La Sclerosi Sistemica

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La sclerosi sistemica (sclerodermia) è una malattia infiammatoria cronica caratterizzata da:

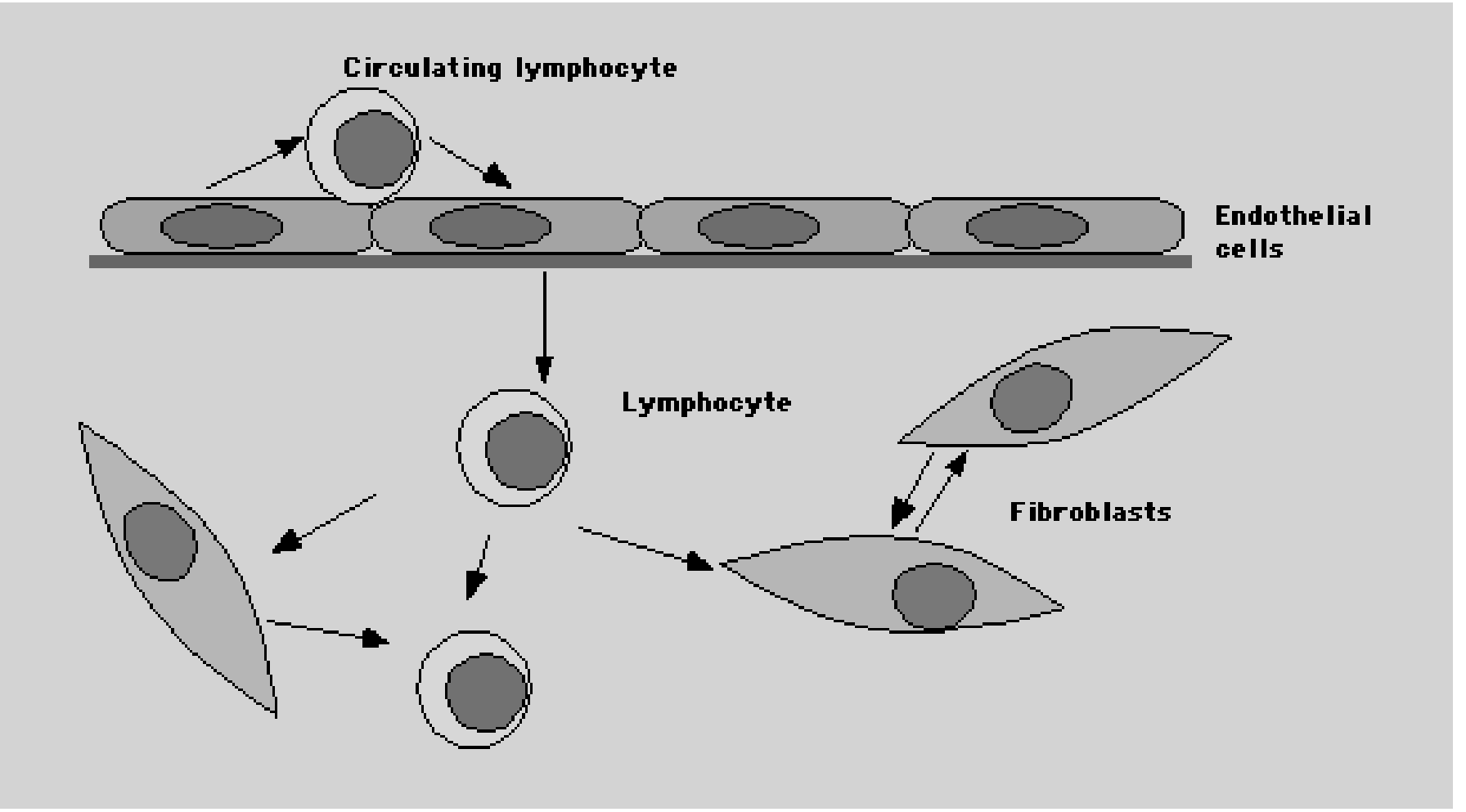
- Alterazioni caratteristiche del microcircolo arteriolare
- Fibrosi della cute e degli organi interni
- Presenza di autoanticorpi diretti contro antigeni nucleari

Caratteristiche epidemiologiche

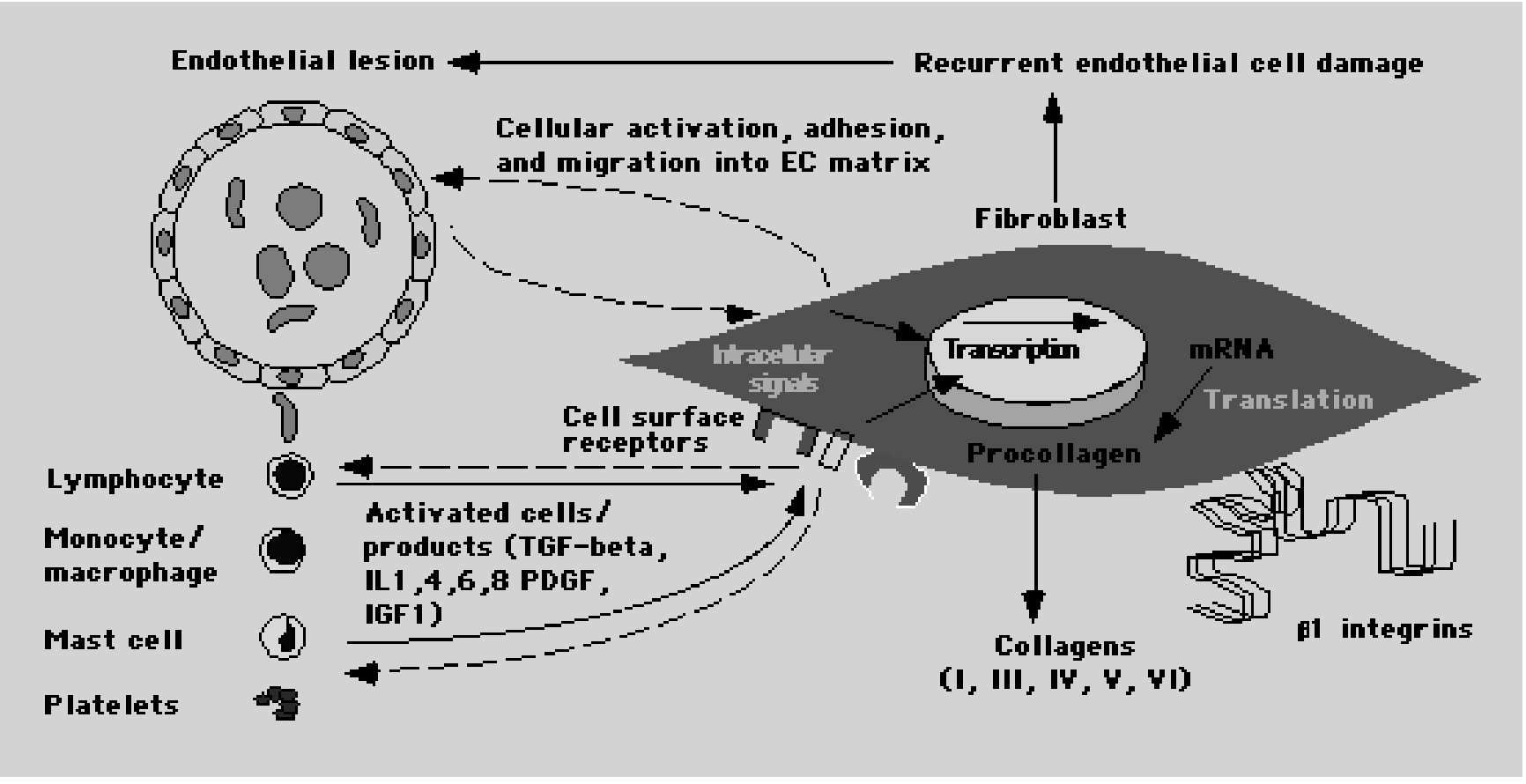
F:M = 9:1

Familiarità per:

f. di Raynaud	5.0 %
SSc	1.4 %
Altre m. autoimmuni sistemiche	3.8 %



Cellular interactions in the pathogenesis of scleroderma Schematic representation of the cellular components implicated in the pathogenesis of scleroderma: the vascular endothelial cells, lymphocytes, and fibroblasts. Interplay between these factors, and between the fibroblasts and noncellular components of the extracellular matrix are likely to play an important role.



Paracrine interactions between cells involved in scleroderma – Activated cells of the immune system, endothelial cells, and fibroblasts are all capable of releasing cytokines and growth factors which might exert a paracrine or autocrine influence on other cells. This could in turn modulate celluar properties and induce production of the same or other factors. Thus, there is the potential for local cytokine loops to initiate and perpetuate the immunologic, vascular, and fibrotic components of scleroderma.

Potential Sources for Cytokines Implicated in Scleroderma Pathogenesis

Cell type	Major cytokine products
Endothelial cells	
Activated or damaged	IL-1, IL-6, IL-8, IGF-1, PDGF, TGF-beta, ET-1
Immune or inflammatory cells	
Monocyte/macrophage	IL-1, TNF,
Lymphocytes	IL-2,-4,-6,-8
Mast cells, neutrophils, eosinophils	bFGF, proteases
Fibroblasts	
Scleroderma fibroblasts	TNF, IL-1, IL-6, TGF-beta, IGF-1, DGF

Effect of Cytokines on Fibroblast Collagen Metabolism

Fibroblast response	Mediators
Increased fibroblast chemotaxis	TGF-beta, IL-4, TNF-alpha and beta, PDGF, IFN gamma, ET-1
Increased fibroblast proliferation	IL-1 alpha and beta, bFGF, aFGF, PDGF, IL-6, EGF, TGF-beta (via PDGF), ET-1, IL-17
Increased collagen synthesis	TGF-ß, IL-1 alpha and beta, IL-4, IGF
Decreased collagen synthesis	bFGF, IFN gamma and alpha, relaxin, EGF, TNF-alpha
Increased collagenase synthesis	IL-1 alpha and beta, bFGF, TNF-alpha and beta
Decreased collagen synthesis	TGF-beta
Increased TIMP synthesis	IL-1 alpha and beta, TGF-beta
Decreased TIMP synthesis	IL-6

Properties of Scleroderma Dermal Fibroblasts in Tissue Culture

Increased

- Collagen I and III mRNA and protein production
- Proteoglycan synthesis
- Fibronectin synthesis
- Prolyl and lysyl hydroxylase enzyme activity
- PDGF receptor expression
- Production of IL-1 and IL-6
- Serum independent proliferation
- Surface expression and shedding of ICAM-1
- Collagenase secretion (?)
- Suceptibility to anti-Fas induced apoptosis (?)

Reduced

- Collagen I mRNA downregulation in collagen gel matrix culture
- Collagenase production
- Proliferative response to recombinant EGF, endothelin-1

Classification of Systemic Sclerosis

Limited cutaneous scleroderma

- Raynaud's phenomenon for years, occasionally decades
- Skin involvement limited to hands, face, feet, and forearms (acral distribution)
- Dilated nailfold capillary loops, usually without capillary drop-out
- A significant (10 to 15 percent) late incidence of pulmonary hypertension, with or without skin calcification, gastrointestinal disease, telangiectasias (CREST syndrome), or interstitial lung disease
- Renal disease rarely occurs
- Anticentromere antibody (ACA) in 70 to 80 percent

Diffuse cutaneous scleroderma

- Raynaud's phenomenon followed, within one year, by puffy or hidebound skin changes
- Truncal and acral skin involvement; tendon friction rubs
- Nailfold capillary dilatation and capillary drop-out
- Early and significant incidence of renal, interstitial lung, diffuse gastrointestinal, and myocardial disease
- Anti-Scl-70 (30 percent) and anti-RNA polymerase-I, II, or III (12 to 15 percent) antibodies

Scleroderma sine scleroderma

- Presentation with pulmonary fibrosis or renal, cardiac, or gastrointestinal disease
- No skin involvement
- Raynaud's phenomenon may be present
- Antinuclear antibodies may be present — anti-Scl-70, ACA, or anti-RNA polymerase-I, II, or III

Environmentally induced scleroderma

- Generally diffuse distribution of skin sclerosis and a history of exposure to an environmental agent suspected of causing scleroderma

Overlap syndromes

- Features of systemic sclerosis which coexist with those of another autoimmune rheumatic disease such as systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, vasculitis, or Sjögren's syndrome.

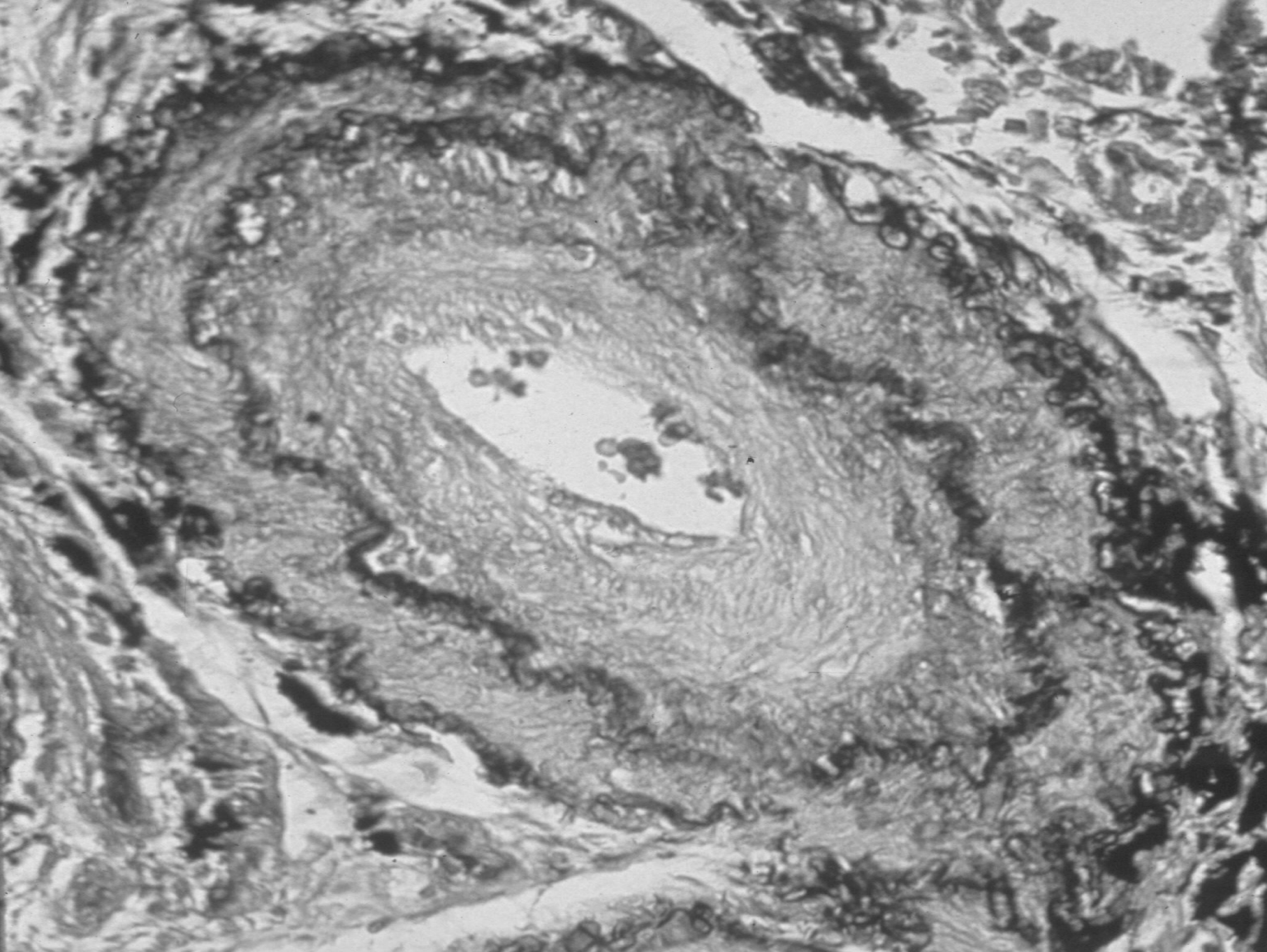
Pre-scleroderma

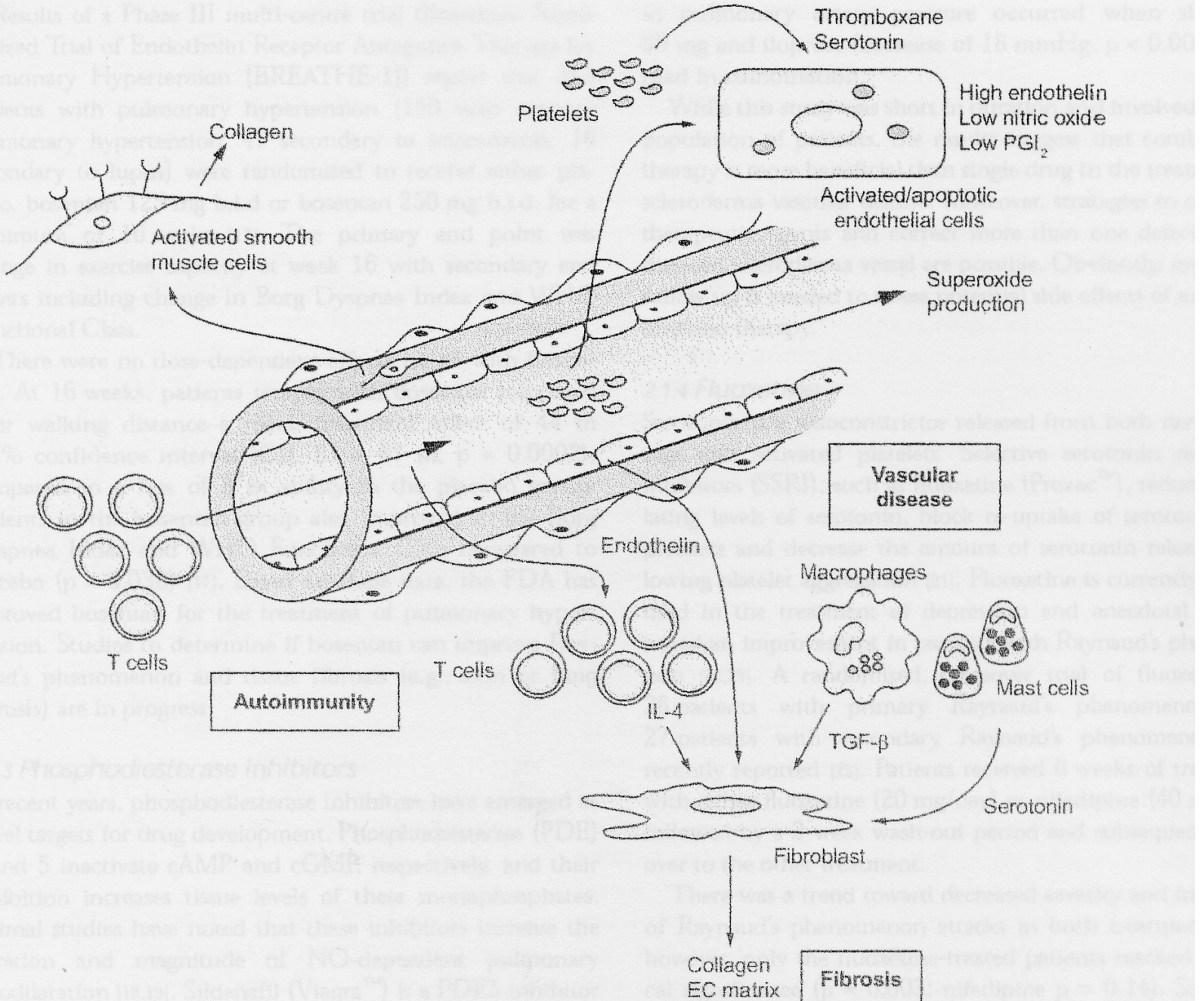
- Raynaud's phenomenon
- Nailfold capillary changes and evidence of digital ischemia
- Specific circulating autoantibodies — anti-topoisomerase-I (Scl-70), anti-centromere (ACA), or anti-RNA polymerase-I, II, or III

Le alterazioni del circolo arteriolare precedono di mesi o anche molti anni l'insorgenza della fibrosi cutanea e/o viscerale; sono caratterizzate da:

- Marcata iperplasia dell'intima
- Ispessimento della tonaca media per proliferazione delle cellule muscolari
- Adesione delle piastrine

Conseguenza: obliterazione vascolare, fibrosi vasale, ischemia tissutale



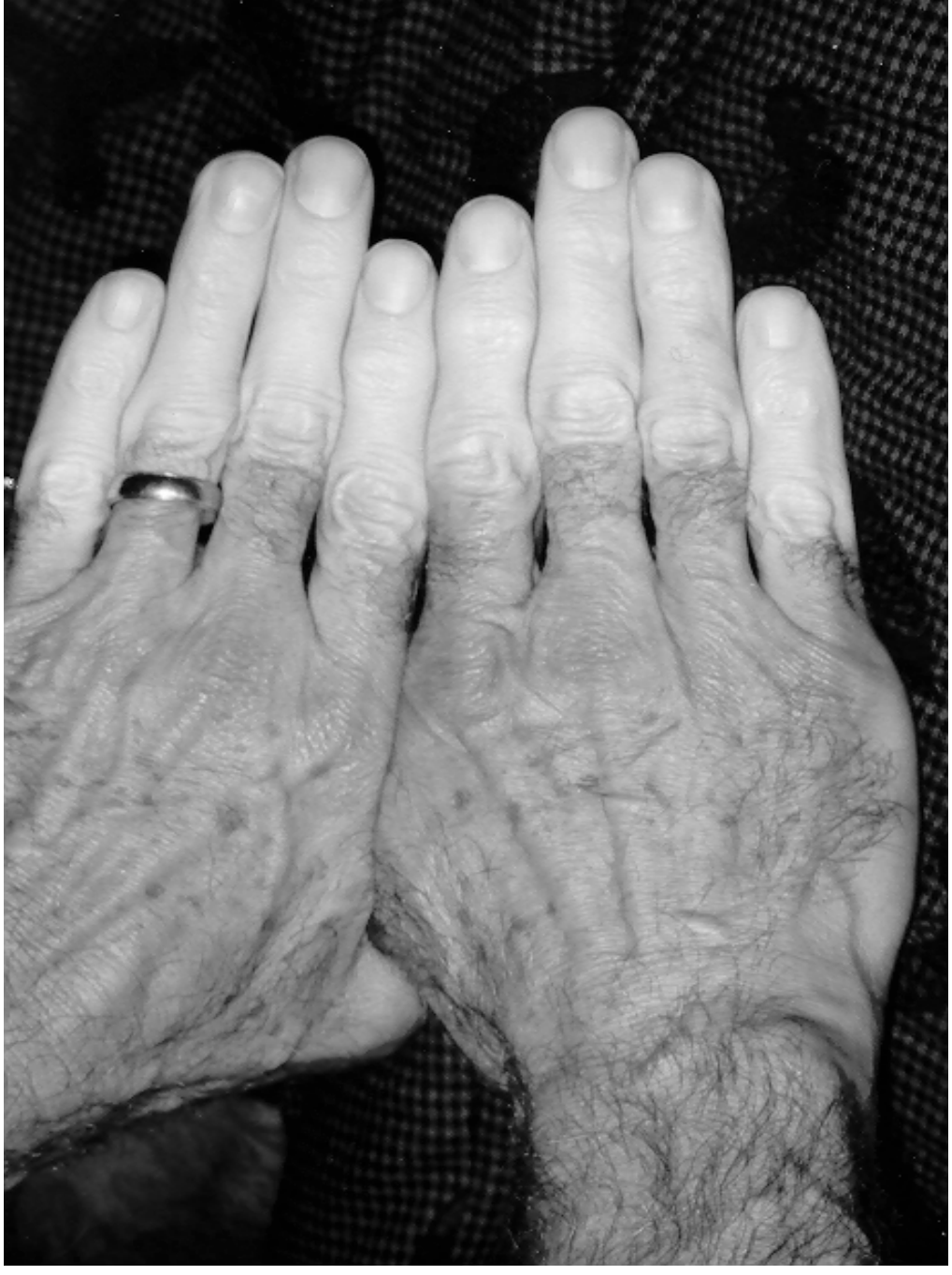

Thromboxane
Serotonin
Platelets
High endothelin
Low nitric oxide
Low PGI_2
Collagen
Activated/apoptotic
endothelial cells
Activated smooth
muscle cells
Superoxide
production
Vascular
disease
Endothelin
Macrophages
T cells
T cells
Autoimmunity
IL-4
Mast cells
TGF-β
Serotonin
Fibroblast
Collagen
EC matrix
Fibrosis

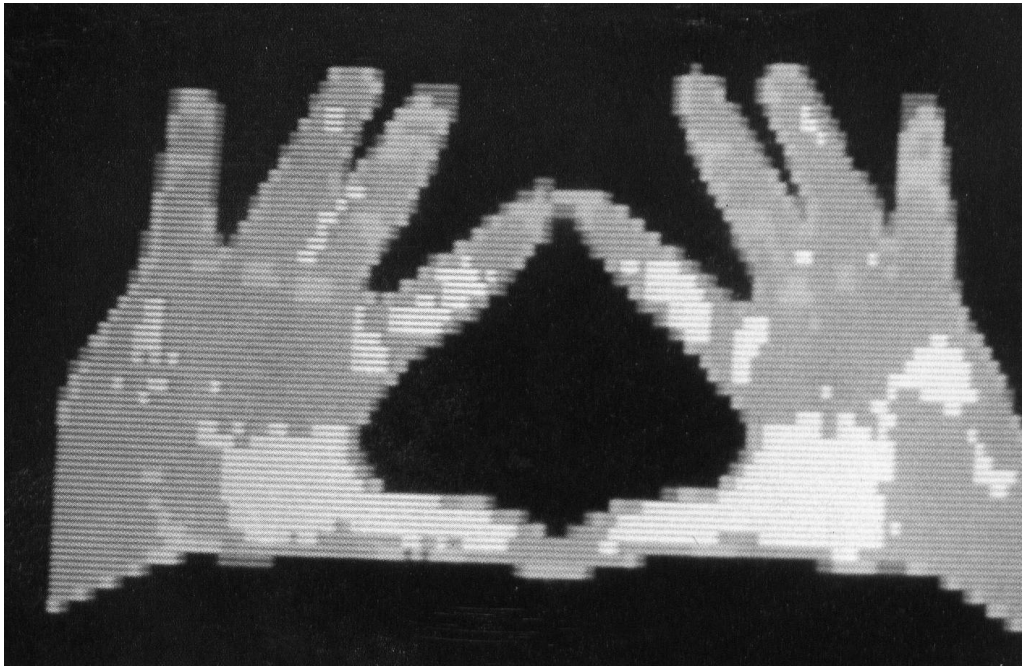
Le alterazioni vascolari sono responsabili del Fenomeno di Raynaud
cambiamento trifasico del colore della cute delle mani e/o dei piedi
scatenato dal freddo o da uno stress emotivo

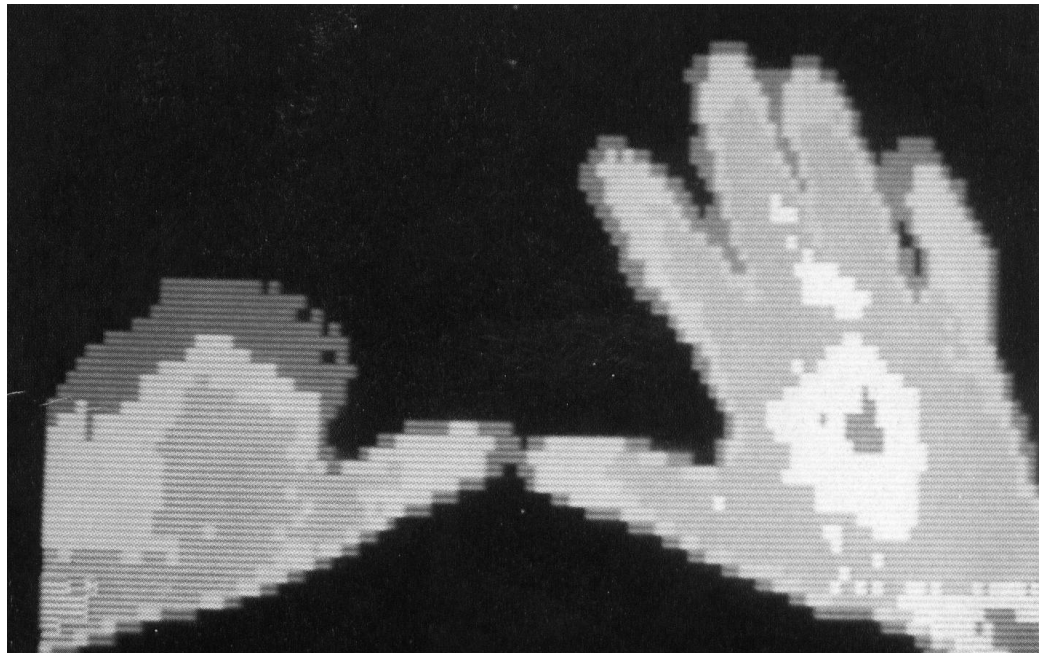
Bianco: fase ischemica, da vasocostrizione

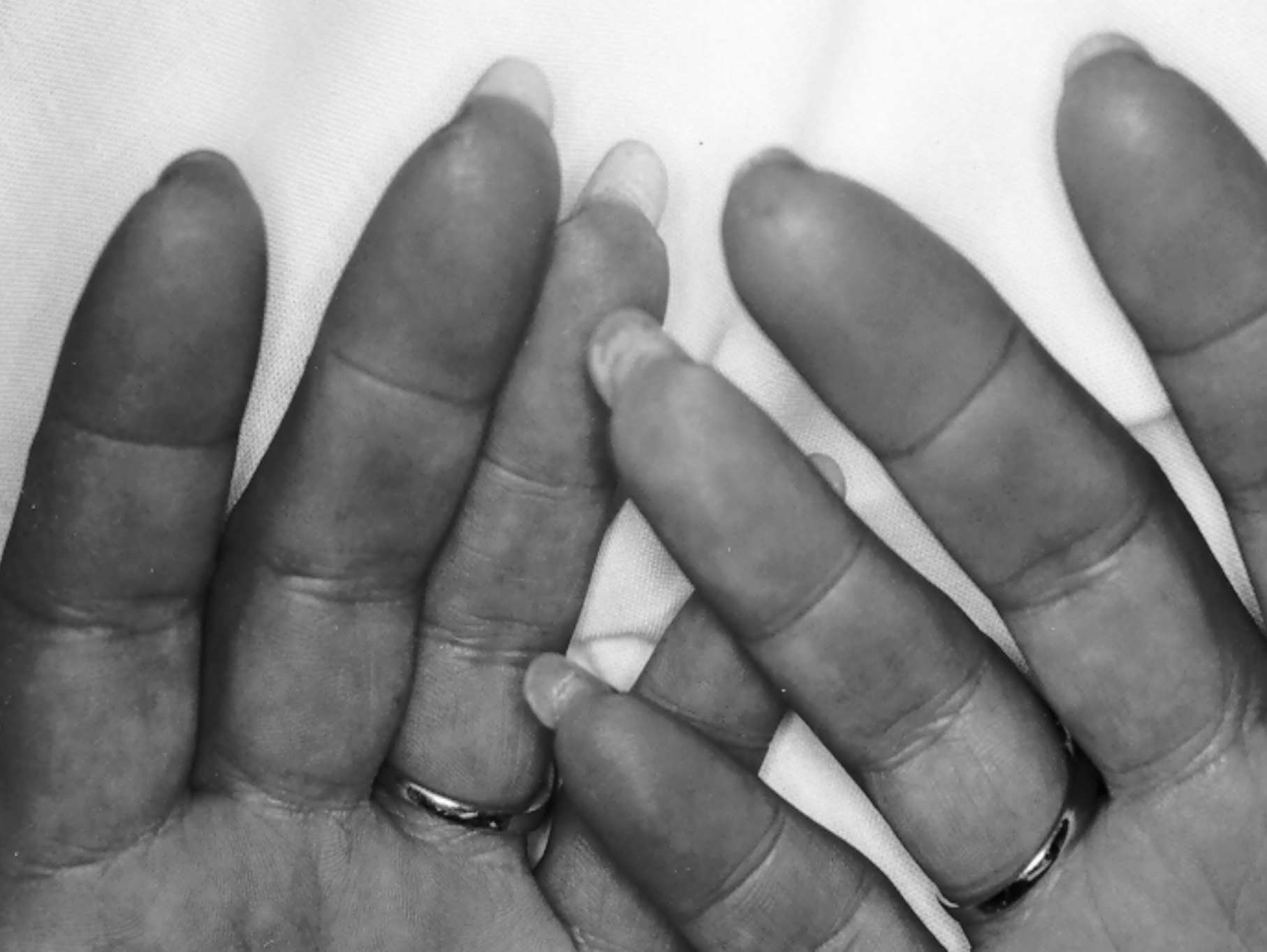
Blu: fase di stasi e dilatazione venulare secondaria all’anossia

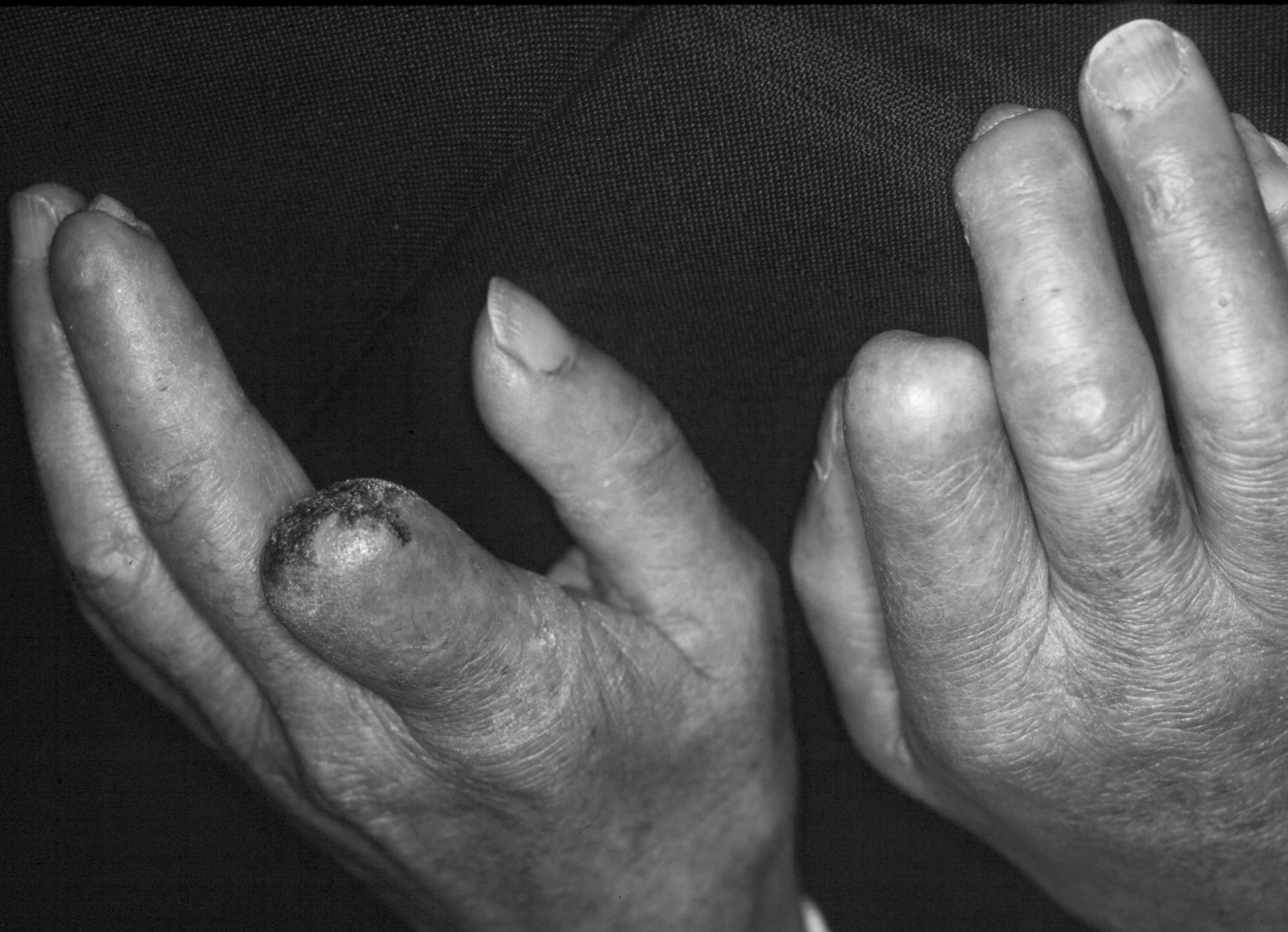
Rossa: fase iperemica, da vasodilatazione arteriolare reattiva

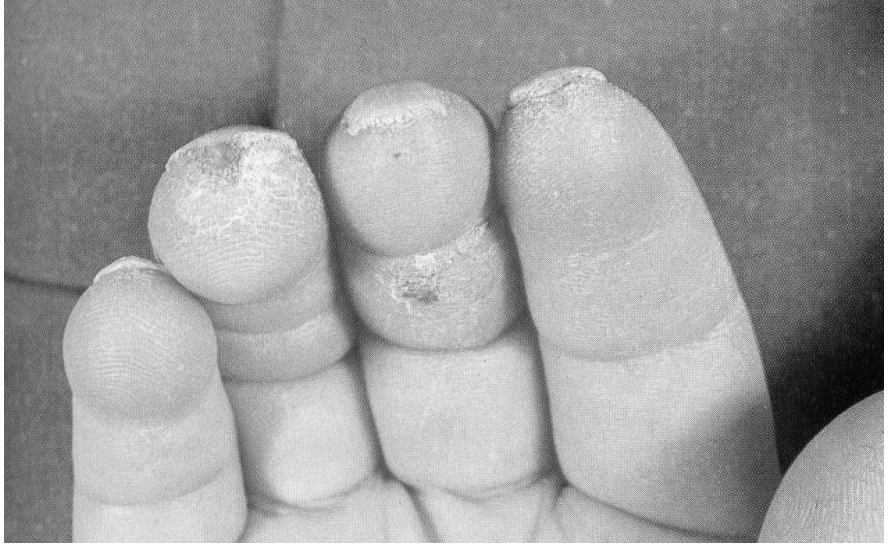


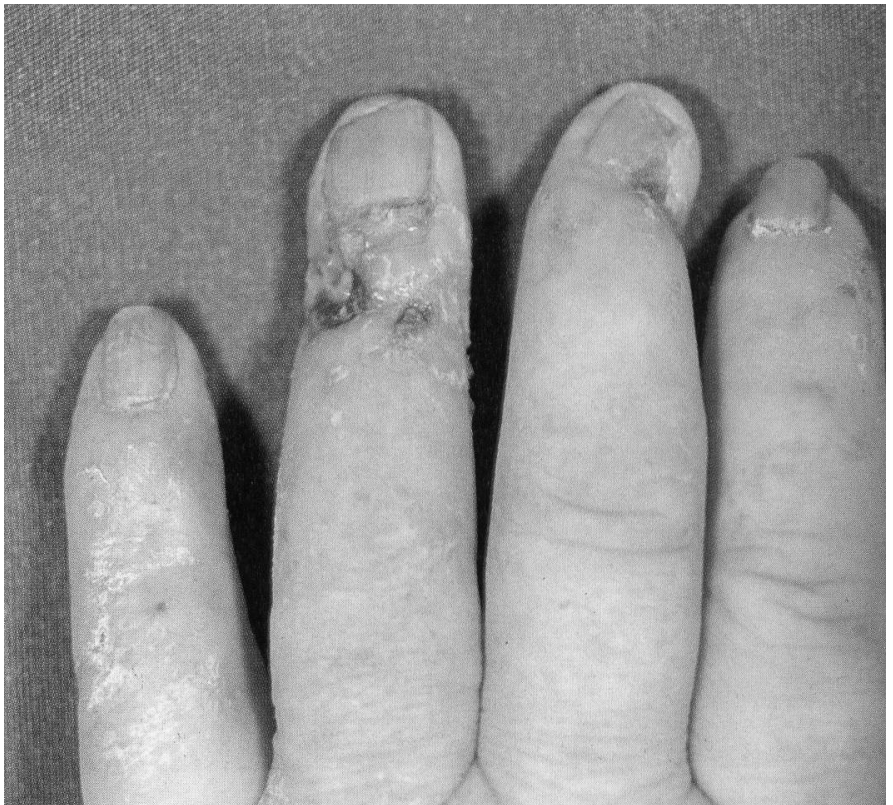








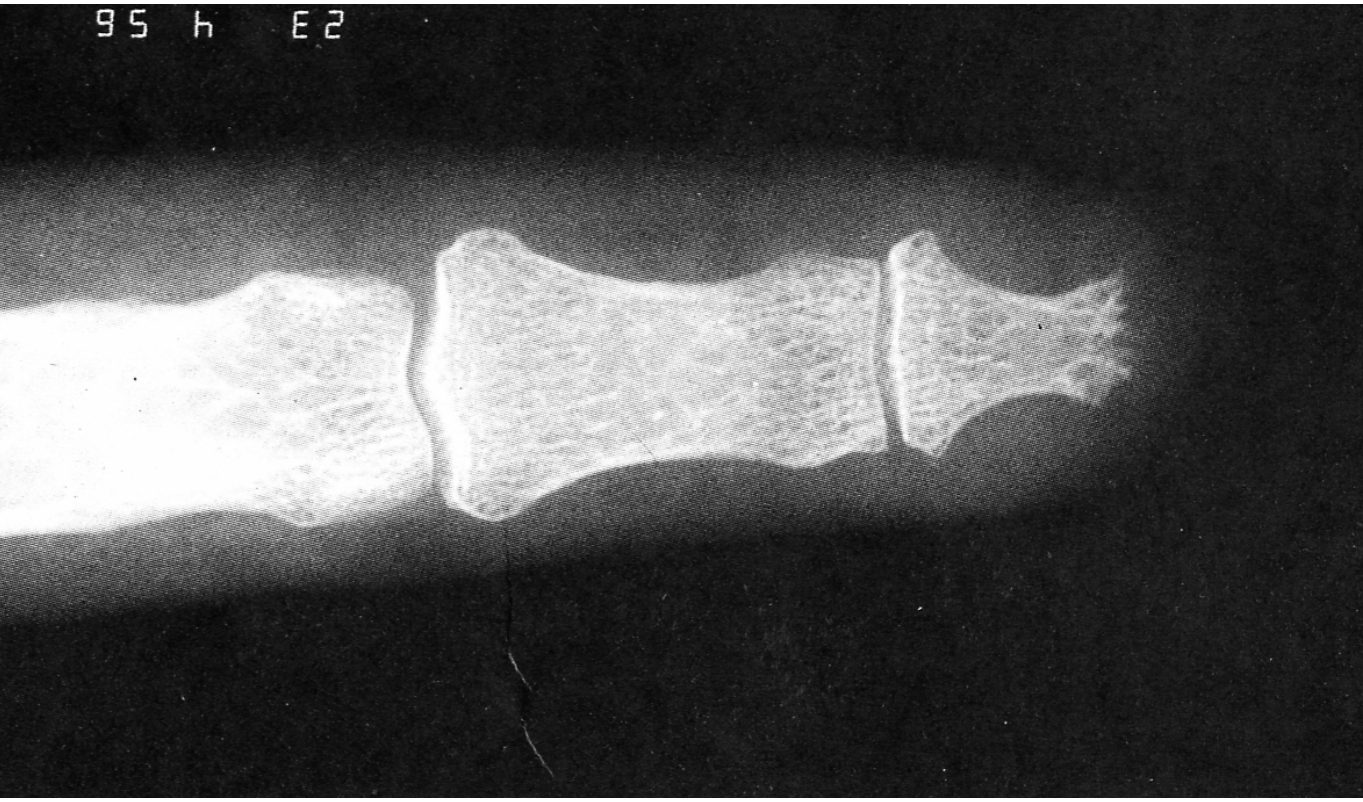




Il fenomeno di Raynaud precede di mesi ma anche di molti anni l'insorgenza della malattia conclamata

Le alterazioni vascolari che sono alla base del fenomeno di Raynaud sono presenti nel circolo arteriolare di tutti i tessuti ed organi e precedono l'insorgenza della fibrosi

Il fenomeno di Raynaud consente la diagnosi di sclerosi sistemica in fase preclinica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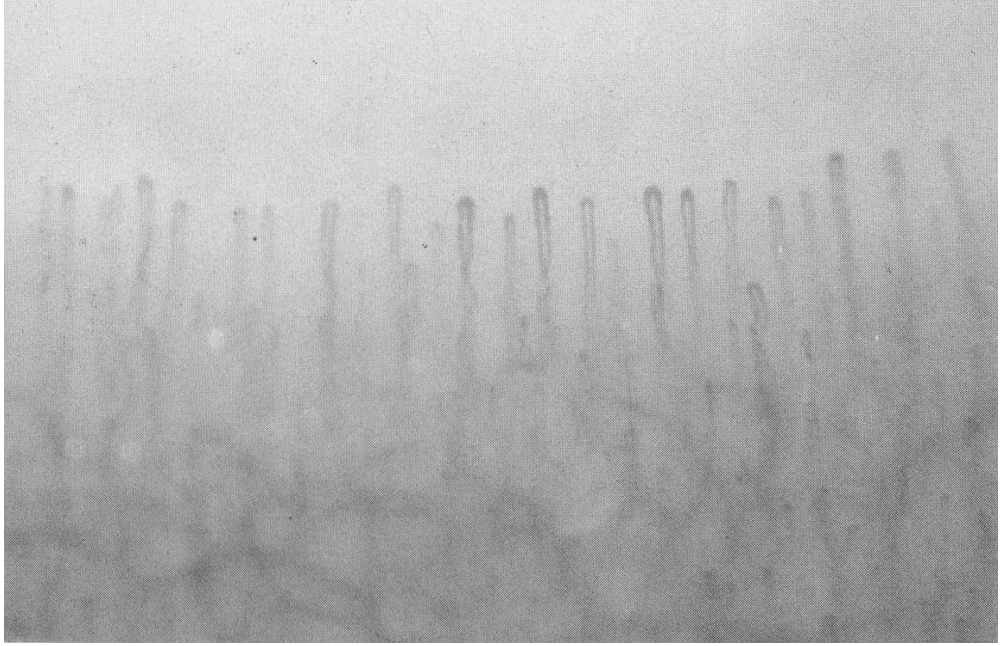
FENOMENO DI RAYNAUD PRIMITIVO O SECONDARIO?

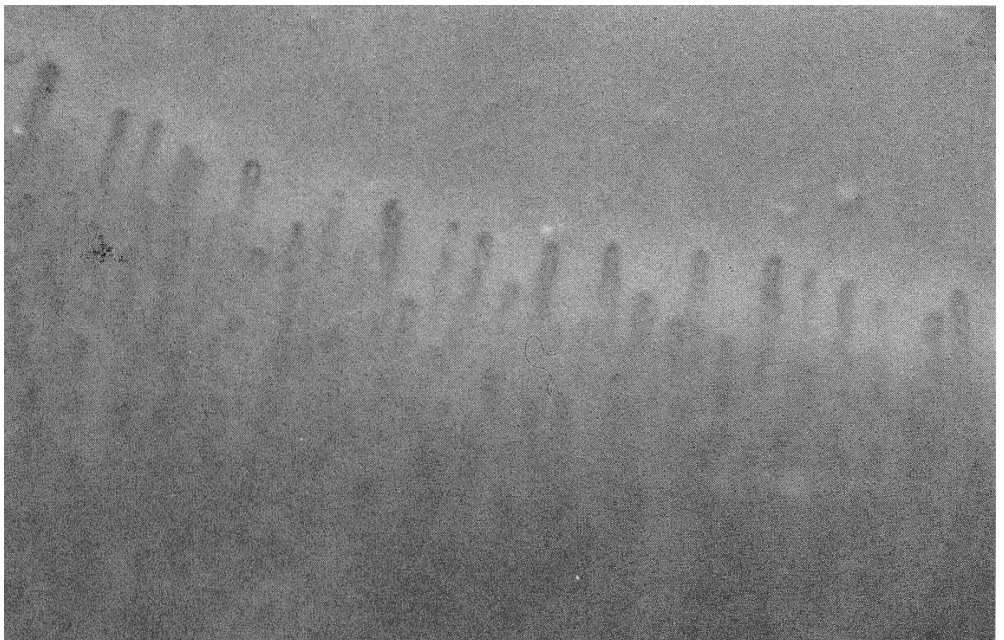
CRITERI	PRIMITIVO	SECONDARIO
Distribuzione	simmetrica	simmetrica
età media insorgenza	14	30
Familiarità	spesso positiva	generalmente negativa
gravità	moderata*	grave**
disturbi trofici	assenti	presenti
capillaroscopia	normale	patologica
autoAb	assenti	presenti

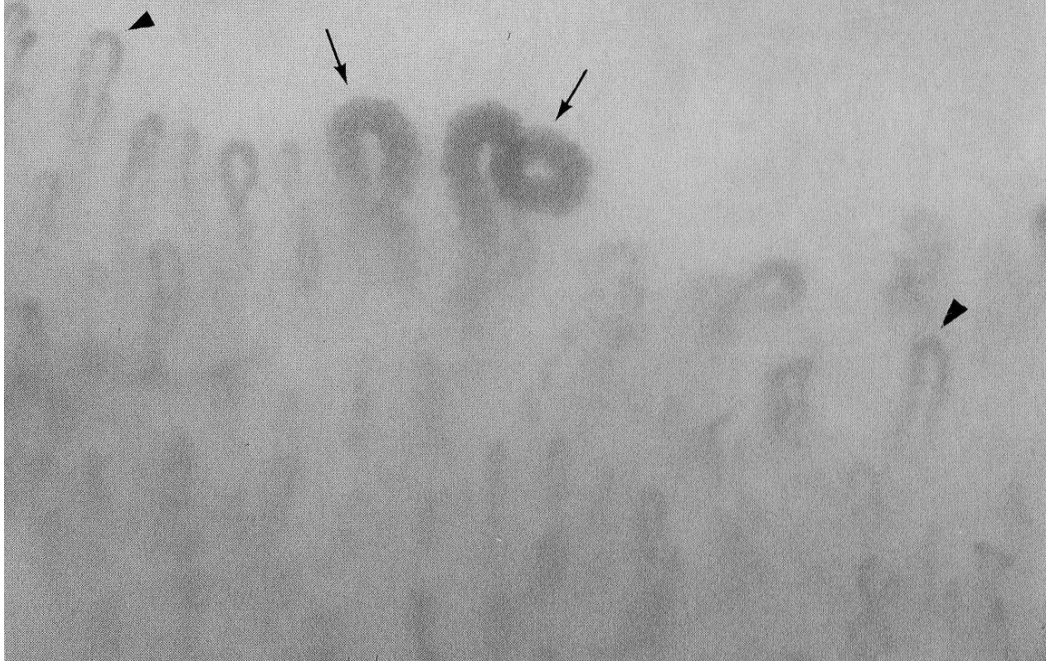
NB solo il 10% circa dei pz. con diagnosi di Raynaud primitivo evolvono vs forma secondaria (mal. autoimmune)

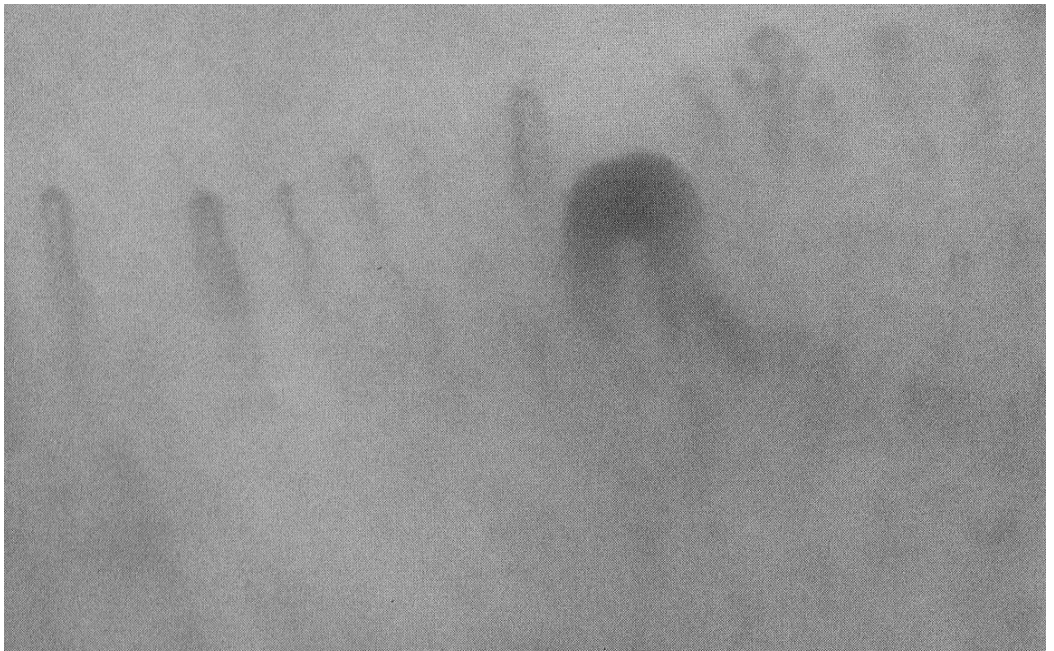
proporzionata all'entità e alla durata dello stimolo

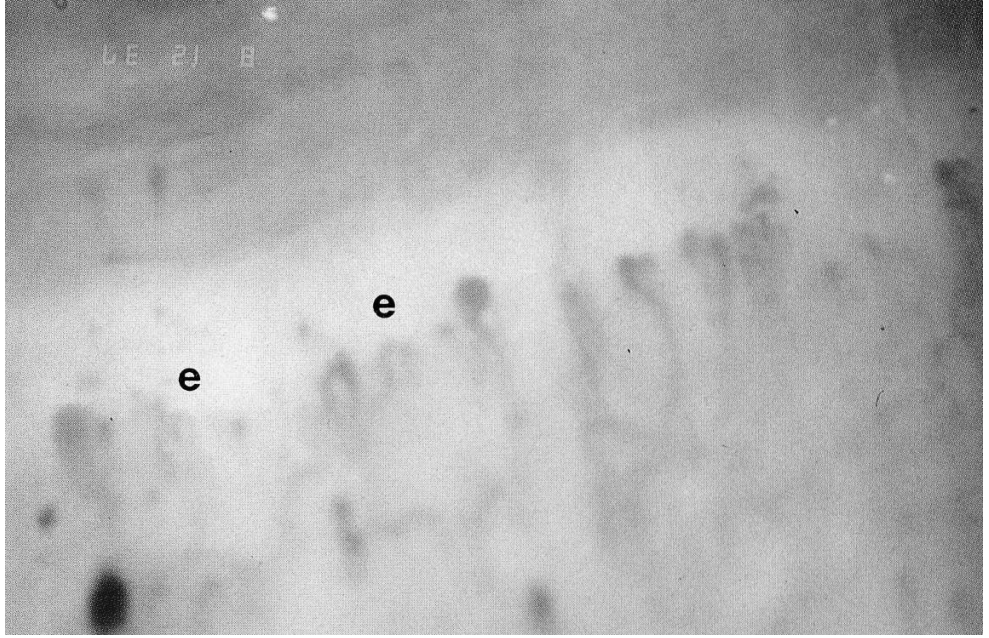
* non proporzionata alla entità e alla durata dello stimolo







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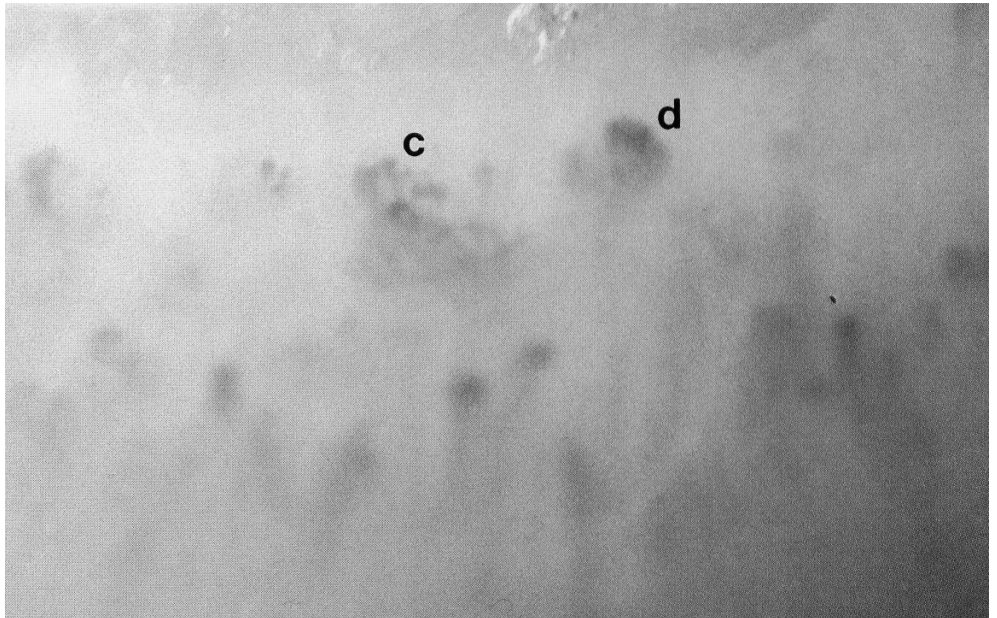
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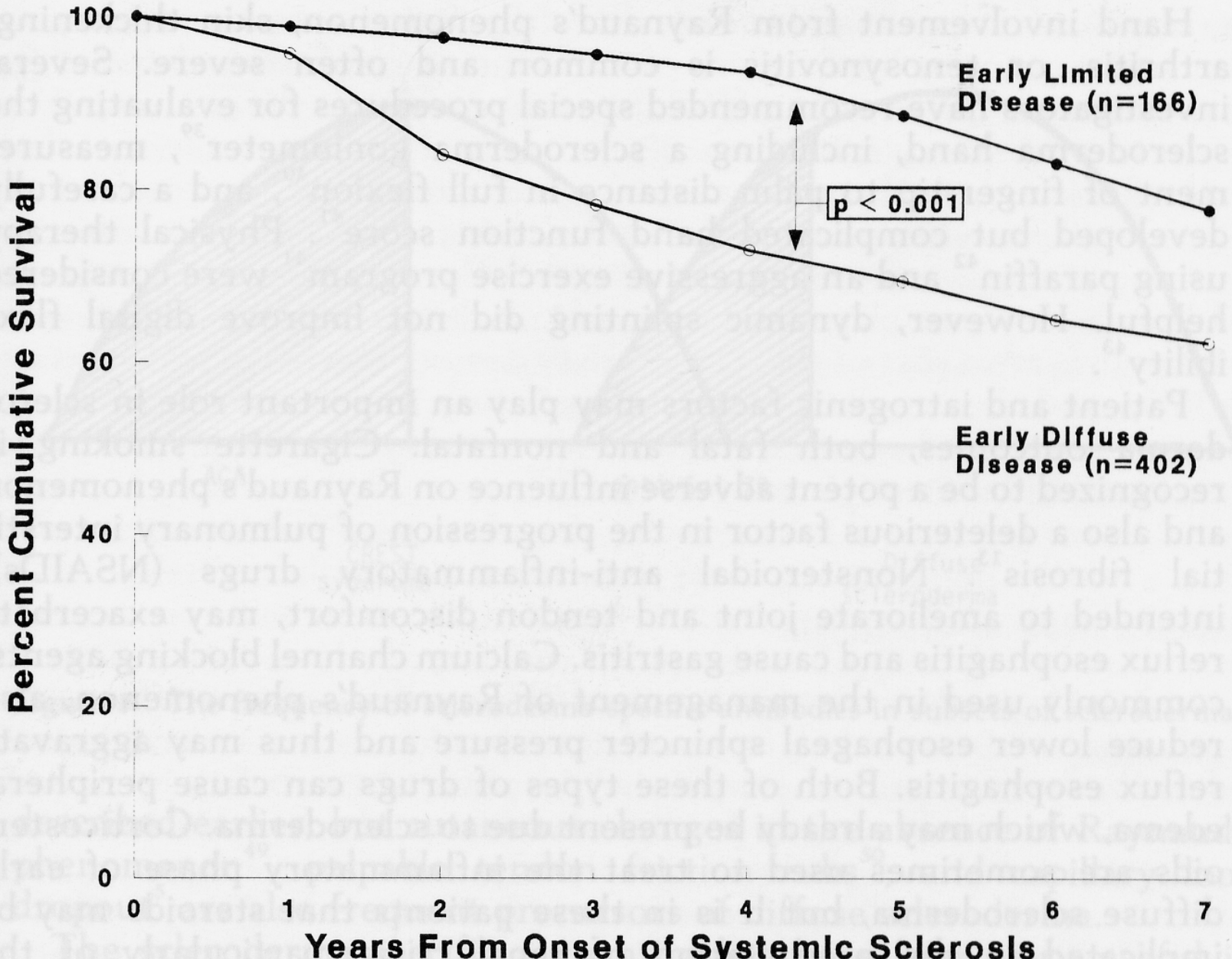
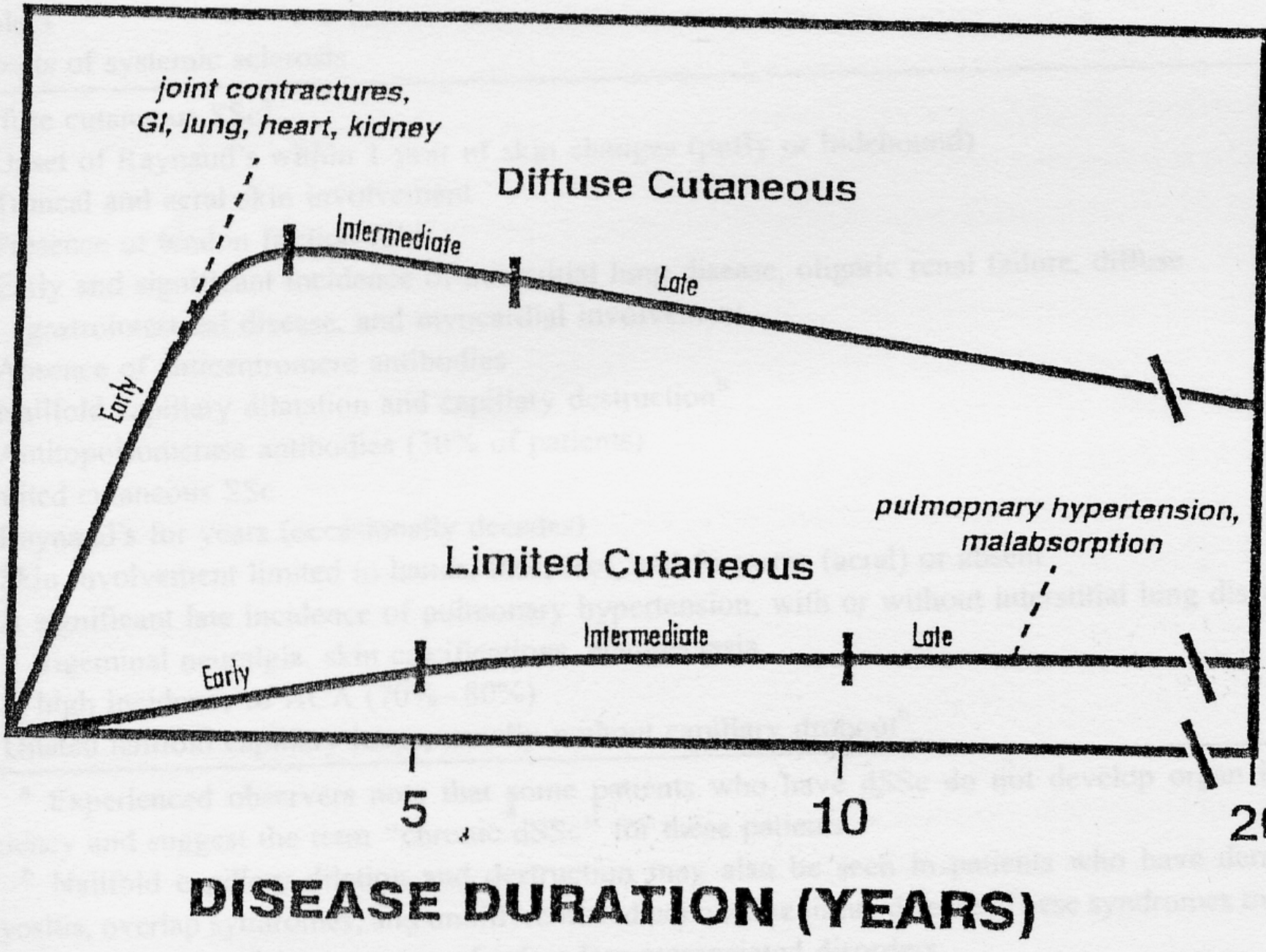
Caratteristiche cliniche ed epidemiologiche dei pazienti seguiti presso l'Immunologia Clinica di Milano (1980-2004)

	dcSSc(n=408)	lcSSc(n=1135)
Età all'ingresso (mediana e range)	**42 (17-65)**	**53 (38-74)**
Anni di follow-up (mediana e range)	**7 (0-20)**	**8.5 (0-20)**
Sesso femminile (%)	**78**	**95**
Coinvolgimento esofageo (%)	**100**	**85**
Coinvolgimento colon (%)	**58**	**35**
Malassorbimento (%)	**6**	**0**
Fibrosi polmonare (%)	**80**	**45**
Ipertensione polmonare (%)	**28**	**33**
Coinvolgimento cardiaco (%)	**70**	**54**
Miosite (%)	**15**	**3**
Calcinosi (%)	**16**	**45**
Sindrome sicca	**10**	**7**
Coinvolgimento renale (%)	**4**	**0**
Anti-centromero (%)	**8**	**57**

PROGNOSIS IN SYSTEMIC SCLEROSIS (SCLERODERMA)



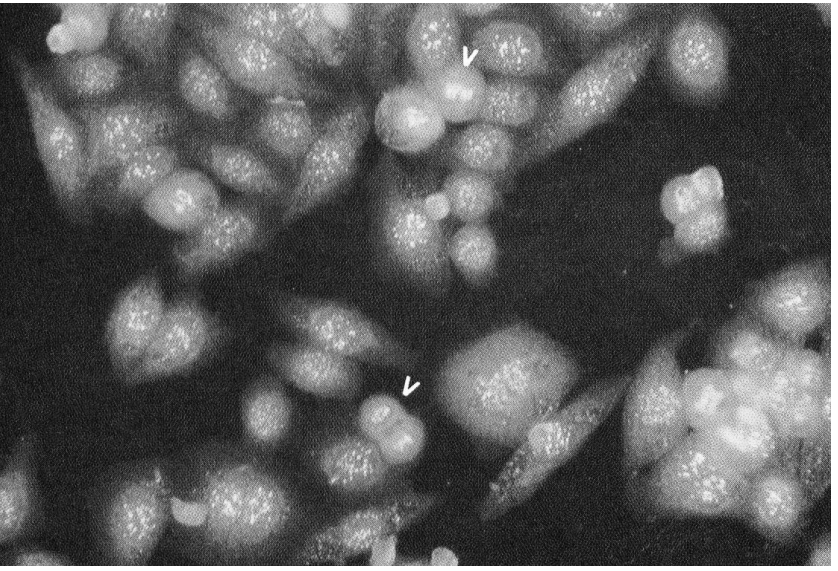

joint contractures,
GI, lung, heart, kidney
Diffuse Cutaneous
Intermediate
Late
Early
pulmopnary hypertension,
malabsorption
Limited Cutaneous
Intermediate
Late
Early
SKIN THICKNESS
5
10
DISEASE DURATION (YEARS)

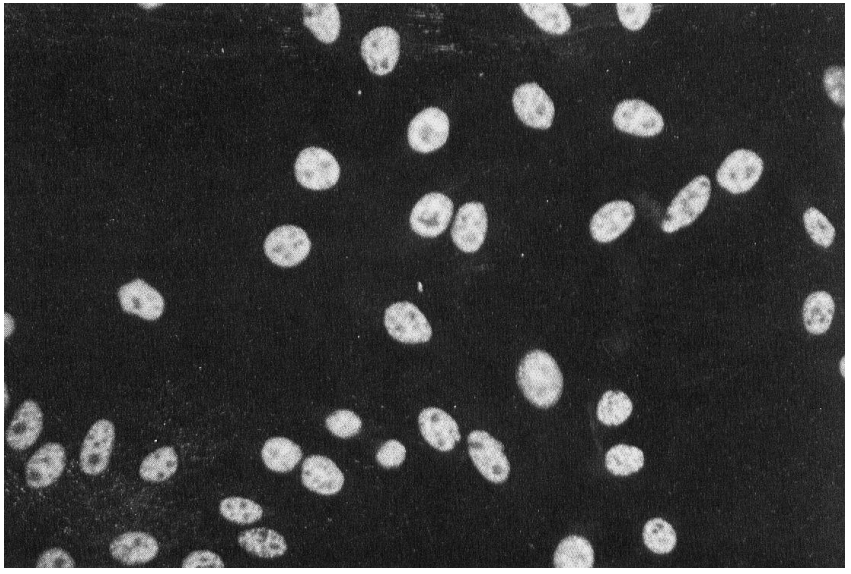
Clinical Features of the Major Systemic Sclerosis Subsets

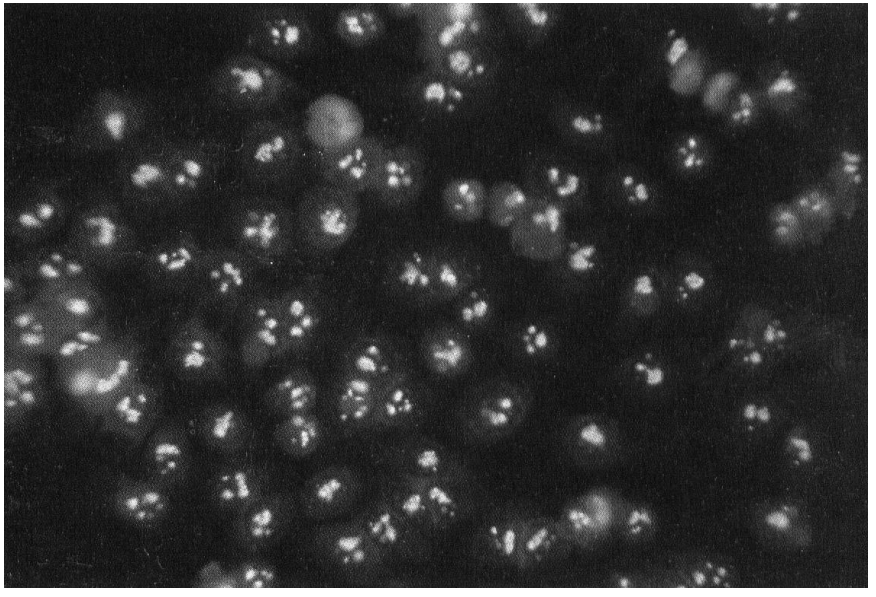
Diffuse cutaneous	Early (< 3 years after onset)	Late (> 3 years after onset)
Constitutional	Fatigue and weight loss	Minimal, weight gain typical
Vascular	Raynaud's often relatively mild	Raynaud's more severe, more telangiectasia
Cutaneous	Rapid progression involving arms, trunk, face	Stable or regression
Musculoskeletal	Prominent arthralgia, stiffness, myalgia, muscle weakness, tendon friction rubs	Flexion contractures and deformities, joint/muscle symptoms less prominent
Gastrointestinal	Dysphagia, heartburn	More pronounced symptoms, midgut and anorectal complications more common
Cardiopulmonary	Maximum risk for myocarditis, pericardial effusion, intersitital pulmonary fibrosis	Reduced risk of new involvement but progression of existing esta-blished visceral fibrosis
Renal	Maximum risk period for scleroderma after 5 years	Renal crisis less frequent, uncommon after 5 years
Limited cutaneous	**Early (< 10 years after onset)**	**Late (> 10 years after onset)**
Constitutional	None	Only secondary to visceral complications
Vascular	Raynaud's typically severe and longstanding telangiectasia	Raynaud's persists, often causing digital ulceration or gangrene
Cutaneous	Mild sclerosis with little progression on trunk, face	Stable, calcinosis more prominent
Musculoskeletal	Occasional joint stiffness	Mild flexion contractures
Gastrointestinal	Dysphagia, heartburn	More pronounced symptoms, midgut and anorectal complications more common
Cardiopulmonary	Usually no involvement	Lung fibrosis may develop, but often progresses slowly, Anti-scl-70 predicts increased risk of severe fibrosis. Maximum risk for developing isolated pulmonary hypertension and secondary right ventricular failure
Renal	No involvement	Rarely involved, anti-RNA polymerase predicts increased risk of renal involvement

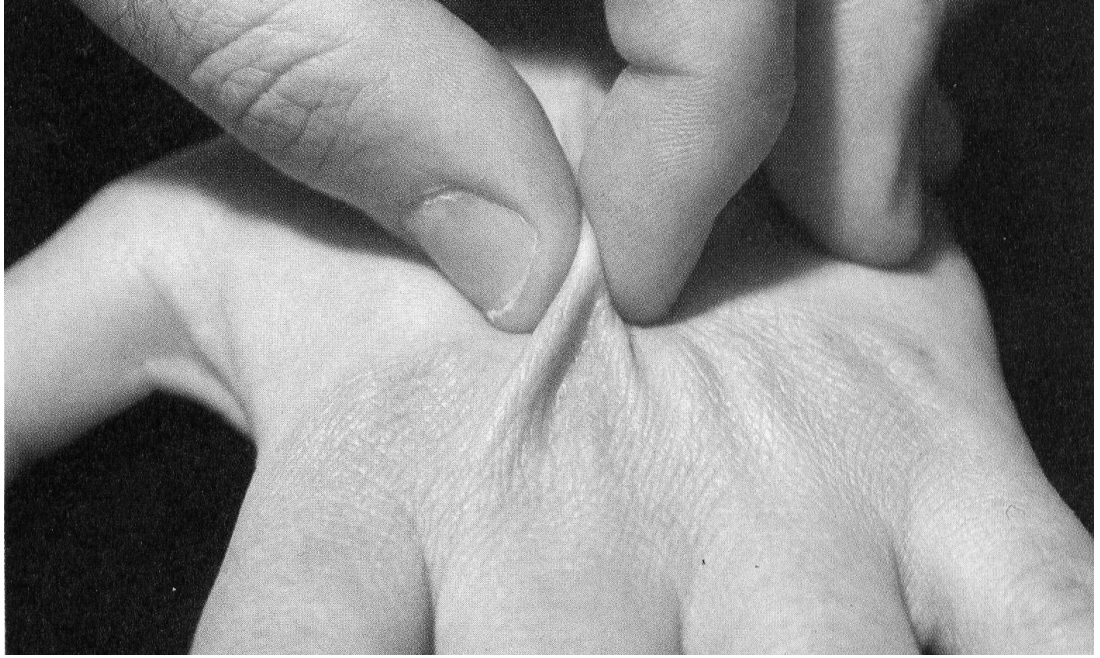
Antigen	ANA staining pattern	HLA associations	Frequency in all patients (percent)	Clinical associations	Organ involvement
Scl-70 topoisomerase-1	Speckled	DR5(DR11) DR3/DR52a DQ7 DQB1	15-20	dcSSc	Interstitial lung fibrosis, "protection" from isolated pulmonary hypertension
RNA I, II, and III	Speckled Nucleolar	?	20	dcSSc	Renal,skin
U3 RNP (fibrillarin)	Nucleolar	?	<5	dcSSc, poor outcome black men	Pulmonary hypertension, muscle
PM-Scl	Nucleolar	DR3 DR52	3-5	Overlap, mixed	Muscle
U1 RNP	Speckled	?	10	lcSSc, blacks, polymyositis overlap	Muscle
Centromere	Centromere (kinotochore)	DR1(DQ5) DQB1 /DR4 (D13 subtypes)	25-30	lcSSc	Pulmonary hypertension, esophageal disease, "protection from lung fibrosis and renal disease
Th(lo)	Nucleolar	?	5	lcSsc	Pulmonary hypertension, small bowel

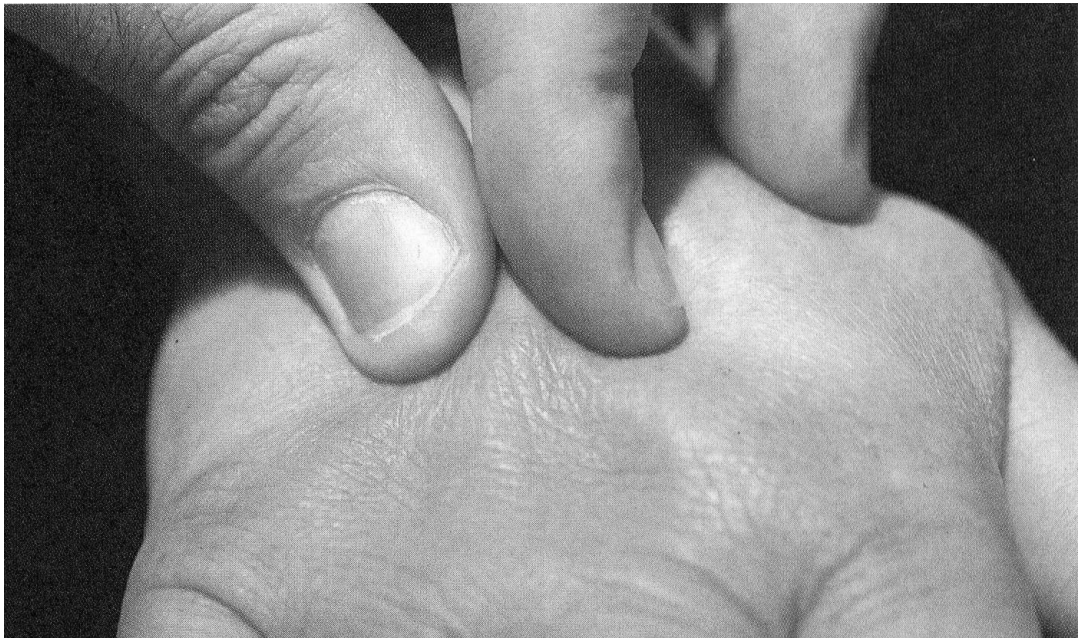
Serum autoantibodies in scleroderma Characteristics and clinical associations of the different autoantibodies that may be seen in scleroderma. dcSSc and lcSSc refer to diffuse and limited cutaneous systemic sclerosis, respectively. (Adapted from Black, CM, J R Coll Physicians Lond 1995; 29:119.)

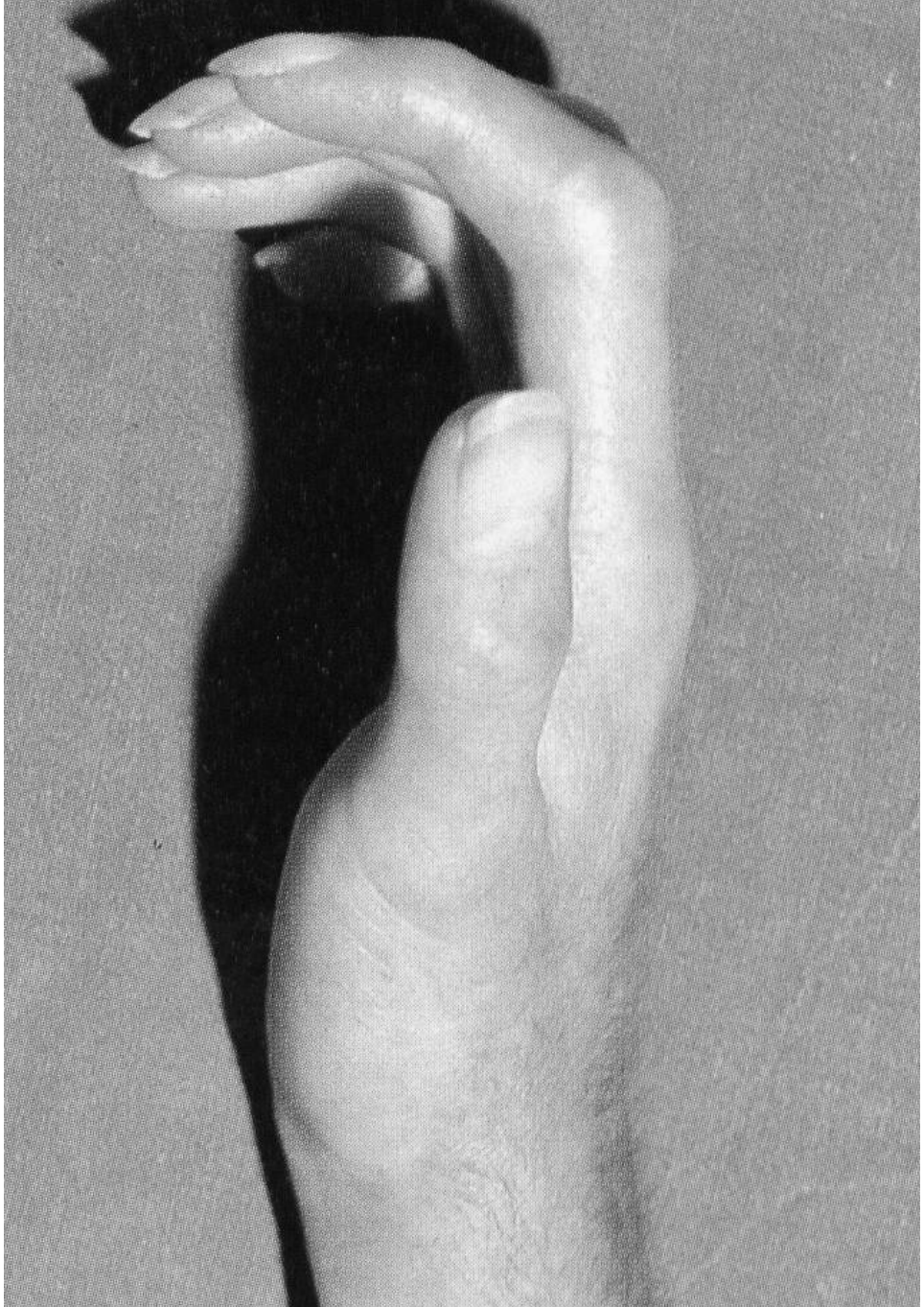


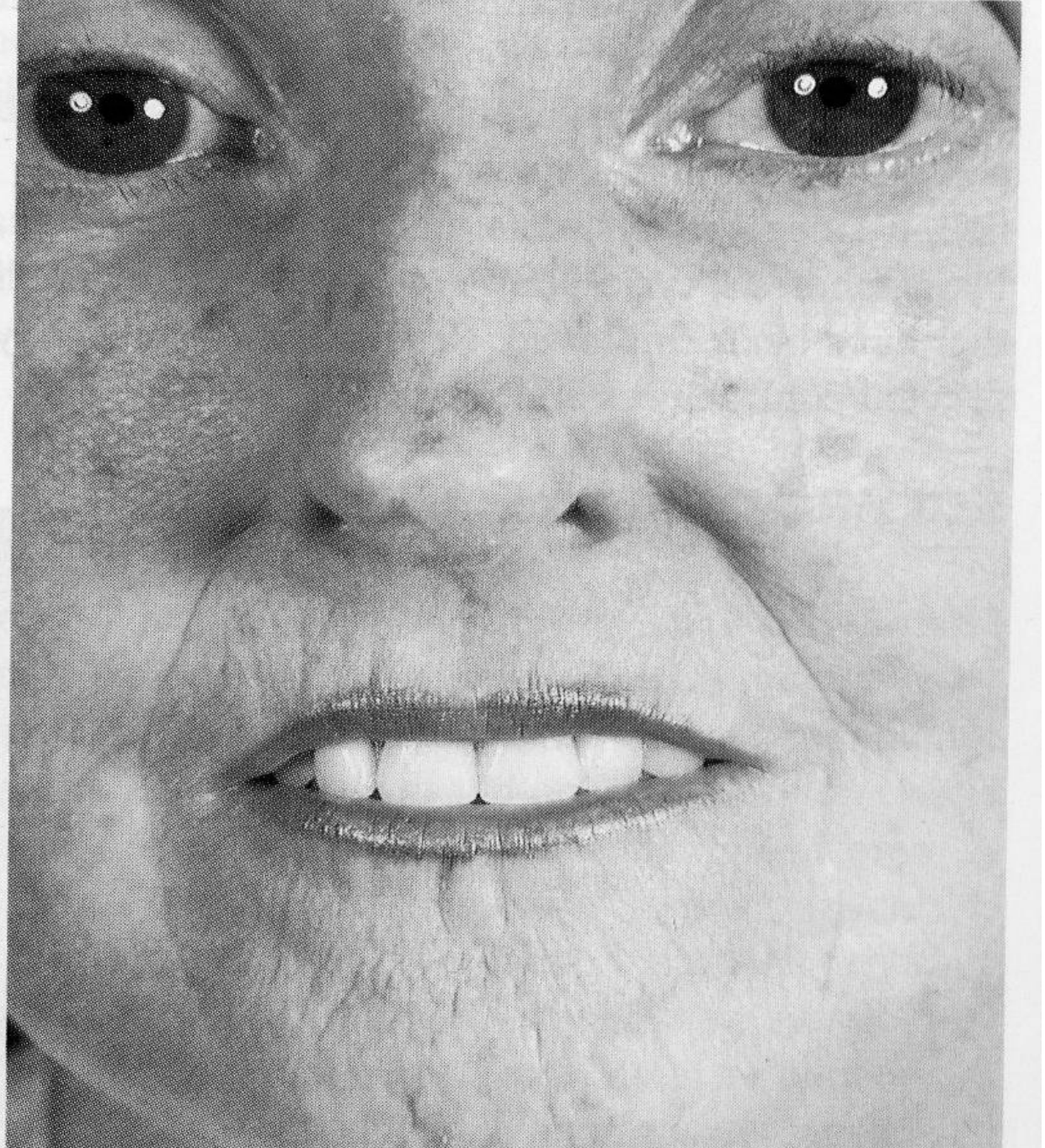


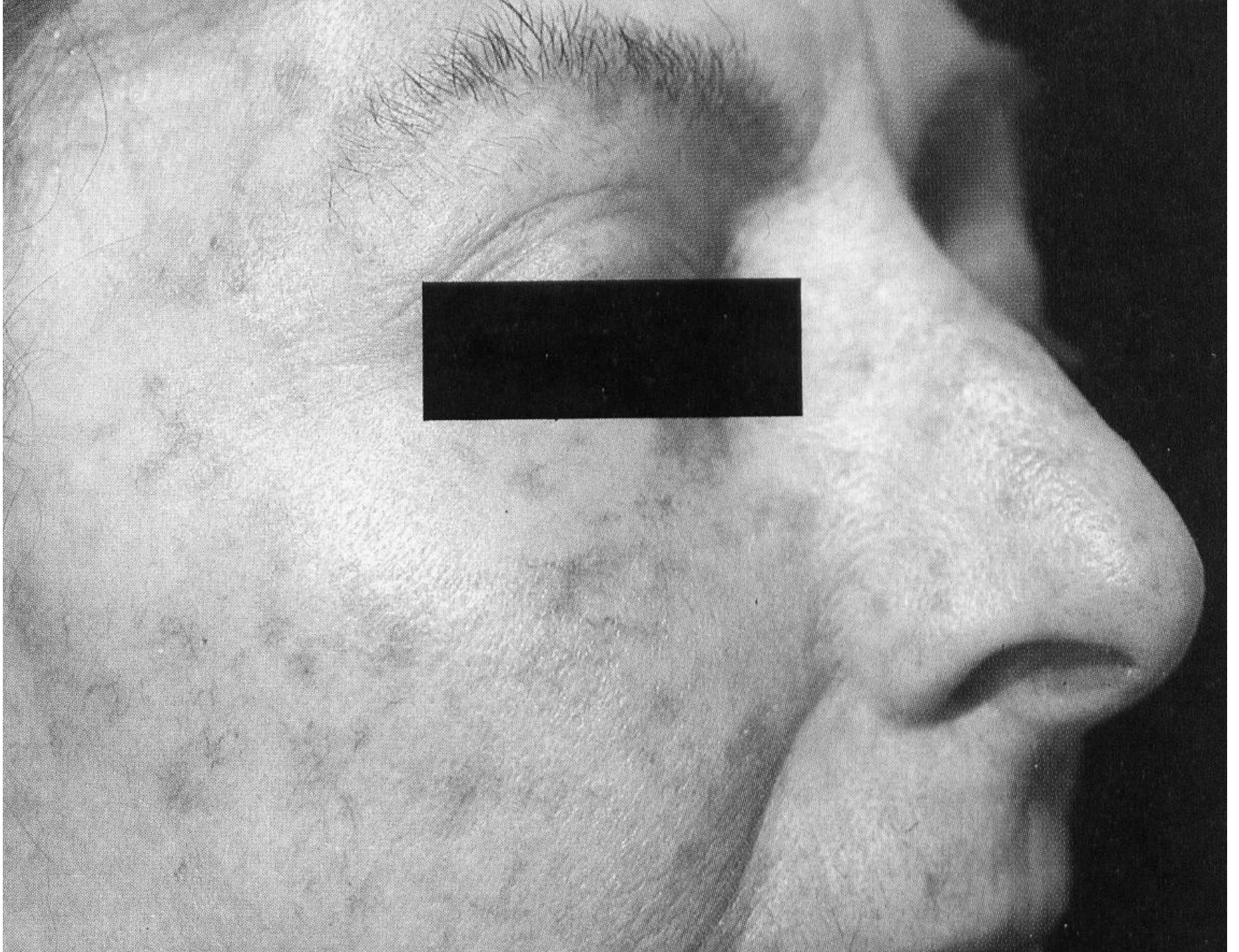


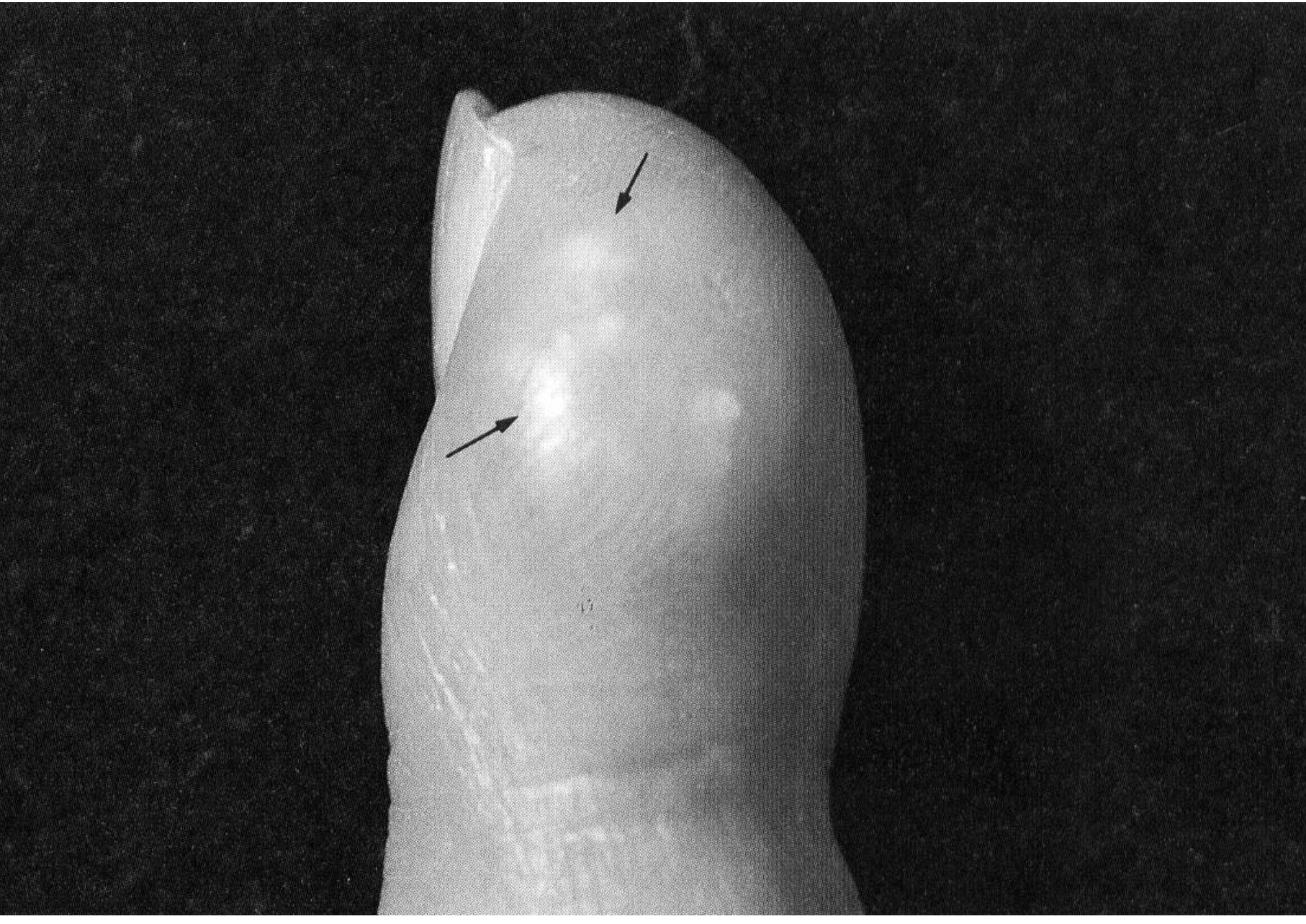


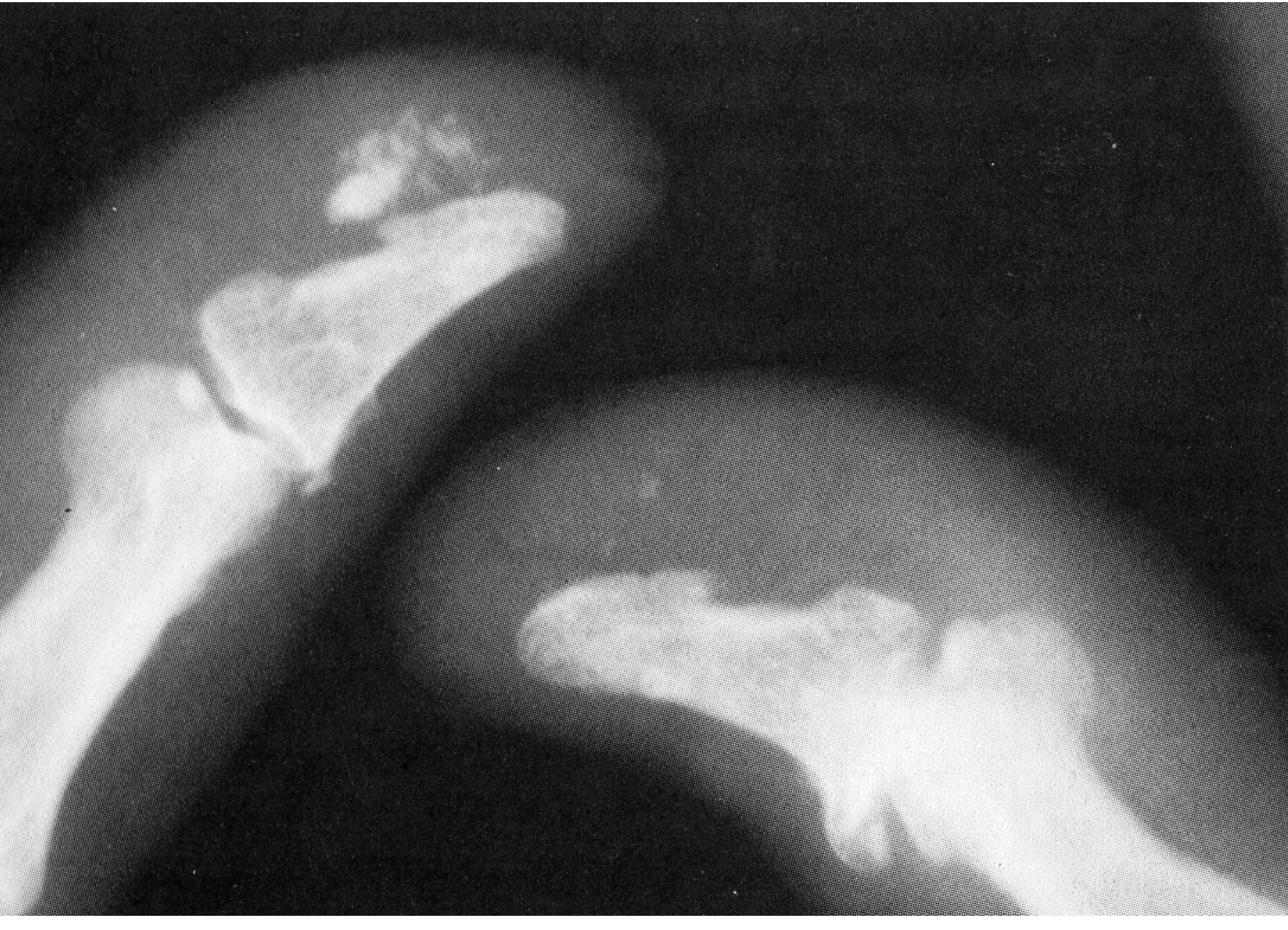












Coinvolgimento dell’apparato digerente

esofagite da reflusso

sanguinamento cronico

disfagia

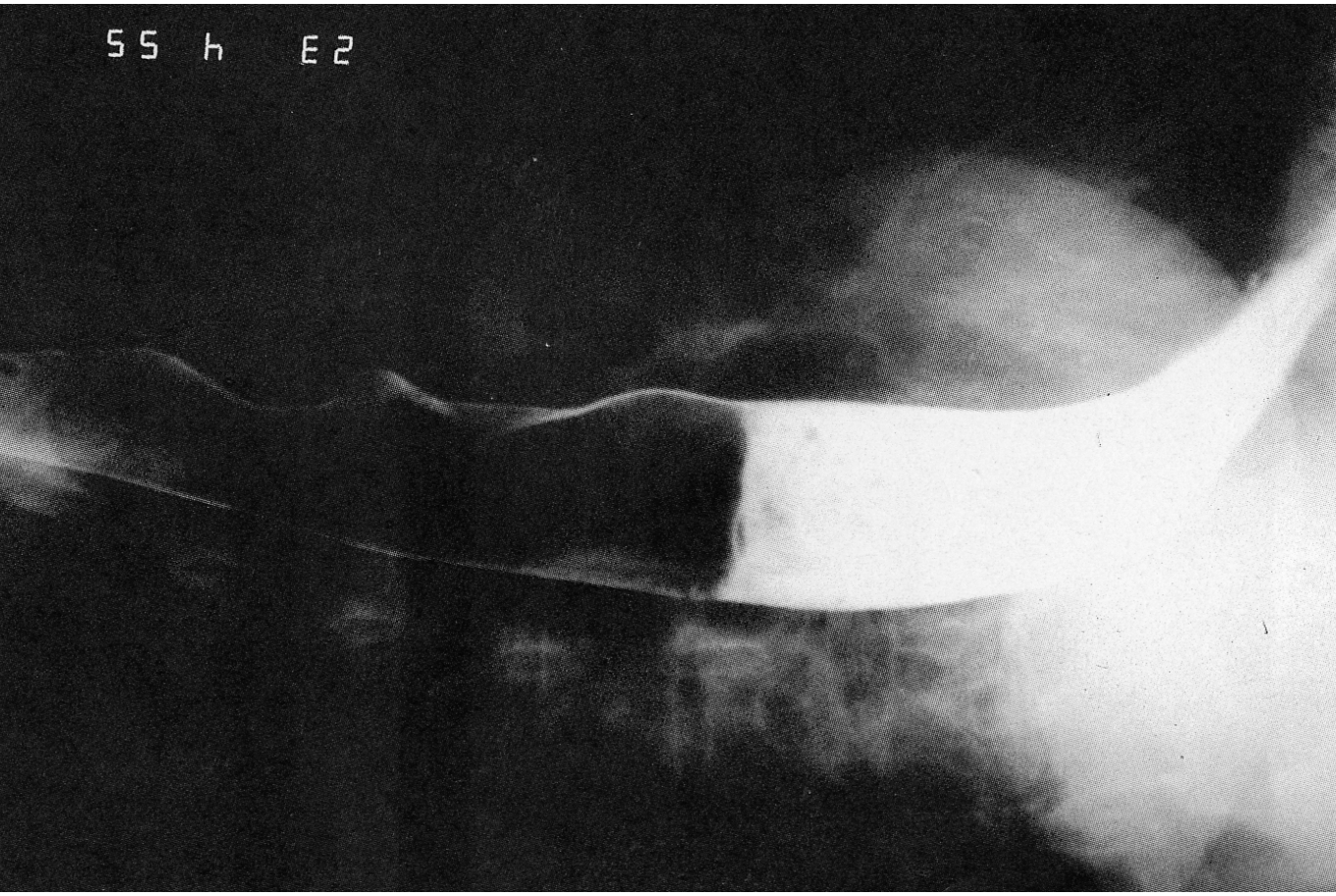
ab-ingestis

stipsi ostinata

crisi subocclusive

diarrea (da ipercrescita batterica)

malassorbimento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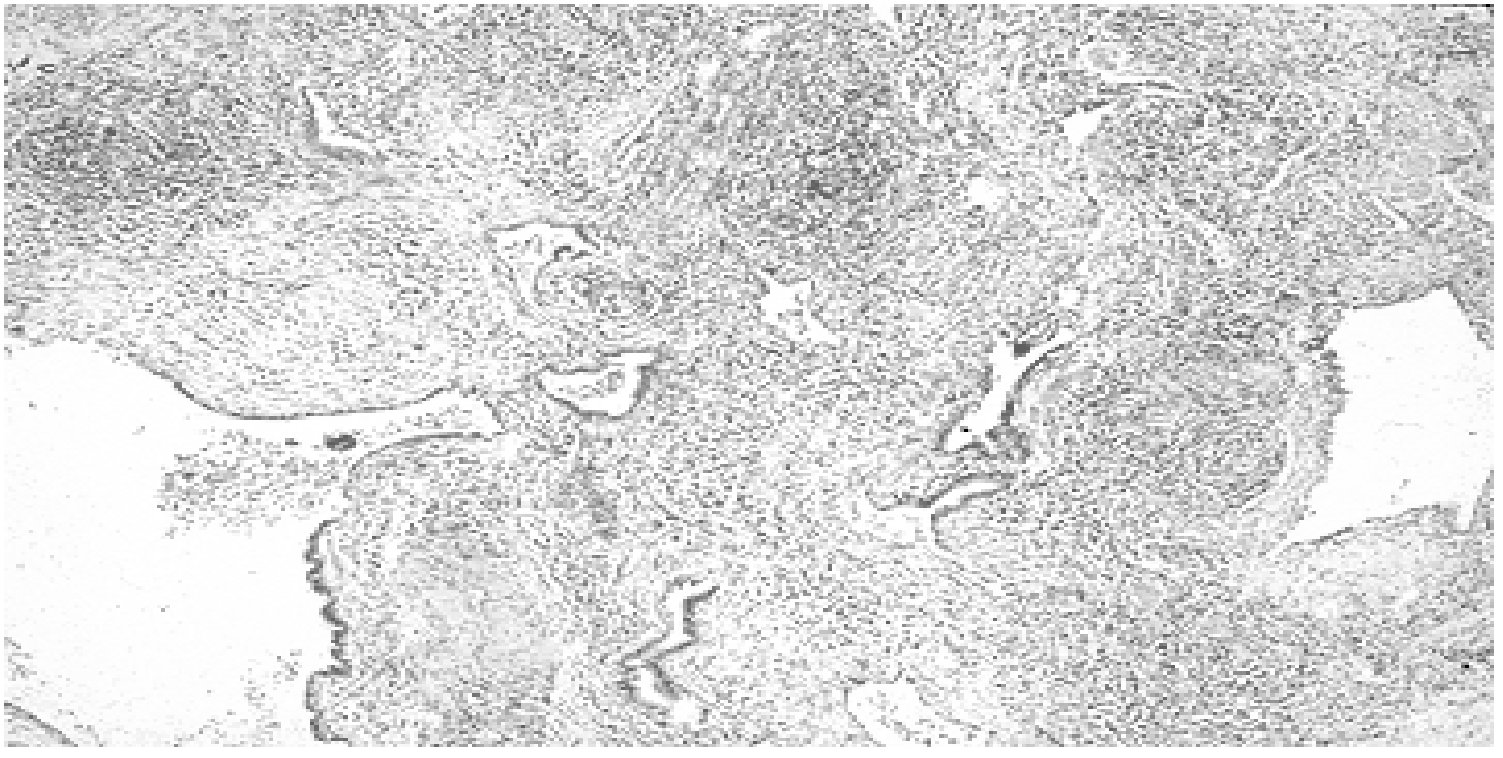
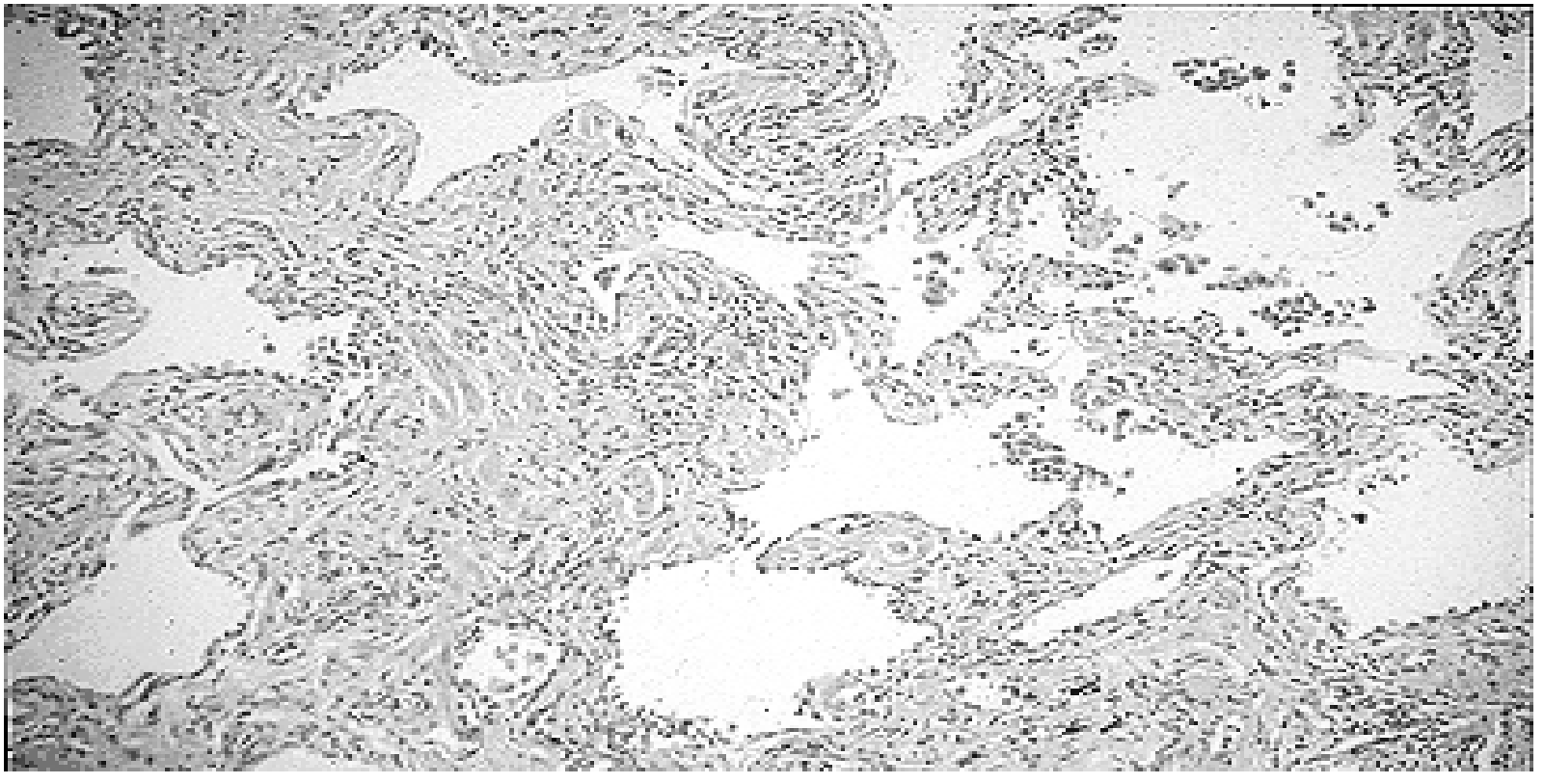
Symptoms and Signs of Lung Disease in Scleroderma

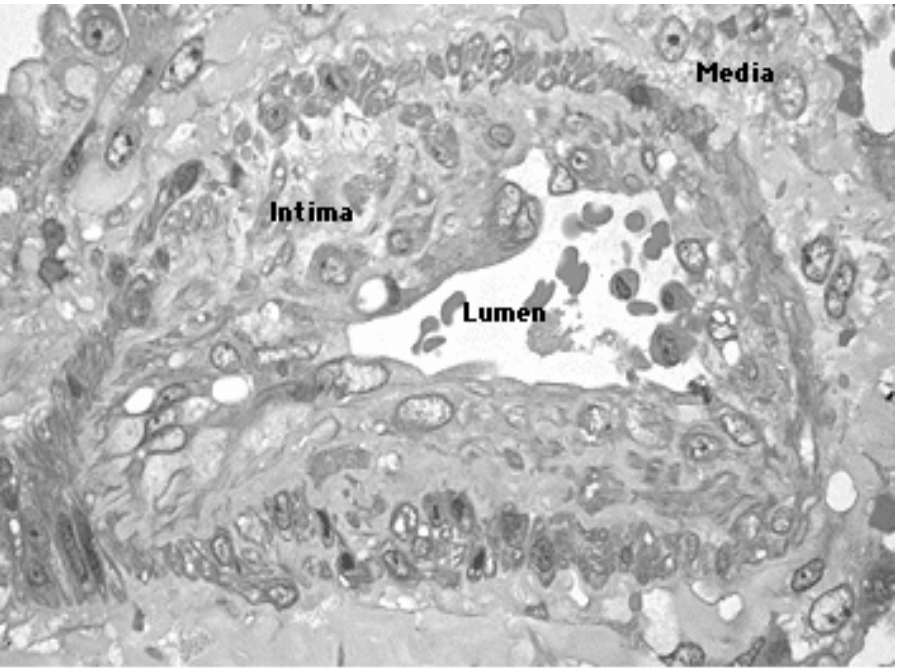
Disease	Symptoms	Signs
Pulmonary fibrosis	Dyspnea Dry cough	Chest expansion Basal crepitations (rales) Clubbing (late, very uncommon)
Pulmonary hypertension	Dyspnea Ankle edema	Loud P2 Right ventricular heave
Pleural involvement	Pleuritic chest pain Dyspnea	Pleural rub Pleural effusion (rare)
Bronchiectasis	Cough with purulent sputum Dyspnea	Basal crepitations
Spontaneous pneumothorax	Chest pain Dyspnea	Resonant percussion Reduced breath sounds
Lung cancer (scar type), especially alveolar cell	Cough Hemoptysis	? Signs of collapse
Respiratory failure due to respiratory muscle involvement	Dyspnea Reduced chest expansion	Hypoventilation



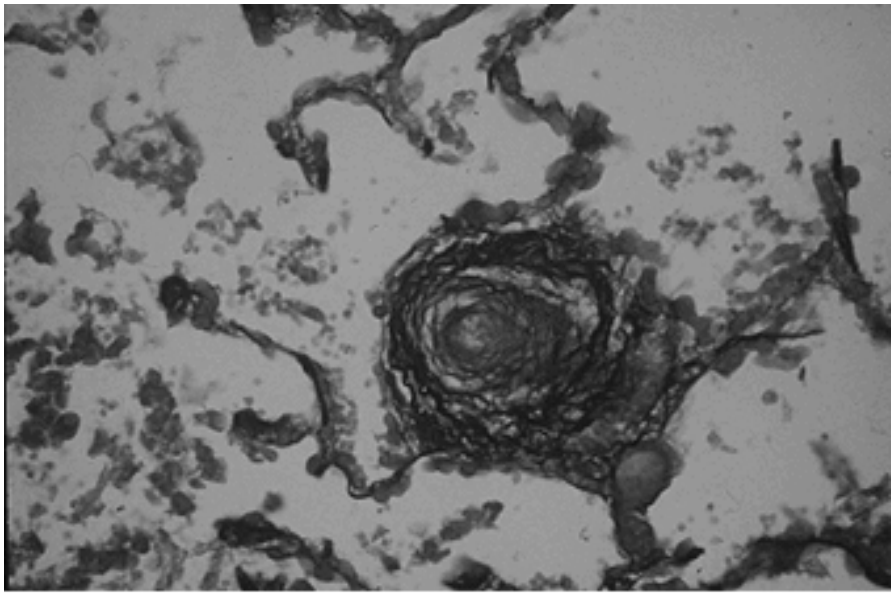
Cellular infiltrate in fibrosing alveolitis Lung biopsy from a patient with scleroderma, fibrosing alveolitis, and ground glass opacification on high resolution CT scan. Note the marked interstitial cellular infiltration. Courtesy of Professor B Corrin, Royal Brompton and National Heart Hospital, London, UK.



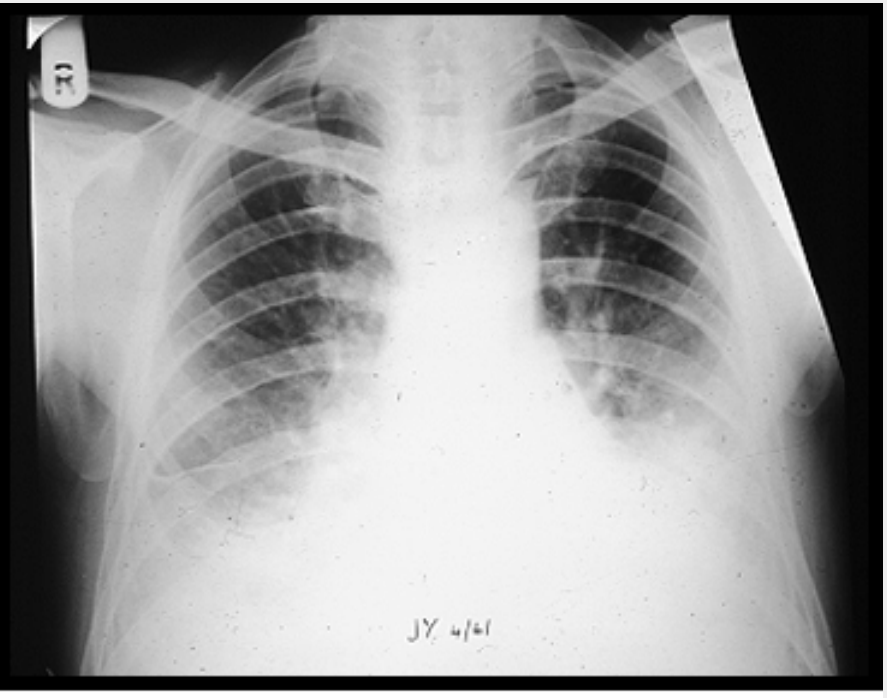
Fibrosis in fibrosing alveolitis Lung biopsy from a patient with scleroderma and a reticulonodular pattern on high resolution CT scan. This later stage of the disease is characterized by fibrosis (stained pink) and tissue destruction. Courtesy of Professor B Corrin, Royal Brompton and National Heart Hospital, London, UK.



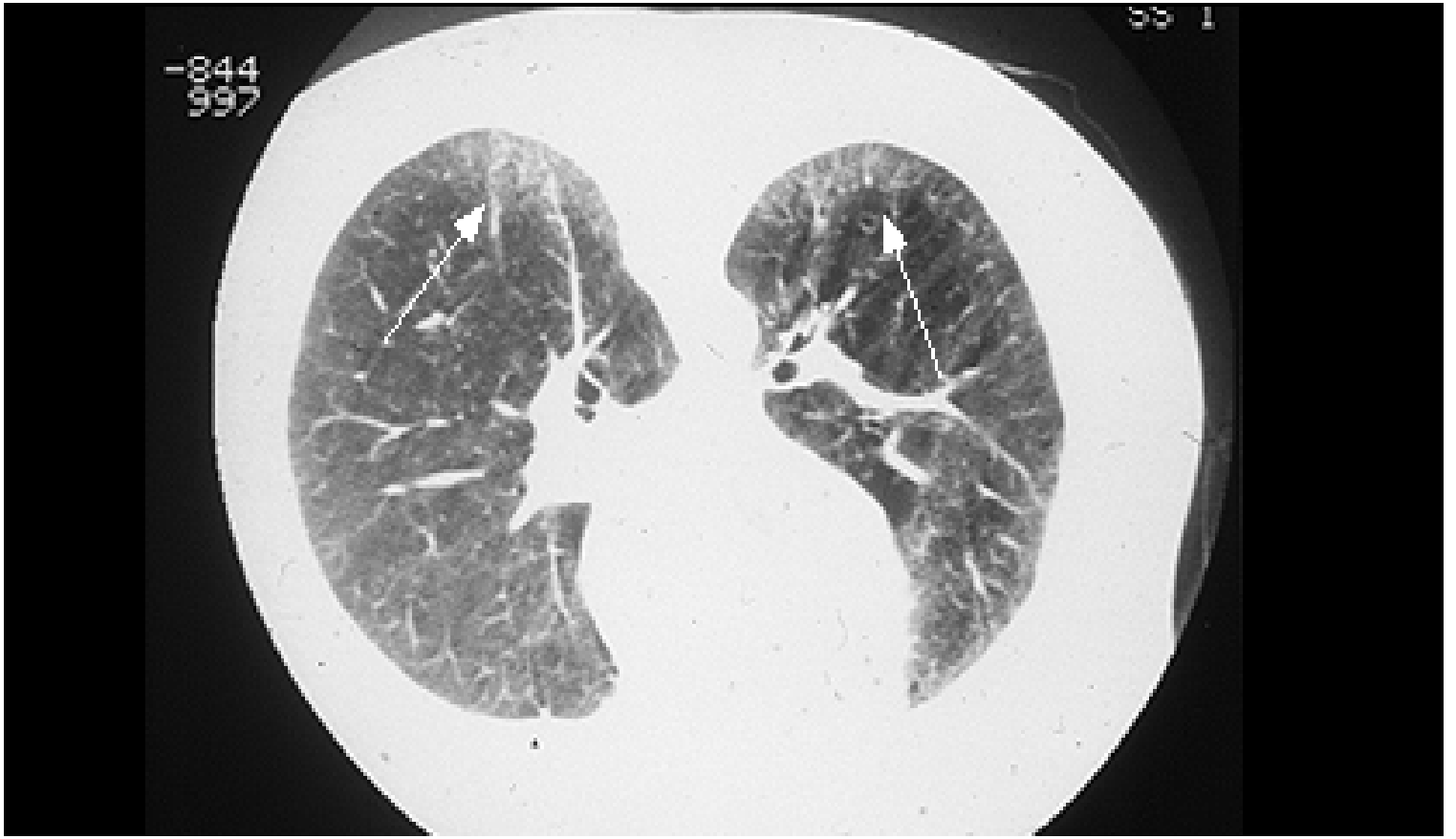
Vascular changes in pulmonary arterial hypertension Pulmonary arteriole in pulmonary hypertension showing both mild medial hypertrophy and marked intimal hyperplasia, leading to partial obstruction of the lumen. Courtesy of Eugene Mark, MD.



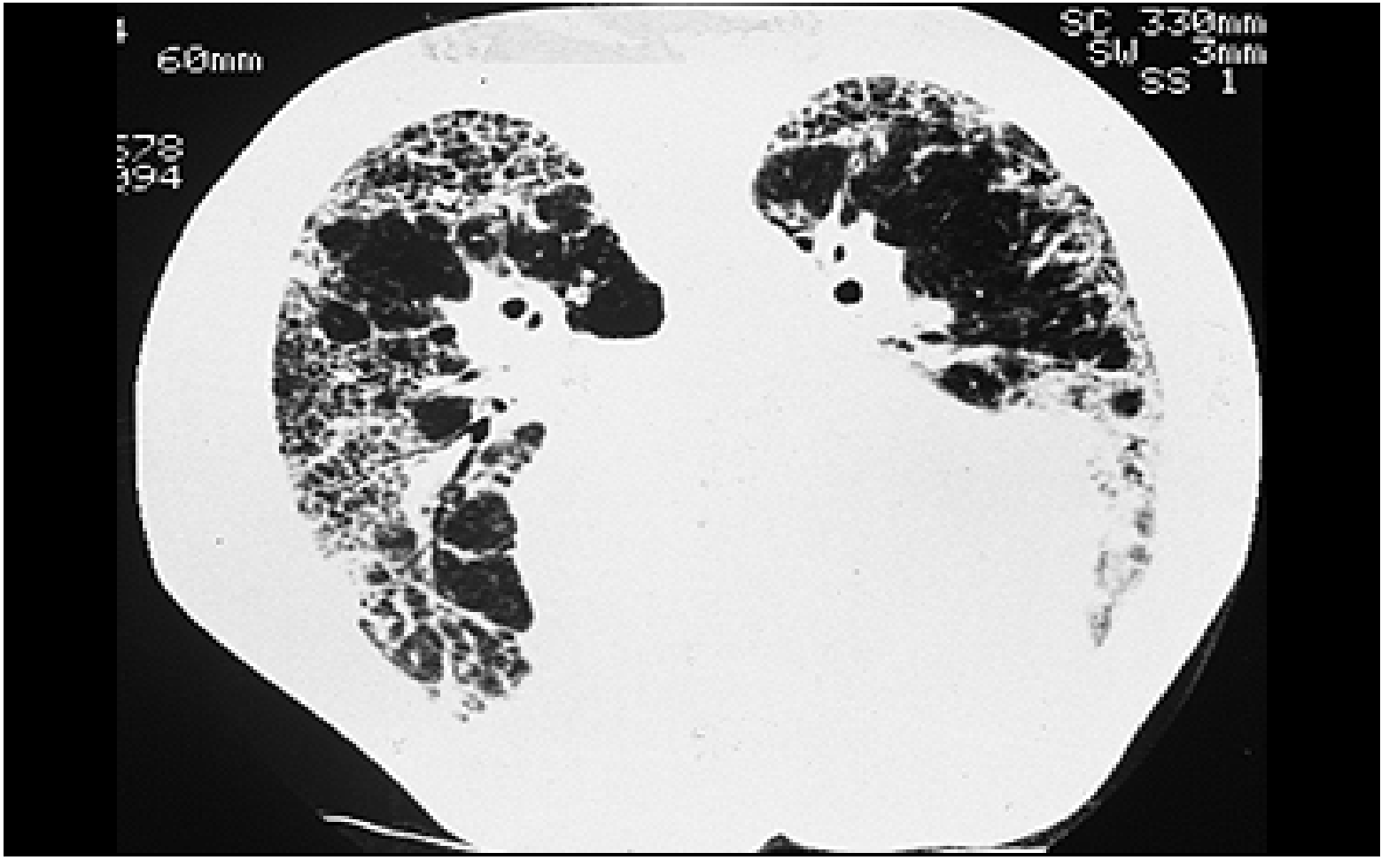
Pulmonary arterial disease in scleroderma Primary pulmonary vascular disease in a patient with scleroderma characterized by marked lamellar intima thickening. Similar "onion-skin" changes can be seen i the small arteries in scleroderma renal disease. Courtesy of Professor B Corrin, Royal Brompton and National Heart Hospital, London, UK.



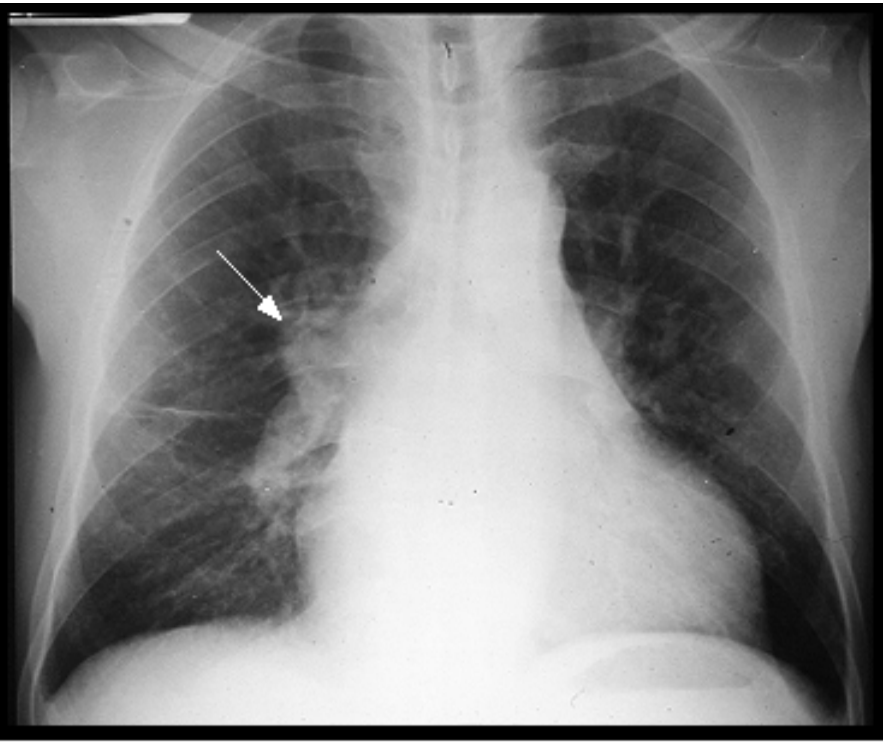
Scleroderma lung disease Chest x-ray of a patient with scleroderma and interstitial lung disease. Note the bilateral basal reticulonodular shadowing. Courtesy of Carol M Black, MD.



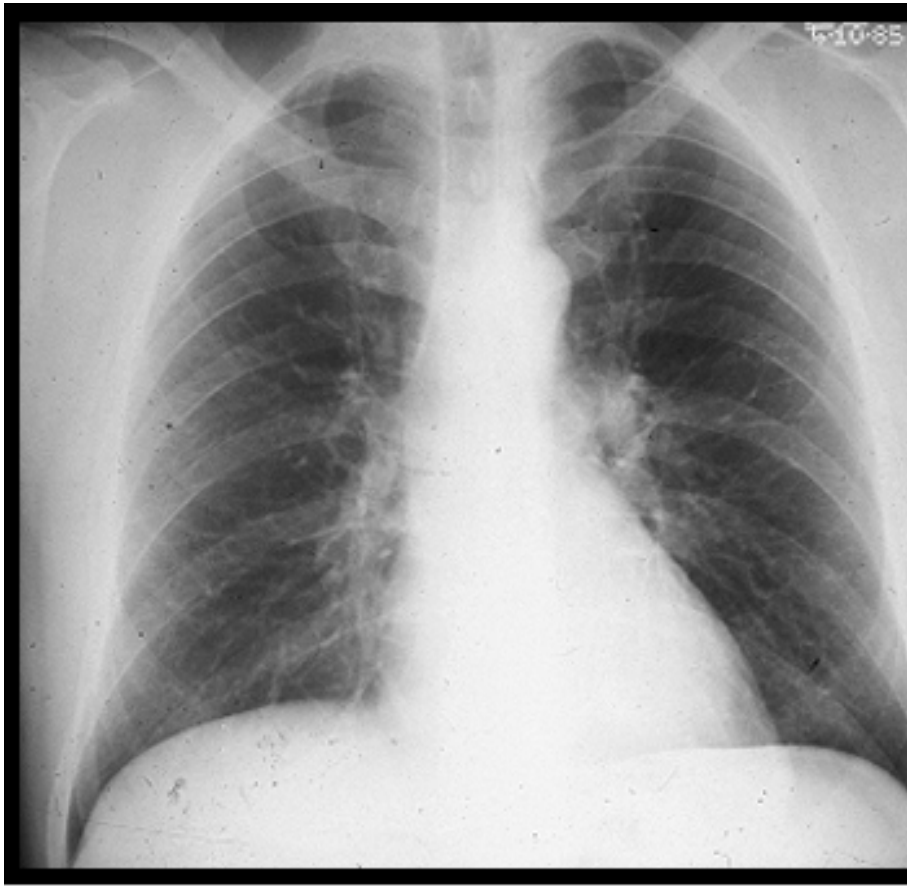
Fibrosing alveolitis in scleroderma High resolution CT scan in a patient with scleroderma and fibrosing alveolitis who had a normal chest radiograph. A peripheral rim of increased density can be seen in both lung fields (arrows). This pattern of ground glass opacification is consistent with a more cellular appearance on lung biopsy. Courtesy of Carol Black, MD.



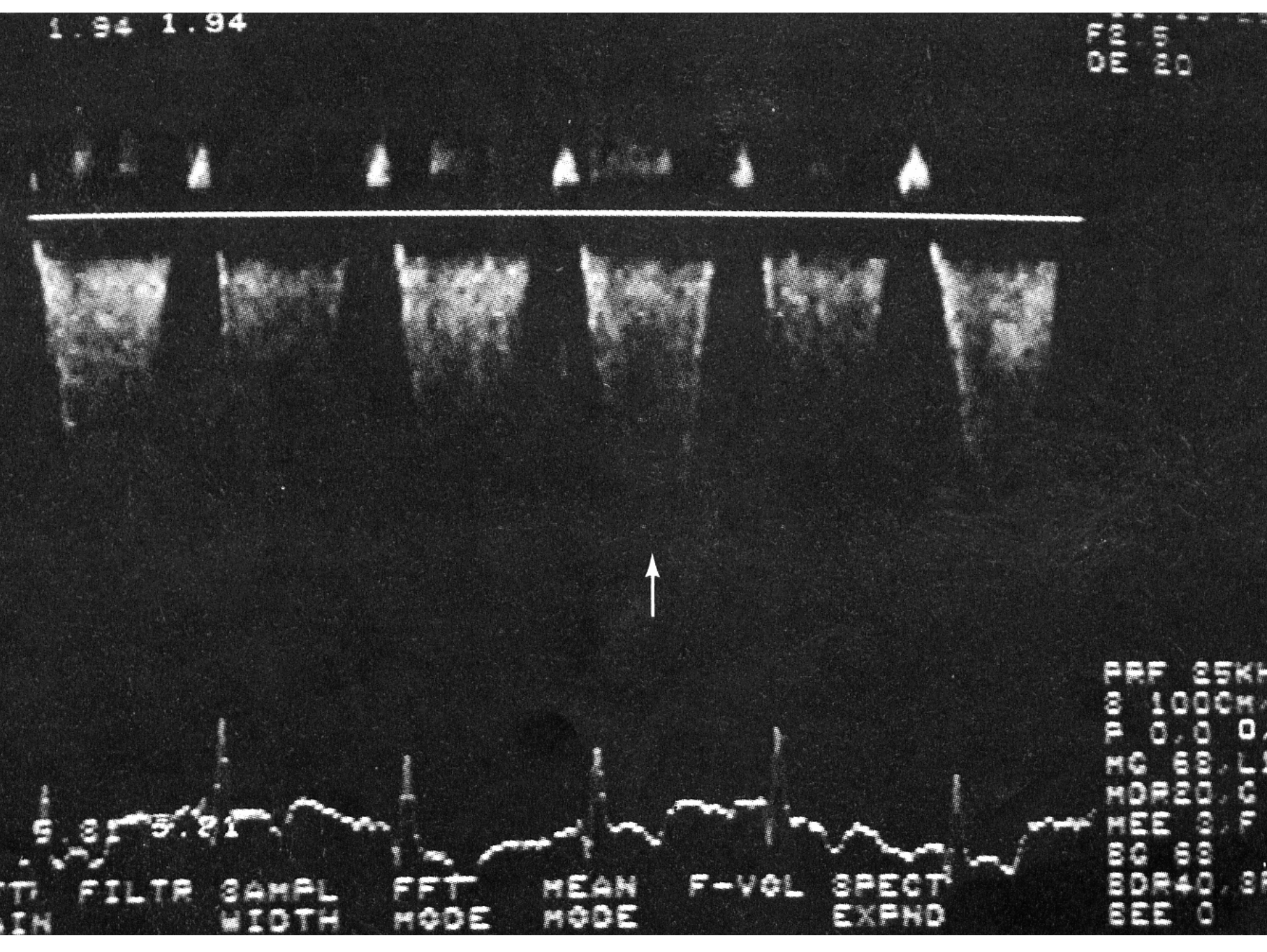
Reticulonodular pattern in fibrosing alveolitis
High resolution CT in a patient with scleroderma and fibrosing alveolitis showing a reticulonodular pattern in both lung fields. This pattern correlates with fibrotic changes on lung biopsy. Courtesy of Carol Black, MD.



Pulmonary hypertension in scleroderma Pulmonary hypertension in a patient with limited cutaneous scleroderma characterized by enlargement of the pulmonary artery (arrow) and attenuation of the smaller vessels. Courtesy of Carol Black, MD.



Normal chest film Posteroanterior view of a norma chest radiograph. Courtesy of Carol M Black, MD.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F-VOL
SPECT EXPND

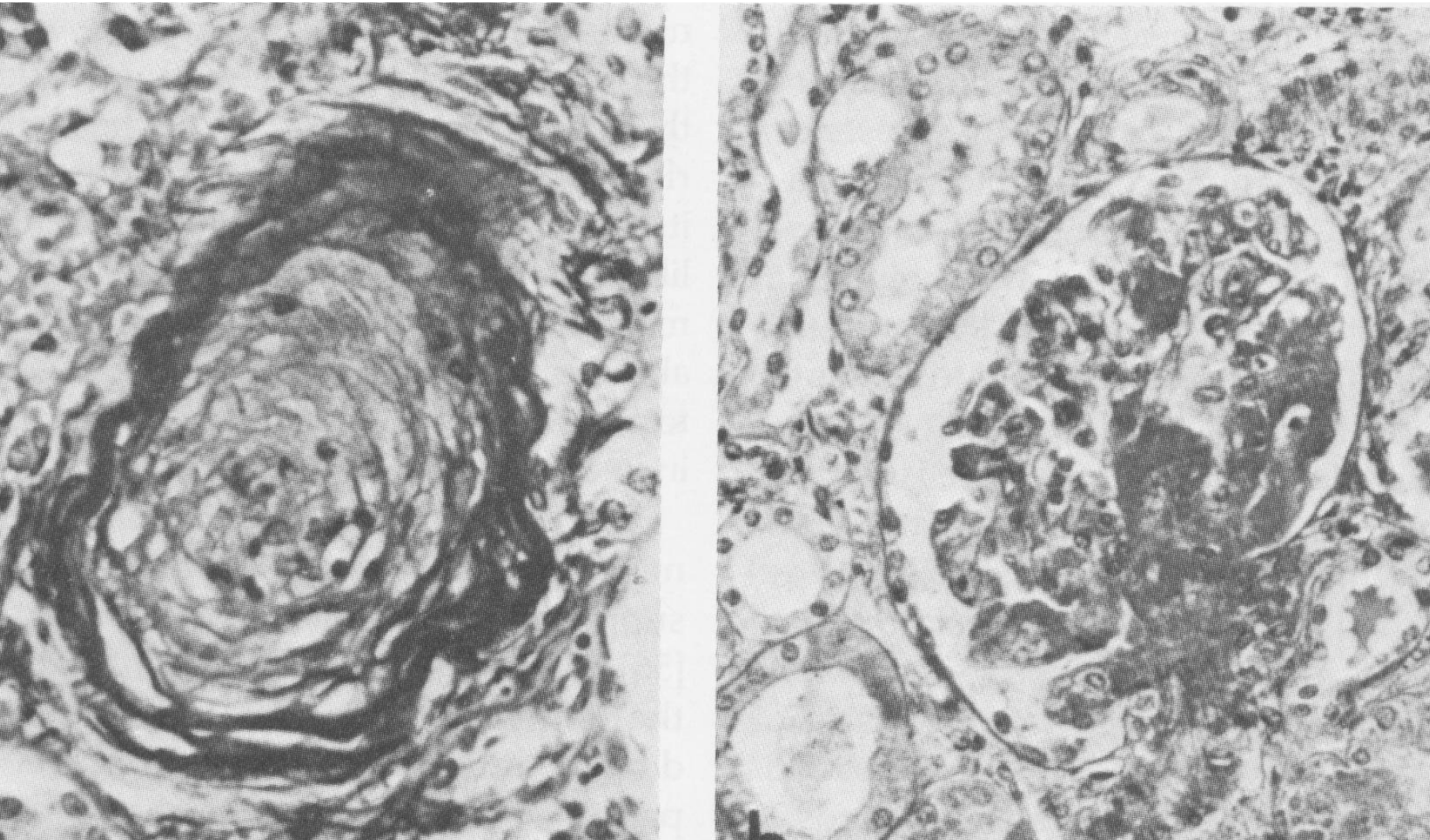
Il coinvolgimento renale nella sclerosi sistemica

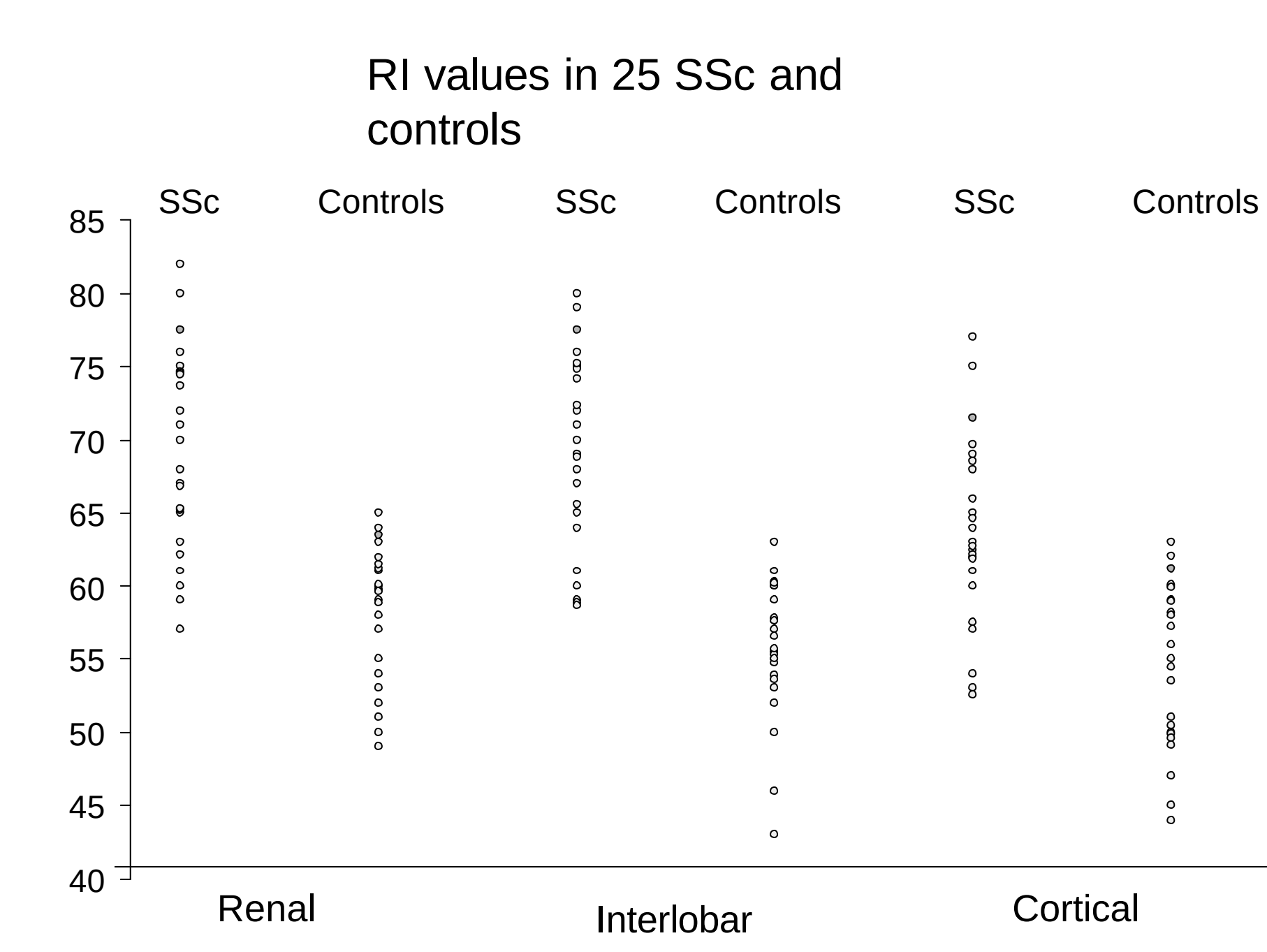
- Riscontrabile all'autopsia nel 60-80% dei pazienti
- Presente in forma subclinica fino al 50% dei pazienti (proteinuria lieve, lieve incremento della creatininemia con o senza ipertensione)
- Crisi renale sclerodermica nel 10-19% del pazienti, meno del 10% nelle casistiche italiane
- Nei pazienti sclerodermici vi è una aumentata produzione di TBX dopo cold-test

Scleroderma "renal crisis".

A: Intimal hyperplasia with complete luminal occlusion of an interlobular
rtery. Note reduplication and fraying of the internal lamina (orcein stain

B: Fibrinoid necrosis of blood vessels in the glomerulus

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70
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55
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45
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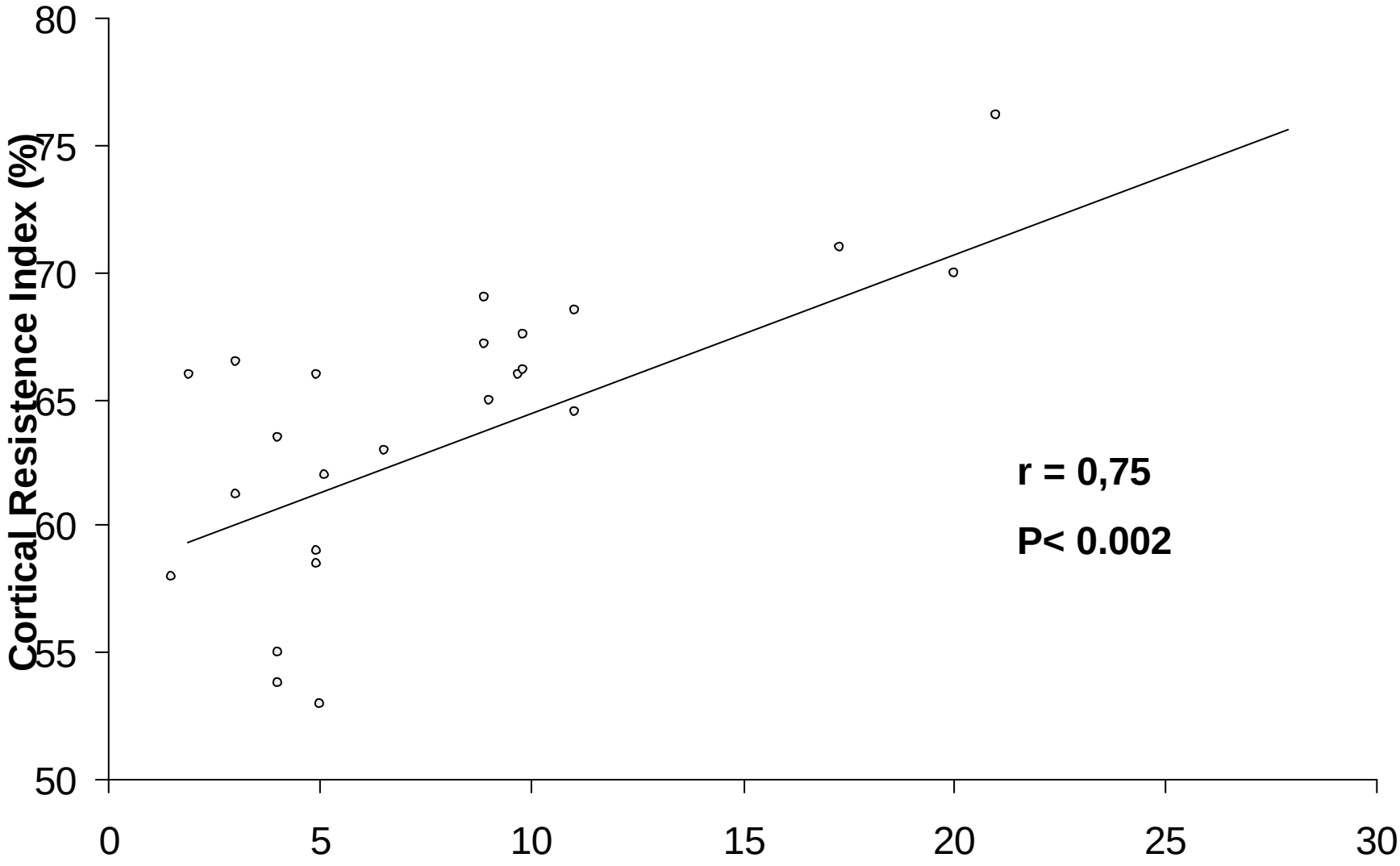
Renal
Interlobar
Cortical

RI and duration of disease



Effect of ACE-inhibitors on the cumulative survival of patients with scleroderma renal crisis