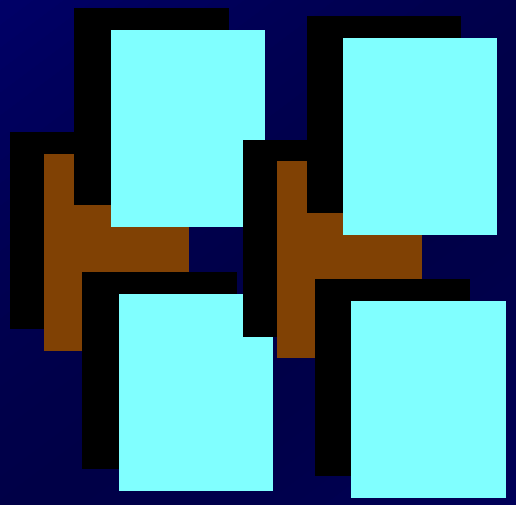
Scleroderma

systemic sclerosis

pss

SSc



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Overview

- Basics
- Epidemiology
- Pathogenesis
- Pathology
- Clinical features
- Laboratory evaluation

Basics

- *Definition*: A **systemic** disorder characterized by accumulation of connective tissue in the skin and visceral organs, causing structural and functional abnormalities
- *Etiology*: Unknown
- *Clinical characteristics*:
  - vascular damage
  - immune activation
  - excessive synthesis and deposition of extracellular matrix (fibrosis)

Pathogenesis

Uncontrolled and irreversible proliferation of normal connective tissue along with striking vascular changes

- Collagen
- Proteoglycans
- Fibronectin
- Laminin

EPIDEMIOLOGY OF SYSTEMIC SCLEROSIS

Peak age (years)	30–50
Sex distribution (F:M)	4:1
Prevalence rate (/100,000)	10–20
Annual incidence (/100,000)	1–2
Geography	Unrestricted
Genetic associations	?? DR5, DRw52, DR4
Relative risk	Unknown

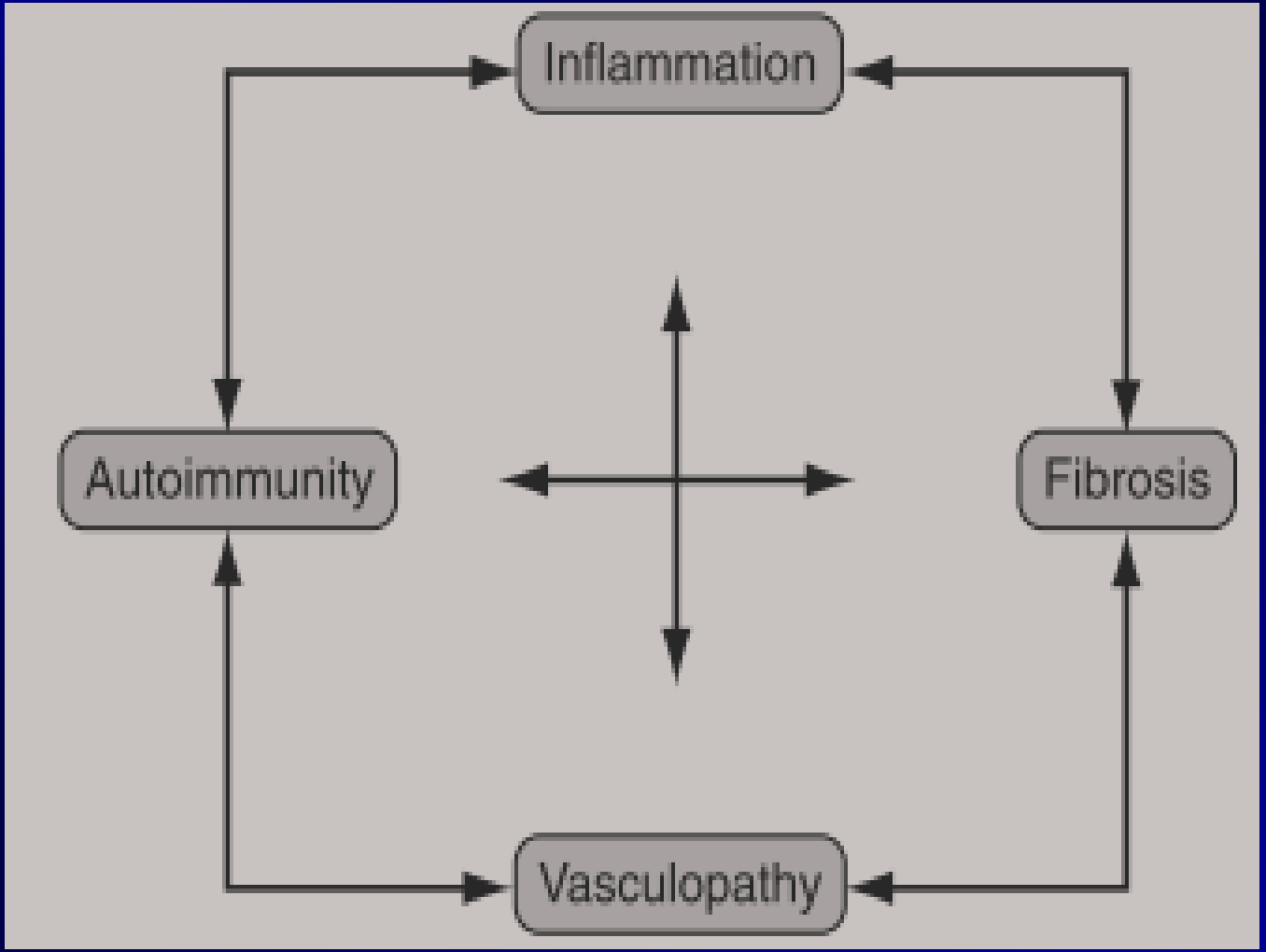
Scleroderma

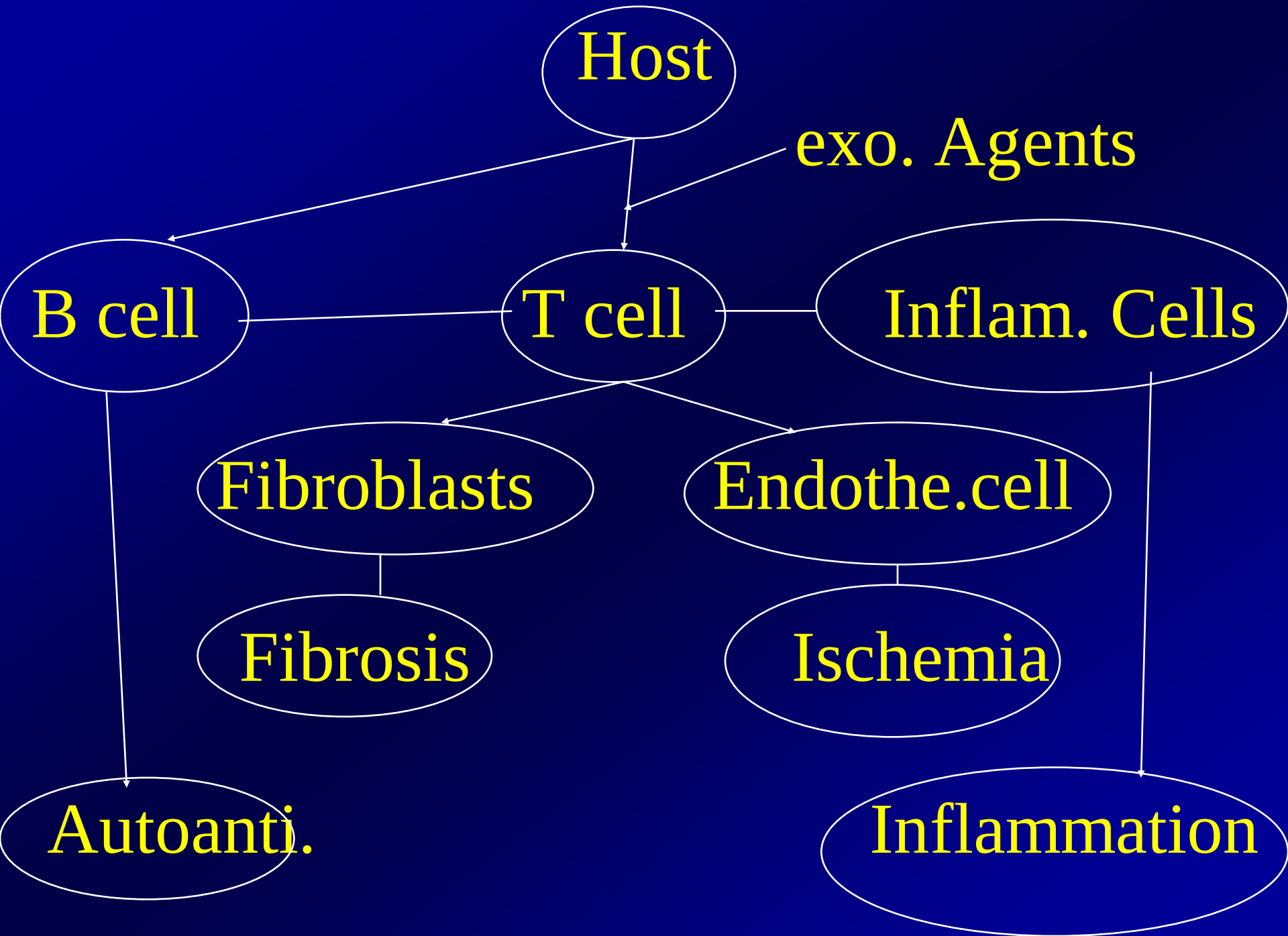
Etiology

Initiating factors are not known

- Numerous environmental agents (PVC)
- Drugs (Bleomycin, Pentezocine)
- Viruses
- Defective immunoregulation
  - Autoantibodies
  - Cellular autoimmunity
  - Genetics and viruses

Pathogenesis




Host
exo. Agents
B cell
T cell
Inflam. Cells
Fibroblasts
Endothe.cell
Fibrosis
Ischemia
Autoanti.
Inflammation

Genetic Risk

- The relative risk among first-degree: 13
- HLA DRB1*1104, DQA1*0501, DQB1*0301

Systemic Sclerosis (SSc) Susceptibility Genes

Locus	Chromosome	Associated SSc Subset
HLA	6	Various
PTPN22	1p3.2	Topo1+ positive
NLRP1	17p13.2	dcSSc, pulmonary fibrosis
IRF5	7q32	dcSSc
STAT4	2q32.3	lcSSc, ACA
BANK1	4q24	dcSSc
TNFSF4	1q25	SSc
T-bet	17.q21.32	SSc

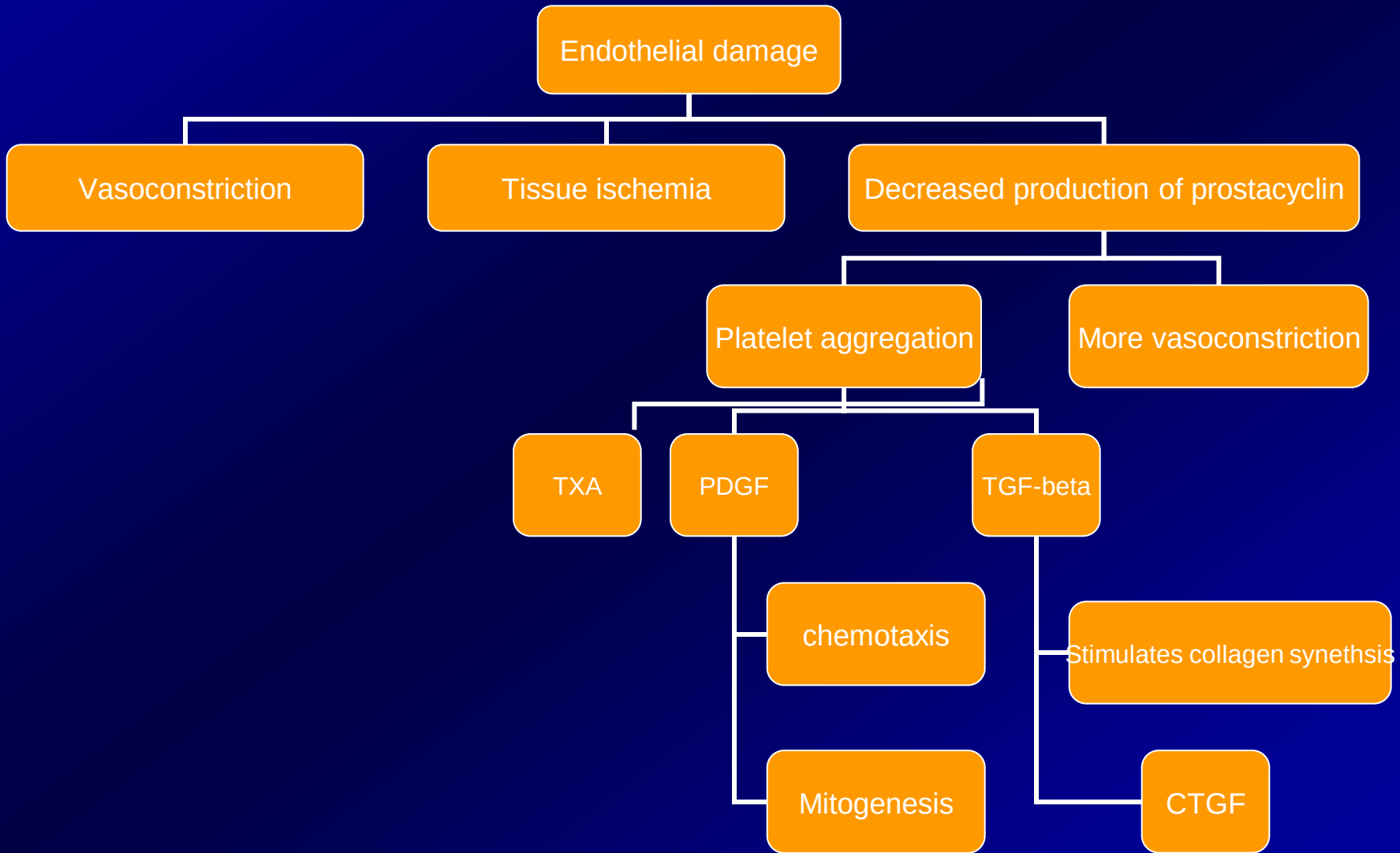
Environmental Agents and Drugs Implicated in Scleroderma-like Syndromes

Chemicals
Silica
Heavy metals
Mercury
Organic chemicals
Vinyl chloride
Benzene
Toluene
Trichloroethylene
Drugs
Bleomycin
Pentazocine
Taxol
Cocaine
Dietary Supplement/Appetite Suppressants
L-tryptophan (contamination)
Mazindol
Fenfluramine
Diethylpropion

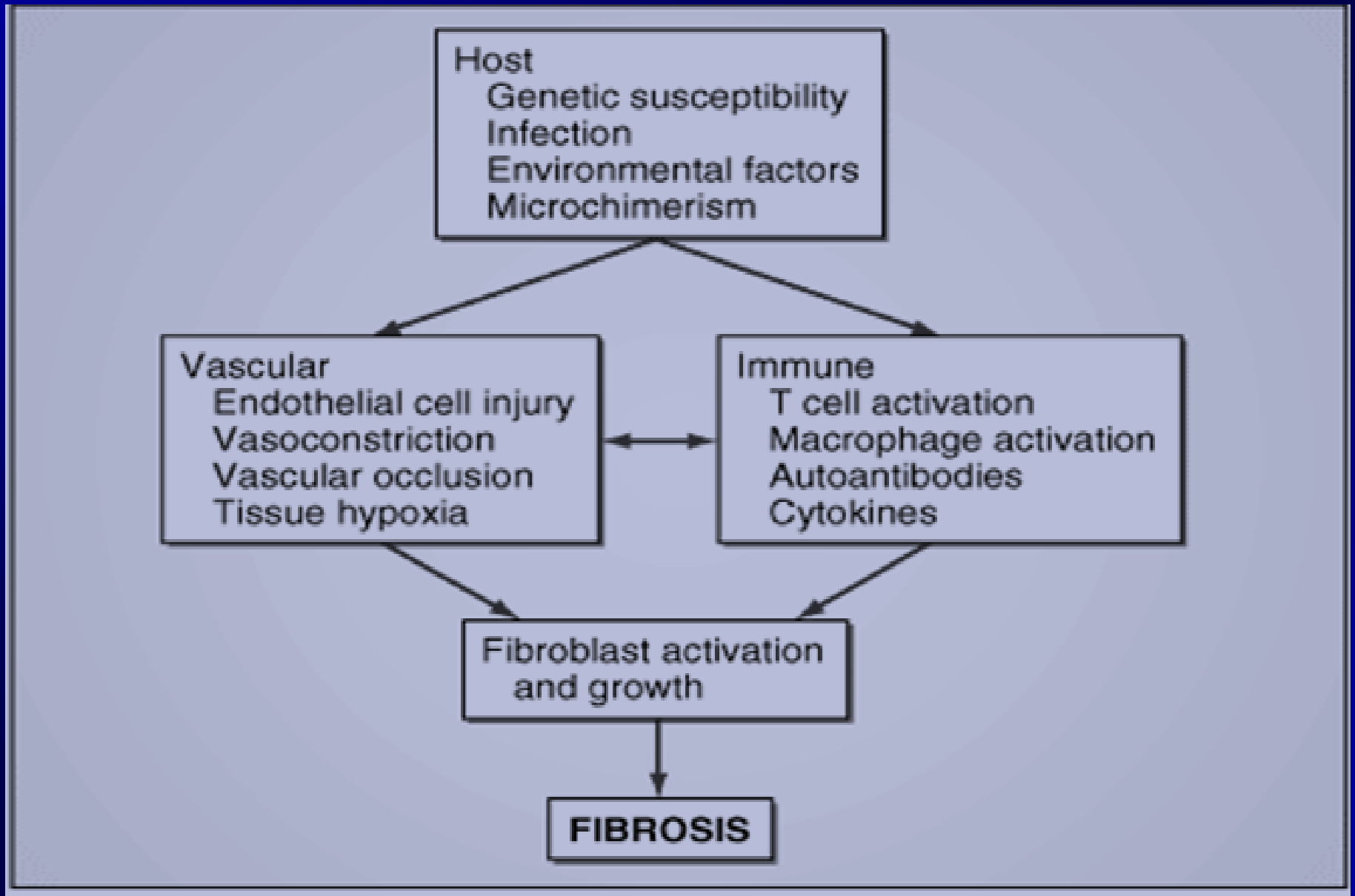
INFECTIOUS AGENTS: VIRUSES

- Human cytomegalo- virus (hCMV)
- Parvovirus B19

Vasculopathy



Fibrosis


Host
Genetic susceptibility
Infection
Environmental factors
Microchimerism
Vascular
Endothelial cell injury
Vasoconstriction
Vascular occlusion
Tissue hypoxia
Immune
T cell activation
Macrophage activation
Autoantibodies
Cytokines
Fibroblast activation and growth
FIBROSIS

Cause of excess production of connective tissue matrix :

PDGF
TGF beta
IL1

MICROCHIMERISM

PATHOLOGY

- In early-stage:

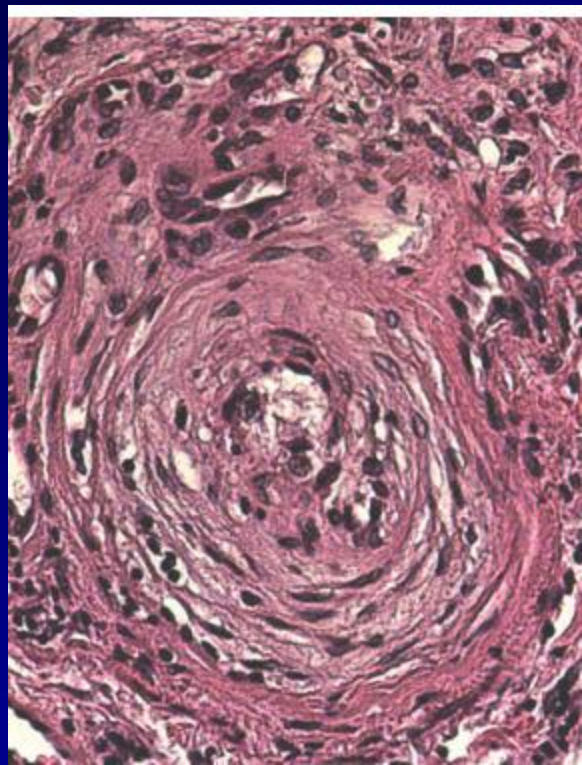
  inflammatory cell infiltrates

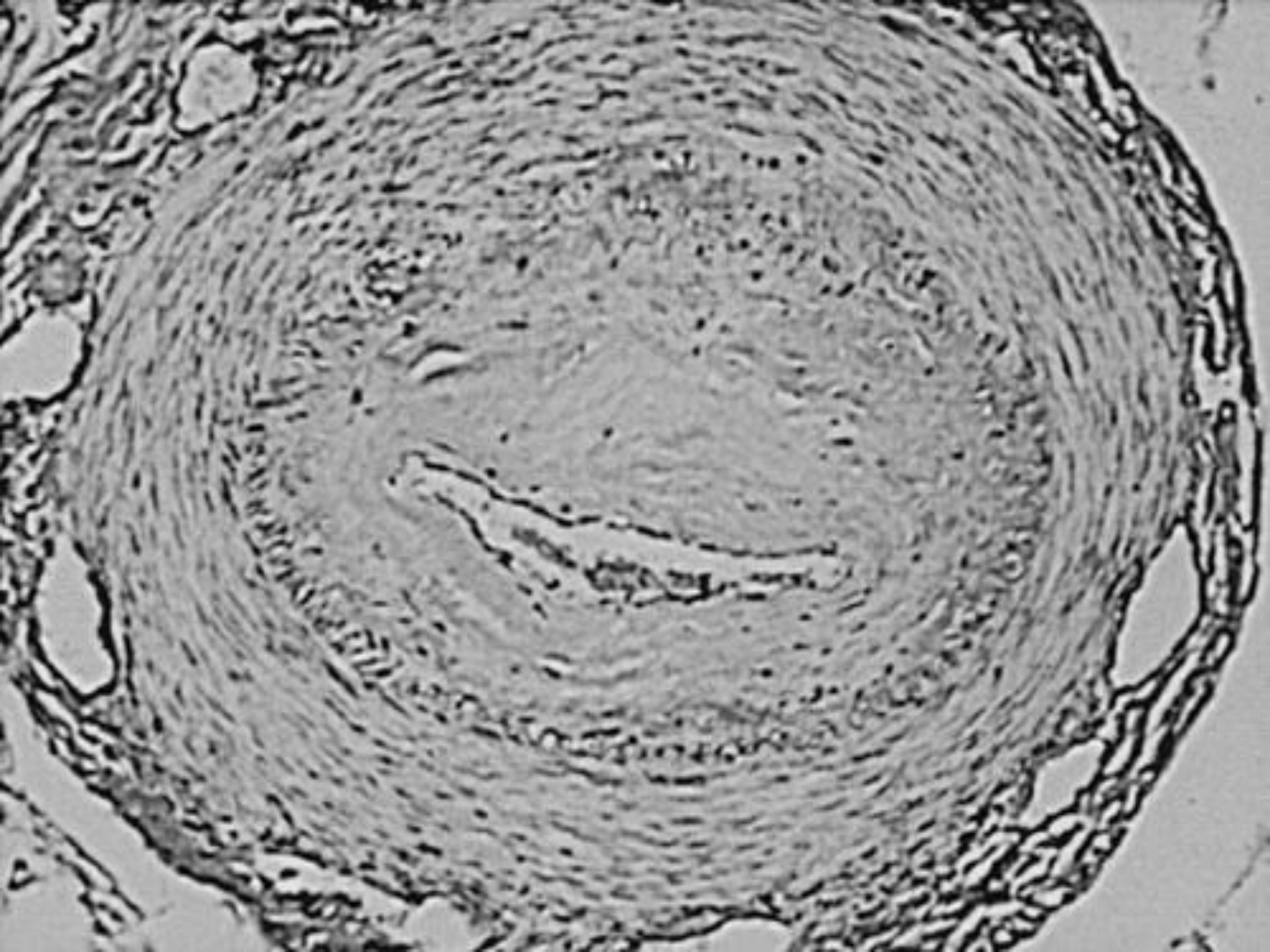
- Noninflammatory proliferative/obliterative vasculopathy

  Fibrosis

Vascular Pathology

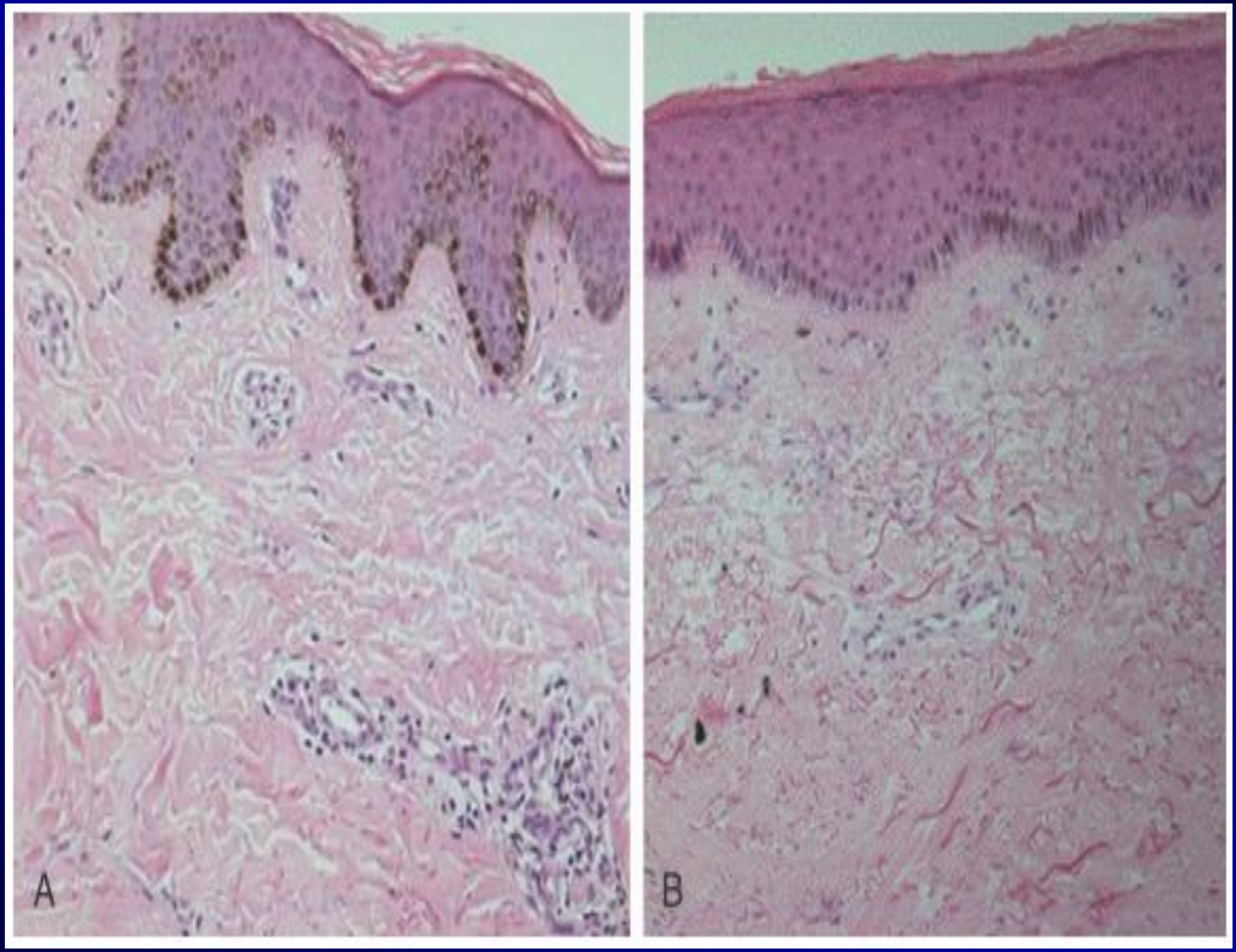
- Intimal proliferation
- Medial hypertrophy





Tissue Fibrosis

- Excessive accumulation of:
- Fibrillar collagens
- Fibronectin
- Elastin
- Proteoglycans,
- Cartilage oligomeric matrix protein (COMP)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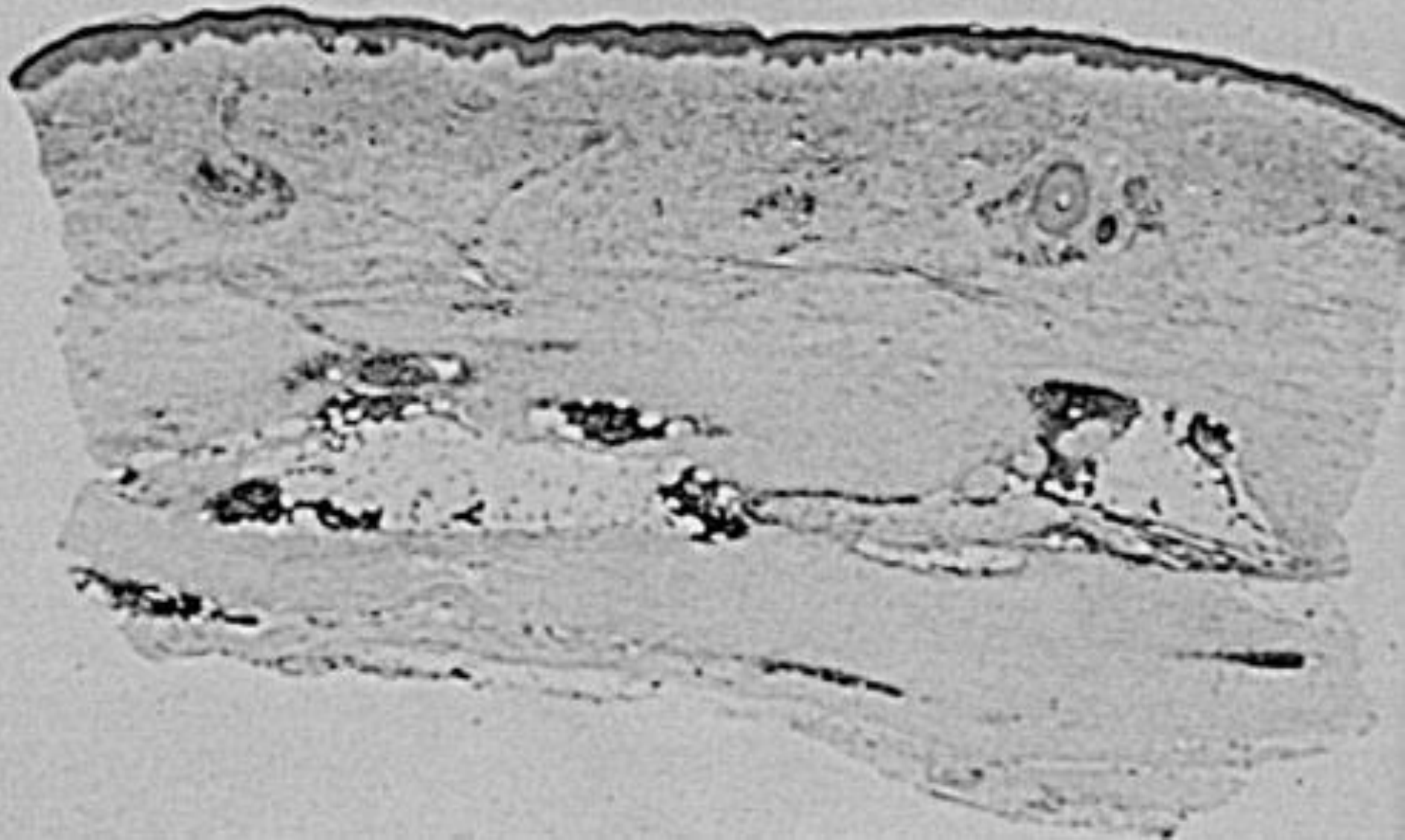
B



Classification

- **Diffuse**
- **Limited**
- **Localized(morphea,linear)**

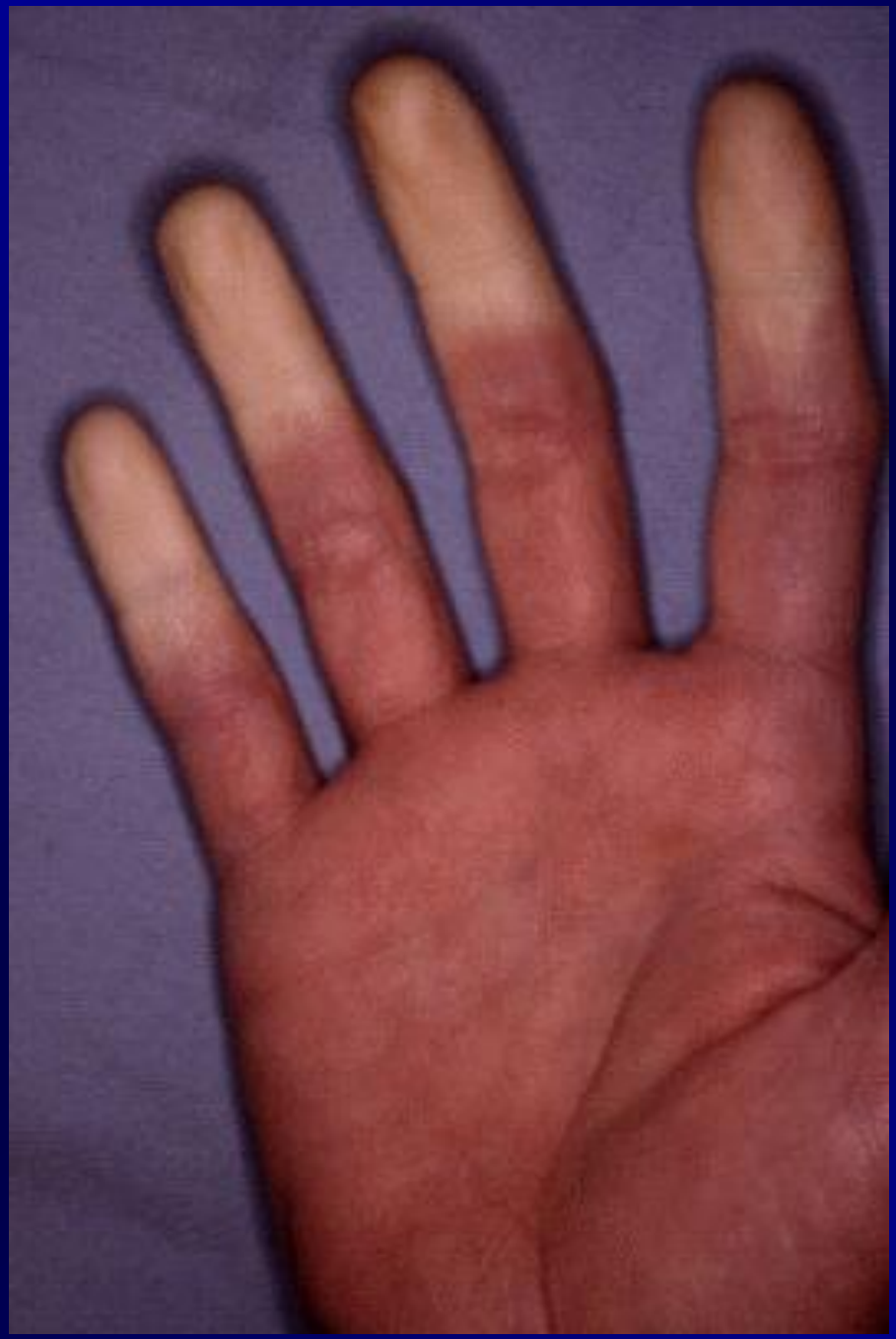
Clinical Features:

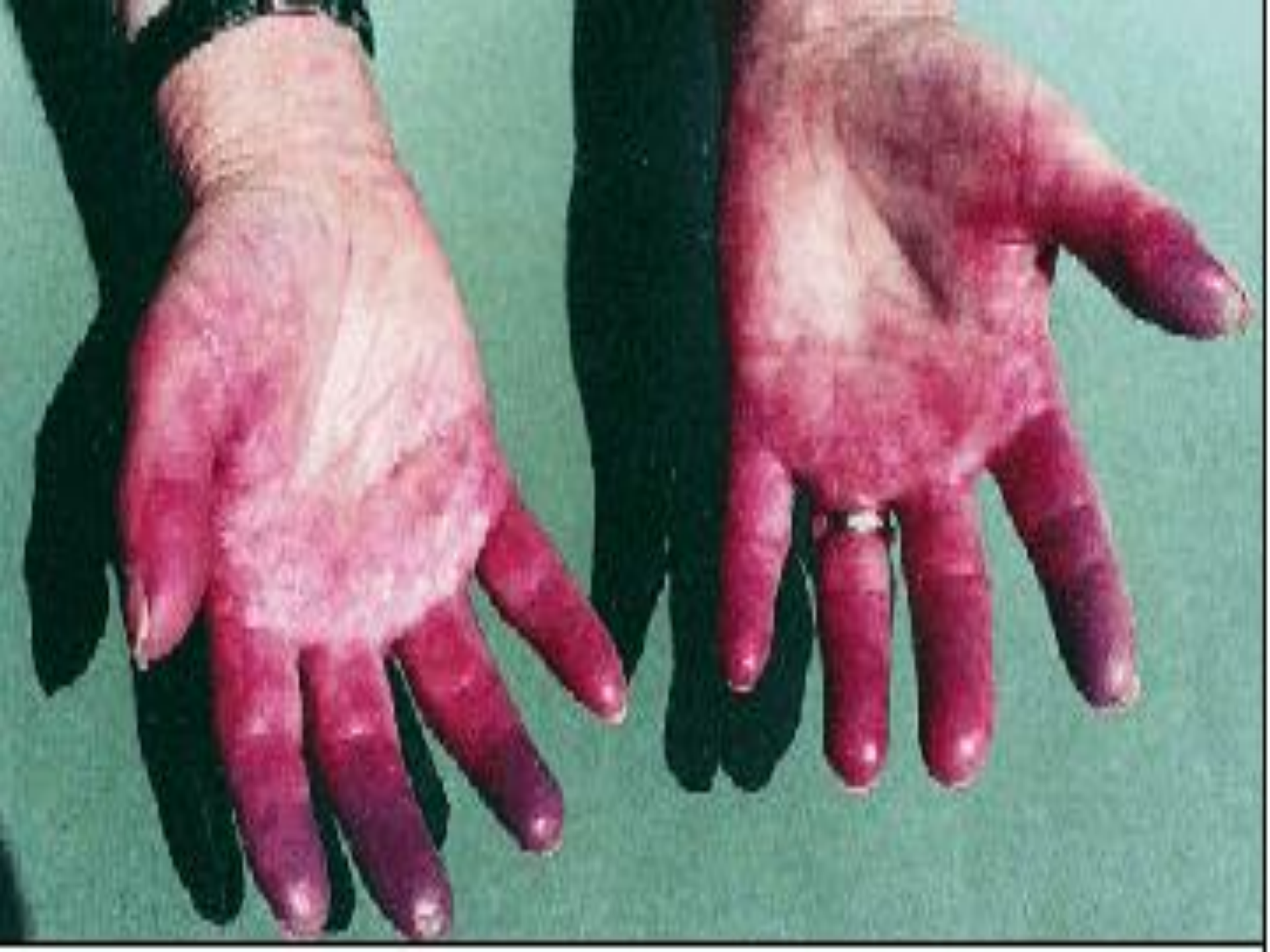
Fibrous thickening affects:

- **Skin**
- **Muscles**
- **Joints**
- **Tendons**
- **Certain internal organs especially esophagus, intestinal tract, lungs and kidneys**

Raynaud's phenomenon

- **An episodic self-limited and reversible vasomotor disturbance manifested as color changes bilaterally in the fingers,toes,and sometimes ears nose and lips**
- **Color changes: pallor,cyanosis,erythema**
- **Numbness,tingling,pain on recovery**





Scleroderma and Raynaud's

- **Frequency :**

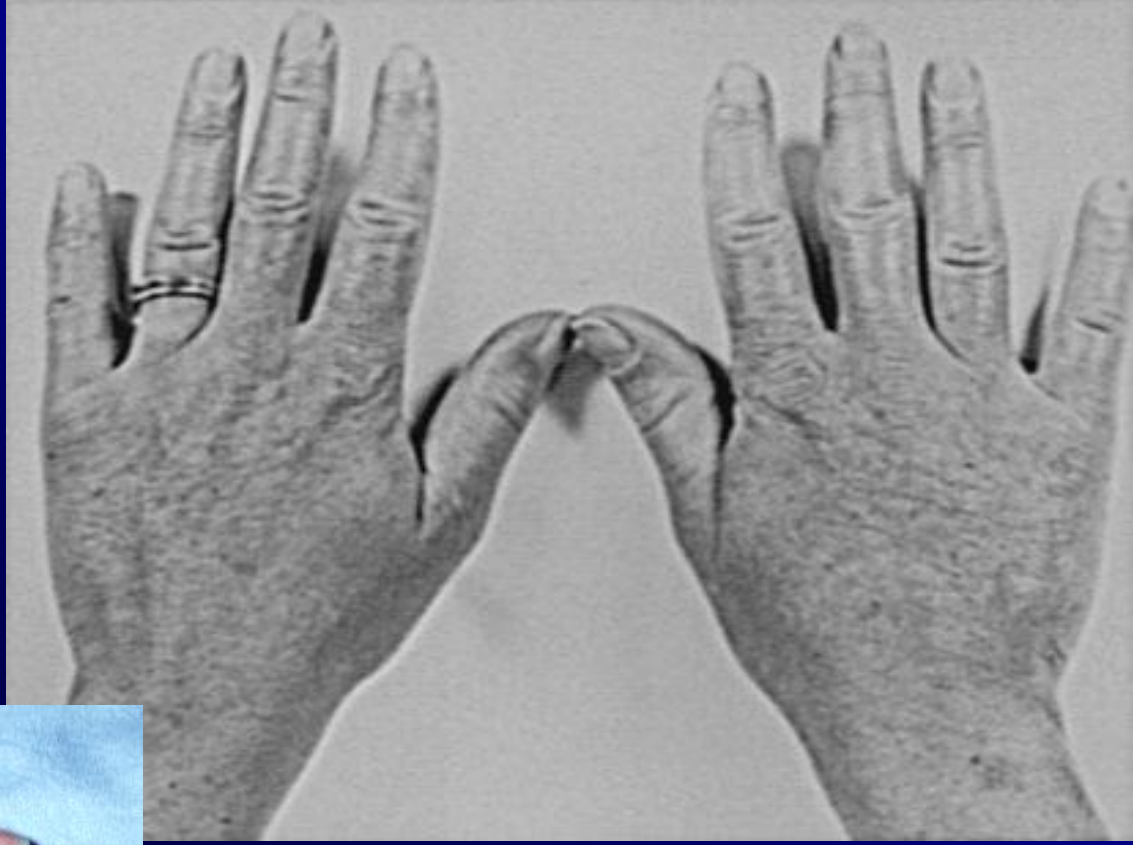
  Diffuse 85%

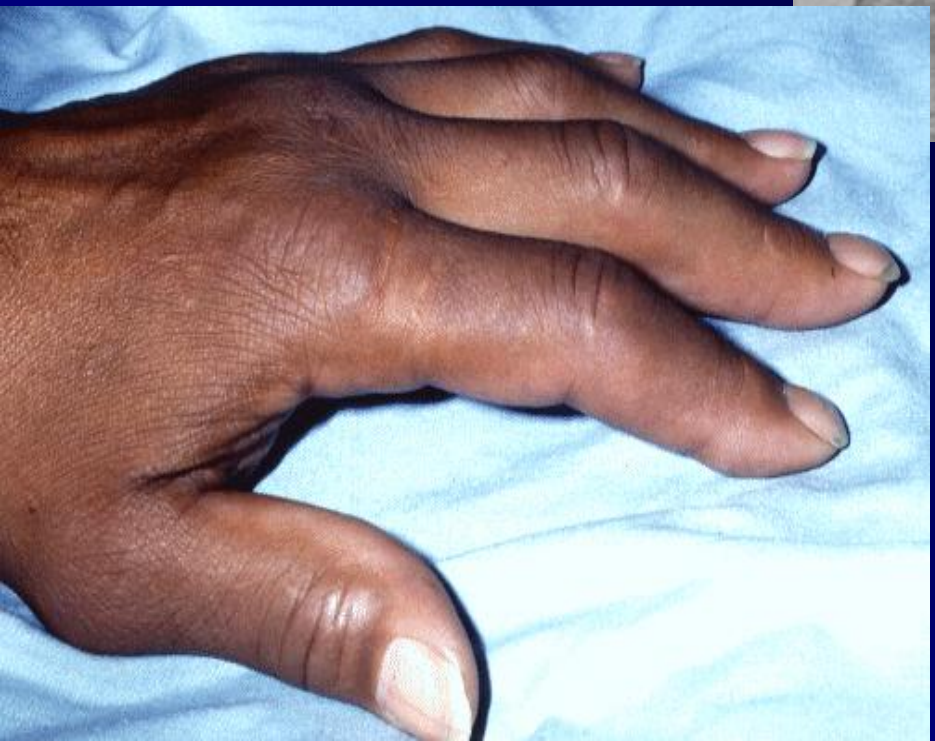
  Limited 95%

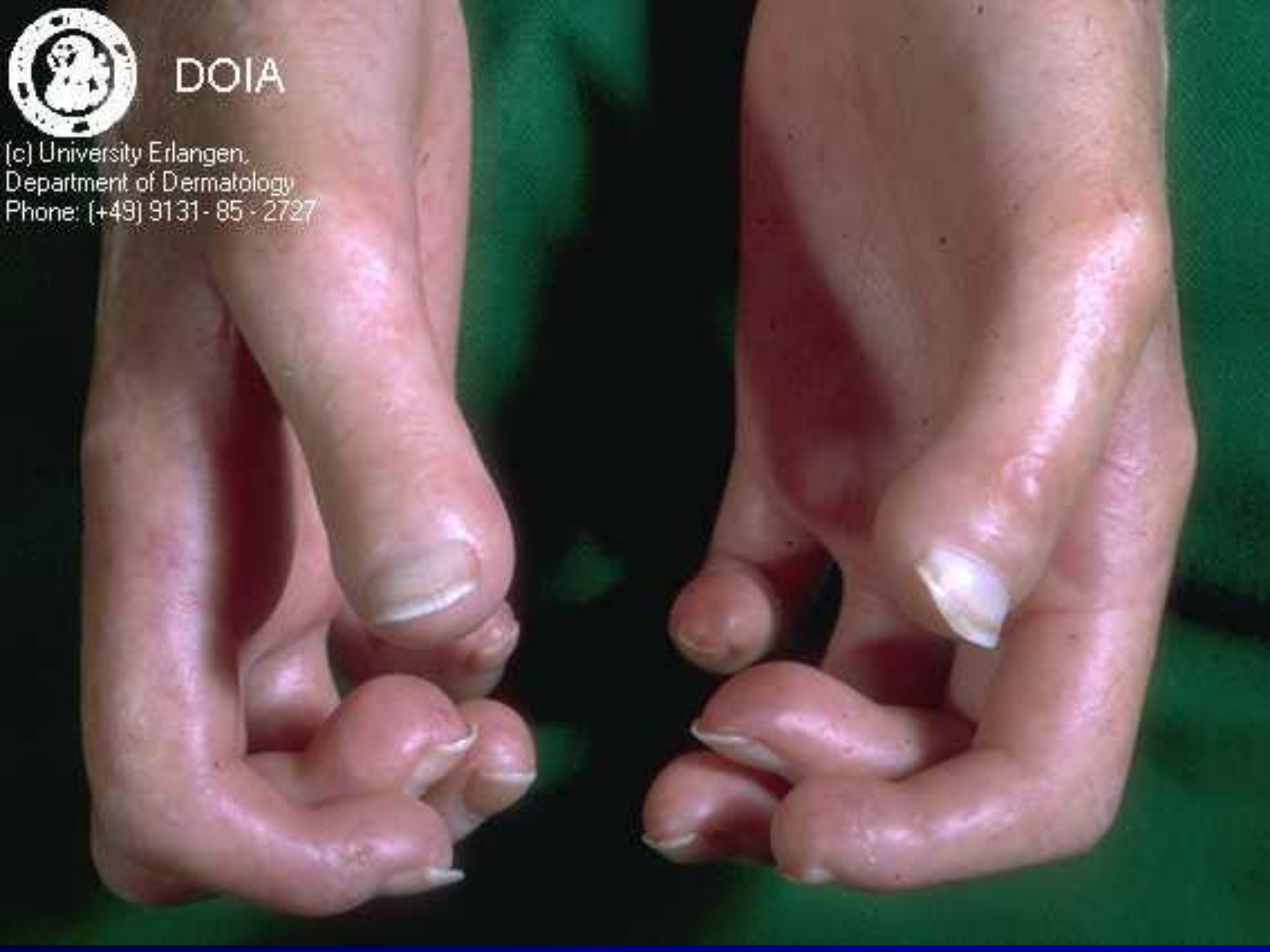
- **In 70% first presentation**

Skin

- Edematous
- Hardening
- Softening






DOIA
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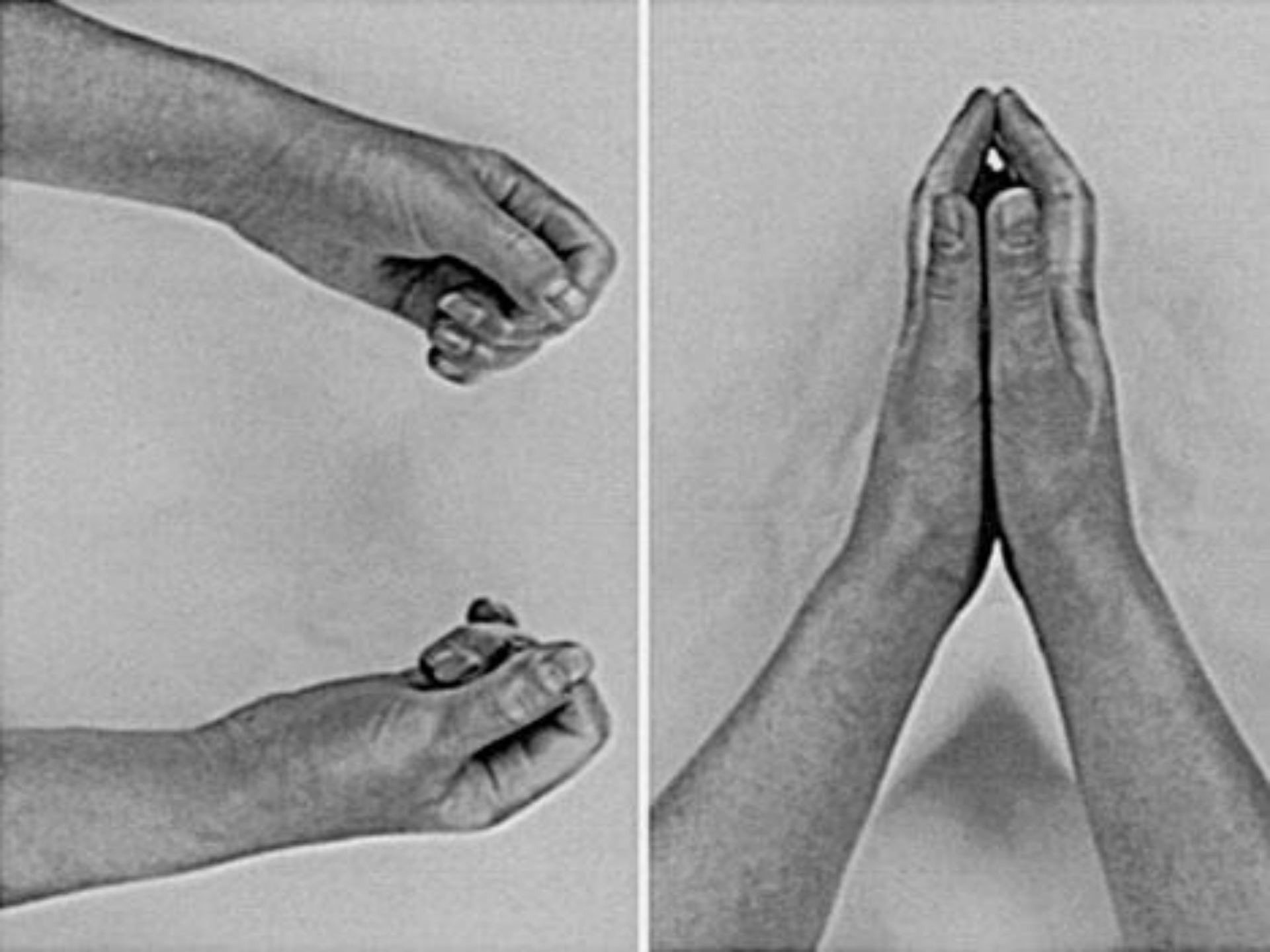
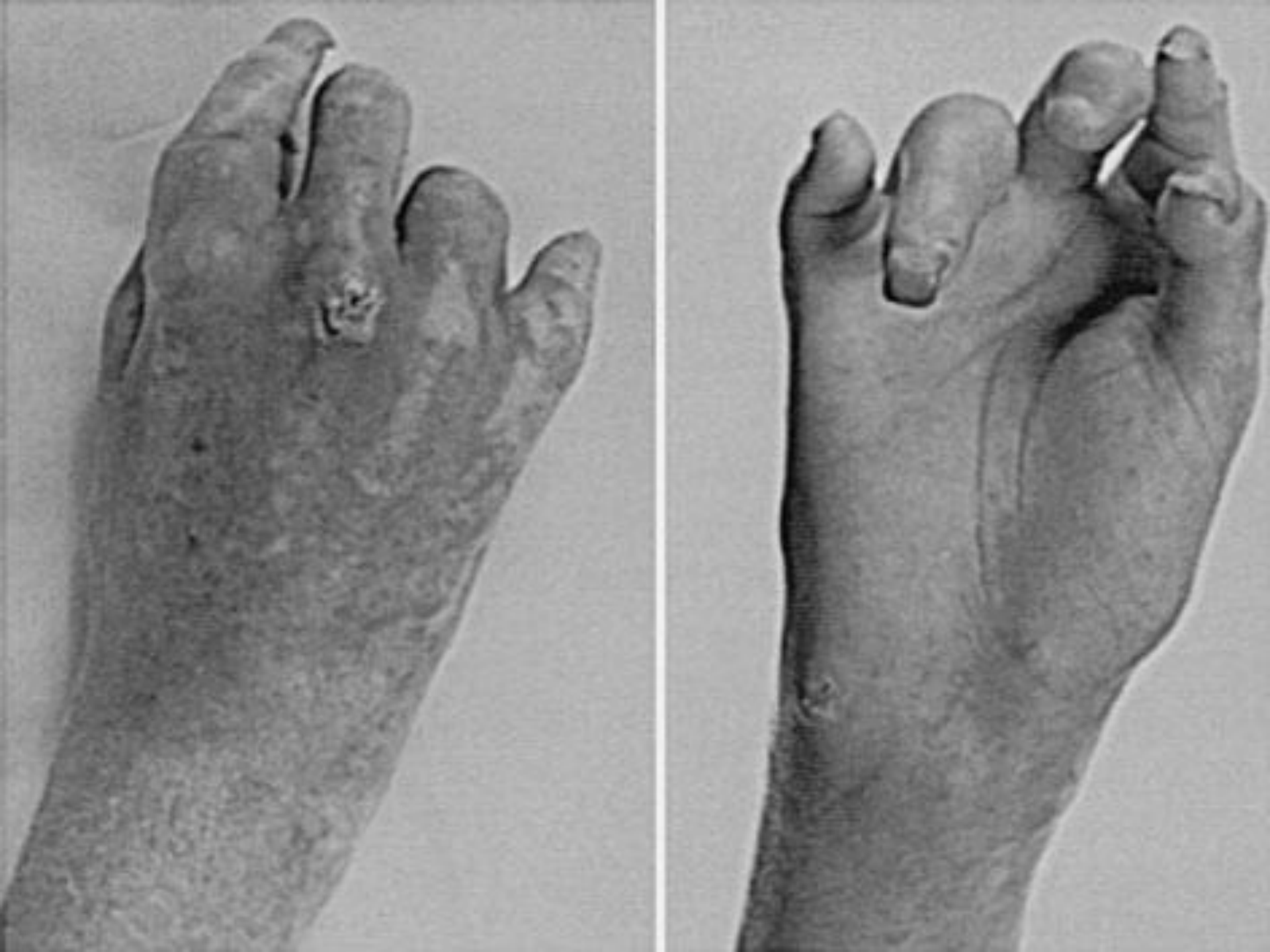
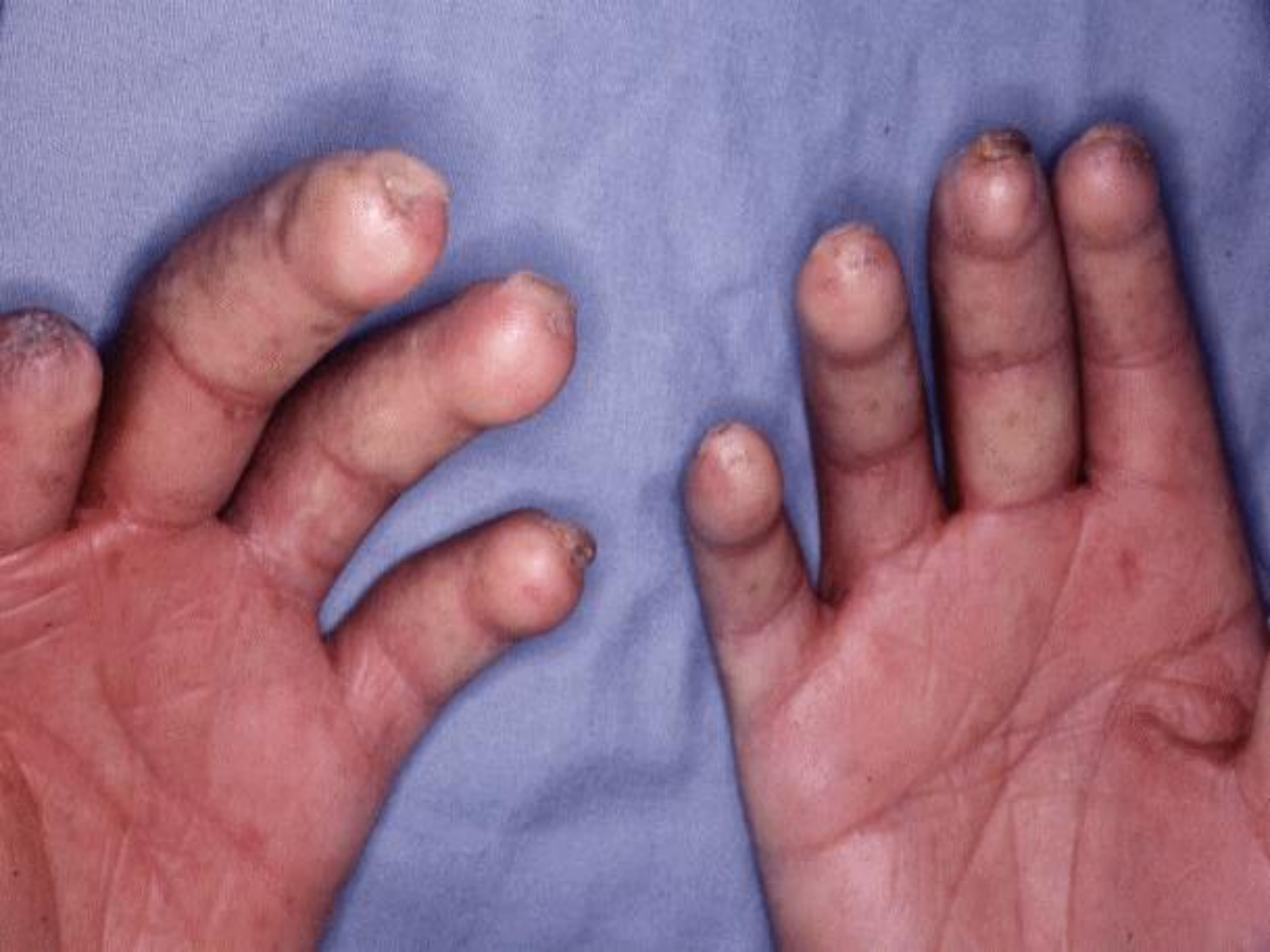
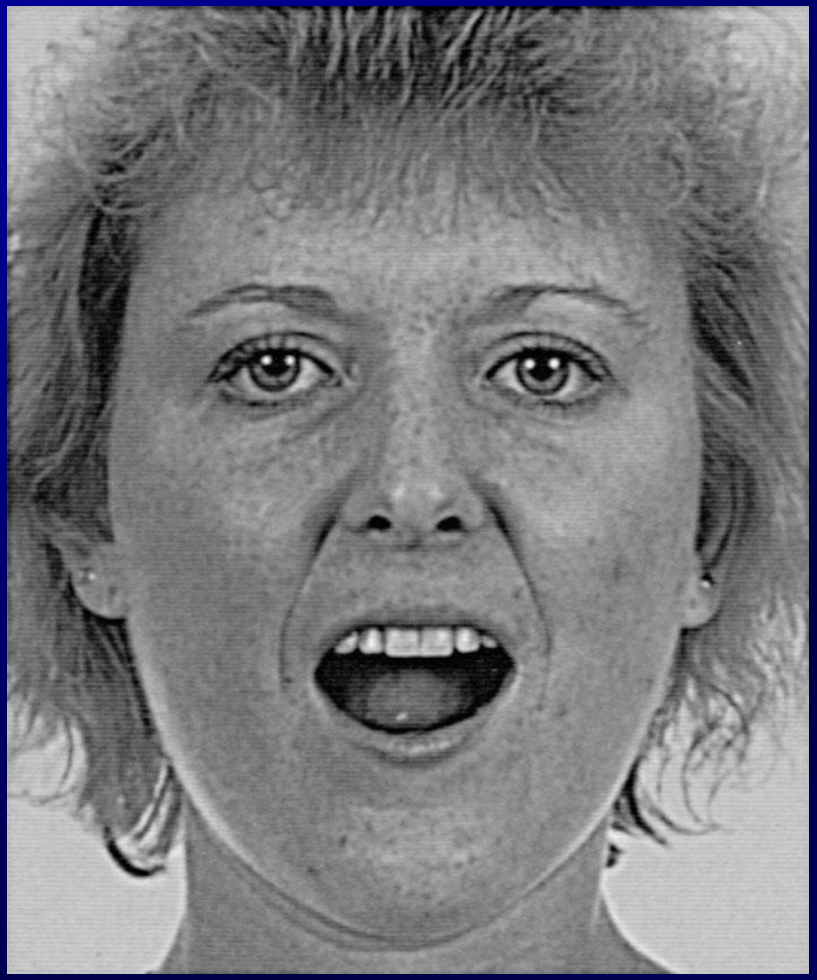
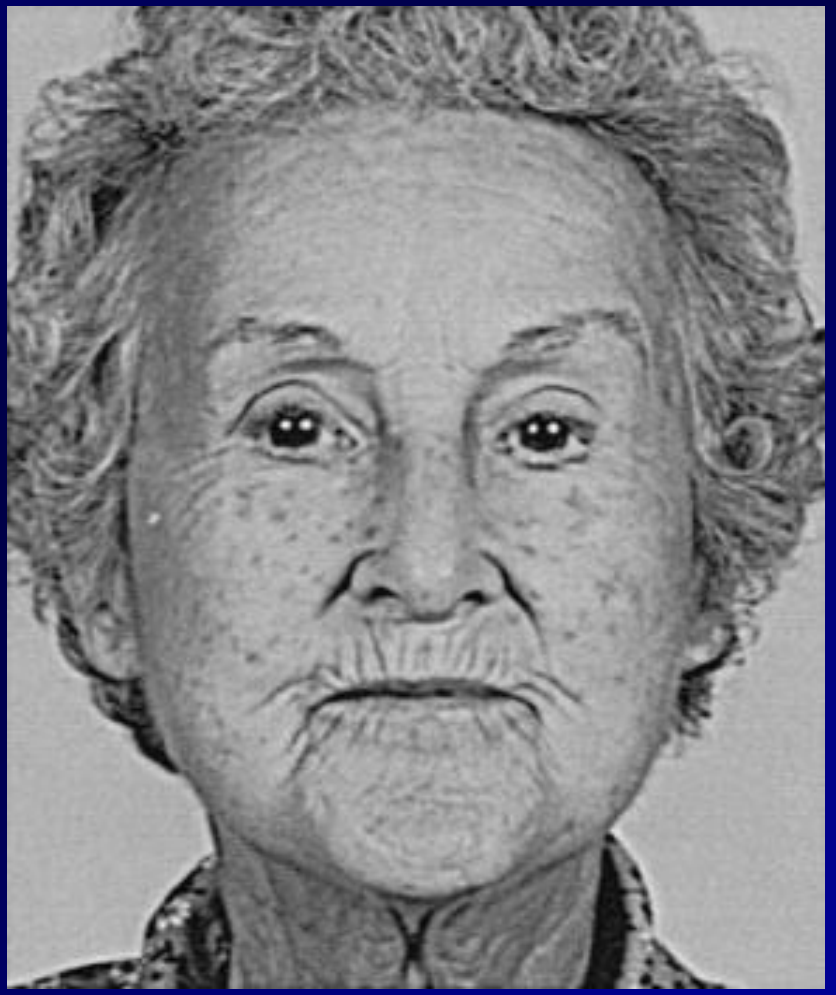
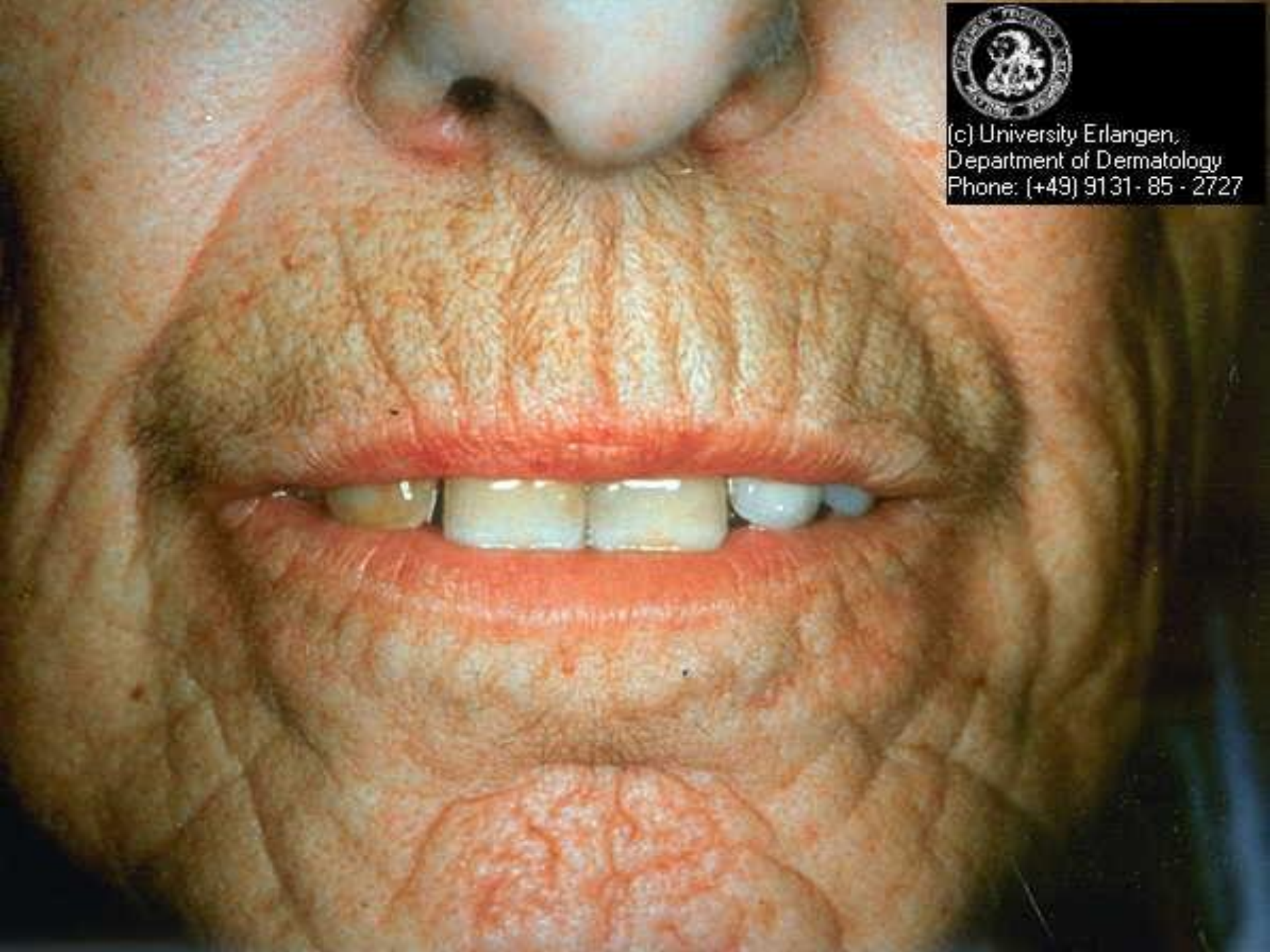


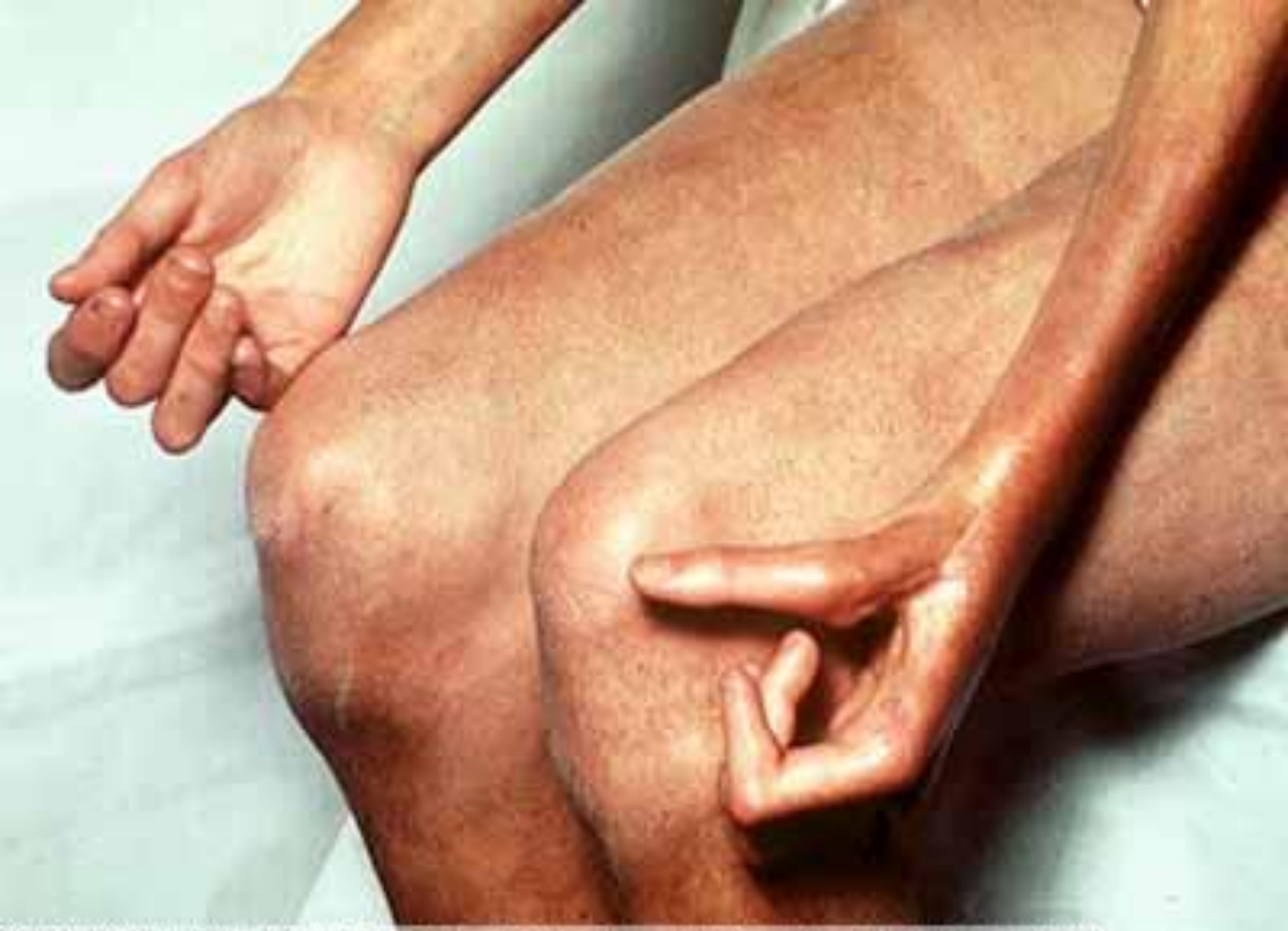


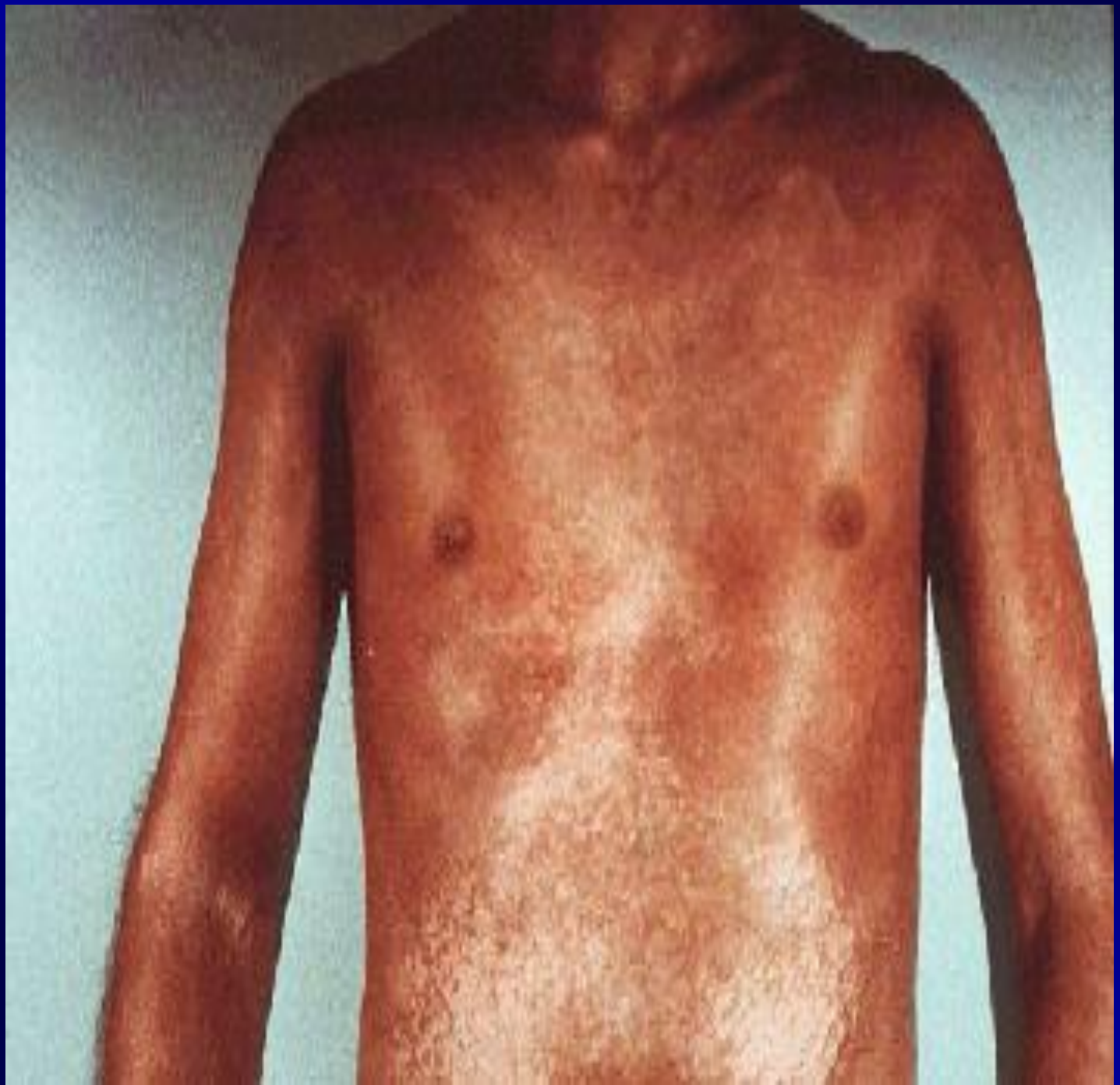


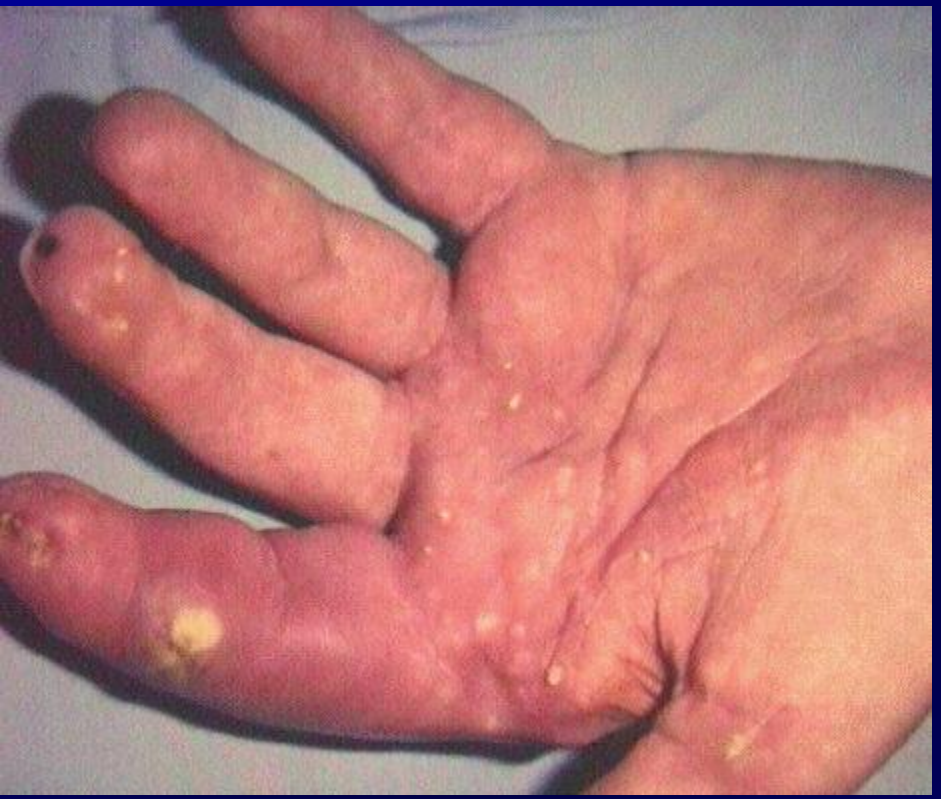


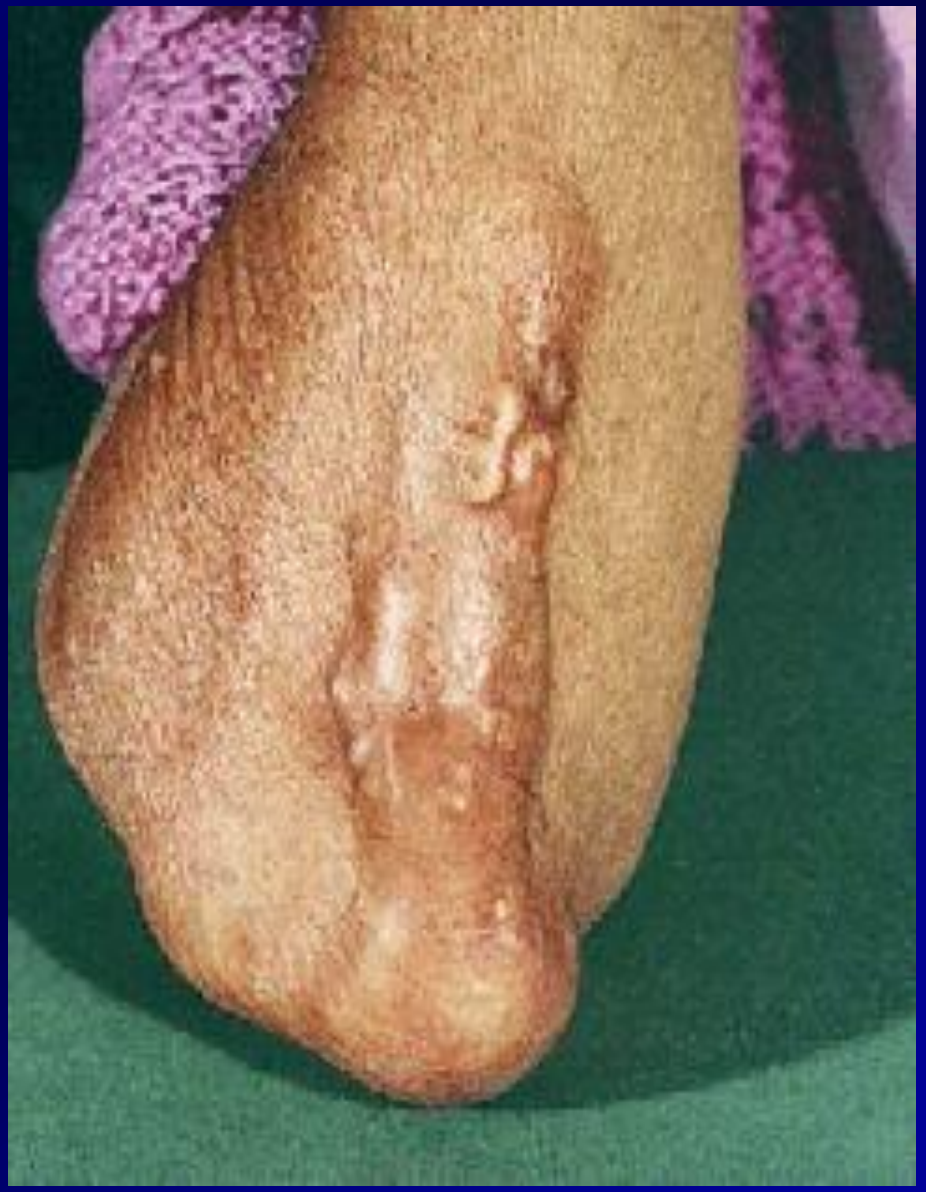


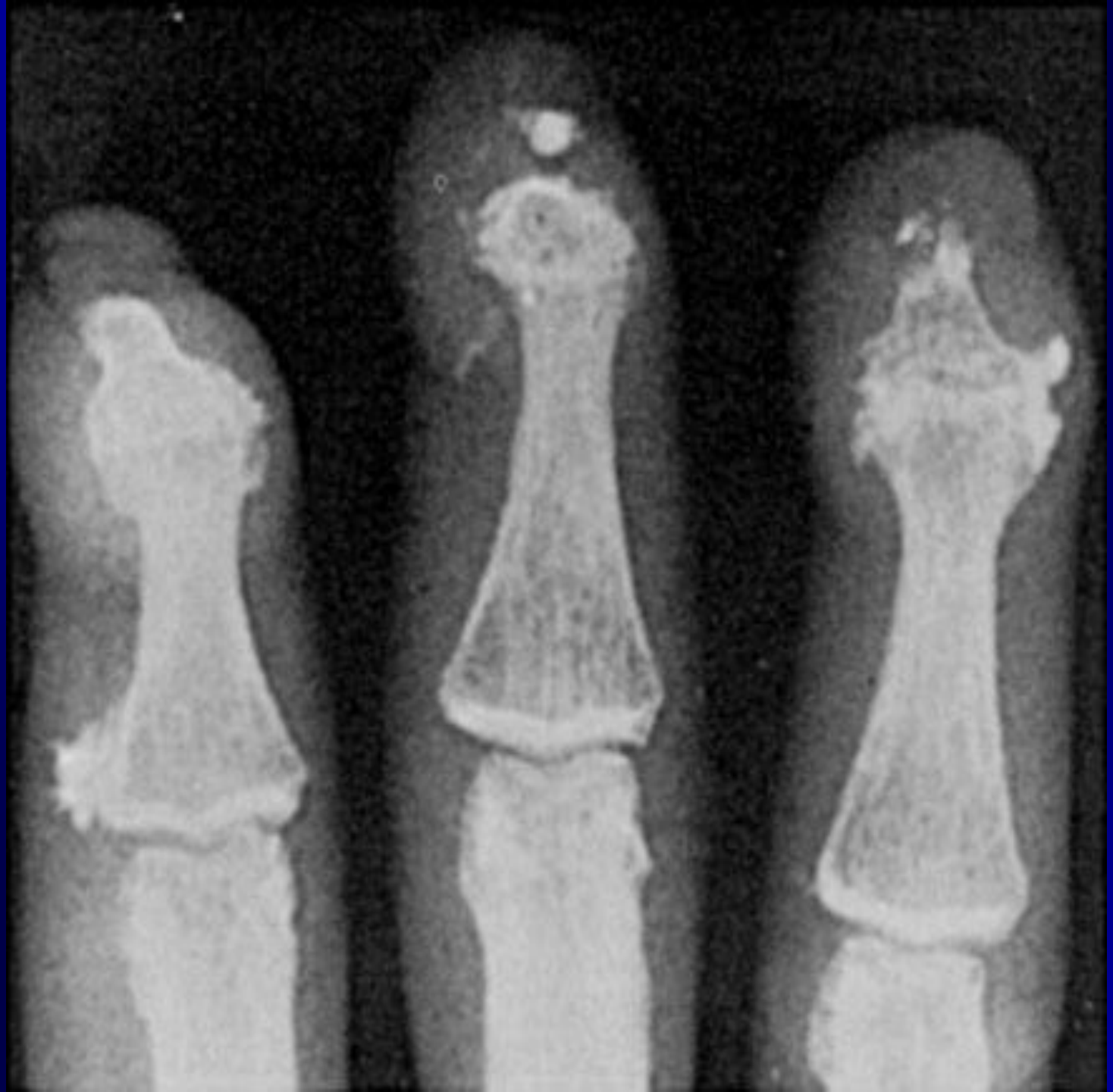












Gastrointestinal Tract

Esophagus

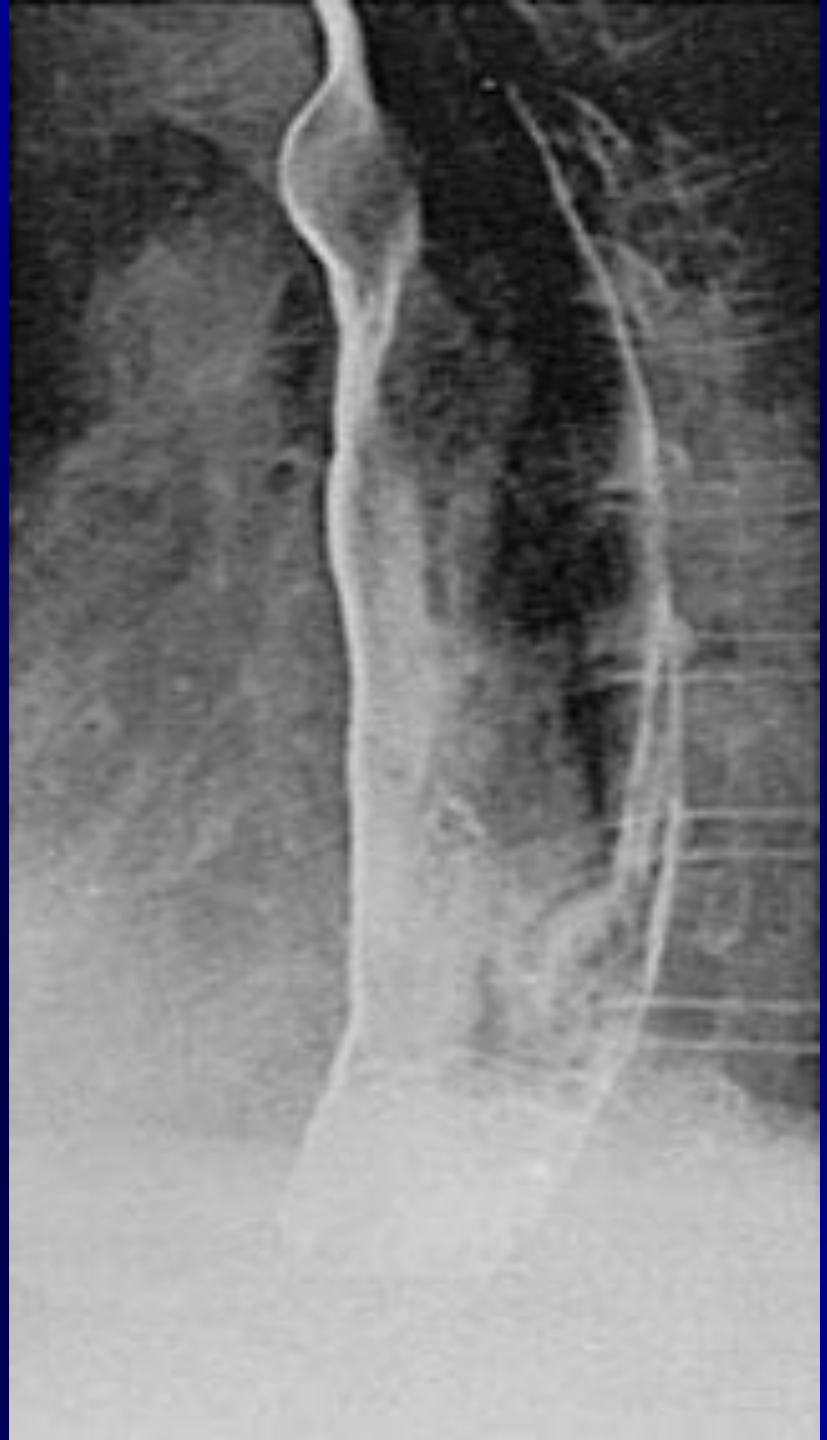
- **Esophageal dysmotility**
- **Dysphagia**
- **GER**

Small bowel

- **Diarrhea**
- **Malabsorbtion**
- **Deficient peristalsis**

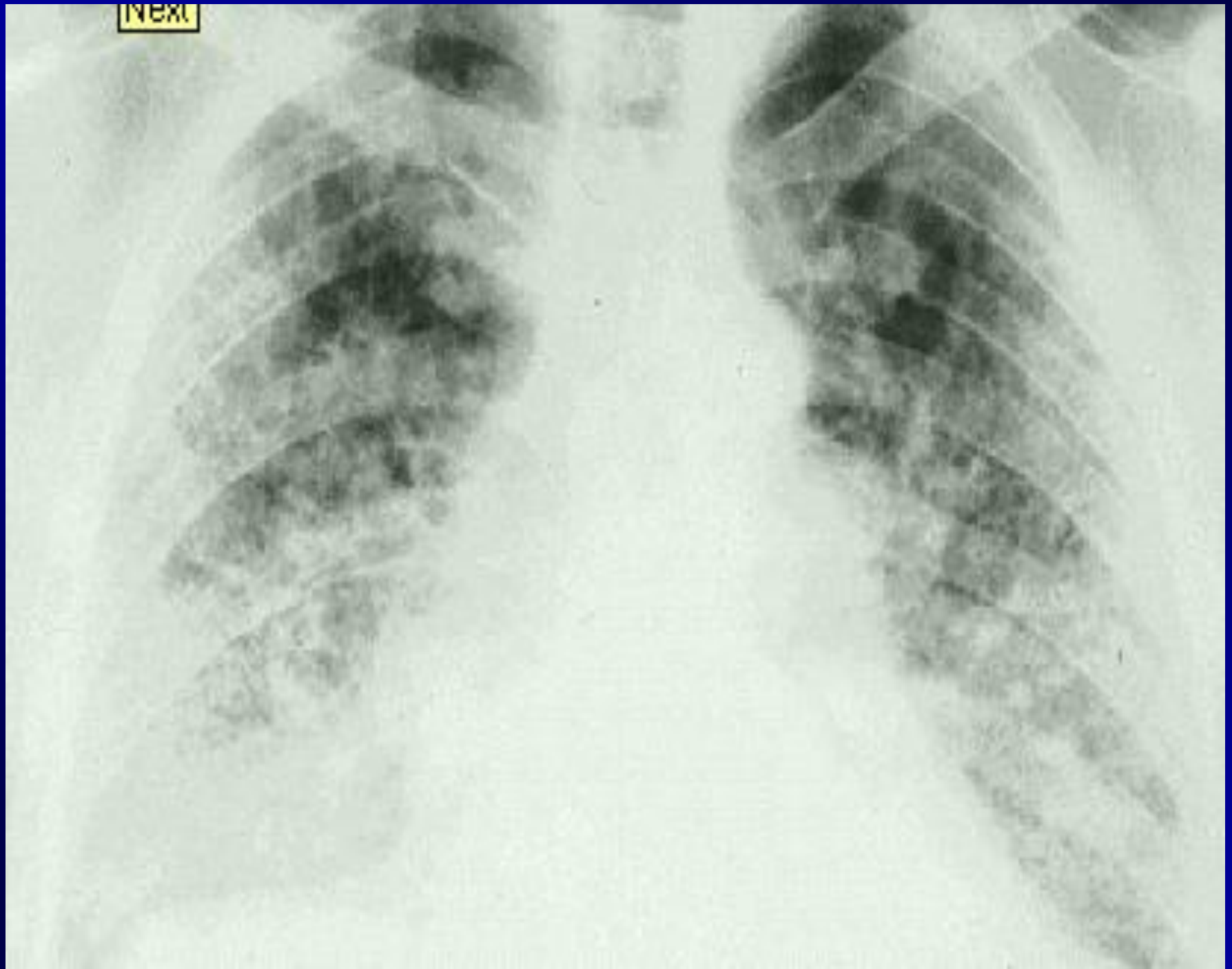
Large bowel

- **Diarrhea**
- **Constipation**
- **Obstruction**
- **Perforation**



Pulmonary Features

- **At least two-thirds of SSc patients and is now the leading cause of death**
- **Pulmonary fibrosis**
- **Vascular lesions :Pulmonary hypertension**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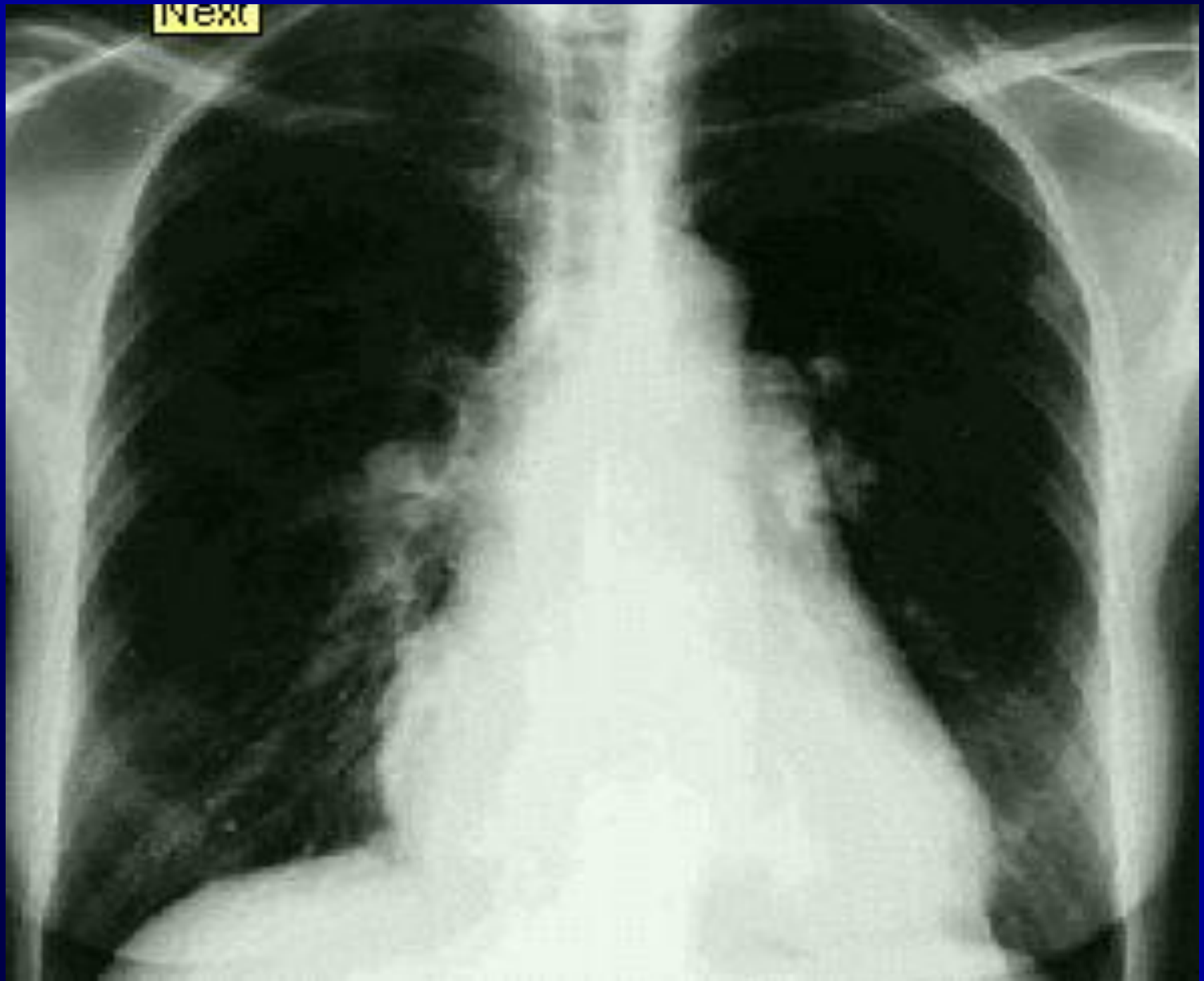
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Renal Features

- Renal failure was the leading cause of death in SSc until the advent of effective treatment
- Mostly in diffuse cutaneous scleroderma
- Renal crisis characterized by malignant hypertension, which can progress rapidly to renal failure

Sicca Syndrome

Scleroderma

Joints

- Polyarthralgia
- Polyarthritis
- Stiff painful muscles

Heart

- Arrythmias
- Conduction defects
- Pericarditis
- Congestive Cardiac failure

Immunological tests

- **Scleroderma 70 antibody (*SCl-70*)**

Associated with diffuse disease

- **Anticentromere antibodies (*ACA*)**

Associated with limited disease

Classification criteria

Major criteria

- **skin change in any location proximal to the metacarpophalangeal joints**

Minor criteria:

1. **sclerodactyly,**
2. **digital pitting scars of fingertips or loss of digital finger pad substance,**
3. **bibasilar pulmonary fibrosi**

Differential Diagnosis

- Digital sclerosis of diabetes mellitus
- Amyloidosis
- Scleroderma
- Scleromyxedema
- Human graft-versus-host disease

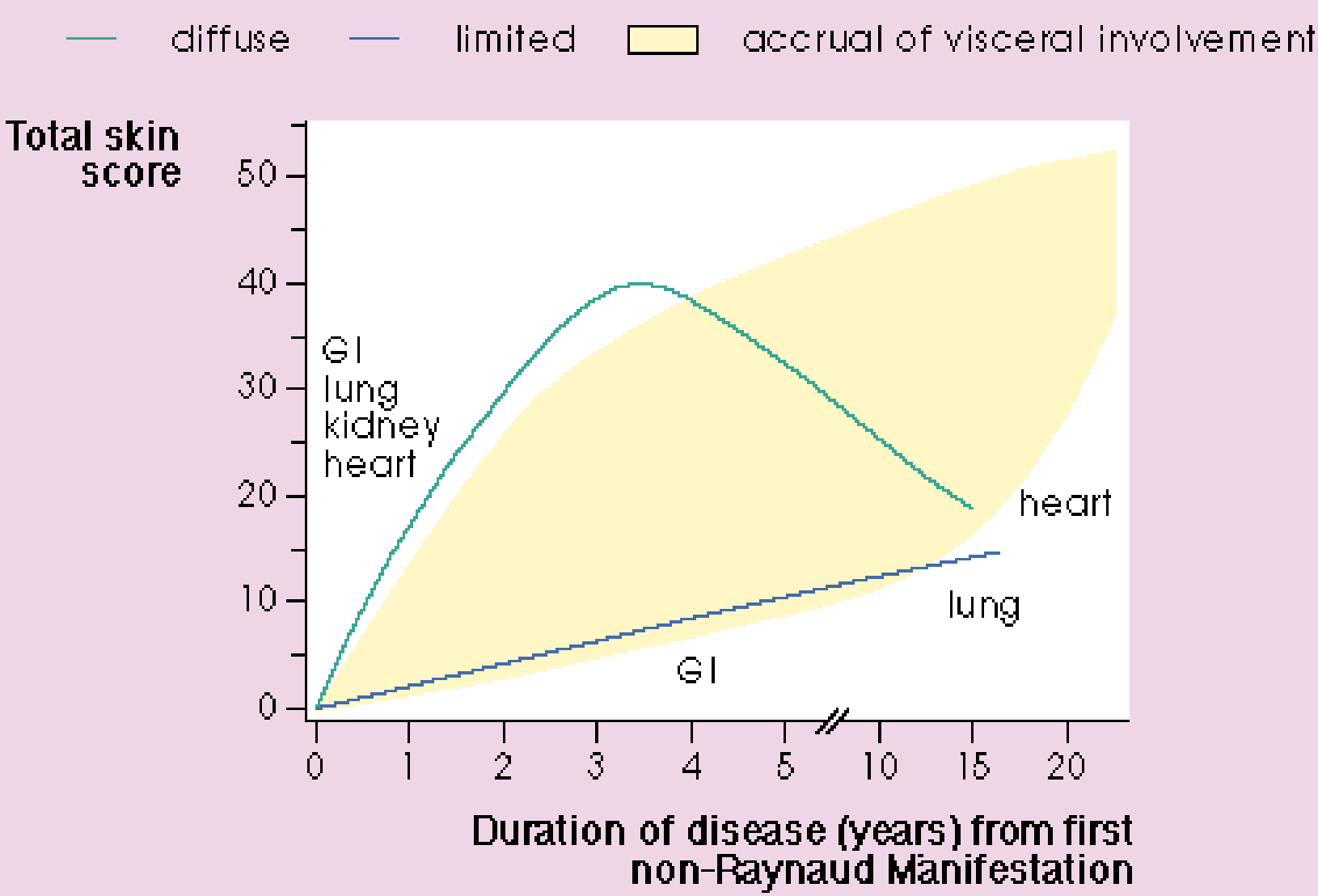
Differential Diagnosis

- Eosinophilic fasciitis
- Porphyria cutanea tarda
- Pentazocine-induced scleroderma

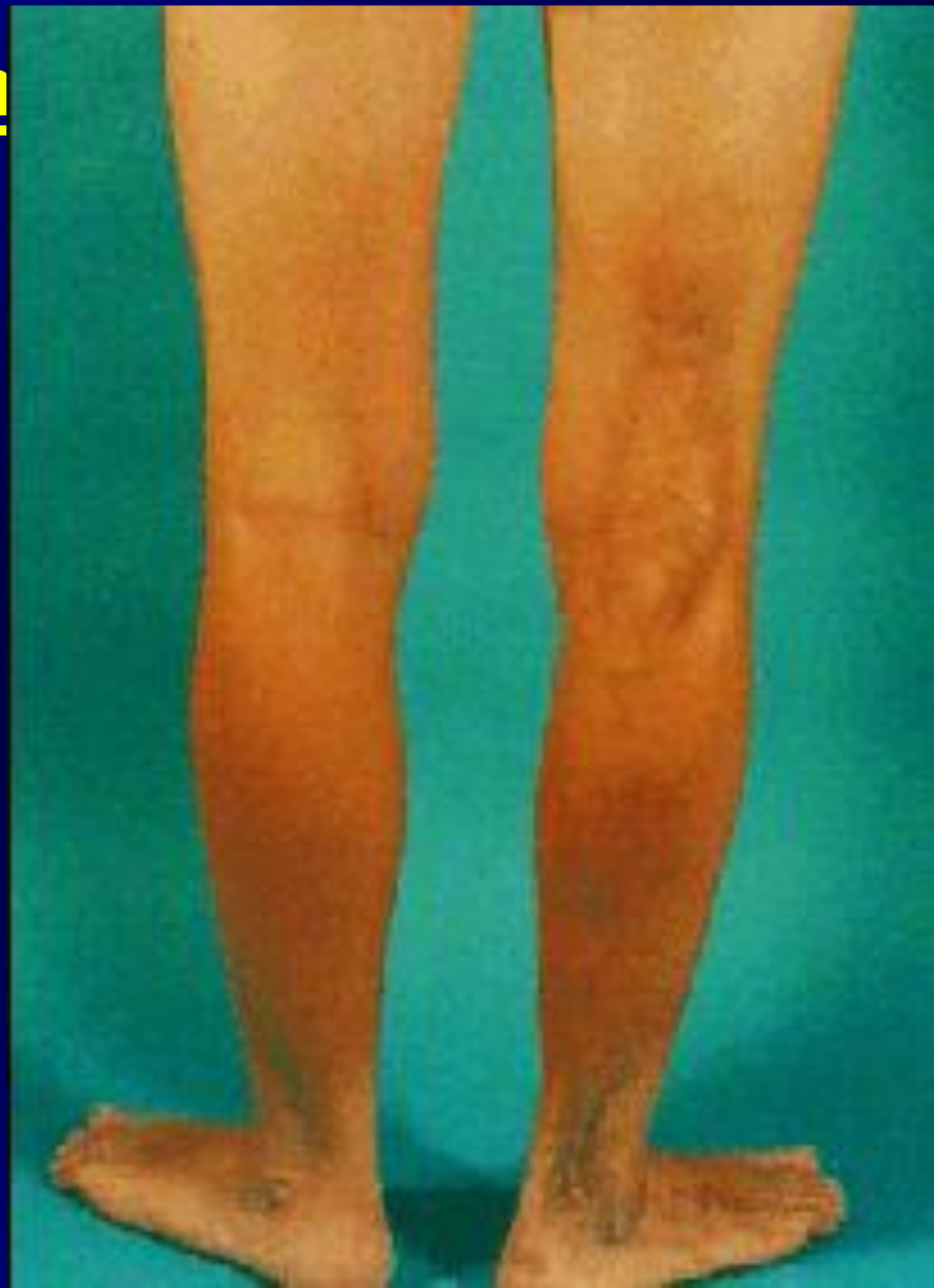
Disorders characterized by similar internal organ involvement

- Primary pulmonary hypertension
- Primary biliary cirrhosis
- Idiopathic pulmonary fibros

THE NATURAL HISTORY OF SYSTEMIC SCLEROSIS BY CLASSIFICATION OF DISEASE



Linear scleroderma



Morphea