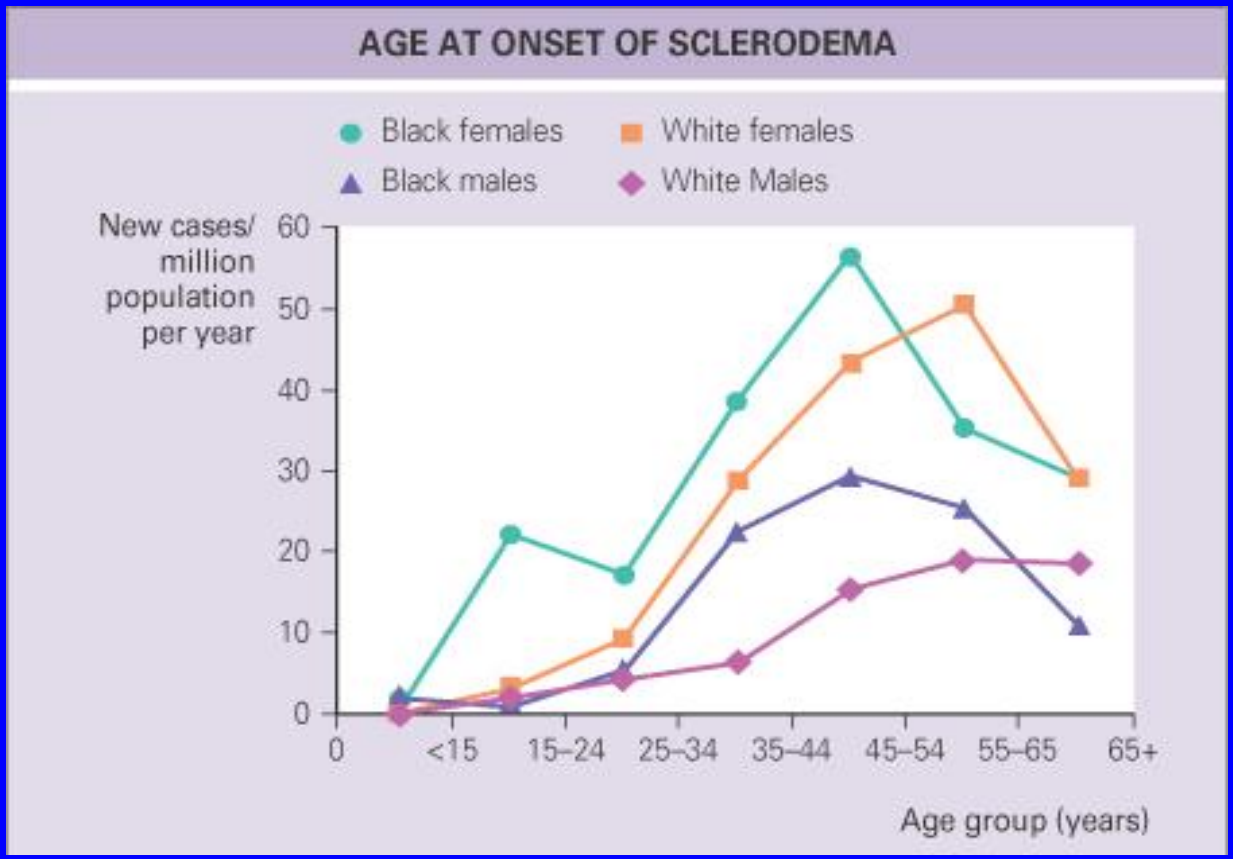
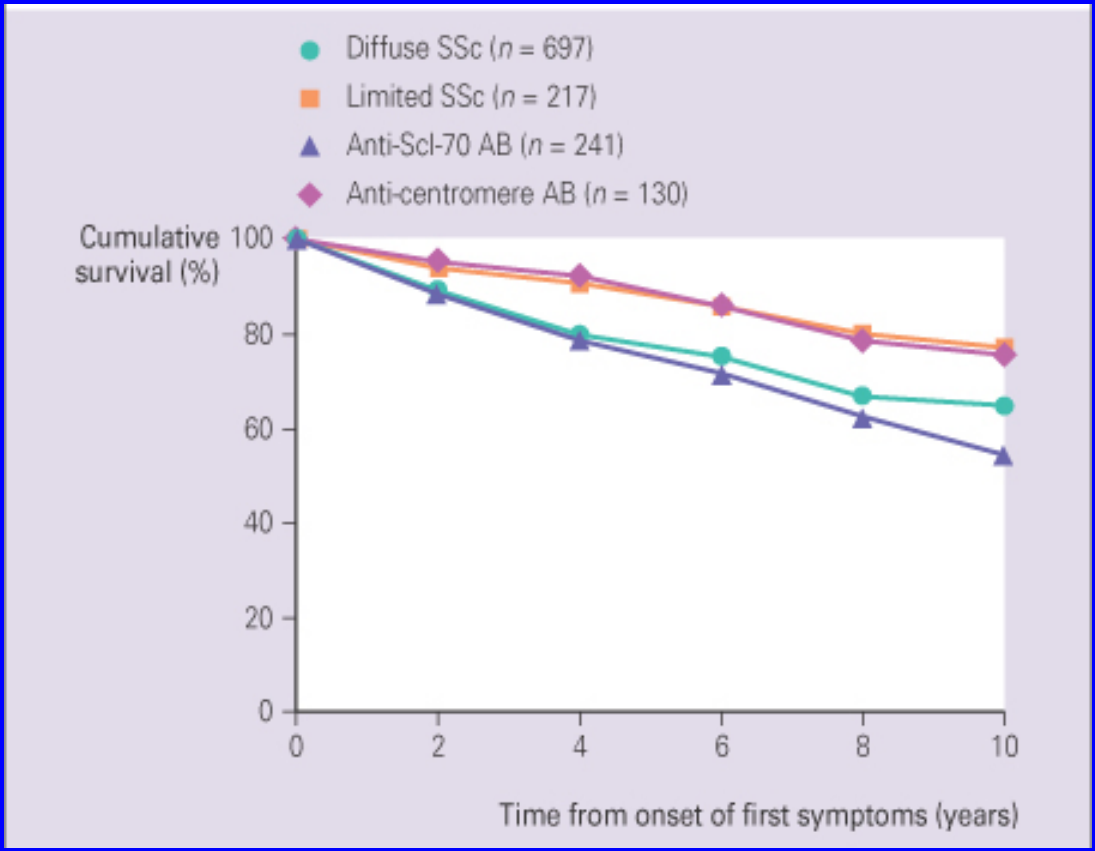
Systemic Sclerosis-Epidemiology

- Rare
- 20 new cases per million per year
- Peak occurrence: 35-65 years of age
- 7:1 female to male ratio
- Occasional family history
- Ethnic background influences survival and disease manifestations

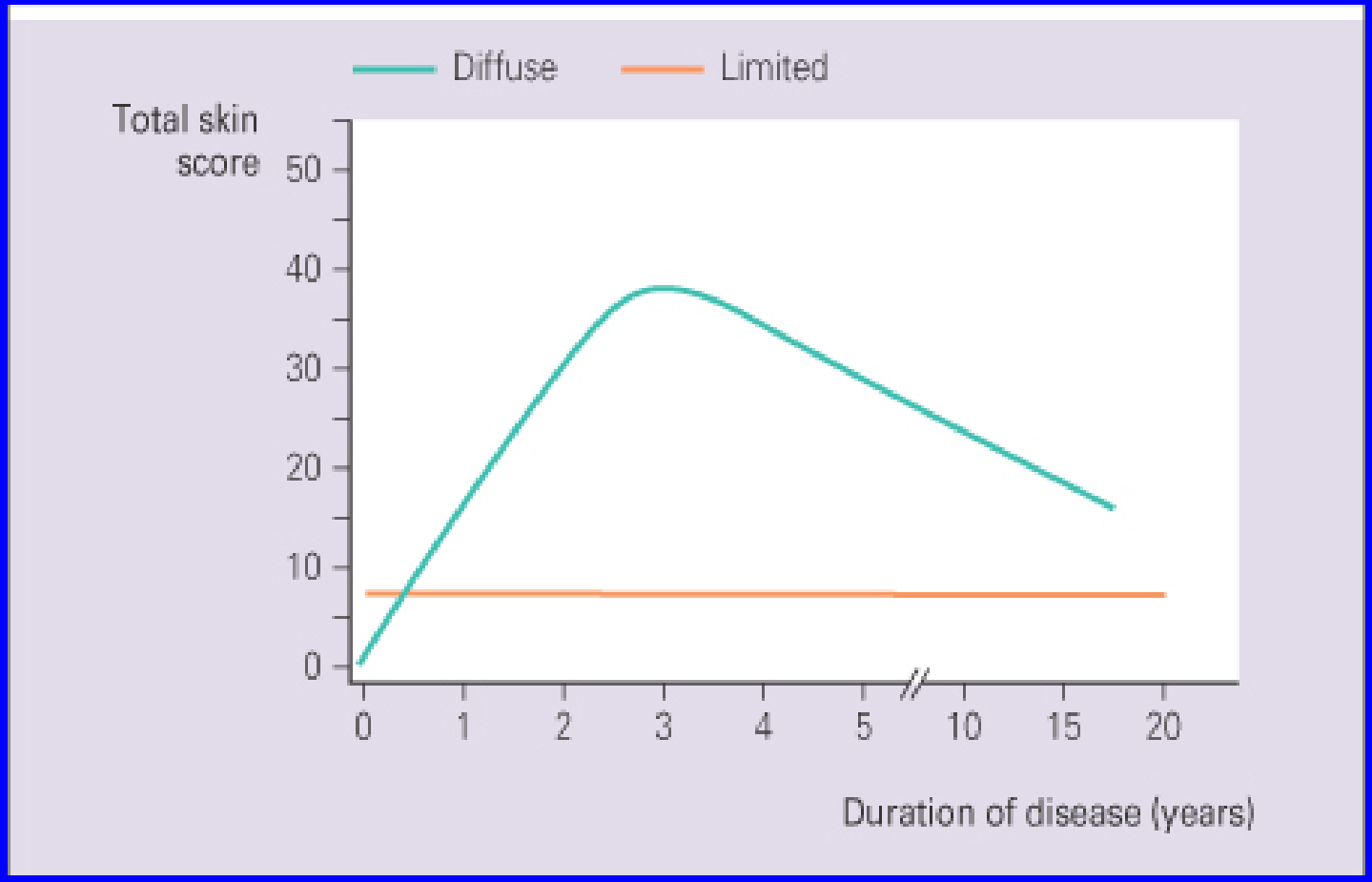
Age Onset of Scleroderma



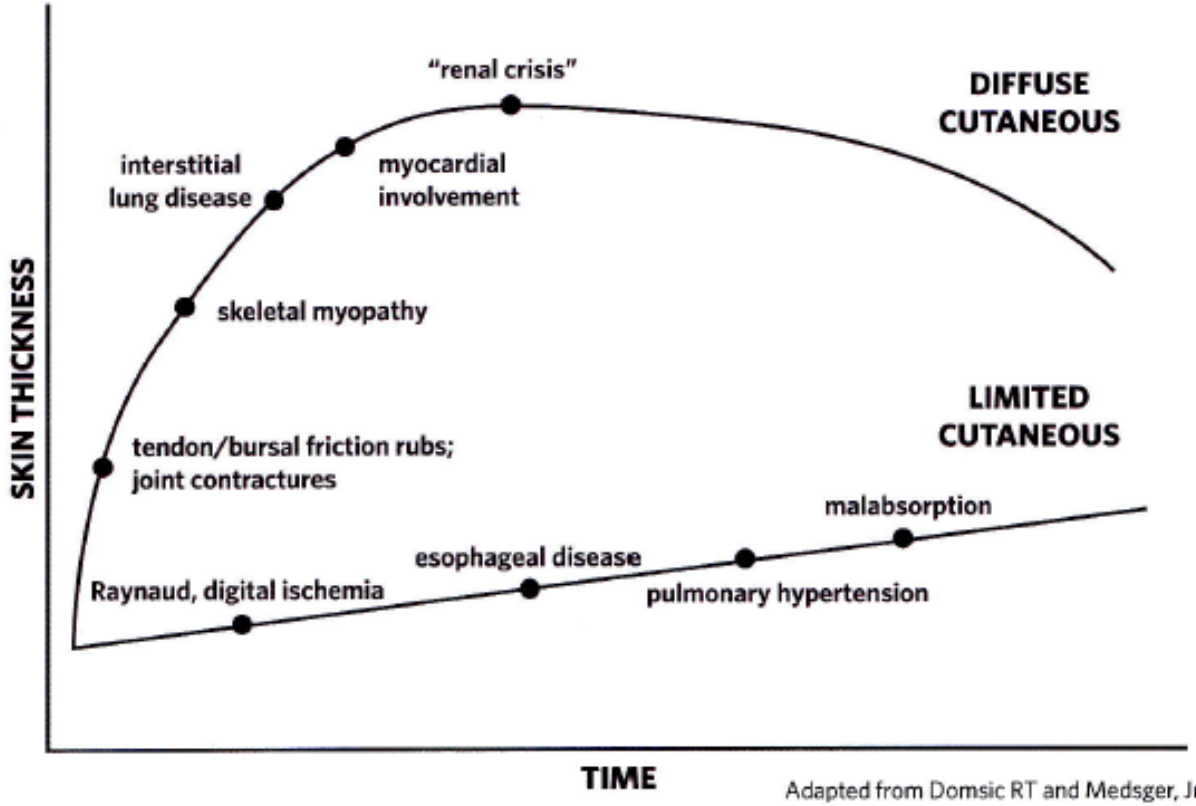
Survival Rates of Scleroderma



Natural History of Scleroderma Skin Involvement



Organ Components of Diffuse and Limited Scleroderma



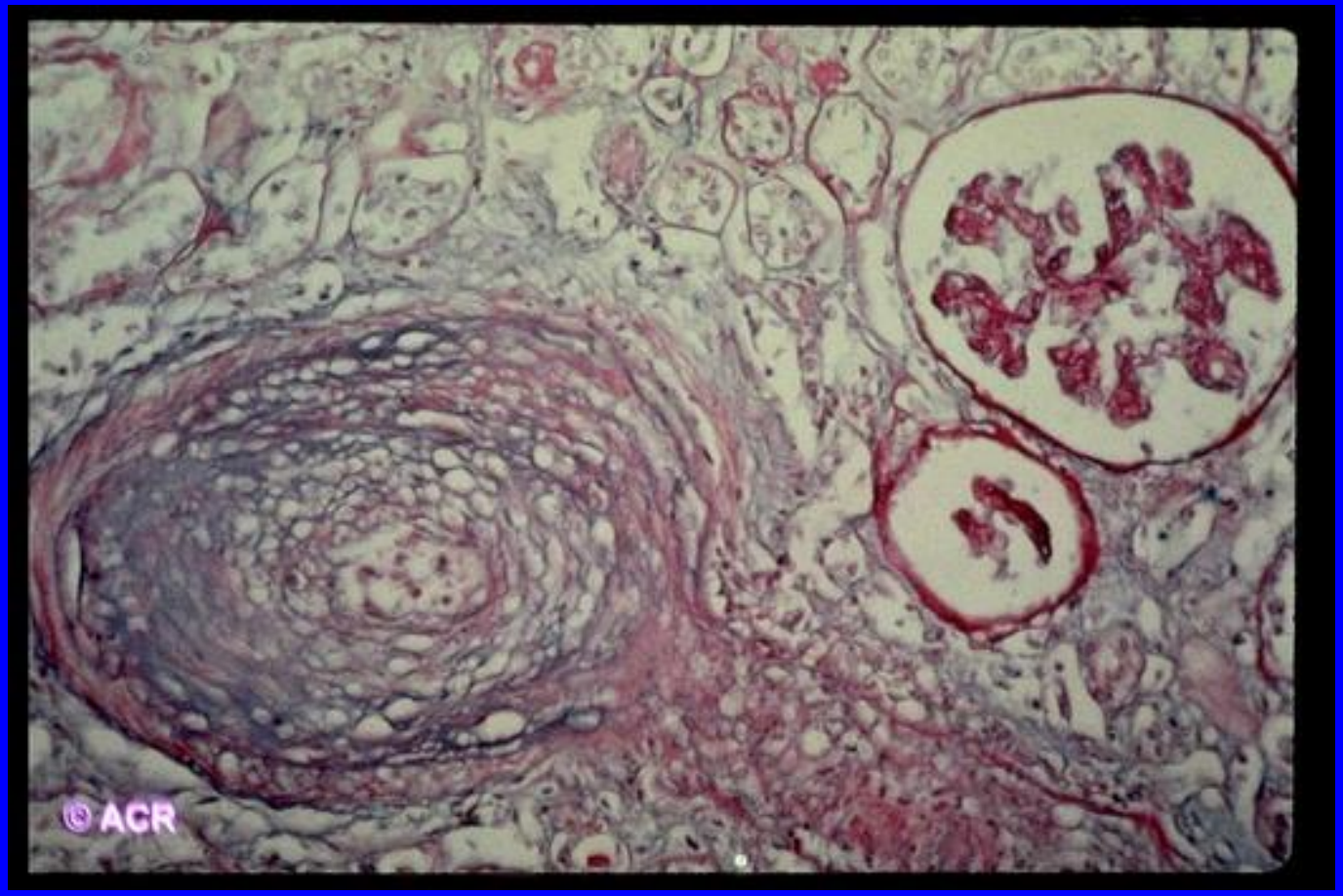
Adapted from Domsic RT and Medsger, Jr, TA. Chapter 6: Disease Subsets in Clinical Practice. Scleroderma: From Pathogenesis to Comprehensive Management. London: Springer Science and Business Media, LLC; 2012.

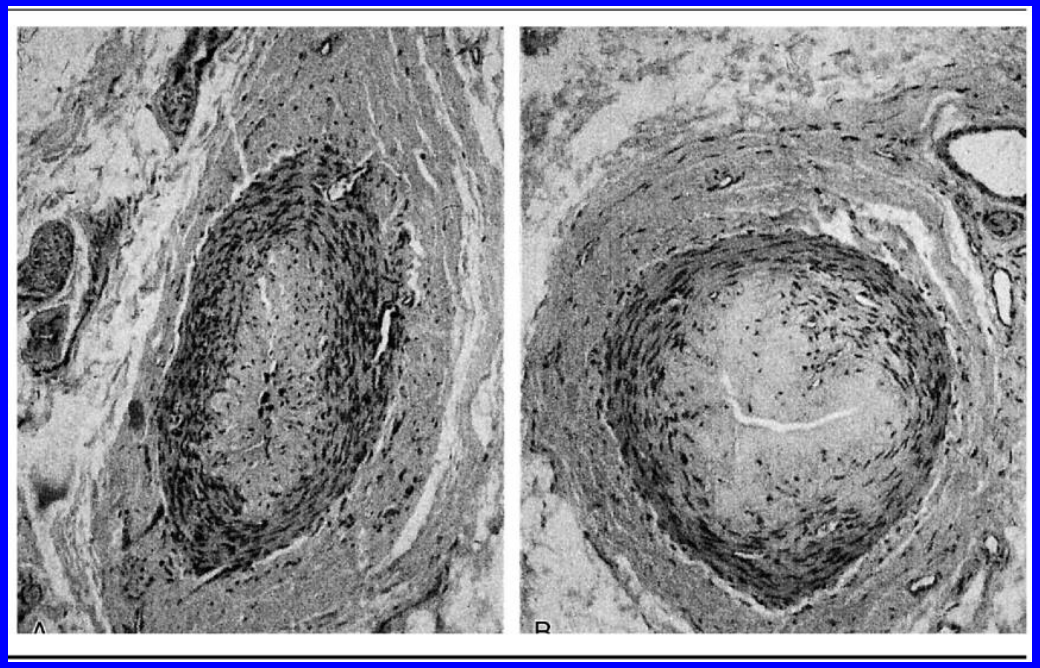
Systemic Sclerosis- Pathology

- Wide spread small vessel vasculopathy
  - small arteries
  - capillaries
  - venules

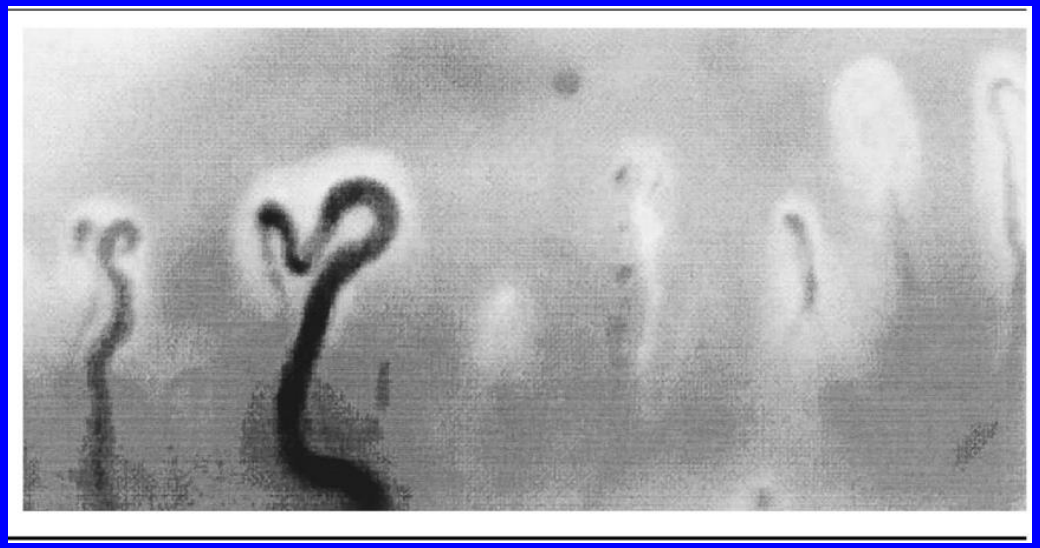
  Ischemia
- Fibrosis
  - skin
  - lungs
  - gastrointestinal tract

Vasculopathy - Kidney

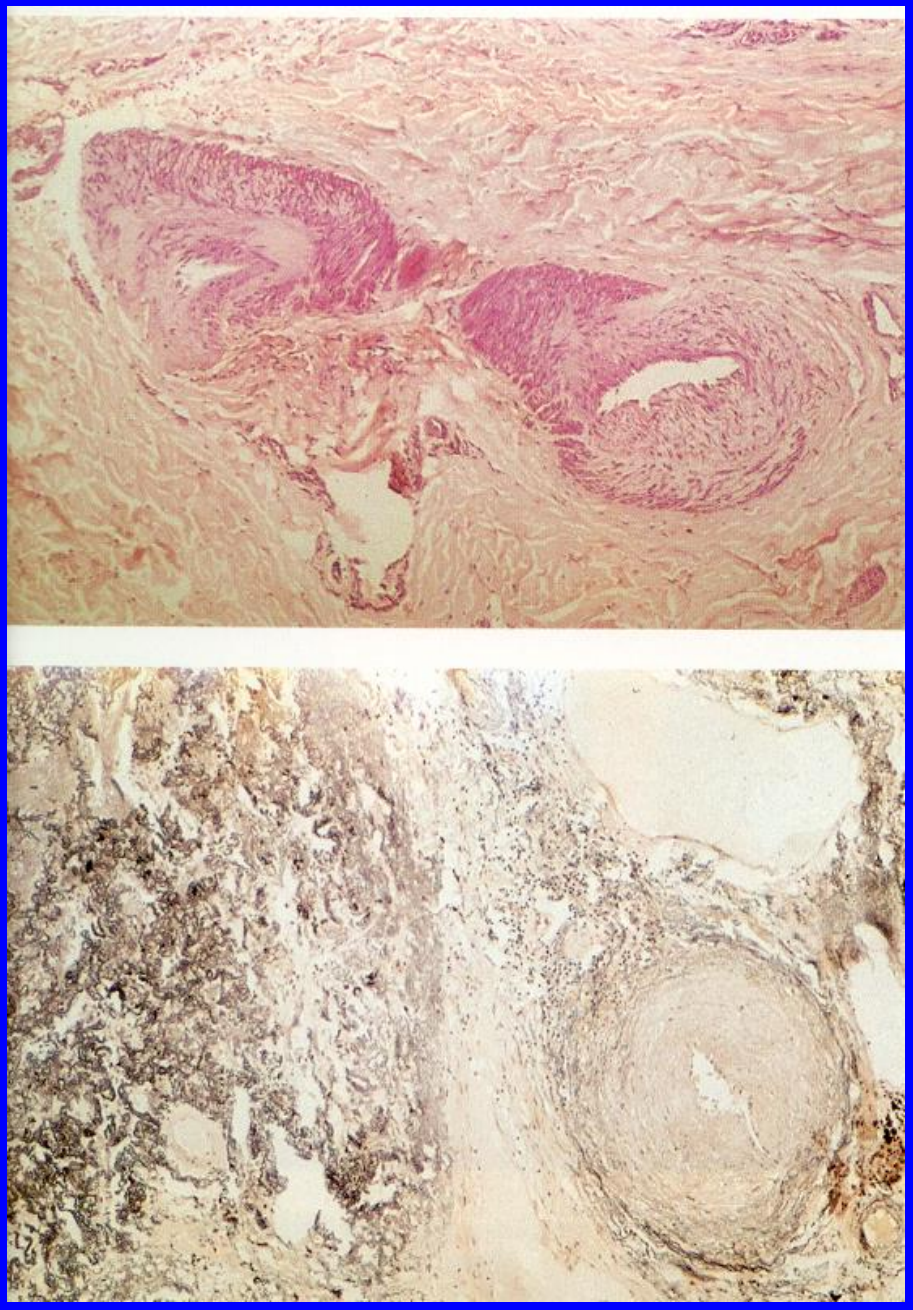




Digital Arteries

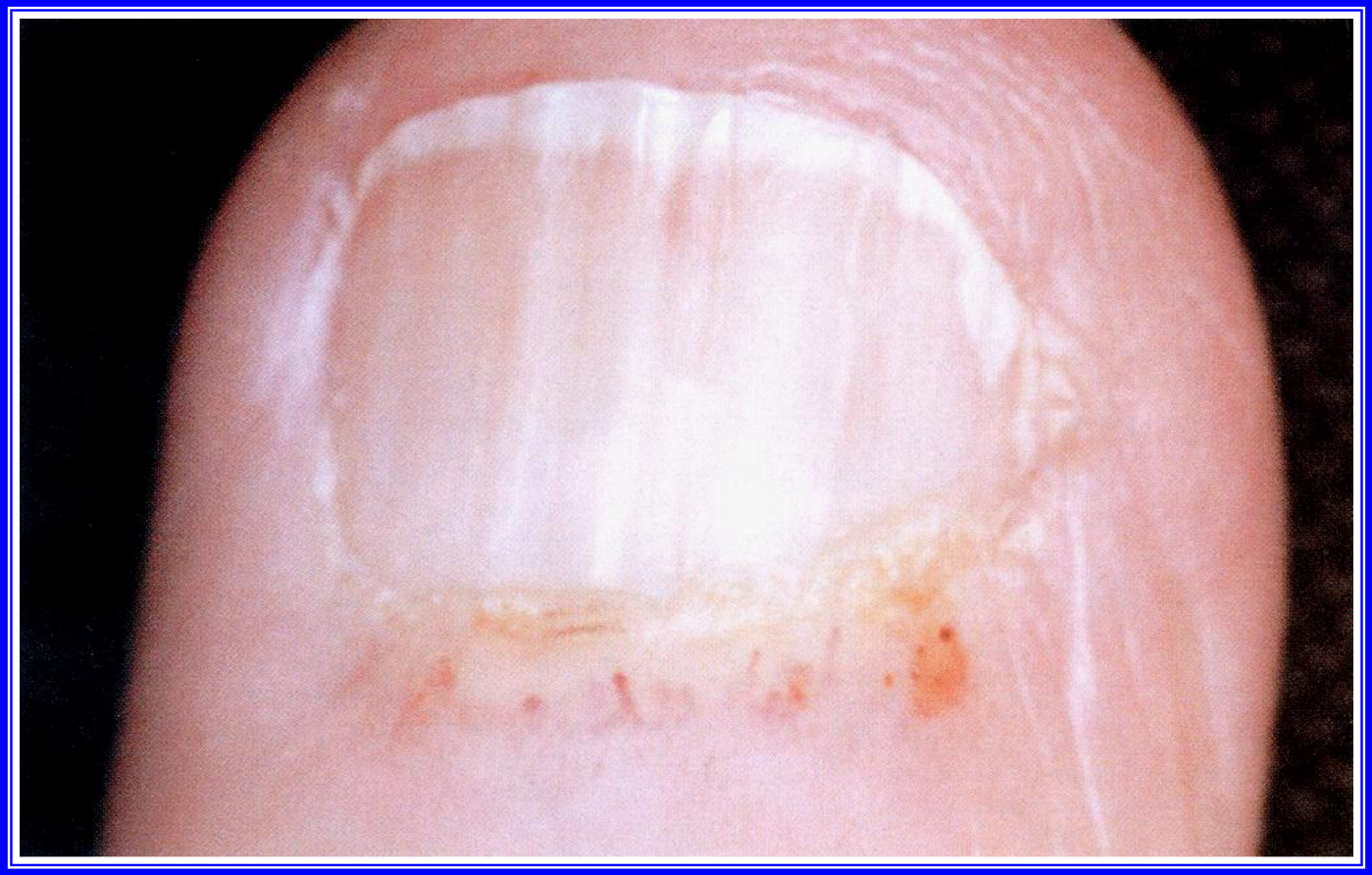


Nailfold Capillary Loops



Vasculopathy in Skin and Lung

Para-Ungual Fold Capillaries



Paraungual Fold Capillaroscopy

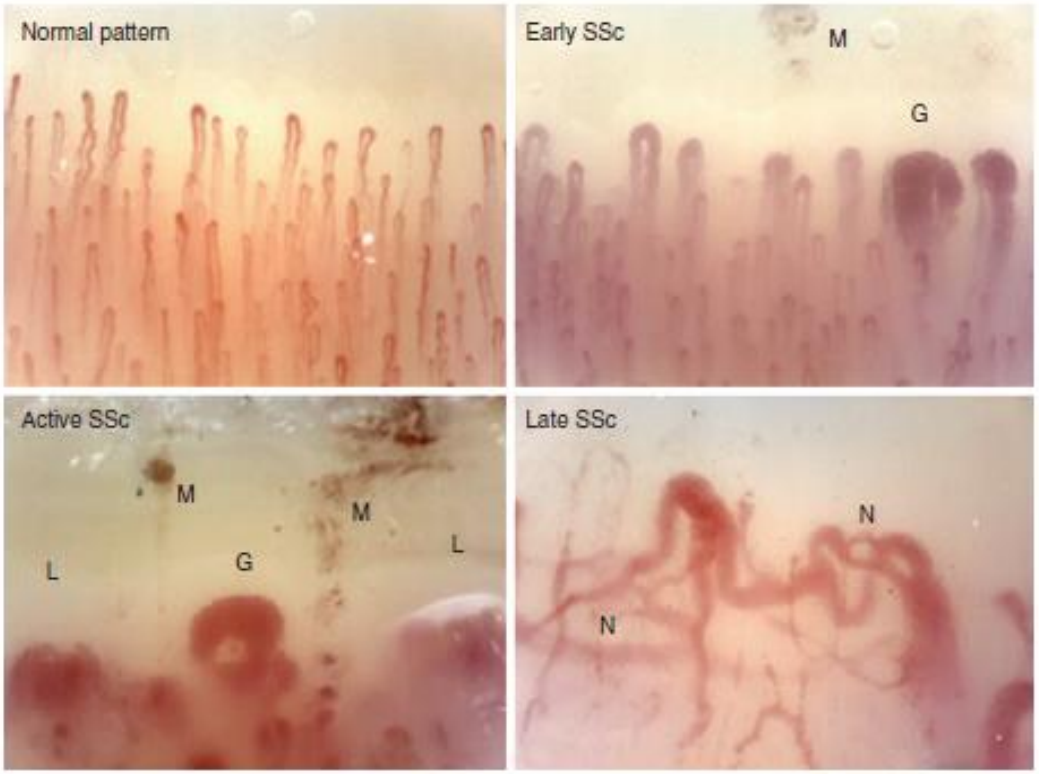
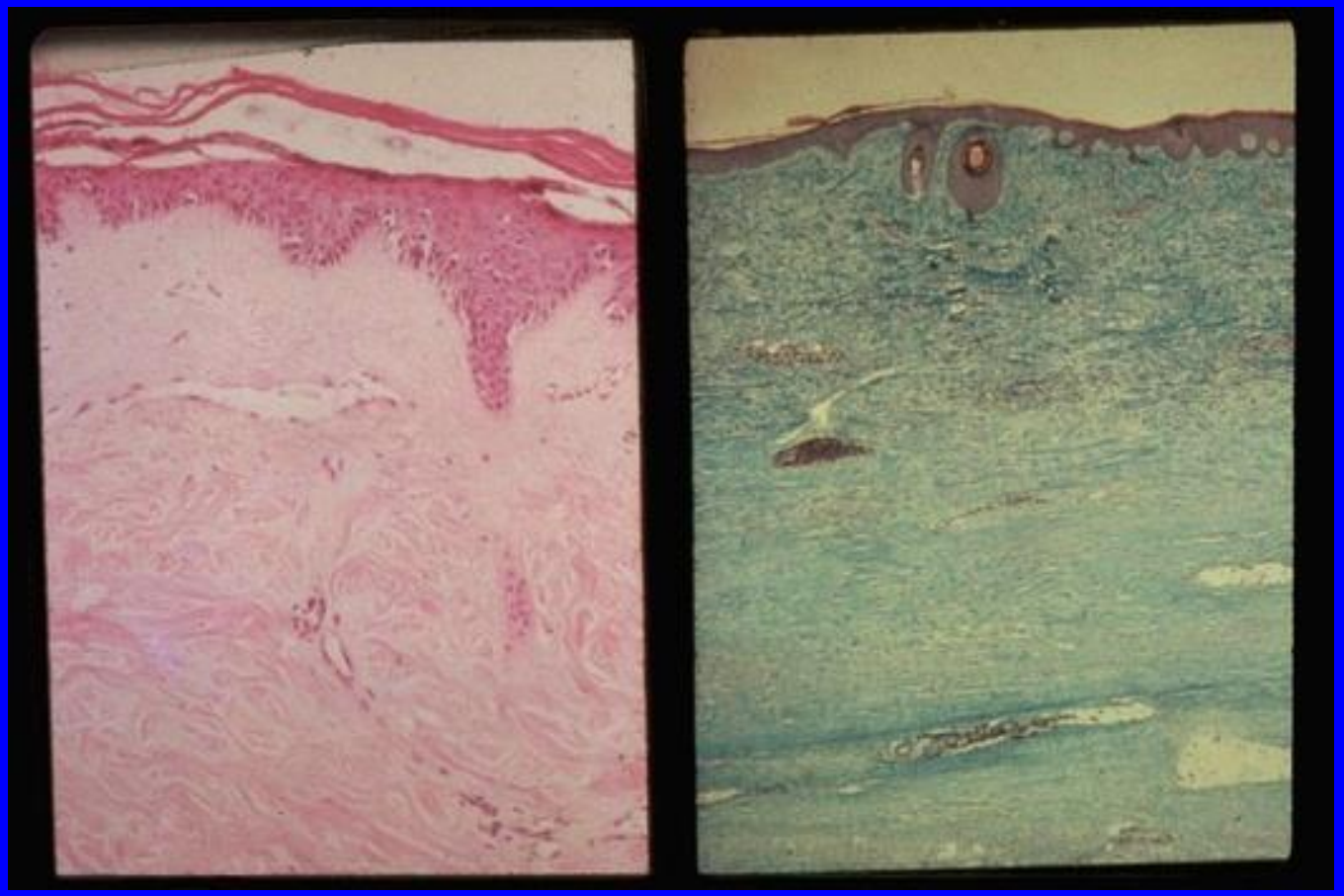
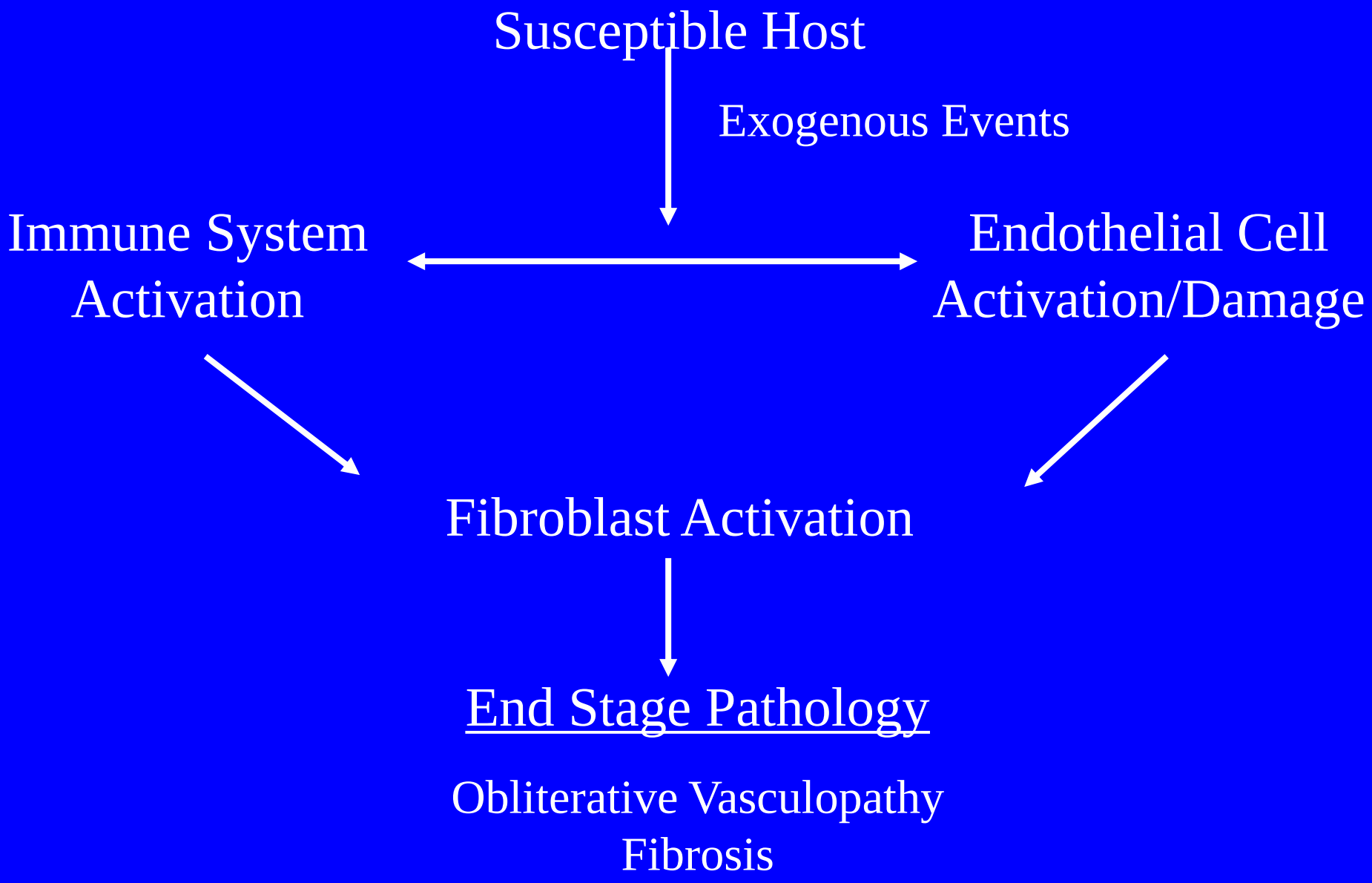


Figure 84-4 Patterns of nail-fold capillary abnormalities assessed by videocapillaroscopy in scleroderma patients. *Top right,* "Early pattern" shows the presence of few enlarged/giant capillaries, few capillary hemorrhages, and no evident loss or distortion of capillaries. *Bottom left,* "Active pattern" presents with frequent dilated capillary loops, frequent microhemorrhages, moderate loss of capillaries, and mild disorganization of the capillary architecture. *Bottom right,* "Late pattern" is characterized by severe loss of capillaries with avascular areas, ramified/bushy capillaries (neovascularization), and disorganization of the normal capillary architecture. G, giant capillaries; L, loss of capillaries; M, microhemorrhages; N, neoangiogenesis; SSc, systemic sclerosis. *(Courtesy Professor Maurizio Cutolo.)*

Fibrosis - Skin




Susceptible Host
Exogenous Events
Immune System Activation
Endothelial Cell Activation/Damage
Fibroblast Activation
End Stage Pathology
Obliterative Vasculopathy
Fibrosis

Systemic Sclerosis - Subsets

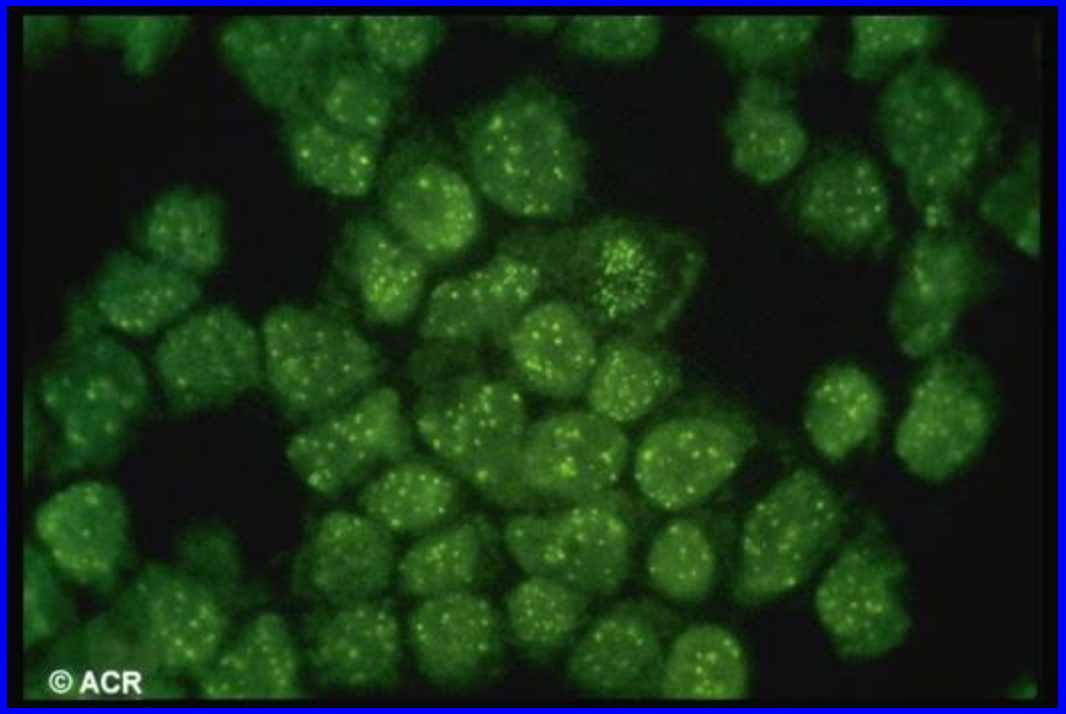
- Diffuse cutaneous systemic sclerosis
- Limited cutaneous systemic sclerosis (CREST syndrome)
- Systemic sclerosis sine scleroderma
- Overlap syndromes and undifferentiated CTD
- Localized scleroderma
  - morphea
  - linear scleroderma

Autoantibodies -Systemic Sclerosis (80-90%)

Autoantigen recognized	Percentage of patients	SSc type
Nuclei	95	Both
Centromere	10–20	lcSSc
Topoisomerase I (Scl-70)	15–25	dcSSc
RNA polymerase I, II, III	10–25	dcSSc
U3-RNP (fibrillarin)	5–45	dcSSc
Th/To RNP	5	lcSSc
U1-RNP	5–35	lcSSc
Pm/Scl	4	lcSSc with myositis

dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; SSc, systemic sclerosis.

Anticentromere Antibodies



Clinical Features of Systemic Sclerosis

- Vascular (Raynaud's Phenomenon)
- Skin
- Musculoskeletal
- Lung
- Gastrointestinal
- Heart
- Kidney
- Miscellaneous

Clinical Features of Systemic Sclerosis

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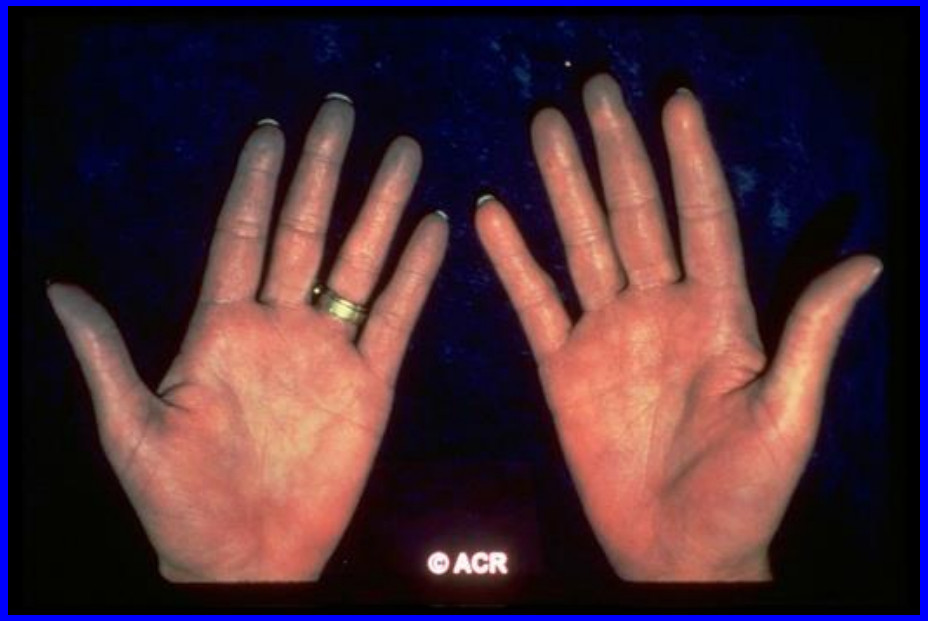
Vascular Involvement - Raynaud's Phenomenon

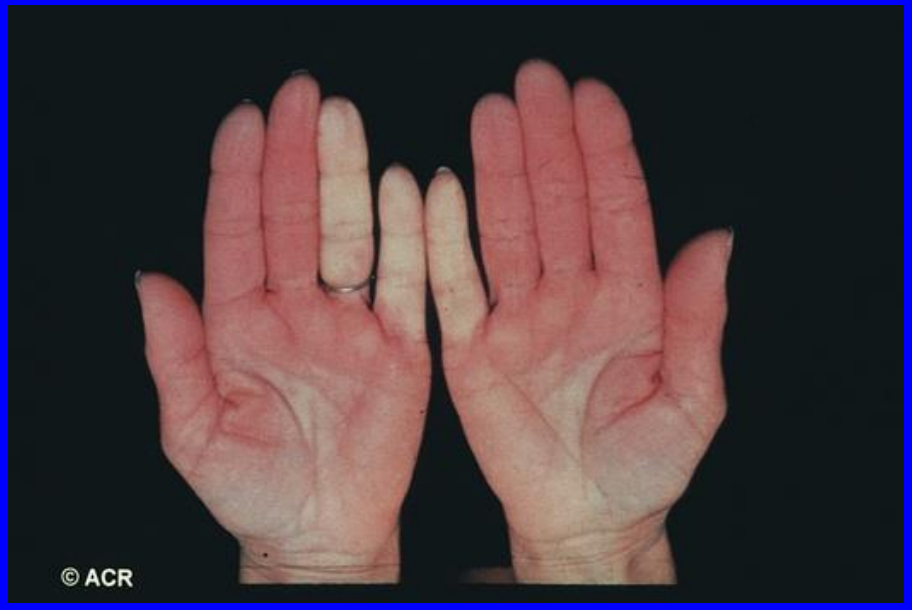
- Early involvement (years before other manifestations)
- Triggered by cold or emotional stress
- White to blue to red
- Primary Raynaud's (disease) vs. secondary Raynaud's (phenomenon)
- Present in 90% of patients with systemic sclerosis

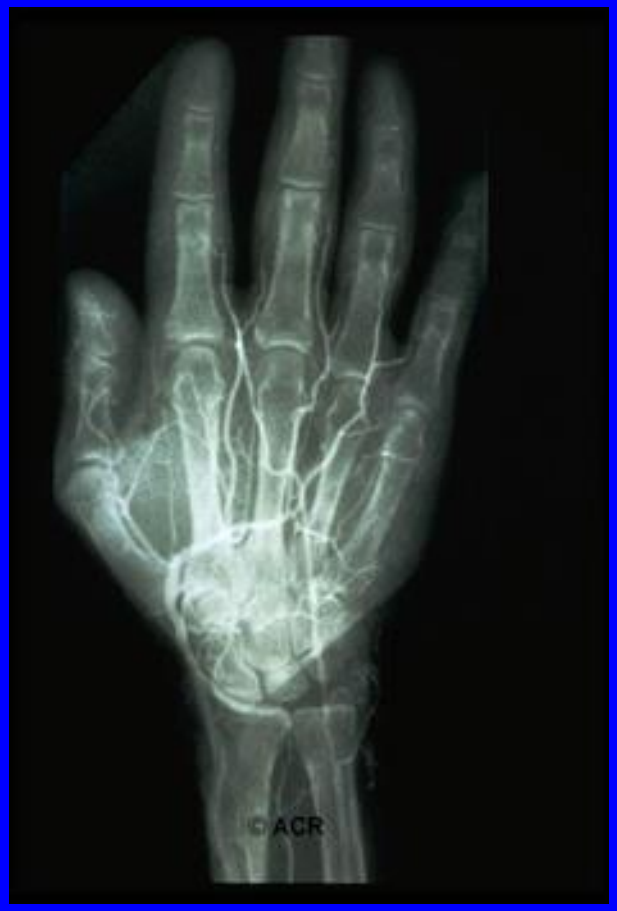
Differential Diagnosis of Raynaud's Phenomenon

Structural vasculopathies	Large and medium arteries	Thoracic outlet syndrome Brachiocephalic trunk disease (atherosclerosis, Takayasu's arteritis)
	Small artery and arteriolar	Systemic lupus erythematosus Dermatomyositis Overlap syndromes Cold injury Vibration disease Arteriosclerosis (thromboangiitis obliterans) Chemotherapy (bleomycin, vinblastine) Polyvinyl chloride disease
Normal blood vessels	Abnormal blood elements	Cryoglobulinemia Cryofibrinogenemia Paraproteinemia Cold agglutinin disease Polycythemias
	Abnormal vasomotion	Primary (idiopathic) Raynaud's phenomenon Drug-induced (ergots sympathomimetics) Pheochromocytoma Carcinoid syndrome Other vasospastic disorders (migraine, Prinzmetal's angina)

Raynaud's Phenomenon







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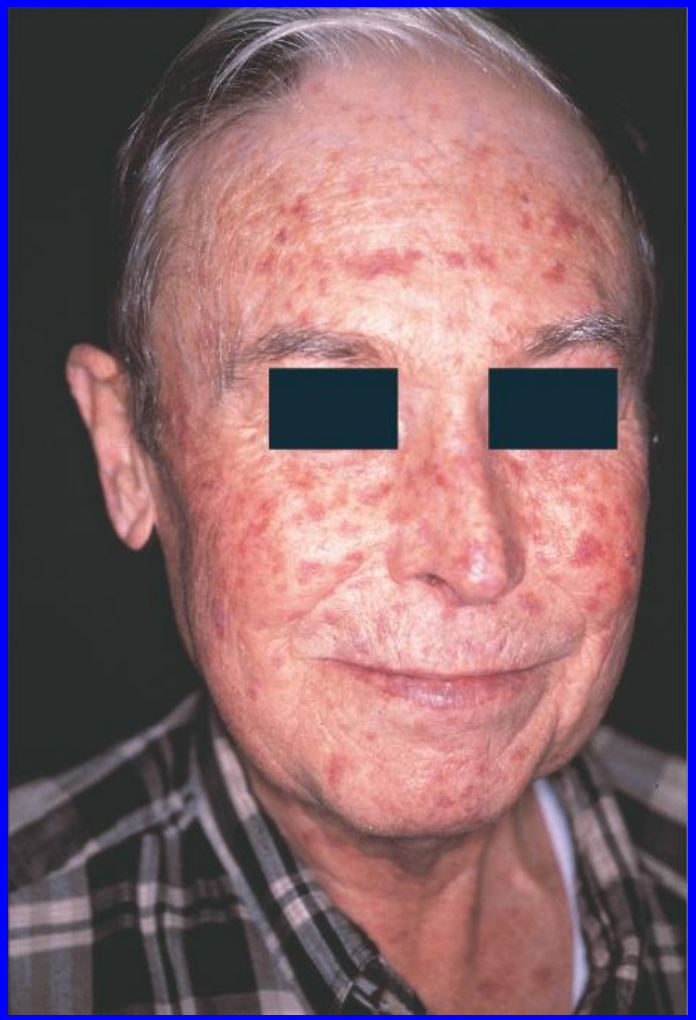
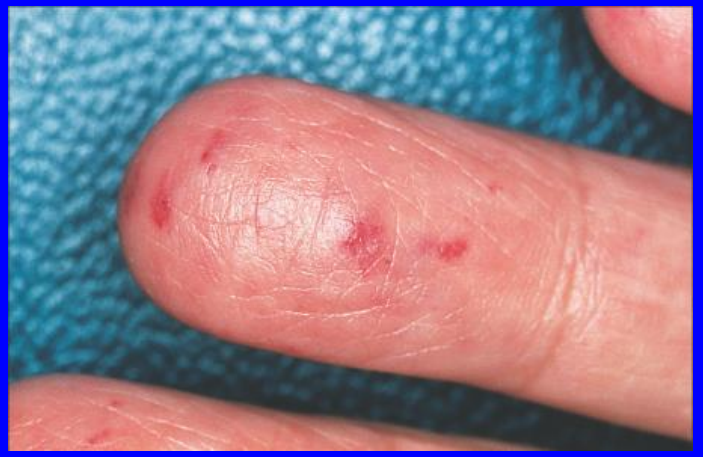
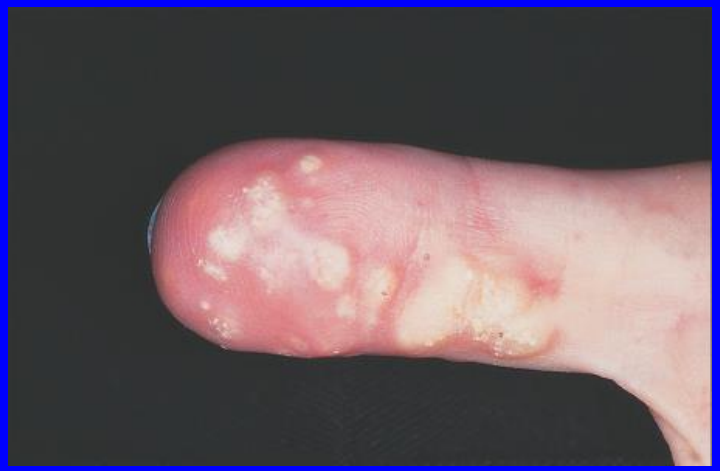
Systemic Sclerosis- Skin

- Phases
  - edematous (earliest)
  - progressive tightening and fibrosis
  - atrophy
- Subcutaneous calcifications (25%)
- Telangectasias
- Pigmentary changes (hyperpigmentation, hypopigmentation, mixed – poikiloderma)

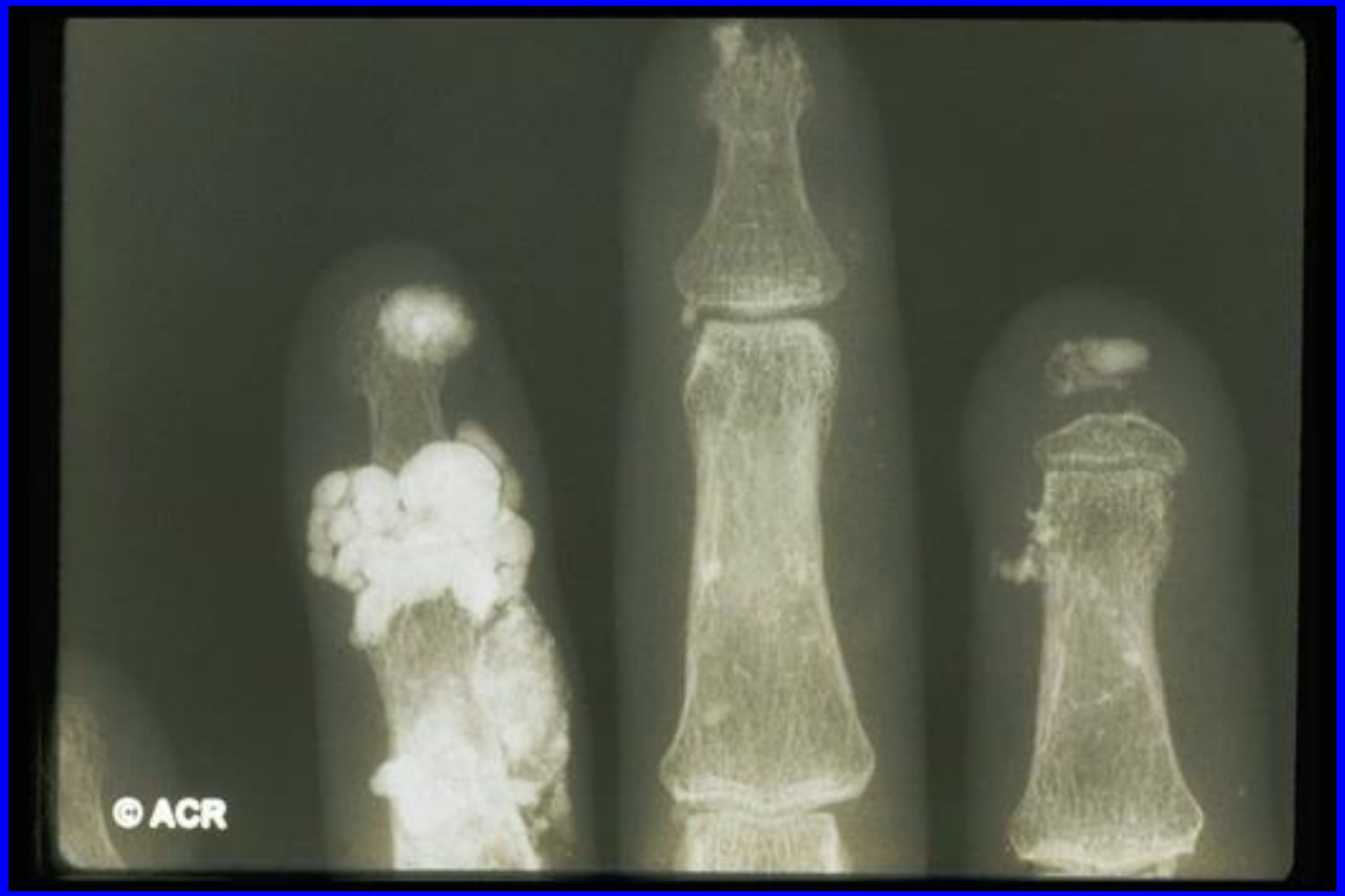
Limited Form - Systemic Sclerosis (CREST)

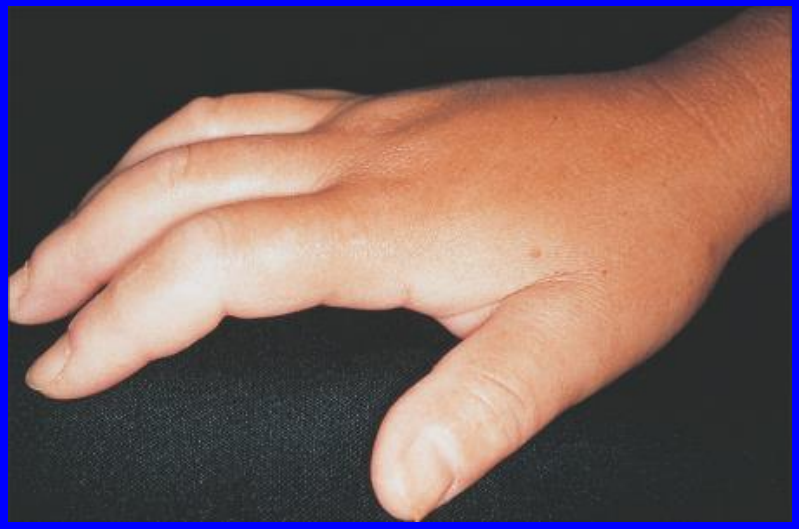




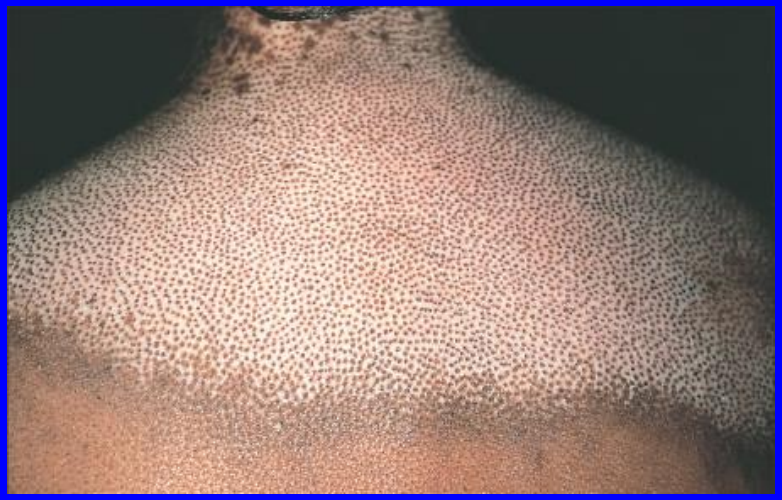


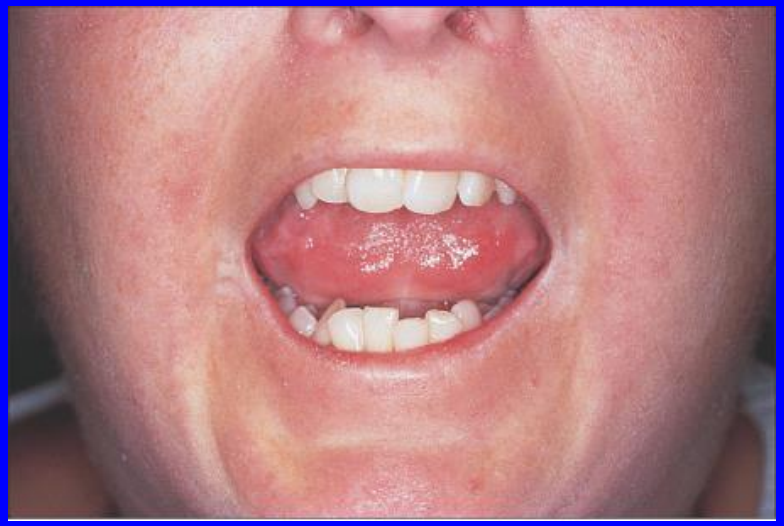
Osteolysis and Calcinosis





Diffuse Form - Systemic Sclerosis





Clinical Features of Systemic Sclerosis

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Systemic Sclerosis - Musculoskeletal

- Nonspecific musculoskeletal complaints
- Joint involvement (12-65%)
- Tendon rubs
- Late findings- muscle atrophy and weakness
- Overlap with polymyositis (10-15%)
- Overlap with rheumatoid arthritis (1-5%)

Clinical Features of Systemic Sclerosis

- Vascular (Raynaud's Phenomenon)
- Skin
- Musculoskeletal
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- Heart
- Kidney
- Miscellaneous

Systemic Sclerosis – Pulmonary Features

- Major cause of mortality
- Pleuritis and pleural effusions
- Intestitial lung disease (ILD)
- Pulmonary artery hypertension (PAH)
- Bronchiolitis, pulmonary veno-occlusive disease
- Thoracic muscle weakness, skin tightness

Systemic Sclerosis – Interstitial Lung Disease

- Nonspecific interstitial pneumonitis (SNIP)
  - 50% of diffuse skin involvement
  - 35% of localized skin involvement
  - Men> women, black>white

  Pulmonary function test: FVC and DLCO are primary parameters

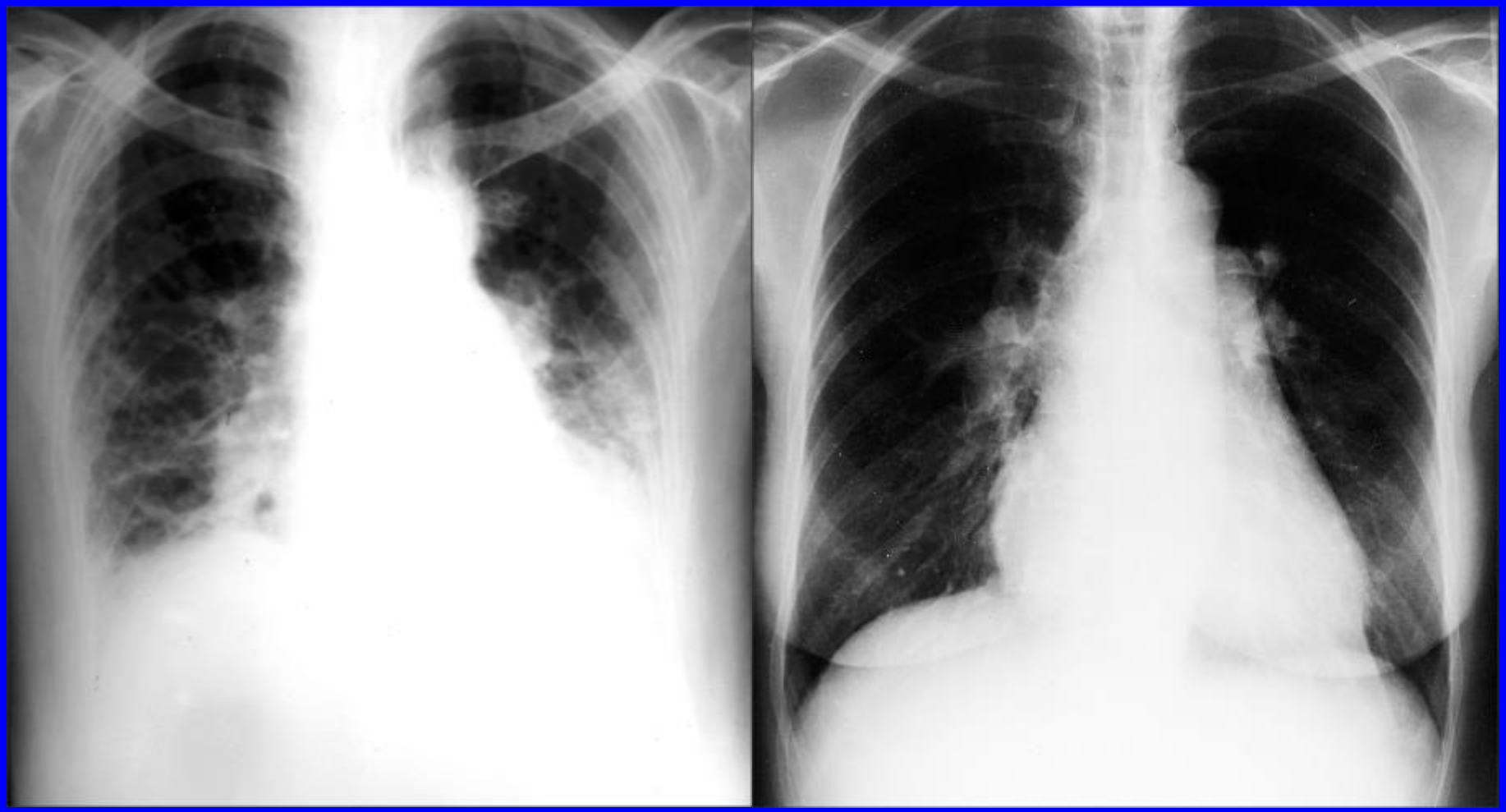
  High resolution CT (thin cuts)

  Strong association with GERD

Systemic Sclerosis – Pulmonary Features

- PAH is present in 10% in SSc
- Early on asymptomatic, then dyspnea
- Advanced: chest pain, right heart failure
- PFTs: FVC/DLCO >1.6
- Echocardiography annually
- Right heart catheterization for confirmation

Systemic Sclerosis –Chest Images



Clinical Features of Systemic Sclerosis

- Vascular (Raynaud's Phenomenon)
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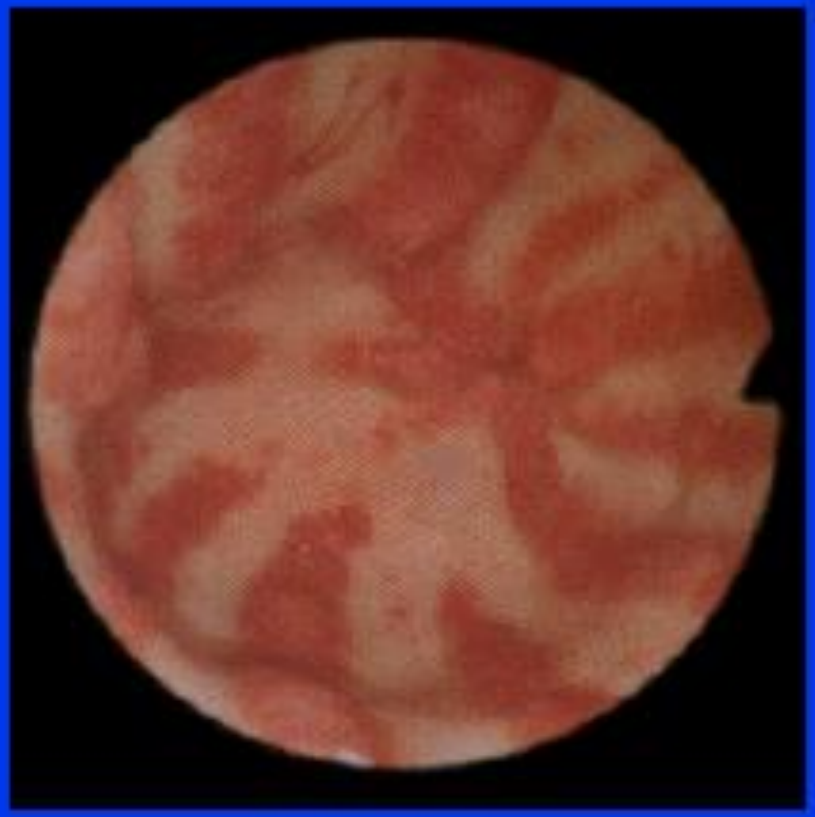
- Miscellaneous

Systemic Sclerosis - Gastrointestinal

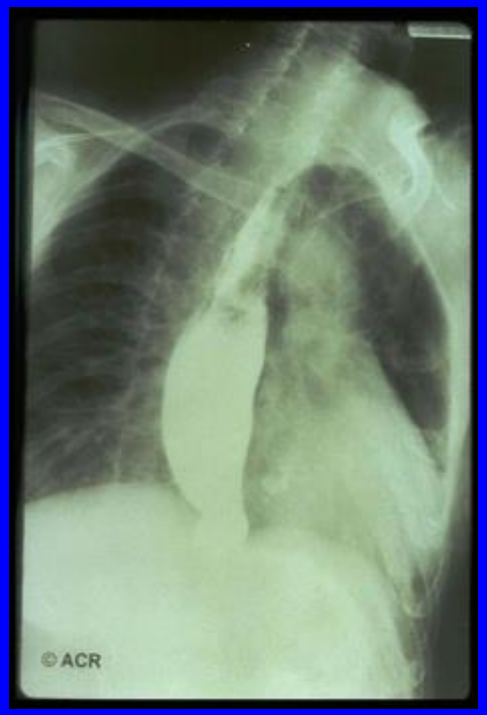
- Small oral aperture
- Esophageal dysmotility (80%) - dysphagia and heartburn
- Loss of secondary peristalsis in lower two-thirds of the esophagus
- Stomach and small bowel dysmotility
- Wide-mouth diverticuli in colon
- Vascular ectasia –stomach and colon bleeding

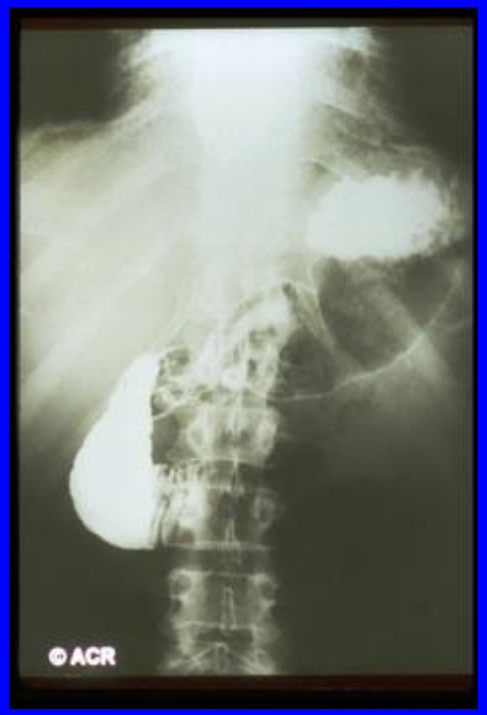
Gastric Antral Vascular Ectasia (GAVE)

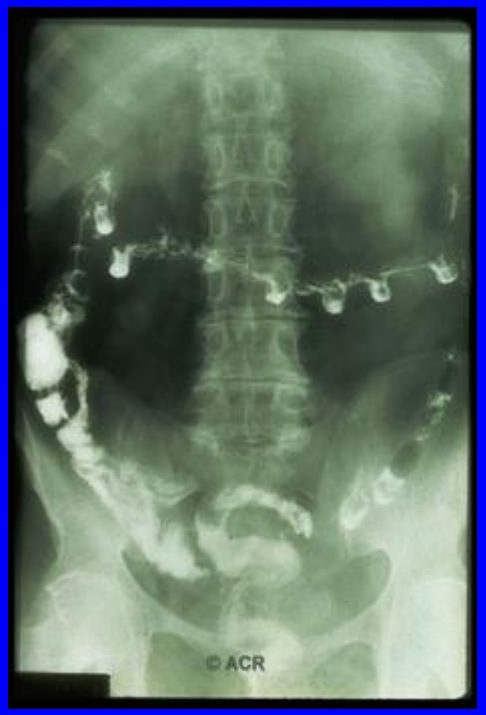
(WATERMELON STOMACH)



Intestinal involvement







Clinical Features of Systemic Sclerosis

- Vascular (Raynaud's Phenomenon)
- Skin
- Musculoskeletal
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- Kidney
- Miscellaneous

Cardiac manifestations

- Usually subtle expression
- Heart failure and arrythmias
- Cardiac injury:
  - Patchy fibrosis of the myocardium
  - Hypoxia/reperfusion injury
- Diastolic dysfunction occurs frequently
- Pericardial effusion (30-40% of patients)

Clinical Features of Systemic Sclerosis

- Vascular (Raynaud's Phenomenon)
- Skin
- Musculoskeletal
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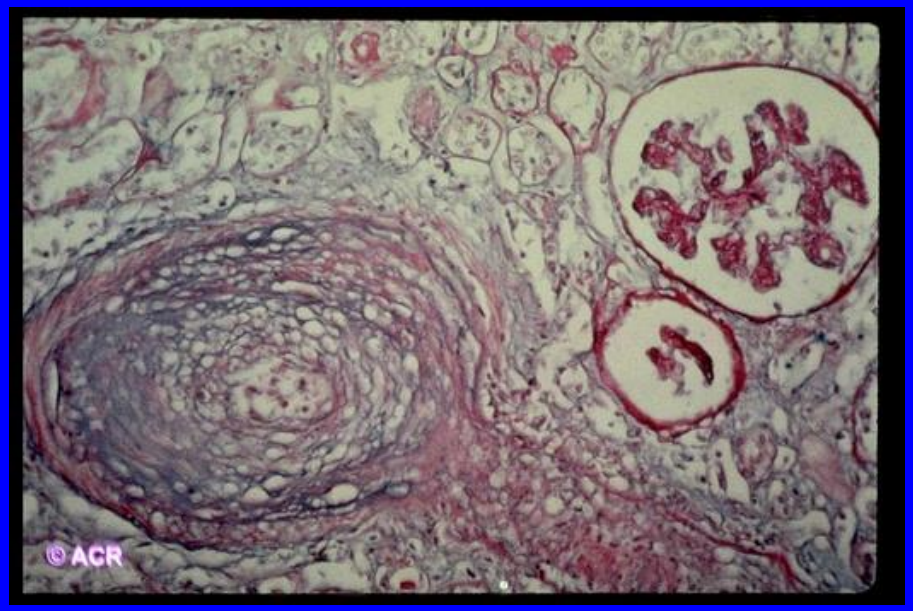
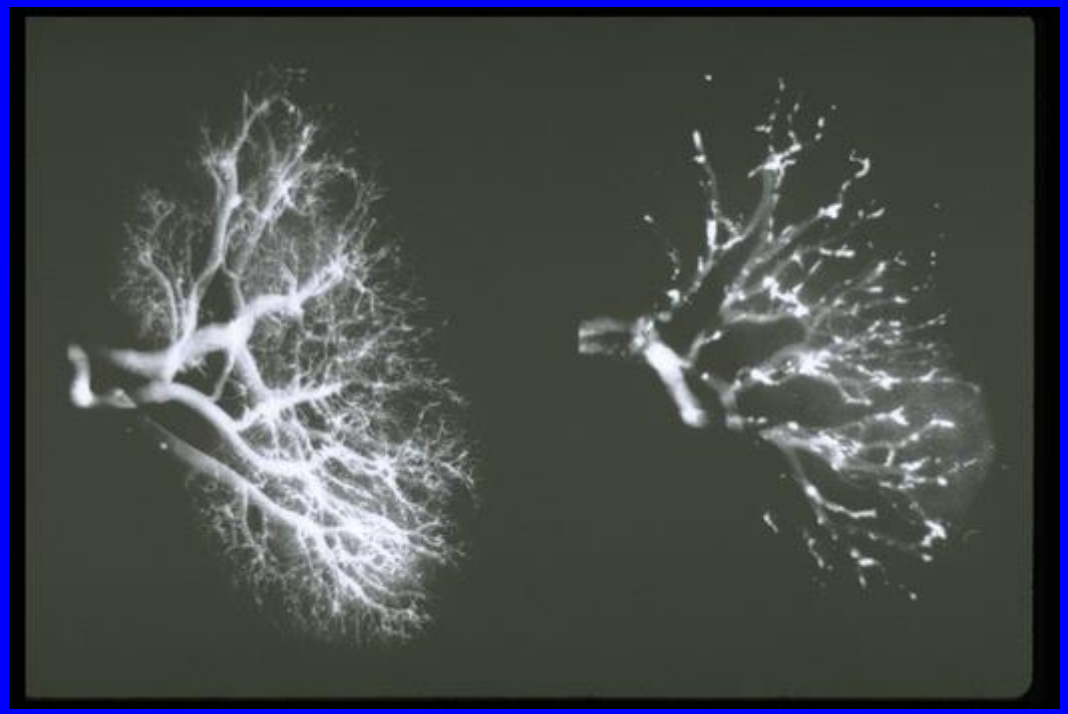
- Gastrointestinal
- Heart
- Kidney
- Miscellaneous

Renal Involvement

- Scleroderma renal crisis (5%)
  - In diffuse variety of SSc
  - 80% occur within the first year
  - Accelerated hypertension and/or rapidly progressive renal failure
  - Laboratory data: proteinuria, microscopic hematuria, increasing serum creatinine levels
  - Can be aborted if identified early
  - Risk factors: moderate/high dose glucocorticoids, anti-RNA polymerase III Abs

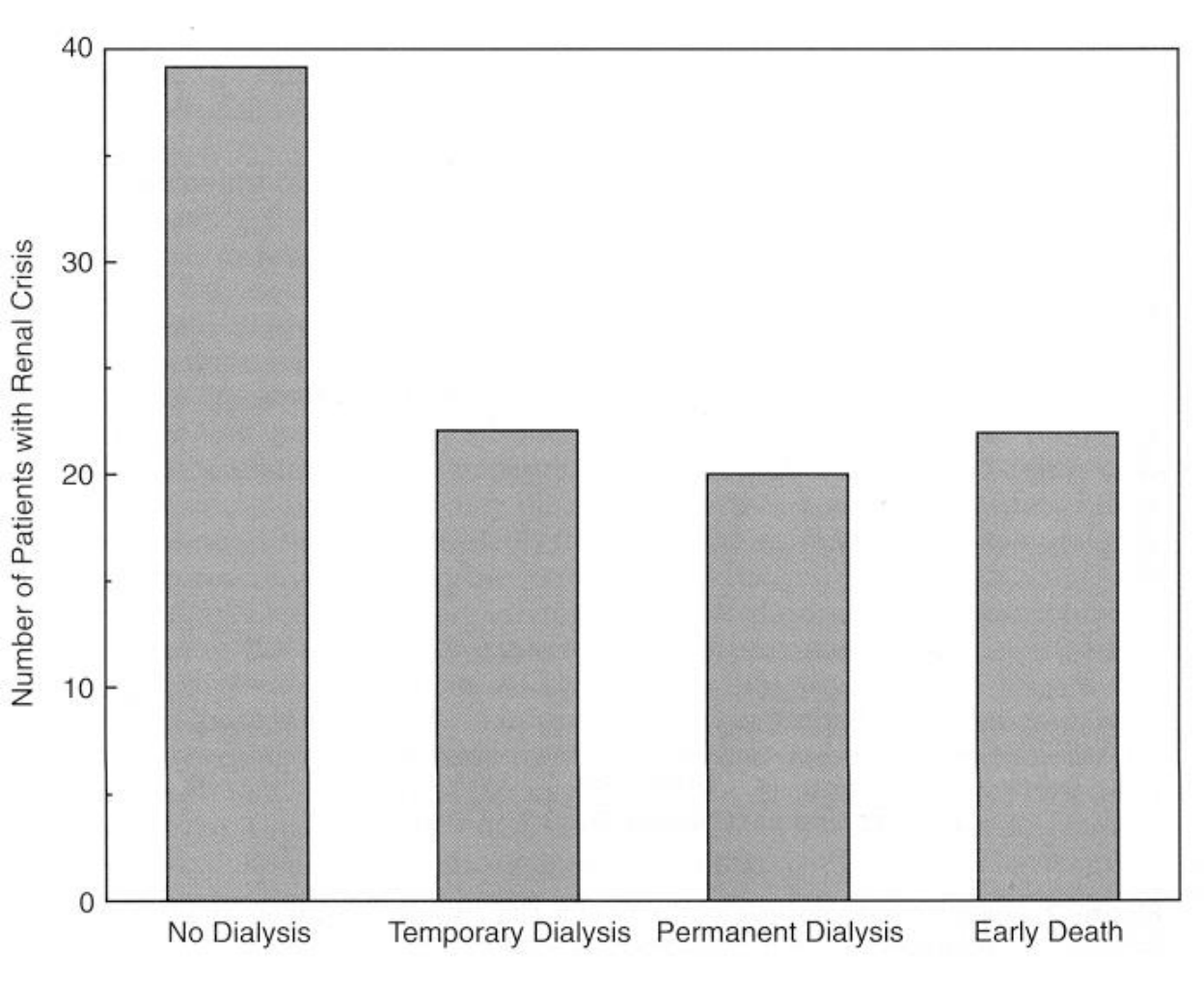


Renal involvement



Scleroderma Renal Crisis - Outcome

100 patients



Systemic Sclerosis- Treatment

- Disease modifying interventions (skin as proxy)
- Methotrexate (immunosuppressant)
- Cyclophosphamide (imunosuppressant)
- Mycophenolate (immunosuppressant)
- Rituximab (B cell inhibitor)
- Nintedanib (tyrosine kinase inhibitor)

Systemic Sclerosis- Treatment (II)

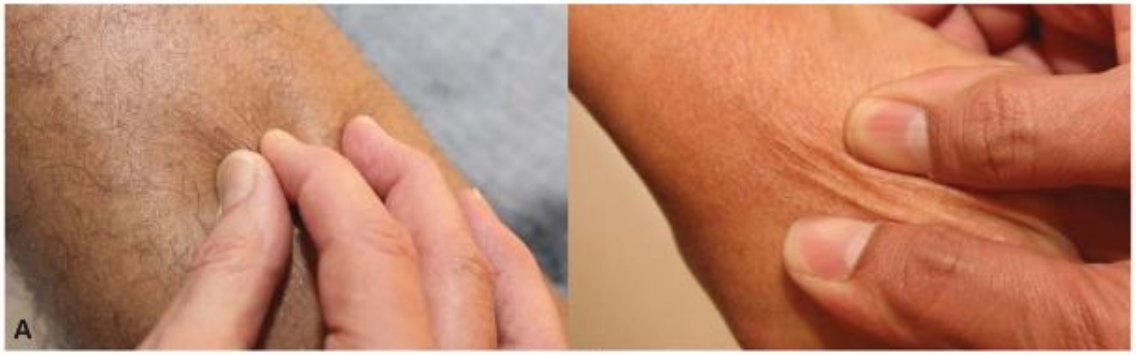
- Symptomatic organ-specific treatments
  - Skin (antihistamines, moisturisers, topical analgesics and antibiotics)
  - Raynaud's phenomenon (avoid cold exposure, gloves, stop smoking, vasodilator therapy, cervical, lumbar and digital sympathectomies)
  - Gastrointestinal (proton pump inhibitors, esophageal dilatation, pro-motility agents, broad spectrum antibiotics)

Systemic Sclerosis- Treatment (III)

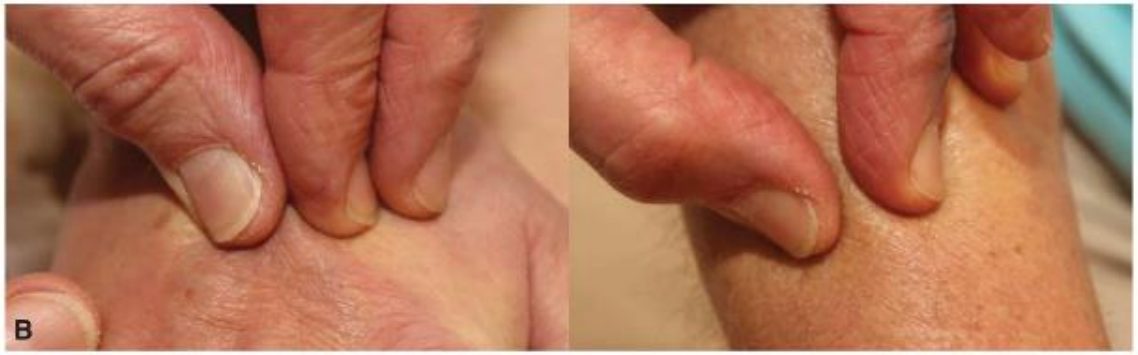
- Pulmonary – interstitial lung disease- (cyclophosphamide, mycophenolate, rituximab), pulmonary hypertension- (continuous IV epoprostenol, endothelin receptor antagonist , PD5 enhancers)
- Renal (ACE inhibitors)
- Musculoskeletal (NSAIDs, physical therapy, corticosteroids/methotrexate)

Scleroderma-Like Conditions

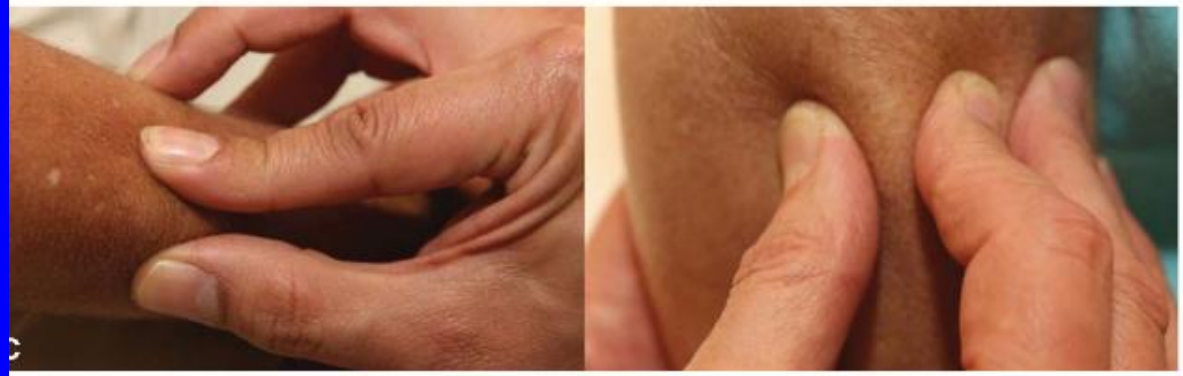
- Eosinophilic fasciitis
- Scleromyxedema
- Occupational or environmental: vinyl chloride disease, jackhammer disease, silicosis, toxic oil syndrome
- Metabolic: porphyria, amyloidosis
- Drug-Induced: bleomycin, tryptophan, carbidopa
- Immunological: Graft-vs-Host disease



Fine wrinkles;
No thickness appreciated

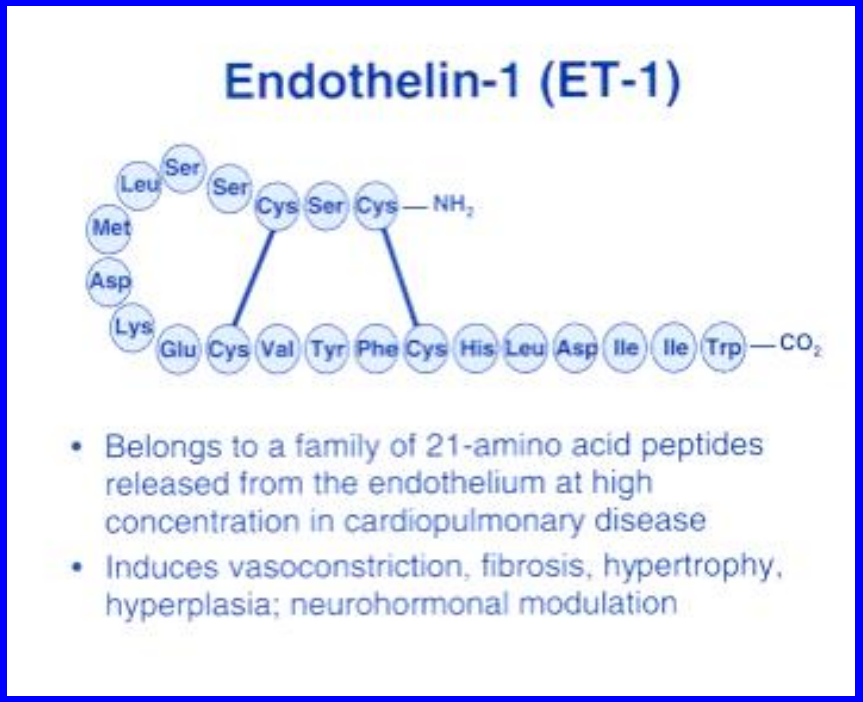


"Mild" skin thickness; easily able to detect
a thickened skin fold between 2 fingers



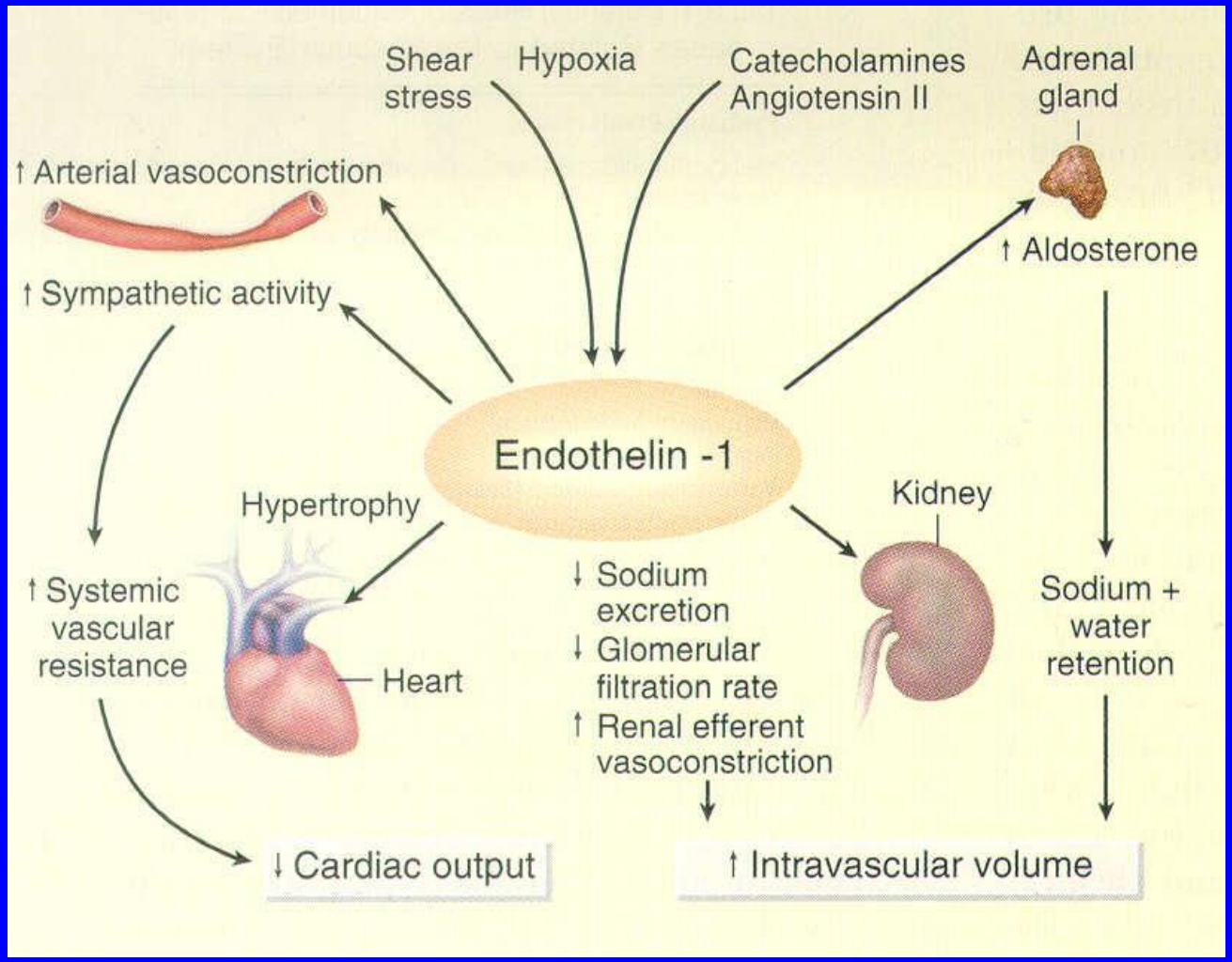
"Moderate" skin thickness; difficulty in making

Rodnan Modified Skin Score (0-3)

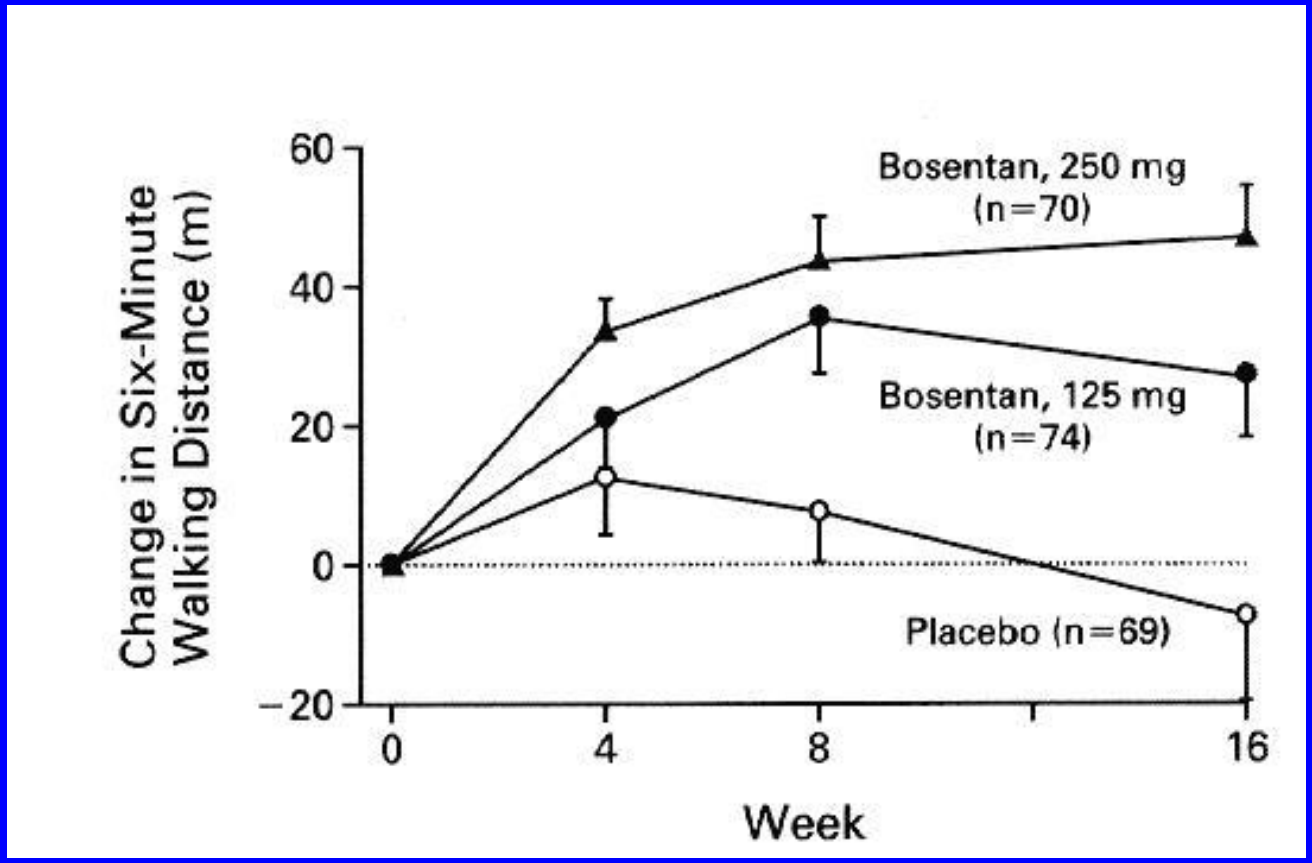


- Produced by a variety of cells
- Endothelin-1 is produced by endothelial cells and smooth muscle cells (SMC)
- Not stored
- Life of molecule is 4-7 minutes
- Cleared by the lungs
- 75% of secretion is towards SMC

Actions- Endothelin-1



Bosentan Therapy - Pulmonary Hypertension



Rubin, N Eng J Med, 2002

Systemic Sclerosis - Subsets

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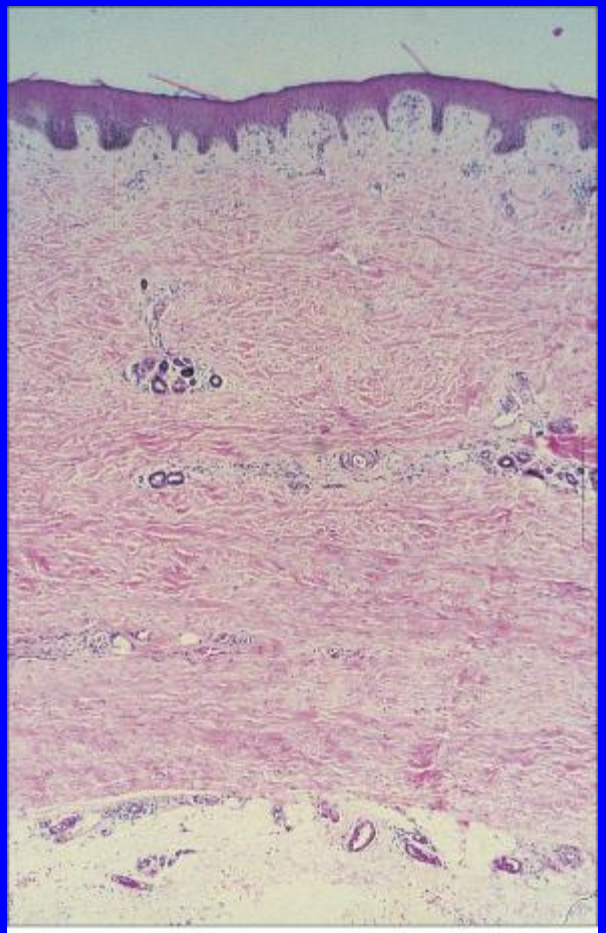
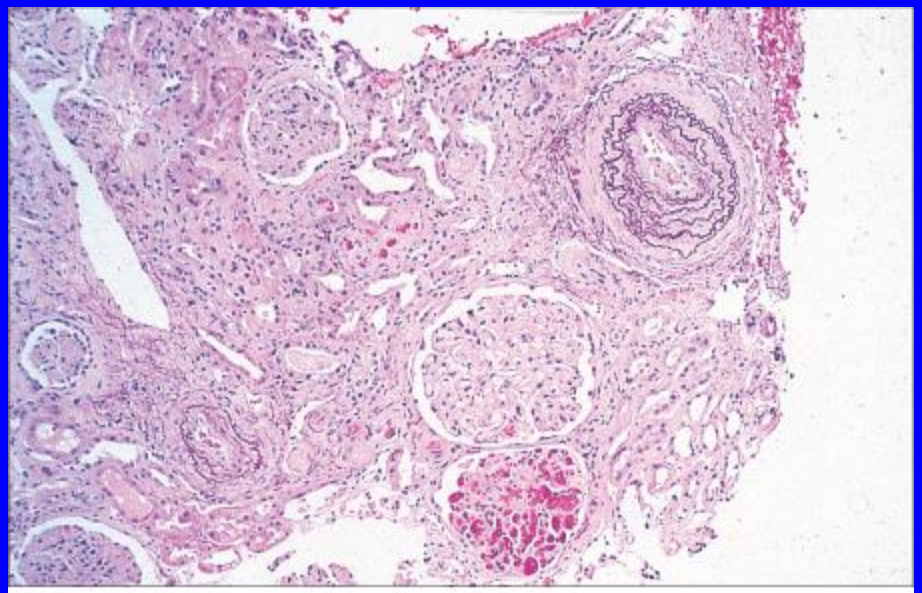
- Limited cutaneous systemic sclerosis (CREST syndrome)
- Overlap syndromes
- Undefined connective tissue disease
- Localized scleroderma
  - morphea
  - linear sclerodrma





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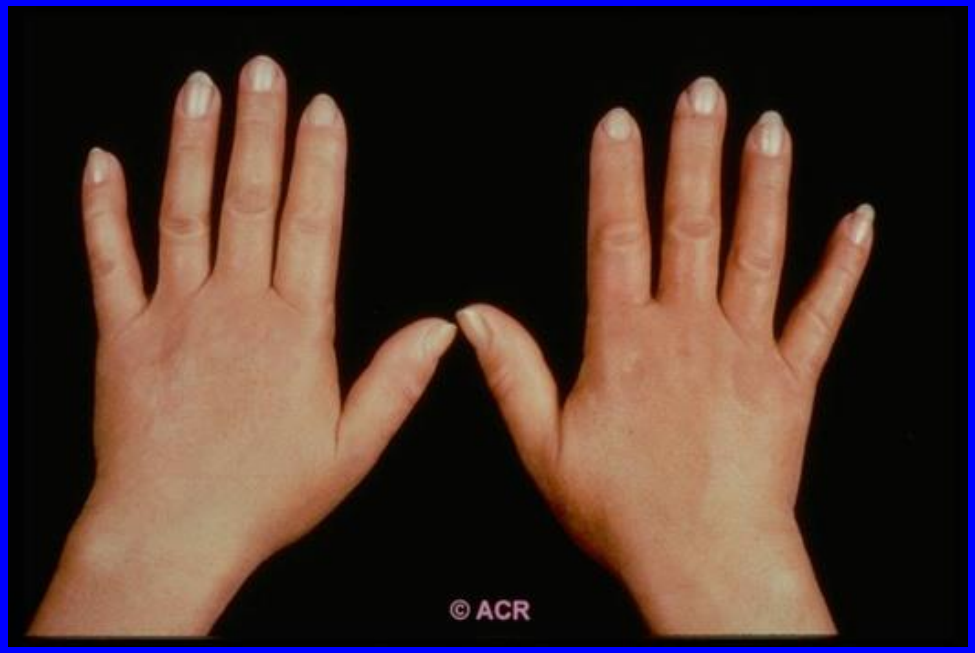
  - capillaries
  - venules

  Ischemia
- Fibrosis
  - skin
  - lungs
  - gastrointestinal tract

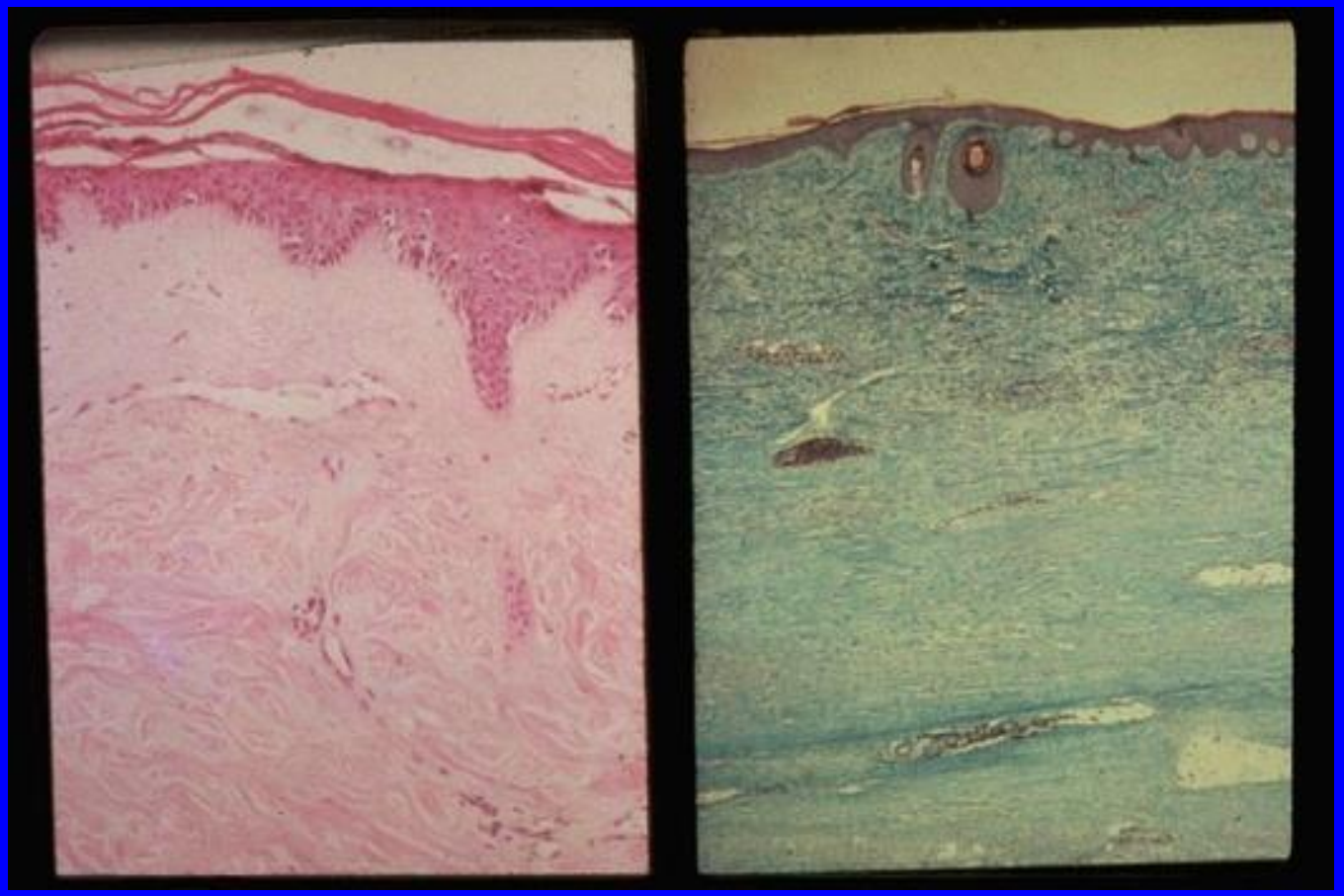
Systemic Sclerosis- Raynaud's Phenomenon

- Color changes of the skin of the digits
- Precipitated by cold or emotional stress
- Pallor followed by cyanosis and then reactive erythema
- > 90% of systemic sclerosis patients
- Both exaggerated vasospasm and narrowing of the lumen contribute to the ischemia

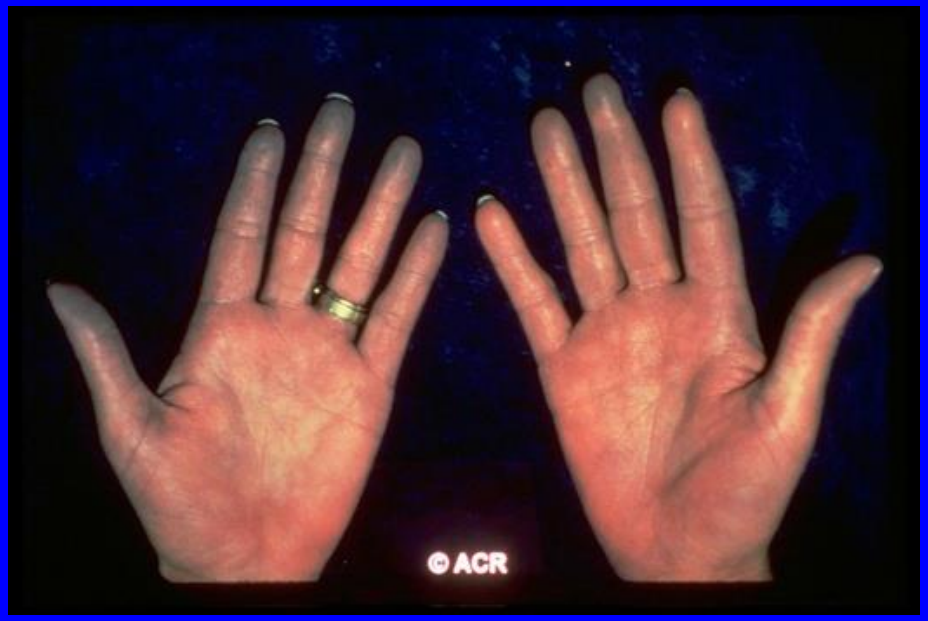


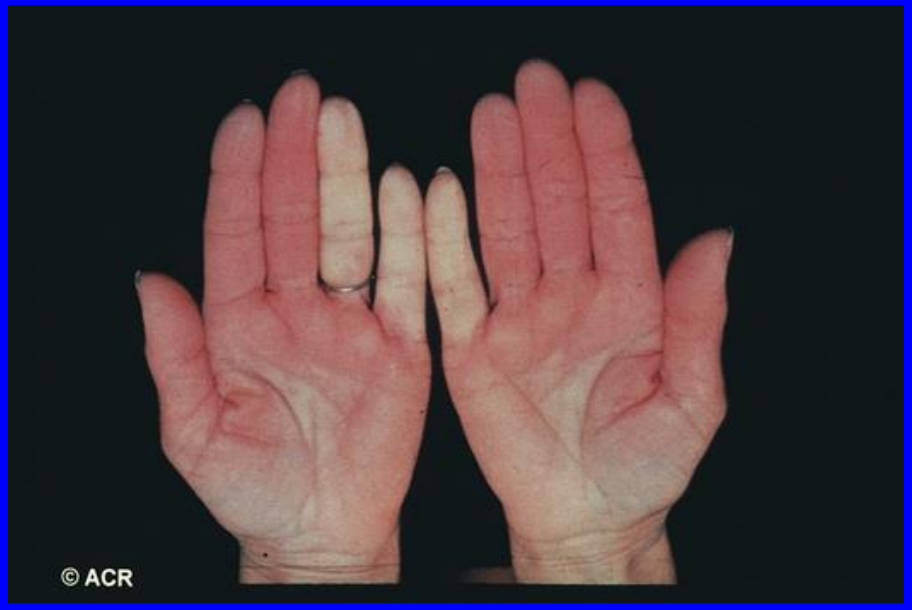
Phases of Scleroderma

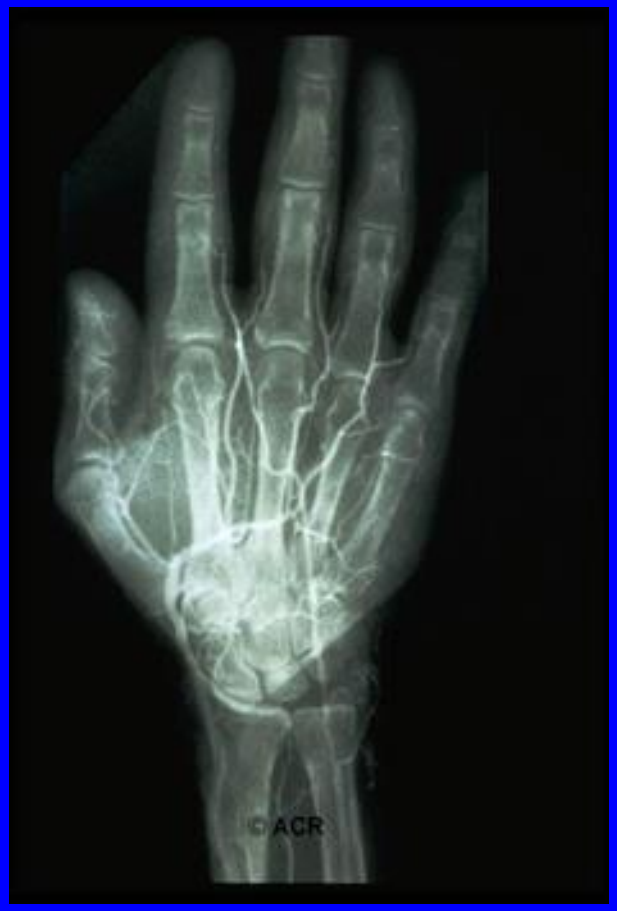
Fibrosis - Skin



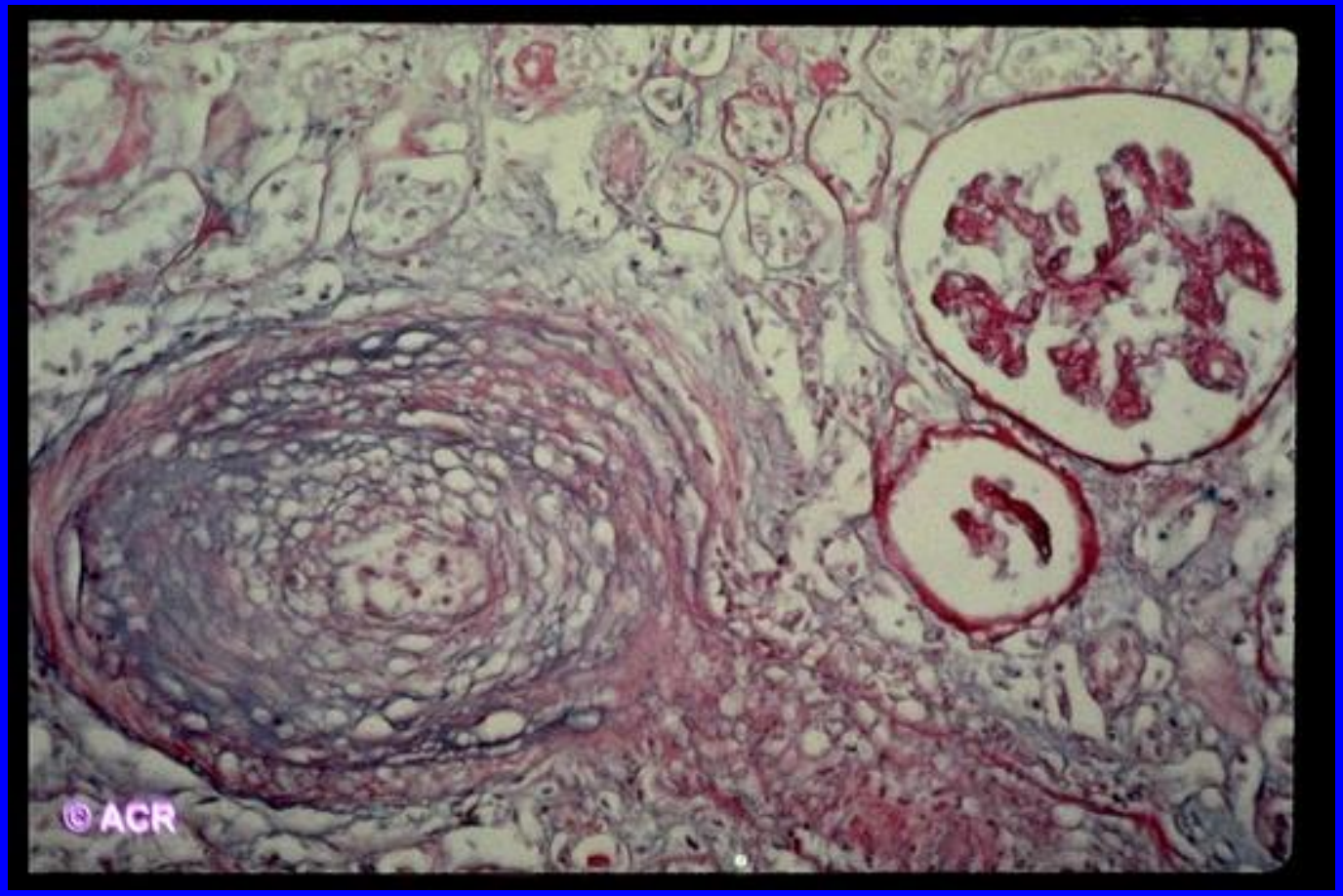
Raynaud's Phenomenon

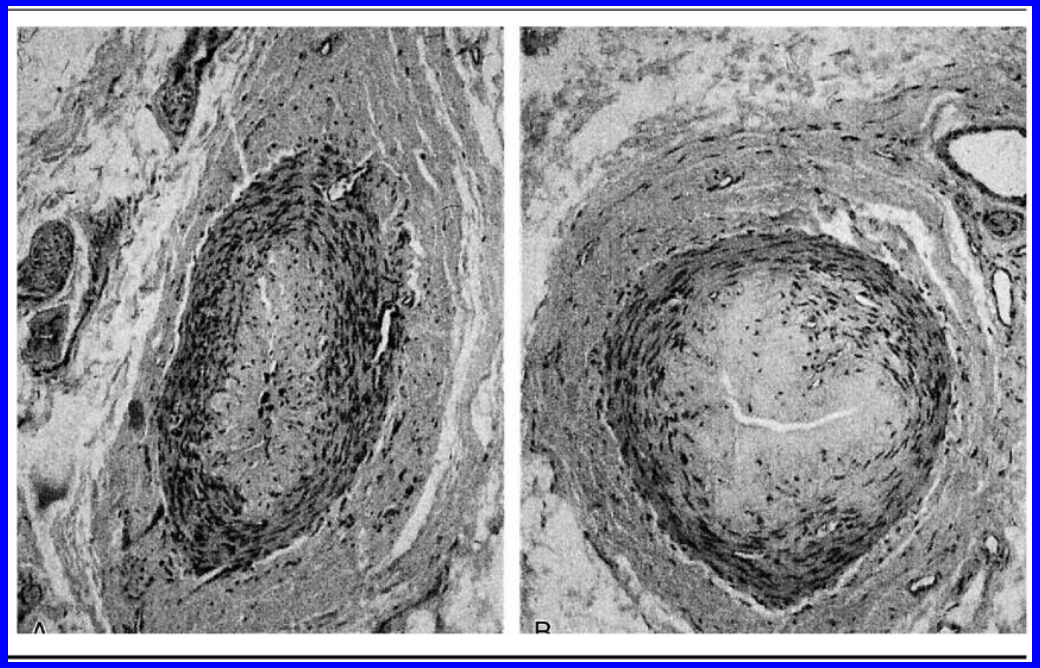




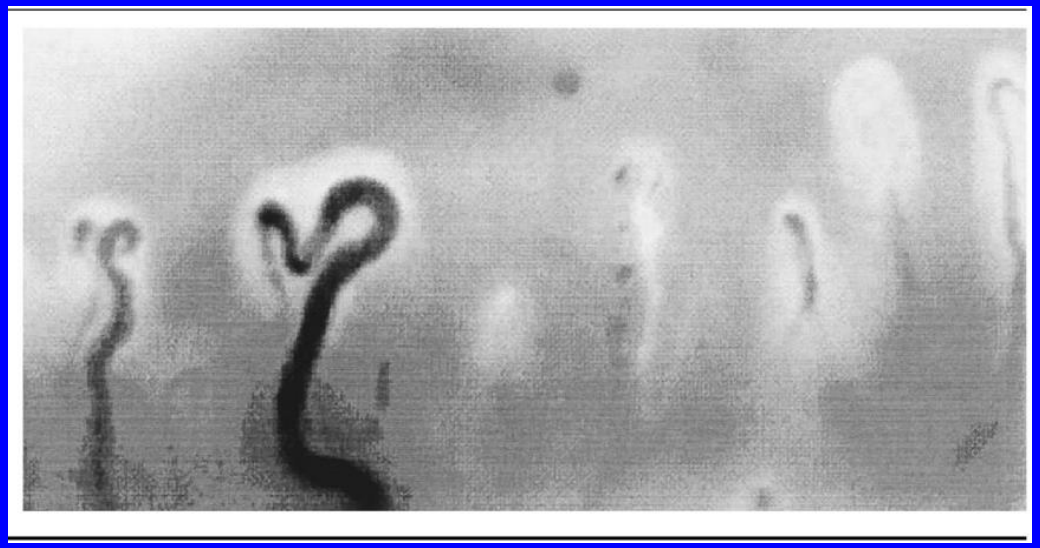


Vasculopathy - Kidney





Digital Arteries



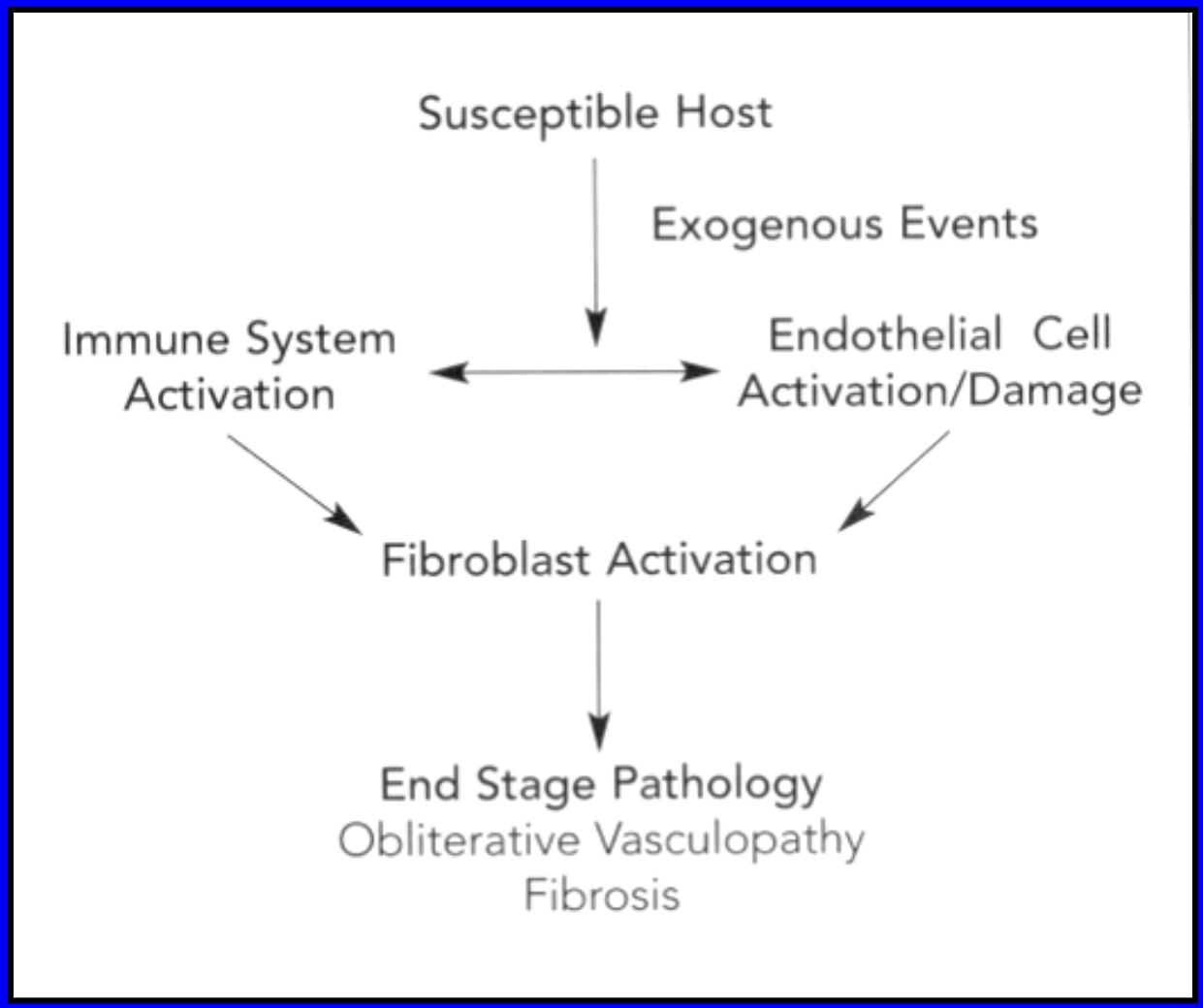
Nailfold Capillary Loops

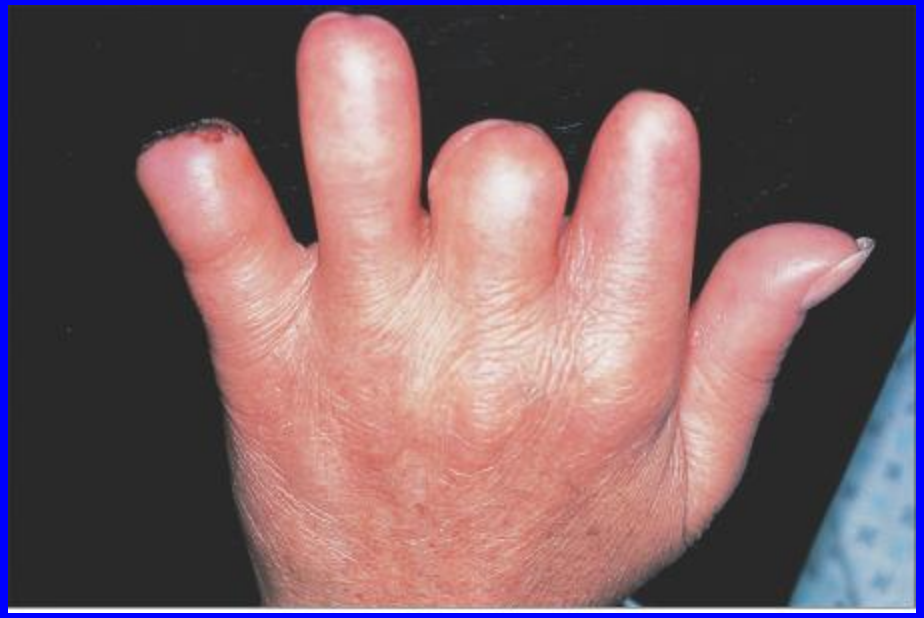
Serum Antibodies - Systemic Sclerosis

Antigen	ANA Staining	Frequency (%)	Association
Scl-70	Speckled	15-20	Diffuse
RNA I, II, III	Speckled/ nucleolar	20	Diffuse
U_3 RNP	Nucleolar	<5	Diffuse (overlap)
PM-Scl	Nucleolar	3-5	Overlap
U_1 RNP	Speckled	10	Limited
ACA	Centromere	25-30	Limited
Th (To)	Nucleolar	5	Limited

Black J R Coll Physicians Lond, 1995

Systemic Sclerosis- Pathogenesis





Raynaud's Phenomenon