

# Scleroderma

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# **Nomenclature Synonyms**

Scleroderma

Progressive Systemic Sclerosis

Systemic Sclerosis

# Scleroderma

- Chronic systemic autoimmune disease characterized by fibrosis of the skin as well as internal organs, e.g., lung, heart, gastrointestinal tract, and kidneys.

## Limited vs. Diffuse Scleroderma

- Cutaneous criteria:
  - Limited: involves skin distal to elbows and knees, as well as face
  - Diffuse: involves skin of proximal extremities and face, as well as trunk
- Implications regarding natural history and prognosis

# Mortality in Scleroderma

- Limited scleroderma
  - 90% 5-year survival
  - 75% 10-year survival
- Diffuse scleroderma
  - 70% 5-year survival
  - 50% 10-year survival

## Swollen Digits in Scleroderma



# Sclerodactyly



## Scleroderma Facial Appearance

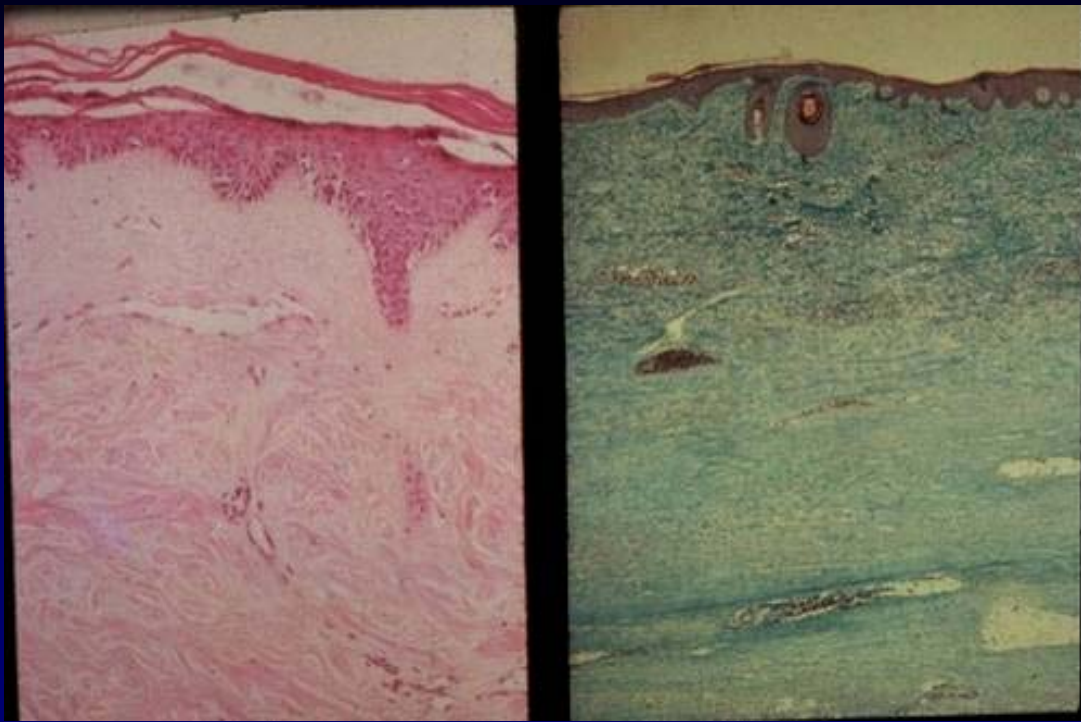




## Diffuse Scleroderma



# Dermatopathology



Excessive Dermal Deposition of Collagen and ECM proteins

## Raynaud's Phenomenon

- Early manifestation of disease in >97% of scleroderma patients, preceding sclerodactyly by months to years
- Vasospasm of the digital microvasculature resulting in:
  - Digital ischemia (pallor)
  - Digital hypoxia (cyanosis)
  - Digital reactive hyperemia (erythema)

# Raynaud's Phenomenon



# Raynaud's Phenomenon



## Digital Arteriogram in Raynaud's Disease



## Digital Capillary Microscopy in Scleroderma



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A II

Normal



C II

Capillary dilatation



D II

Capillary "dropout"

## Facial Telangiectasias in Limited Scleroderma





# Epidemiology of Scleroderma

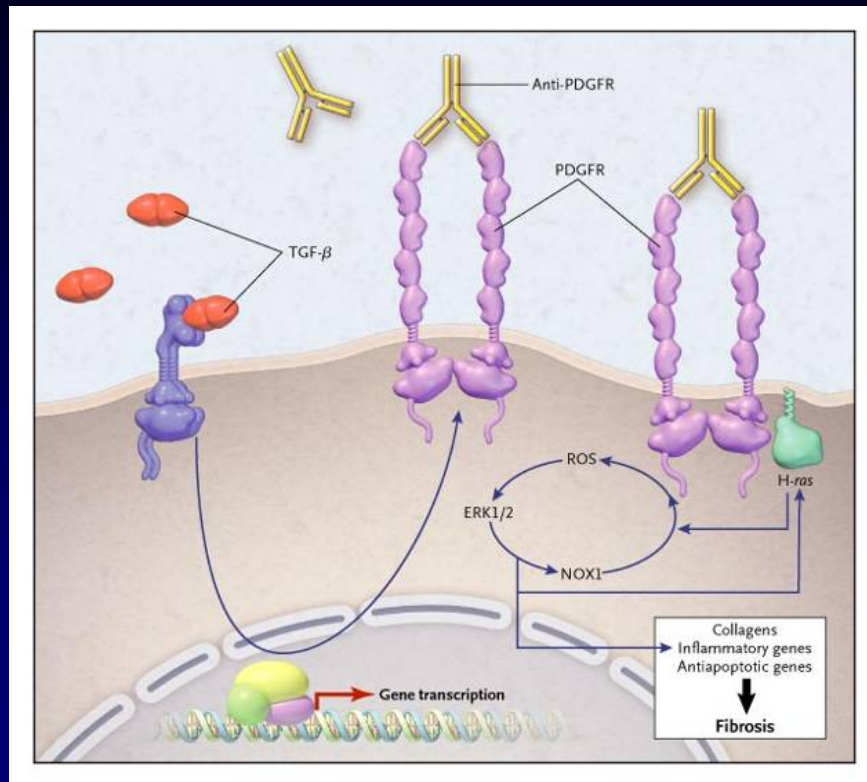
- Incidence: 2 per 100,000
- Prevalence: 25-75 per 100,000
- Sex: F:M 3:1
- Racial Distribution
  - Occurs in all populations
  - African Americans > Caucasians (2:1)
  - Choctaw Native Americans (Oklahoma)
    - Prevalence: 450 per 100,000

# Autoantibodies in Scleroderma

- > 98% exhibit antinuclear antibodies (+ANA)
- Limited Scleroderma
  - 60-70% exhibit anticentromere Ab
- Diffuse scleroderma
  - 30% exhibit antitopoisomerase 1 Ab (anti-Scl 70 Ab)
  - 20-30% exhibit anti-RNA polymerase Ab

# Autoantibodies in Scleroderma

## Anti-PDGF Receptor Antibodies



Tan F. *N Engl J Med* 2006;354:2709-2711

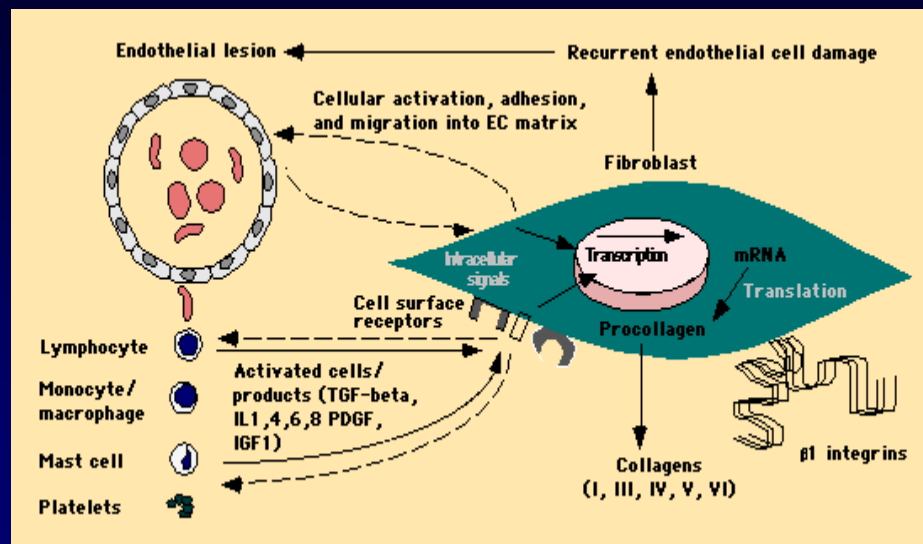
# Immunogenetics of Scleroderma

- HLA associations:
  - Limited scleroderma (anticentromere Ab)
    - HLA-DR $\beta$ 1\*0101
    - HLA-DQ $\beta$ 1\*0501
  - Diffuse scleroderma (antitopoisomerase 1 Ab)
    - HLA-DR $\beta$ 1\*1101 (African Americans, Caucasians)
    - HLA-DR $\beta$ 1\*1104 (African Americans, Caucasians)
    - HLA-DQ $\beta$ 1\*0301 (African Americans, Caucasians)
    - HLA-DR $\beta$ 1\*1502 (Japanese)
    - HLA-DR $\beta$ 1\*1602 (Choctaw Native Americans)

# Pathogenesis of Scleroderma

- Endothelial activation
  - Vasospasm in Raynaud's disease
- Immune activation
  - B cells and autoantibody generation
  - T cells and HLA associations
  - Macrophages and cytokine secretion
    - TGF- $\beta$ , PDGF, TNF $\alpha$ , IL-1
- Fibroblast activation
  - Tissue fibrosis by excessive collagen deposition

# Pathogenesis of Scleroderma



## Limited vs. Diffuse Scleroderma

### Limited Scleroderma

- Pulmonary
  - Pulmonary Hypertension
- Kidney disease uncommon
- Heart disease uncommon
- Gastrointestinal
  - Esophageal dysmotility and gastroesophageal reflux disease

### Diffuse Scleroderma

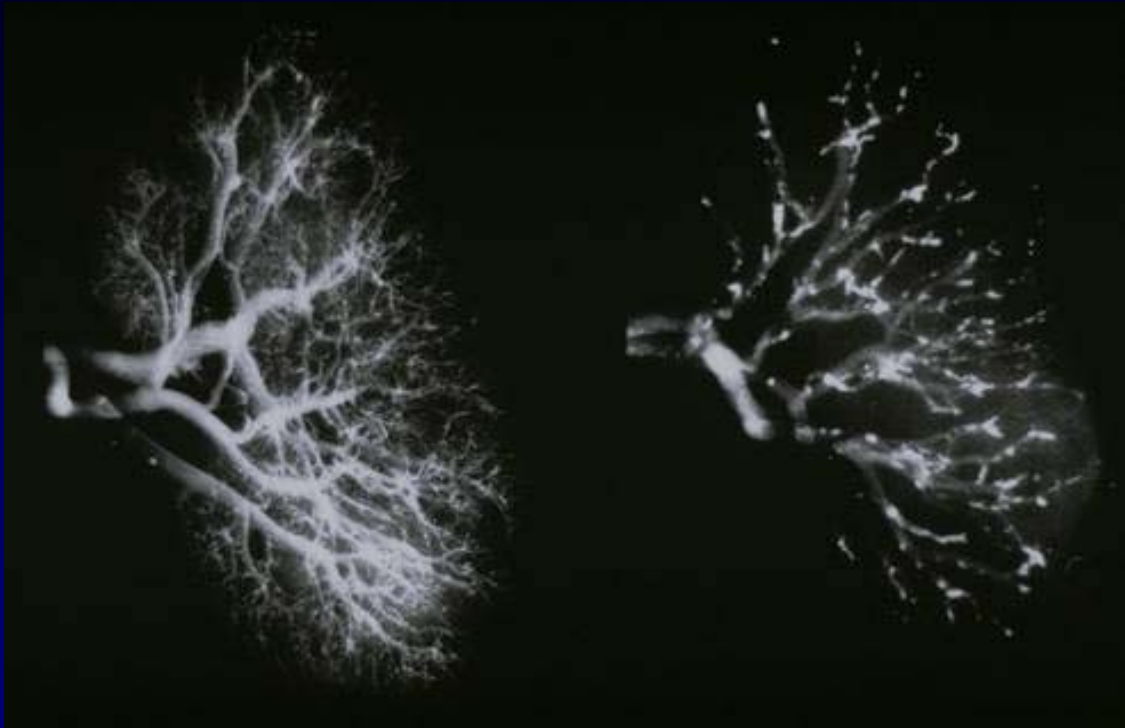
- Kidney
  - Acute renal failure 2° renovascular hypertension
- Pulmonary
  - Pulmonary Hypertension
  - Pulmonary Fibrosis
- Heart
  - Myocardial Fibrosis
- Gastrointestinal
  - Esophageal dysmotility and gastroesophageal reflux
  - Gastroparesis
  - Small bowel stasis and bacterial overgrowth
  - Colonic diverticular disease

## Kidney Disease in Diffuse Scleroderma

- Renovascular disease causing hypertensive crisis resulting in acute renal insufficiency
- Usually an early manifestation



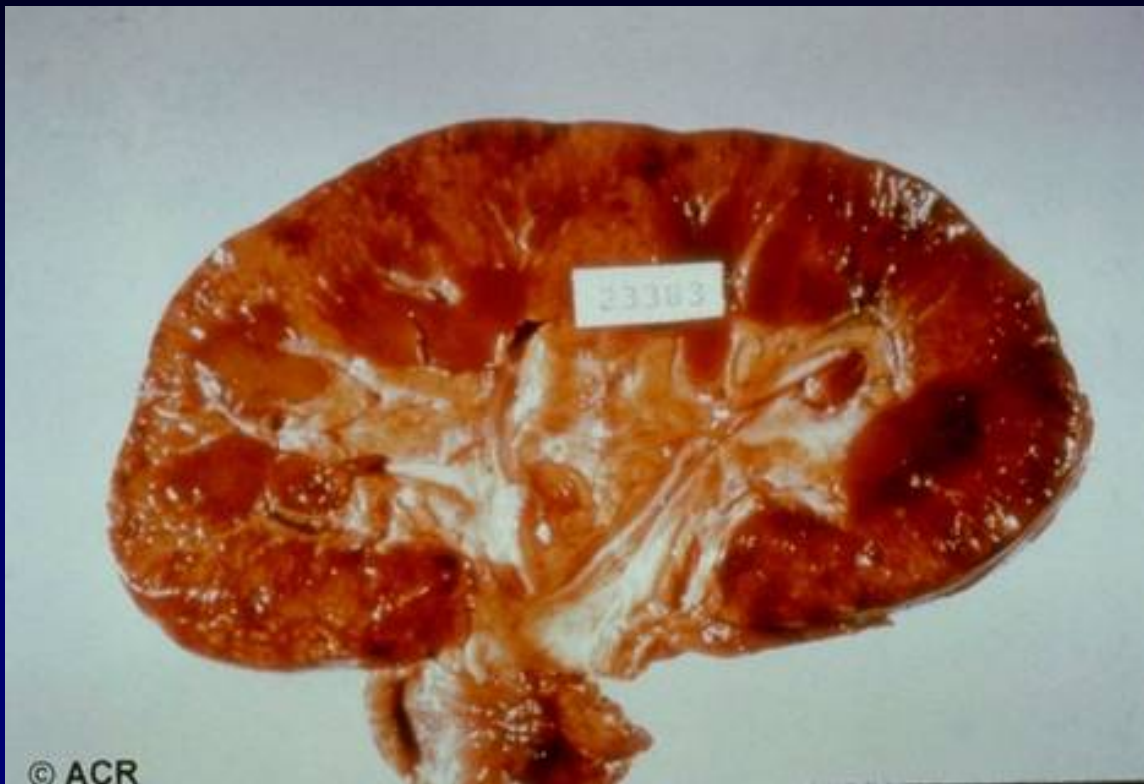
# Renal Arteriogram



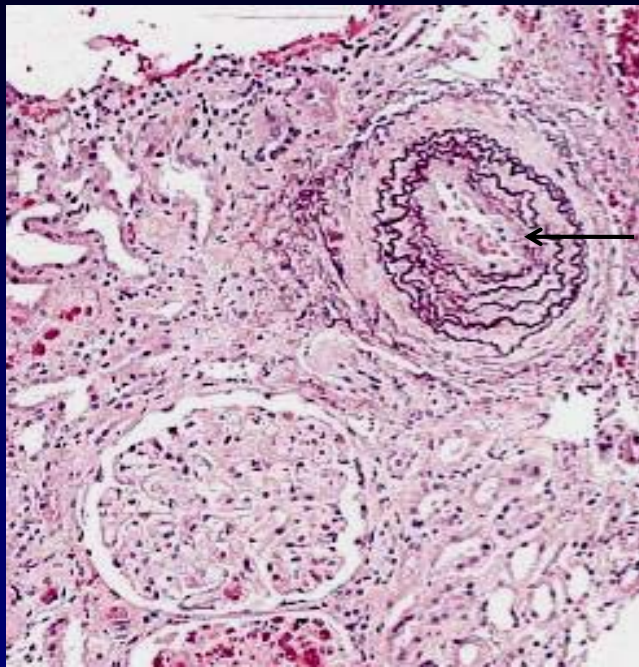
**Normal**

**Scleroderma**

# Scleroderma Kidney Infarctions



# Kidney Histopathology



← vessel lumen occlusion

## Approach to Scleroderma Kidney Disease

- Prophylactic administration of Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
  - Prior to ACE inhibitors: >90% mortality within one year
  - After ACE inhibitors: >60% survival after 10 years

# Pulmonary Disease\*

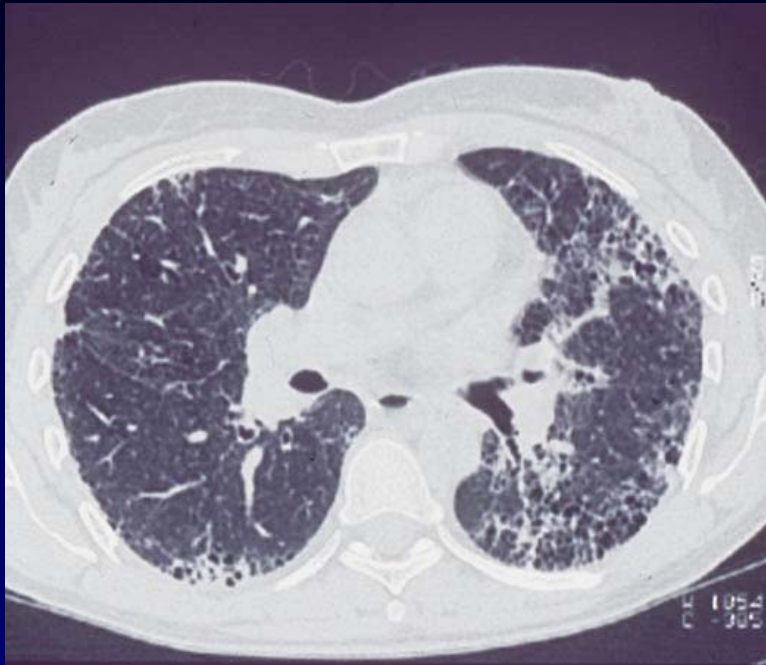
- Parenchymal involvement (interstitial lung disease)
  - Pulmonary fibrosis
- Vascular involvement
  - Pulmonary hypertension

*\*Major cause of mortality in Scleroderma*

# Pulmonary Fibrosis

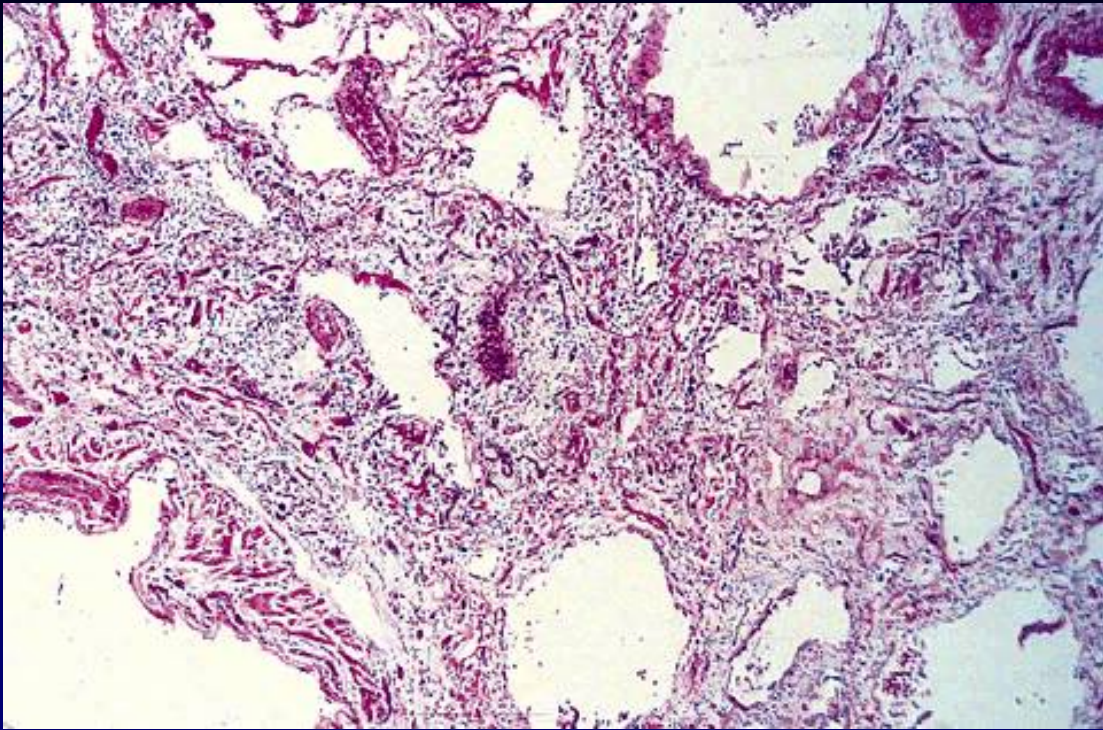


# Pulmonary Fibrosis



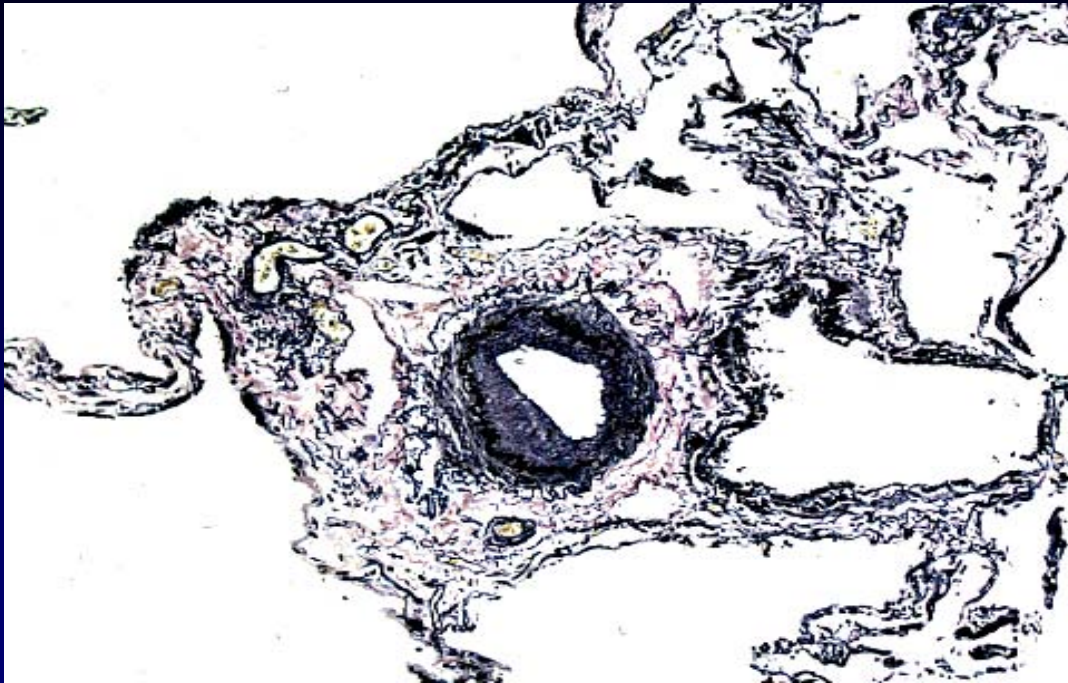
*Chest CT scan*

# Interstitial Lung Disease





# Pulmonary Artery Involvement



# Therapy of Pulmonary Hypertension

- Calcium channel blockers (e.g., diltiazem)
- Endothelin receptor blockers
  - Bosentan (Tracleer)
  - Ambrisentan (Letairis)
- Phosphodiesterase 5 inhibitor
  - Sildenafil (Revatio)
- Prostacyclin analogs
  - Epoprostenol (Flolan) intravenous
  - Treprostinil (Remodulin) intravenous
  - Iloprost (Ventavis) inhalation

# Therapy of Interstitial Lung Disease

- Corticosteroids plus cyclophosphamide?
- Autologous stem cell transplant?

## Gastrointestinal Involvement

- Principal cause of symptoms is a fibrosing process of the medial layer of the GI tract resulting in the replacement of smooth muscle with collagen
- Can involve the entire gastrointestinal tract
- Significant cause of morbidity in scleroderma

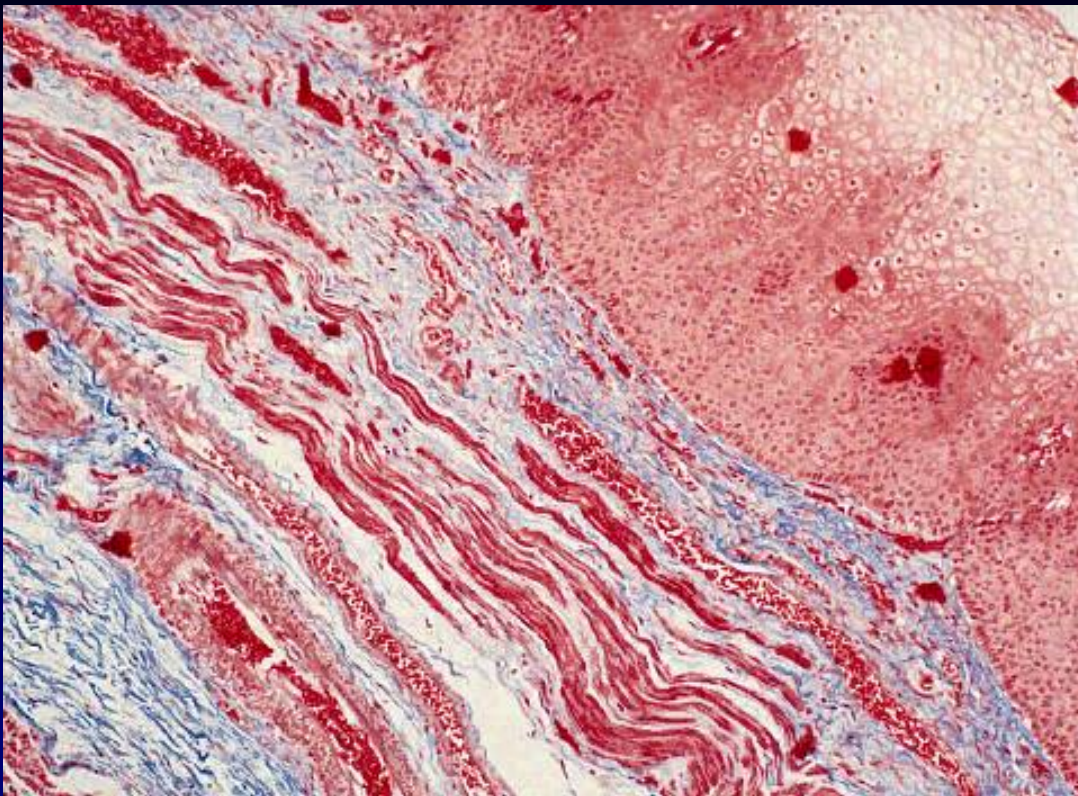
# Esophageal Involvement

- Esophageal Dysmotility
  - Dysphagia
- Gastroesophageal Reflux due to incompetence of the lower esophageal sphincter
  - Dyspepsia or heartburn

# Esophageal Disease

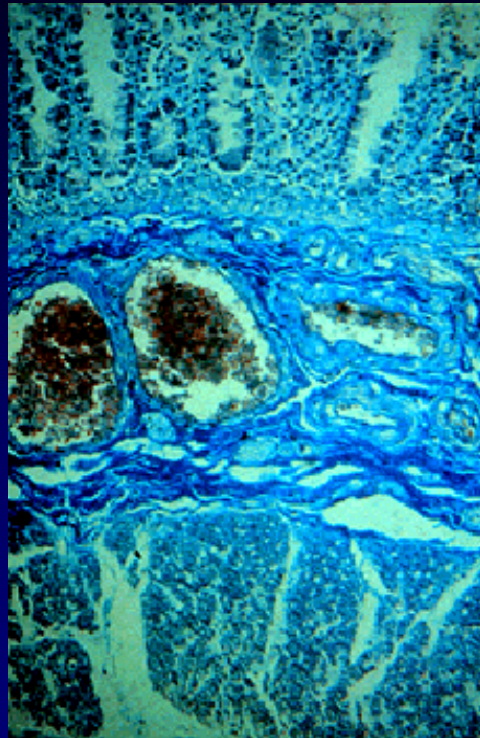


# Esophageal Histopathology



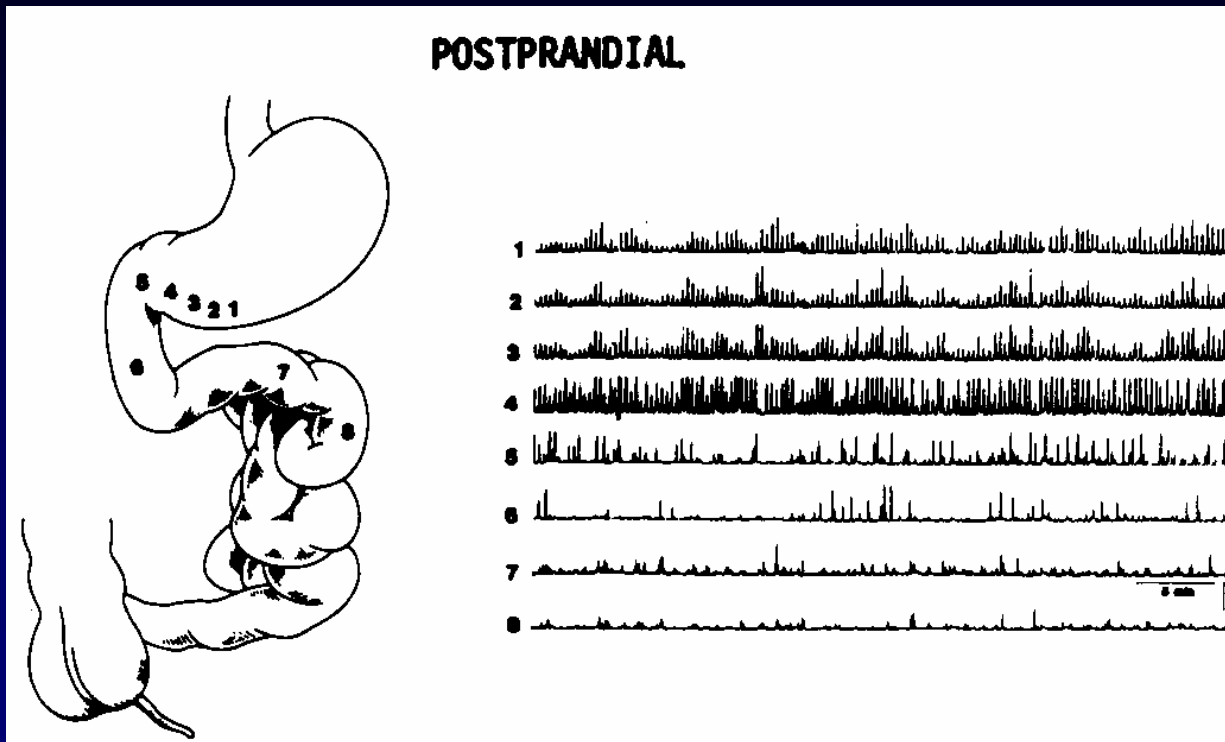
# Duodenal Histopathology

Brunner's glands →

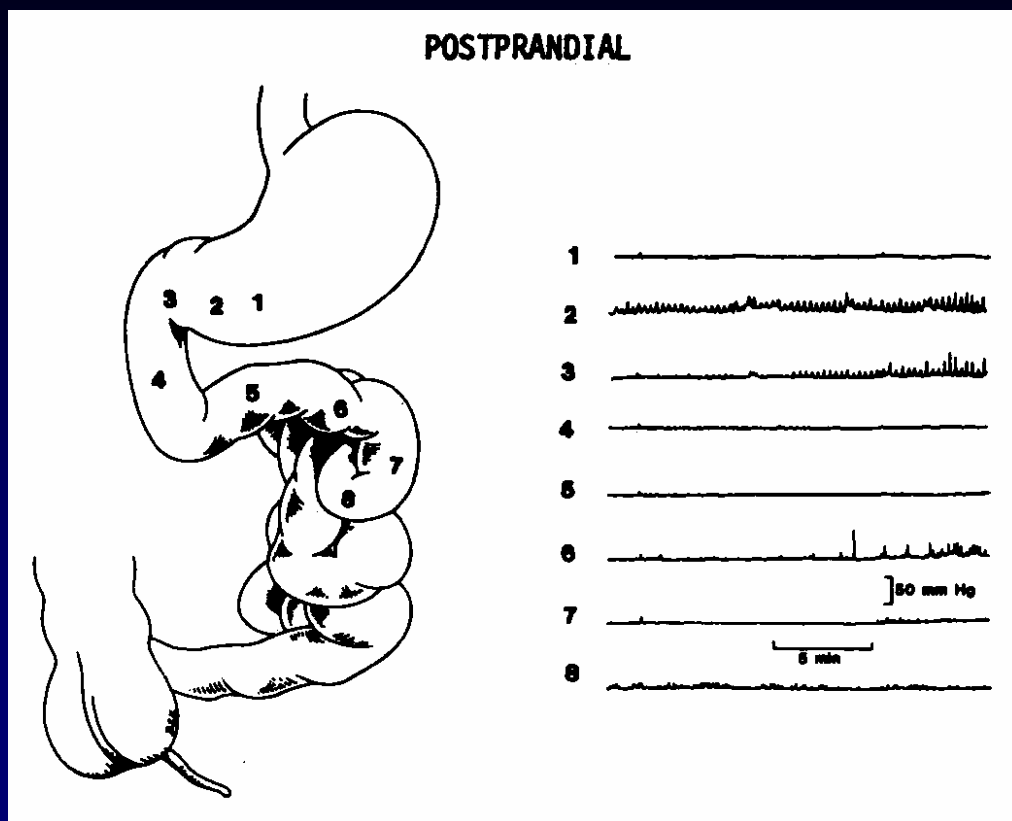




# Normal GI Manometry



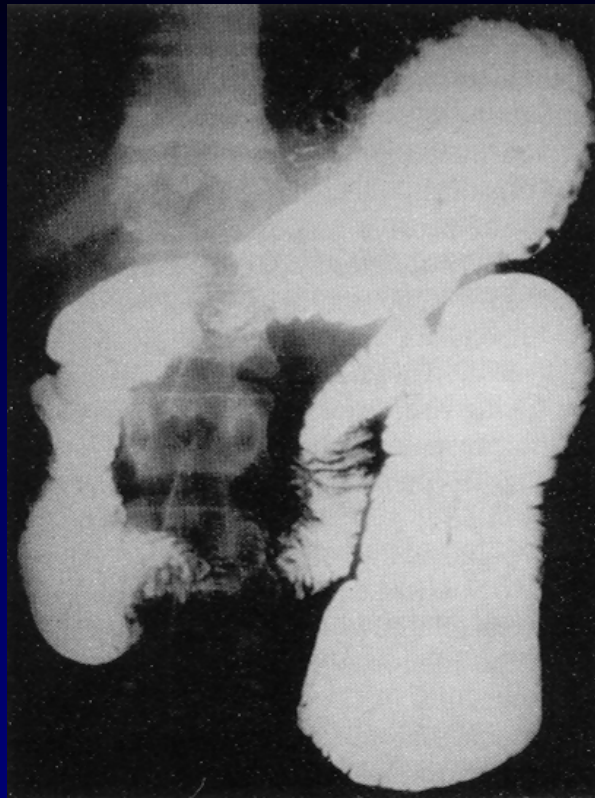
# GI Manometry in Scleroderma



# Small Intestine Involvement

- Hypomotility
  - Stasis of intestinal contents
- Bacterial Overgrowth
  - Malabsorption
- Pseudo-obstruction
  - Abdominal pain

## Dilatation of Proximal Jejunum



# Large Intestine Involvement

- Diverticuli
  - Perforation
- Hypomotility
  - Constipation
- Pseudo-obstruction
  - Abdominal pain

## Colonic Diverticuli



# Colonic Diverticuli



# Approach to Gastrointestinal Disease

- Gastroesophageal reflux
  - Antisecretory agents, e.g., proton pump inhibitors
- Malabsorption 2° to bacterial overgrowth
  - Antibiotic therapy
- Hypo- or dysmotility related symptoms
  - Symptom control
    - e.g., constipation → laxatives



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