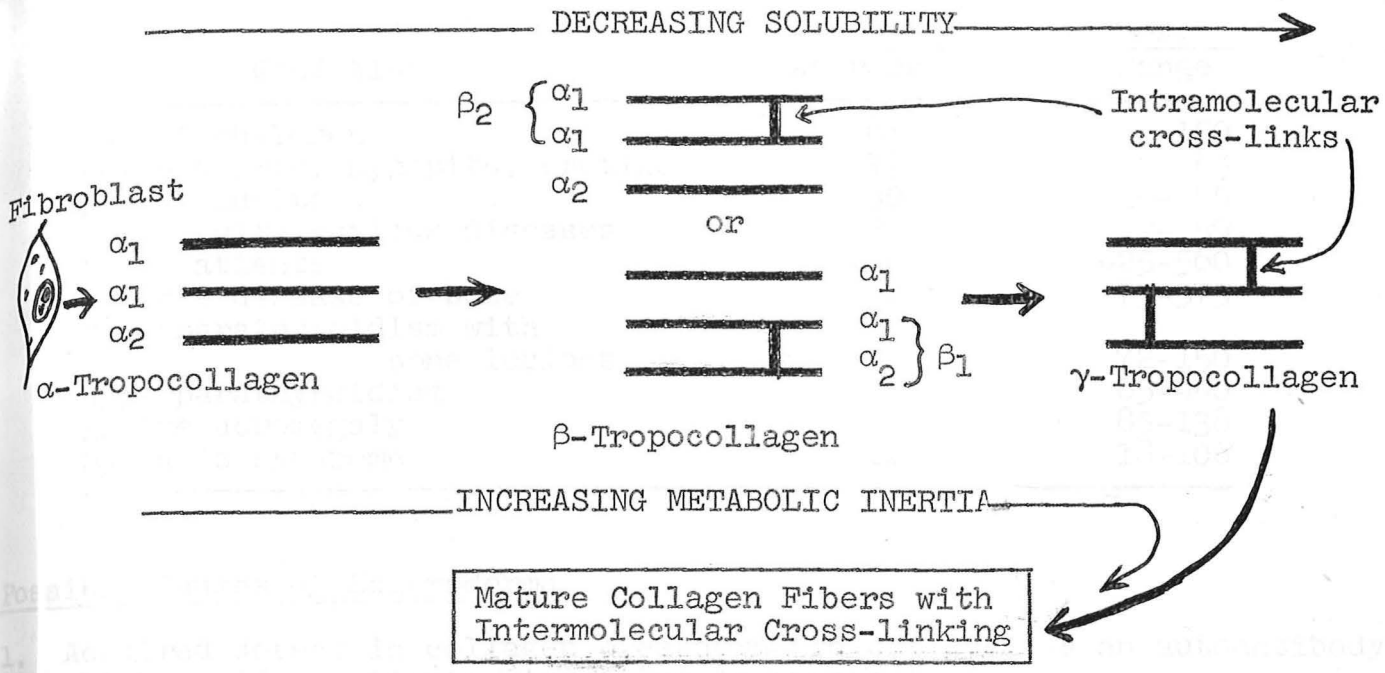
The ankylosis of the right elbow, inability to completely close either hand because of tightness of the skin of the fingers, ? trophic changes of fingertips, small depigmented areas over PIP's, tight facial skin and an immobile facial expression were compatible with scleroderma. Skin biopsy of the hand showed "marked thickening and condensation of collagen fibers in the underlying dermis with normal blood vessels. . . not incompatible with early scleroderma."

Other findings: BP 120/80, normal heart and esophagus x-rays, normal EKG, BUN 18, Hgb 10.9, WBC 17,500, 51% lymphs, cryoglobulin, L.E. prep negative, TVC 50% of predicted, FEV 0.5 sec 90% of total, chest x-ray "heavy markings bilaterally tending toward confluence centrally especially in the region of the apices of the lower lobes suggesting a process, at once diffuse and localized, consistent in appearance with an acute infiltrate in the course of a collagen disease." (Bonte)

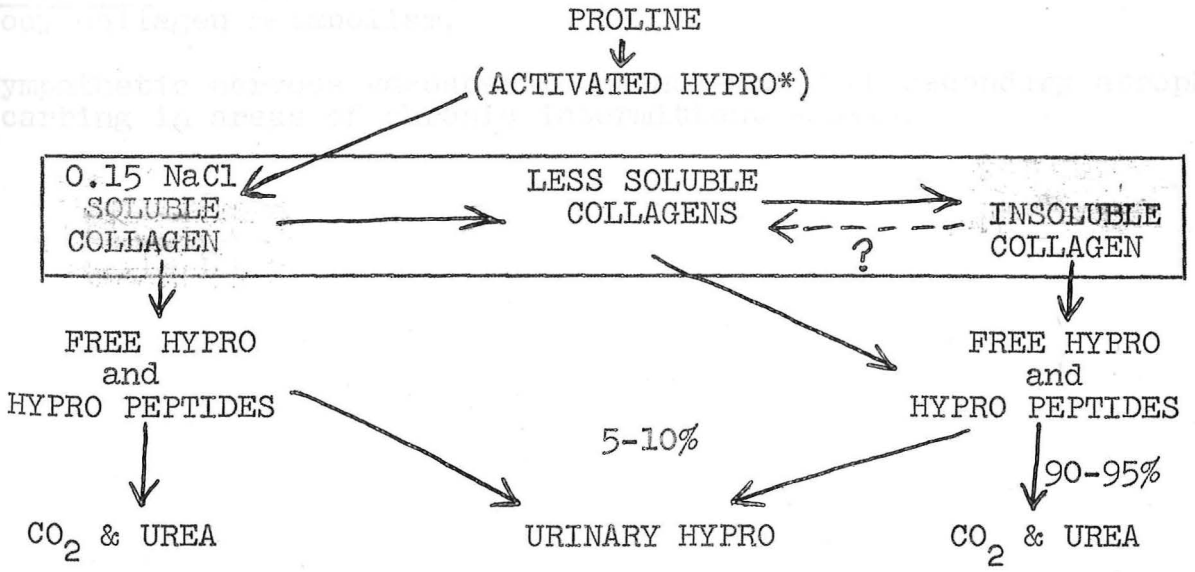
During the next 2 years he gained weight to 102 lbs., but experienced occasional chest pain and dyspnea, and observed continued tightening of the skin of his hands, forearms, face and legs. On [redacted]-60, the distal phalanx of the left 4th digit became gangrenous requiring amputation. Two courses of intravenous disodium versenate (Endrate) produced no objective changes in his disease.

The diffuse fluffy lung infiltrate of the admission of [redacted]-62 seems best explained by a bout of acute sarcoidosis. A scalene node at that time revealed non-caseating granuloma, and resolution was progressive and nearly complete in x-rays taken a few months later. On [redacted]63, EKG showed increased rt. ventricular hypertrophy and anterolateral ischemia, the esophagus was now dilated and immobile by barium swallow fluoroscopy, antinuclear was positive 1/4 dilution, Latex fixation negative, and BUN was 9. At the time of his last clinic visit [redacted]-63, he was planning to visit an uncle in Utah, and has not returned for further follow-up.

Crosslinking in Collagen Formation



Relationship of Urinary Hydroxyproline* Excretion to Overall Collagen Metabolism



Urinary Hydroxyproline in Normal Individuals and in Various Disease States

Condition	Mg. HOP/24 hrs. Average	Range
Normal children	65	15-150
Child dwarfs, hypopits. cretins	17	5- 48
Normal adults	30	15- 55
Adults with various diseases	35	19- 59
Burn patients	470	425-560
Paget's disease of bone	150	75-575
Hyperparathyroidism with bone lesions	90	72-150
Hyperparathyroidism	150	65-440
Active acromegaly	115	85-138
Marfan's syndrome	62	18-106

Possible Causes of Scleroderma

1. Acquired defect in collagen breakdown process such as an autoantibody which could inactivate tissue "collagenases."

2. Loss of hormonal stimulus for collagen turnover, either from decreased hormone or receptor cell deficit.

3. Localized stimulus to new collagen deposition not reflected in overall body collagen metabolism.

4. Sympathetic nervous vasospastic phenomenon with secondary atrophy and scarring in areas of chronic intermittent anoxia.

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