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Rheumatoid Arthritis/Pathogenesis and Clinical Presentation of Joint Inflammation and Destruction

M2 Musculoskeletal Sequence

Fall 2008

David A. Fox, M.D.

Reading Assignment

Primer on the Rheumatic Diseases, 13th edition
Chapter 6A, pp 114-121
Chapter 6B, pp. 122-132

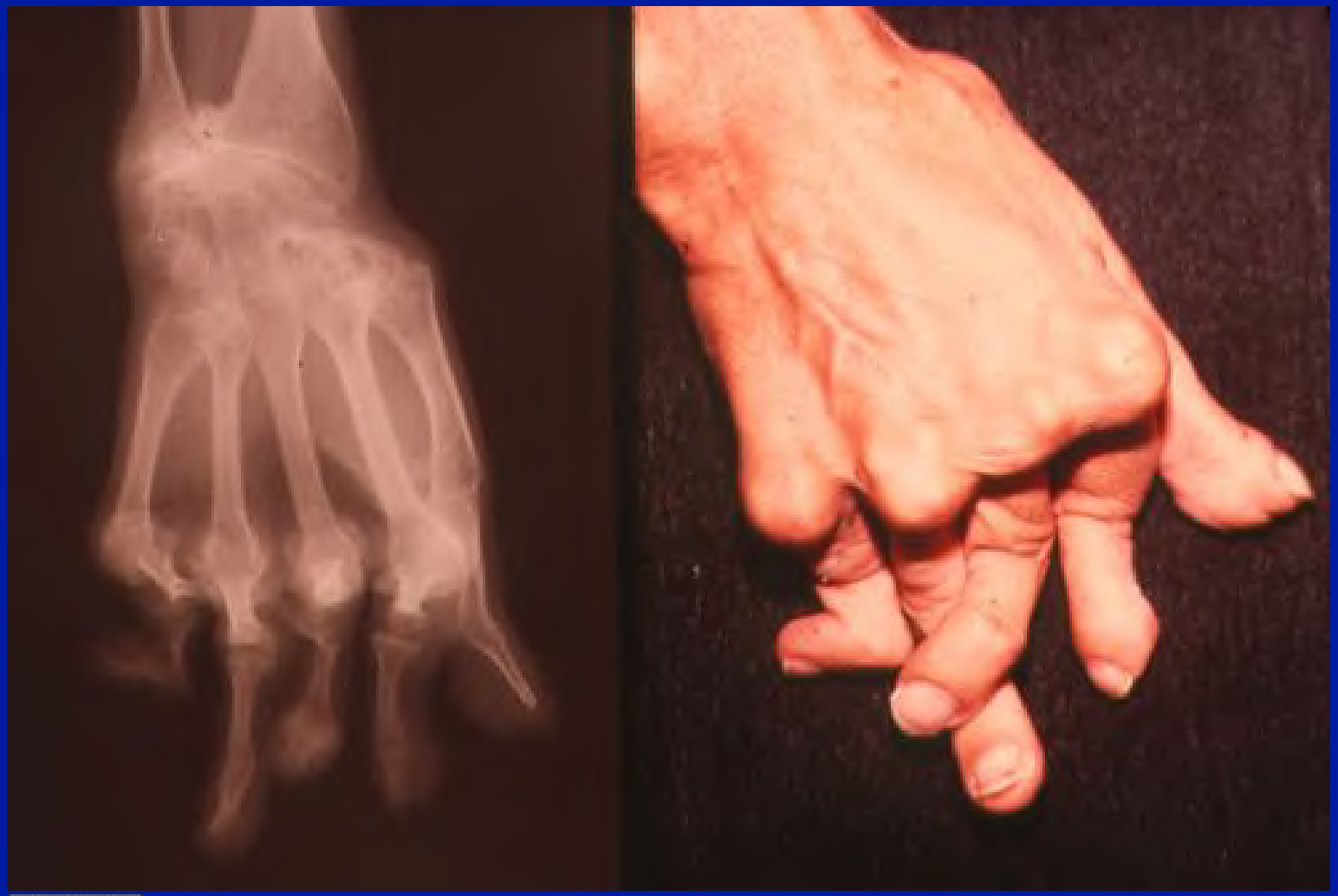
Optional in-depth reading

Arthritis and Allied Conditions – A textbook of Rheumatology, WJ Koopman, Ed.
Chapter 52, pp. 1089-1115, 15th Edition

Learning Objectives

1. Understand how to distinguish rheumatoid arthritis (RA) from other forms of arthritis, such as osteoarthritis.
2. Understand the main clinical features of RA in the joints.
3. Understand the major theories concerning the cause of RA.
4. Understand mechanisms of tissue destruction in the RA joint.
5. Understand the role of TNF (tumor necrosis factor) and other key cytokines in RA.

NOTE: The lecture will include interaction with a patient who has had RA for 29 years, and demonstration of some changes that RA can cause in the joints – material that is not included in this handout. The first half hour will focus on an interview with the patient, including opportunities for the students to ask questions.



NB is a 71-year old woman who was diagnosed with rheumatoid arthritis in 1977, involving the hands, wrists, elbows, shoulders, feet and eventually cervical spine. Family history is notable for autoimmune disease affecting both of the patient's daughters, one with rheumatoid arthritis and the other with systemic lupus. During the first ten years of her illness medical treatment included salicylates, non-steroidals, intramuscular gold, oral gold and prednisone. Methotrexate was first administered in 1989 and her initial visit at the University of Michigan was in 1993. Due to the rheumatoid arthritis the patient had to retire from her position as a high school English teacher.

Rheumatoid Arthritis: 1987 Revised Diagnostic Criteria

Patients must have 4 of 7 criteria:

- *Morning stiffness lasting at least 1 hour
- *Simultaneous arthritis of 3 or more joints
- *Arthritis of hand joints
- *Symmetrical arthritis
- Rheumatoid nodules
- Abnormal serum rheumatoid factor
- Typical changes on PA x-ray film of hand and wrist

* Must persist for at least 6 weeks
Patients may also have another rheumatic disease so long as RA criteria are met.
RA no longer to be designated classical, definite, or probable.

Adapted from Arnett FC, Edworthy SM, Bloch DA, et al: *Arthritis Rheum 1988; 31:319.*

Factors Useful for Differentiating Early RA from Osteoarthrosis (Osteoarthritis)

	RA	Osteoarthrosis
Age of onset	Usually age 20-65 peak incidence in 50's	Increases with age
Predisposing factors	HLA-DR4	Trauma, obesity (OA of the knee), congenital abnormalities (e.g., shallow acetabulum)
Symptoms, early	Morning stiffness	Pain increases through the day and with use
Joints involved	Hands (metacarpophalangeal , proximal interphalangeal joints) wrists, elbows, shoulders, hips, knees, ankles, feet cervical spine. The thoracic spine, lumbar spine and distal interphalangeal joints of the hand are almost never affected.	Distal interphalangeal joints (Heberden's nodes), proximal interphalangeal joints (Bouchard's nodes), weight-bearing joints (hips, knees), spine (any region).
Physical findings	Soft tissue swelling, warmth, deformities	Bony osteophytes, minimal soft tissue swelling early
Radiographic findings	Periarticular osteopenia, marginal erosions	Subchondral sclerosis, osteophytes, cartilage loss
Laboratory findings	Increased erythrocyte sedimentation rate: rheumatoid factor, anemia, thrombocytosis, hypoalbuminemia	Normal

Causes of Chronic Inflammatory Polyarthritis (a partial list)

- Rheumatoid arthritis
  - Systemic rheumatic disease
    - Systemic lupus
    - Scleroderma
    - Polymyositis
    - Vasculitis
  - Spondylarthropathies
    - Ankylosing spondylitis
    - Reiter's syndrome
  - Psoriatic arthritis
  - Gout
  - Pseudogout
  - Rheumatic fever
  - Juvenile rheumatoid arthritis

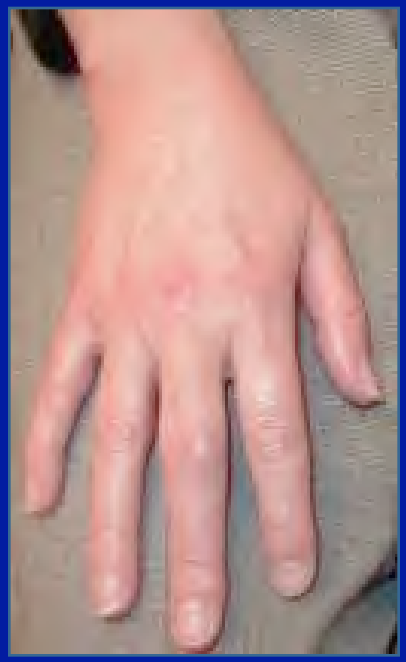
Specific Joint Involvement in Polyarthritis

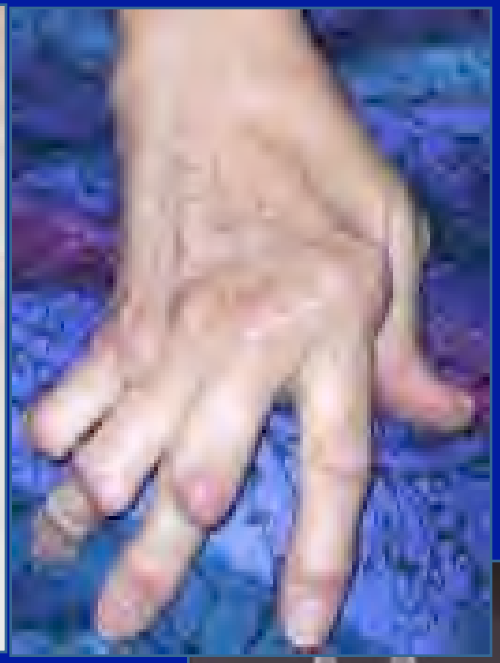
Joints Involved	Common With	Rare In
Temporomandibular	Rheumatoid arthritis, juvenile rheumatoid arthritis	Gout
Larynx (crico-arytenoid)	Rheumatoid arthritis	All other
Elbows, wrists, metacarpophalangeals	Any synovitis	Osteoarthritis
Distal interphalangeal joints (hand)	Osteoarthritis, psoriatic arthritis	Rheumatoid arthritis
Hips	Osteoarthritis, rheumatoid arthritis	Gout
Cervical spine	Rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, osteoarthritis, spondyoarthropathies	Gout
Thoracolumbar spine	Spondyloarthropathies: Ankylosing spondylitis Psoriatic arthritis Reiter's syndrome Inflammatory bowel disease-associated arthritis Osteoarthritis	Gout, Rheumatoid Arthritis

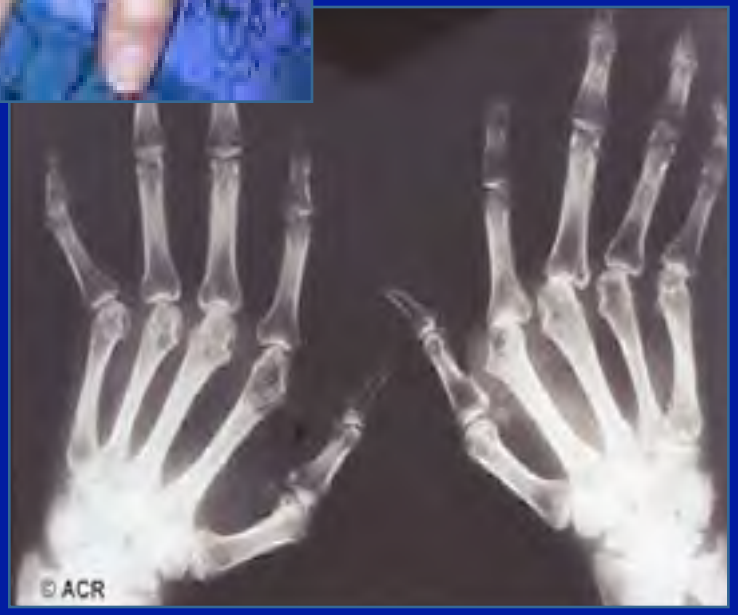
Synovial Fluid Leukocyte Count ($x10^3$)

Condition	0	1	2	4	8	16	32	64	128	PUS
Normal	xxx									
Osteoarthritis	xxxxxxxx									
Rheumatoid arthritis					xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx					
Juvenile rheumatoid arthritis					xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx					
Gout						xxxxxxxxxxxxxxxxxxxxx				
Septic arthritis								xxxxxxxxxxxxxxxxxx		

Clinical Spectrum of RA

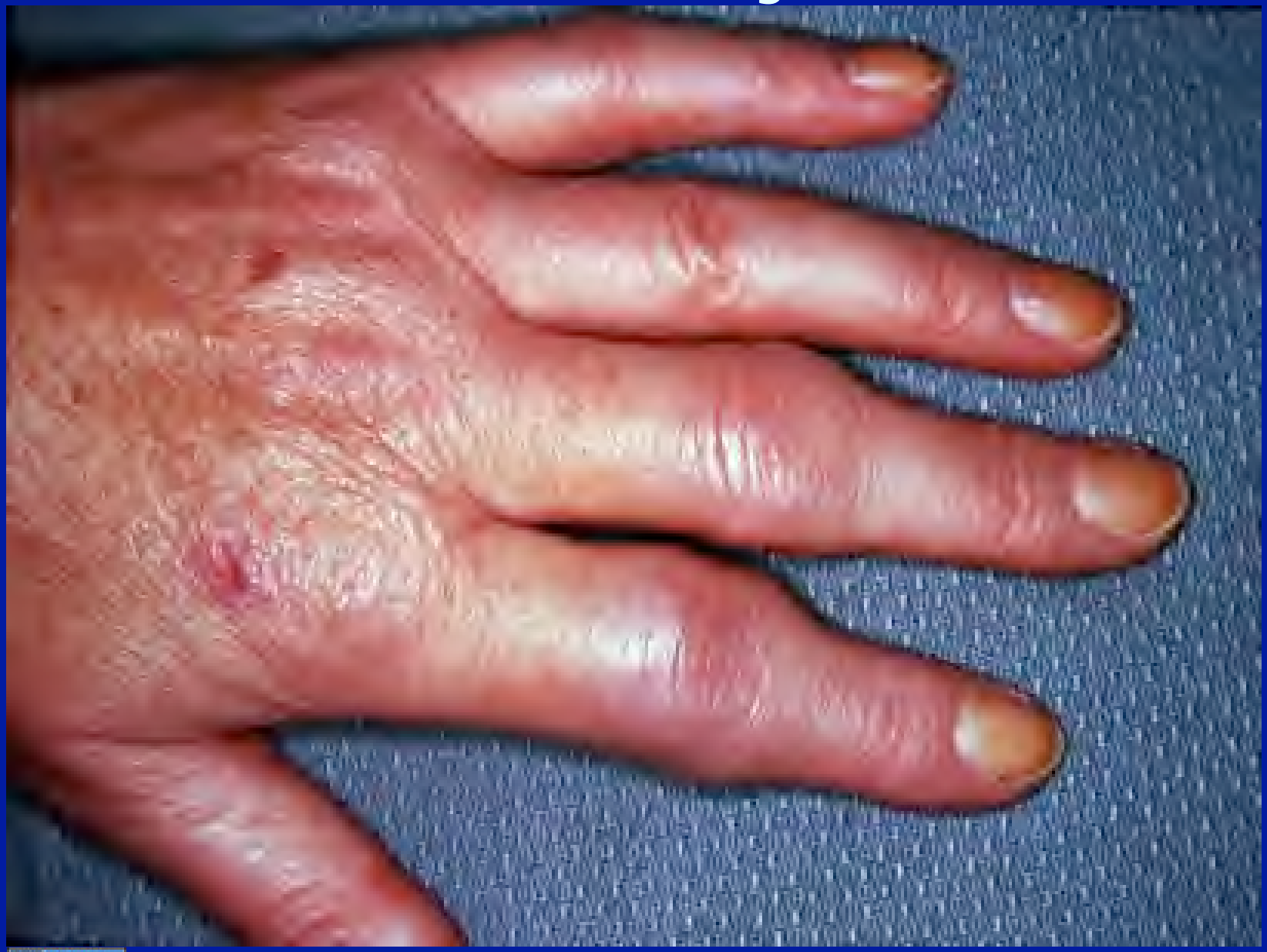




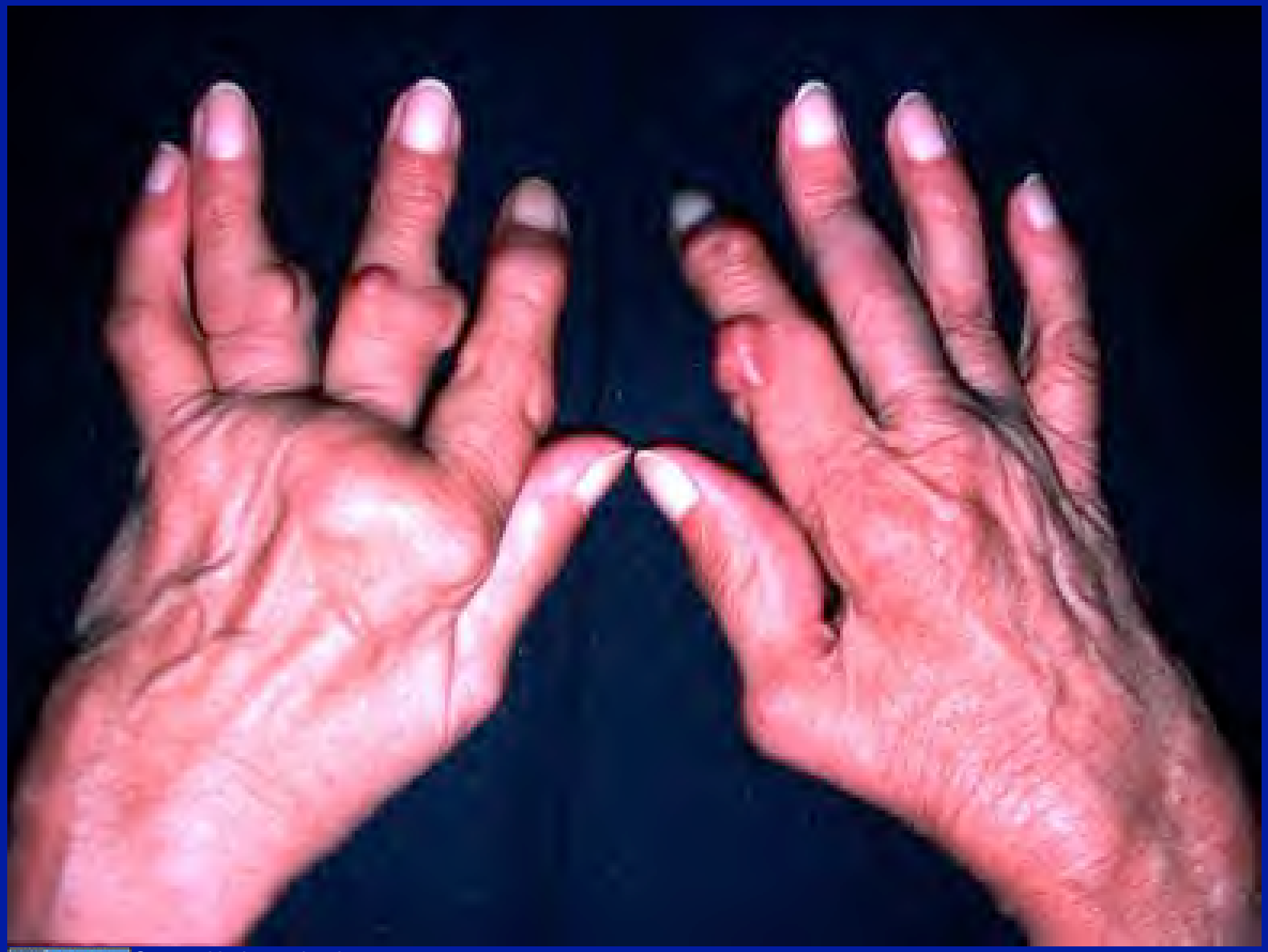


 J. Cush, 2002. (All images)

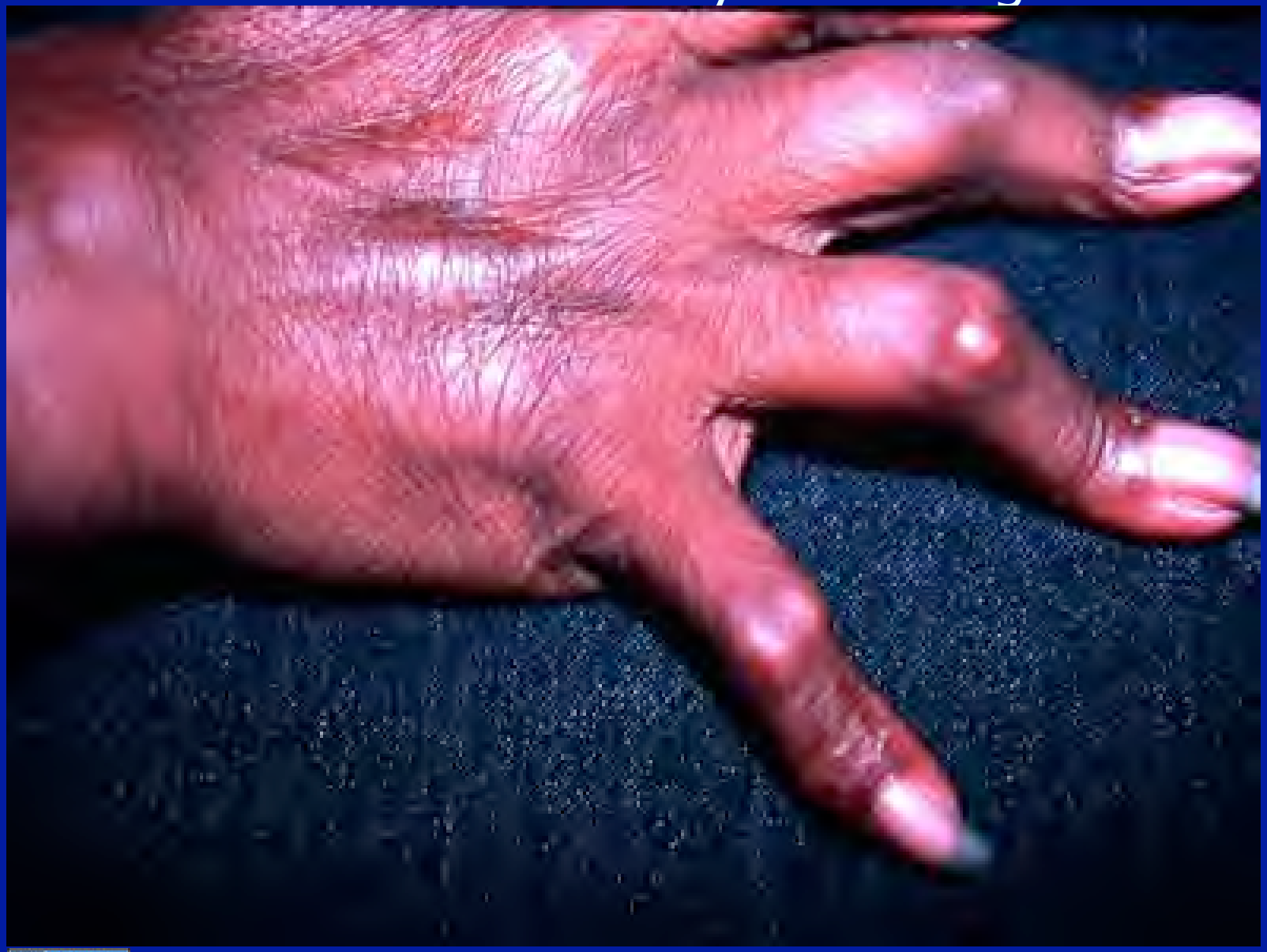
PIP swelling



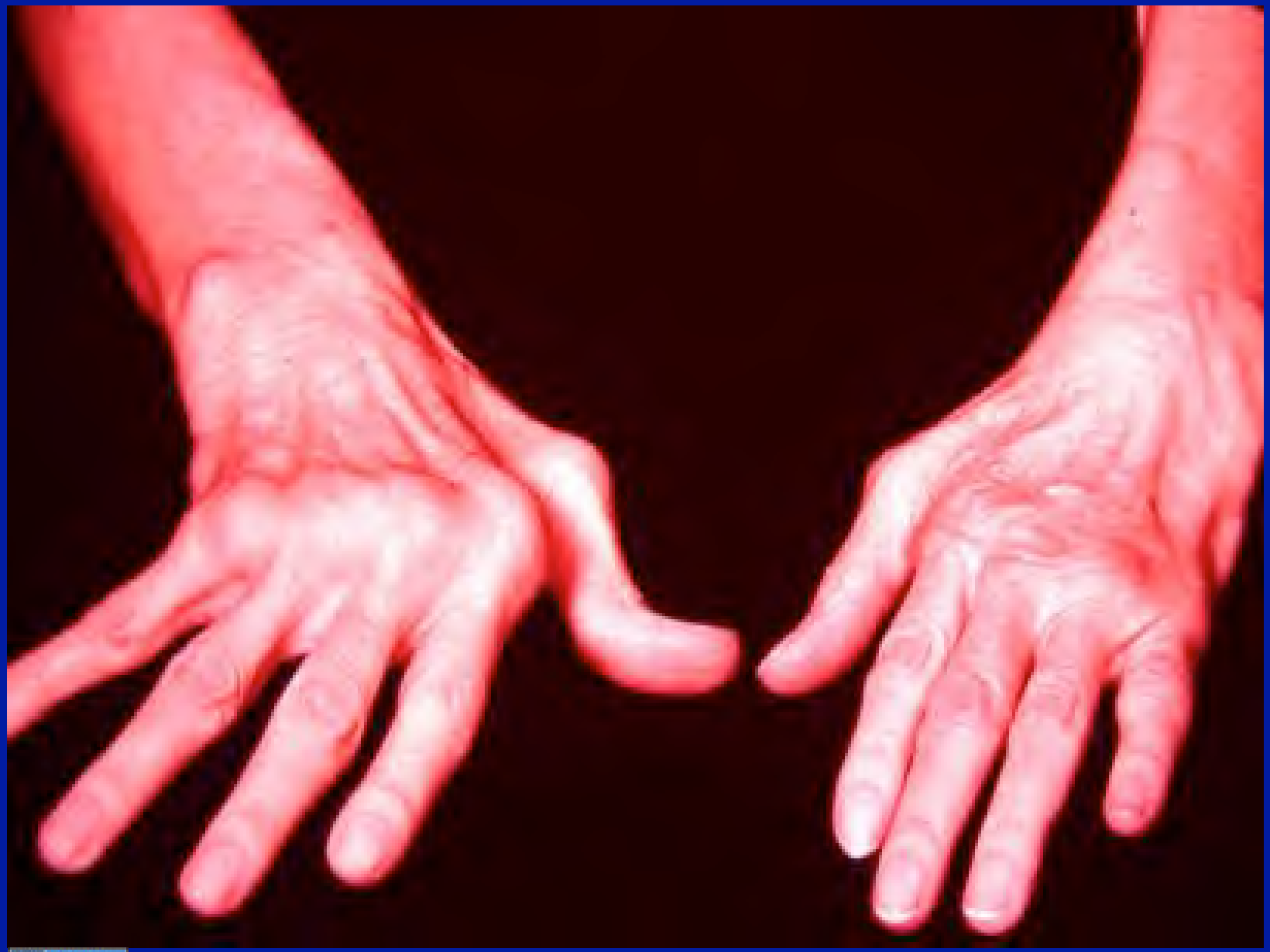
PIP nodules, MCP swelling/subluxation



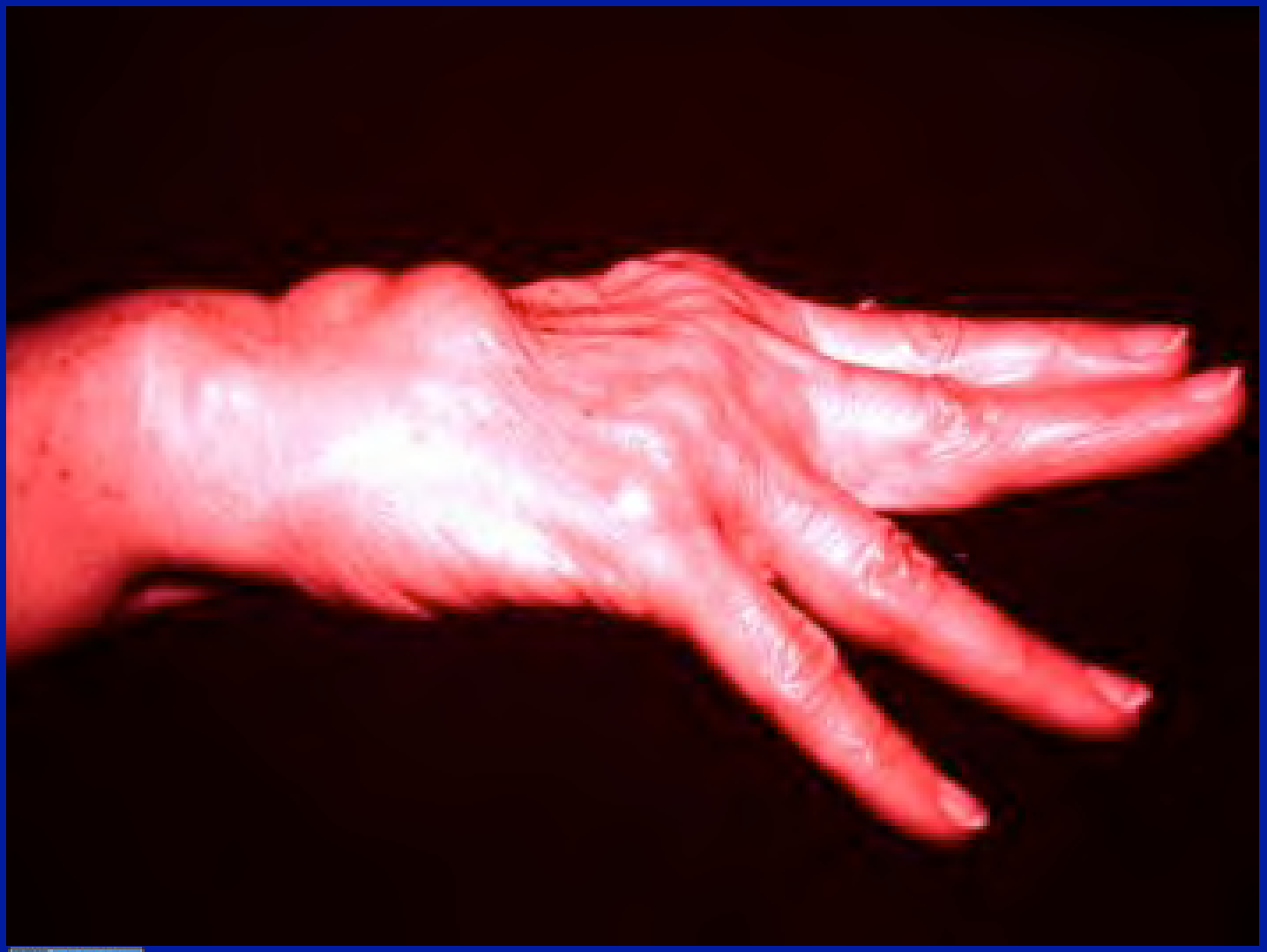
Boutoniere deformity of the fingers



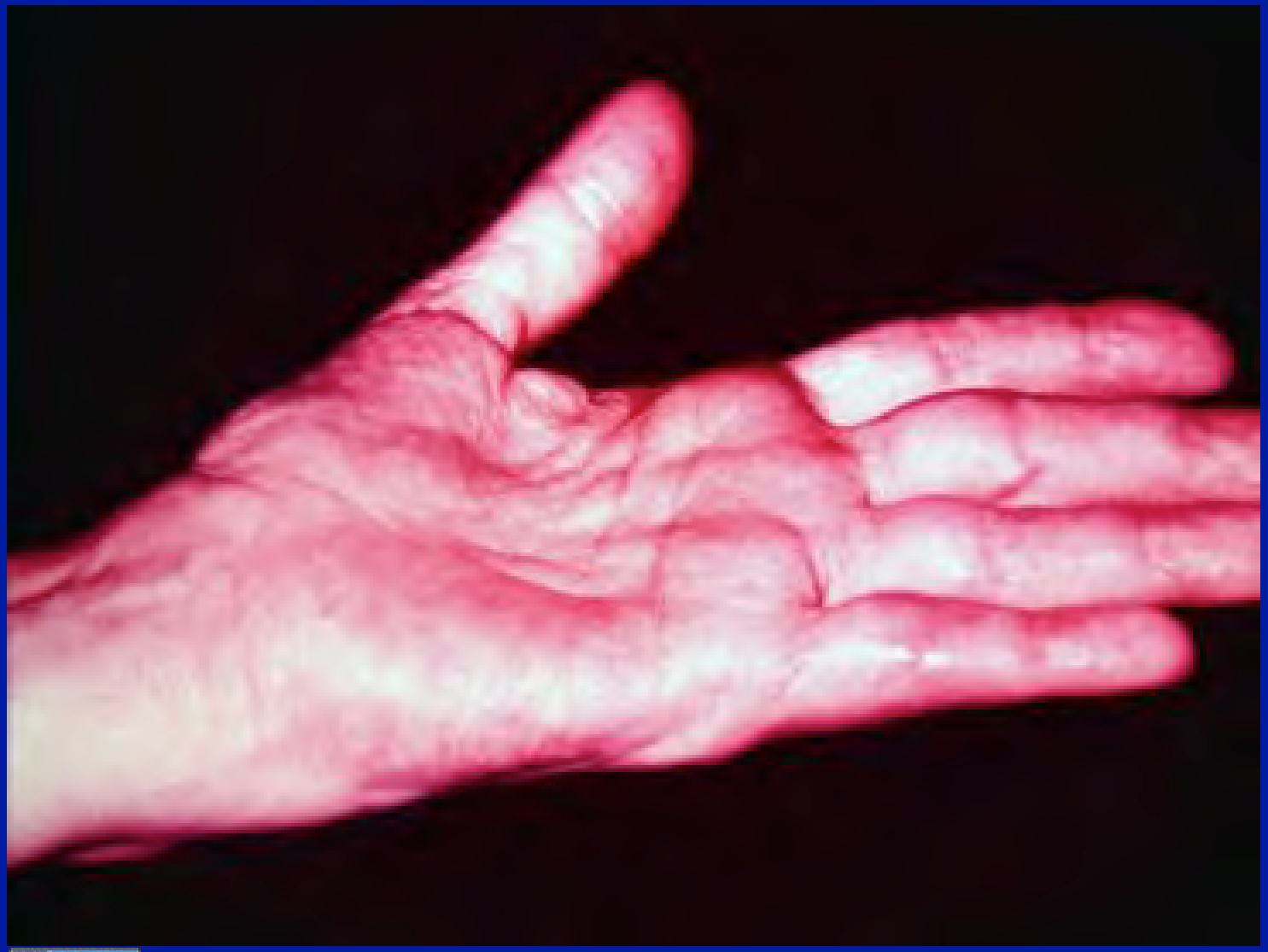
Ulnar deviation, MCPs of right hand



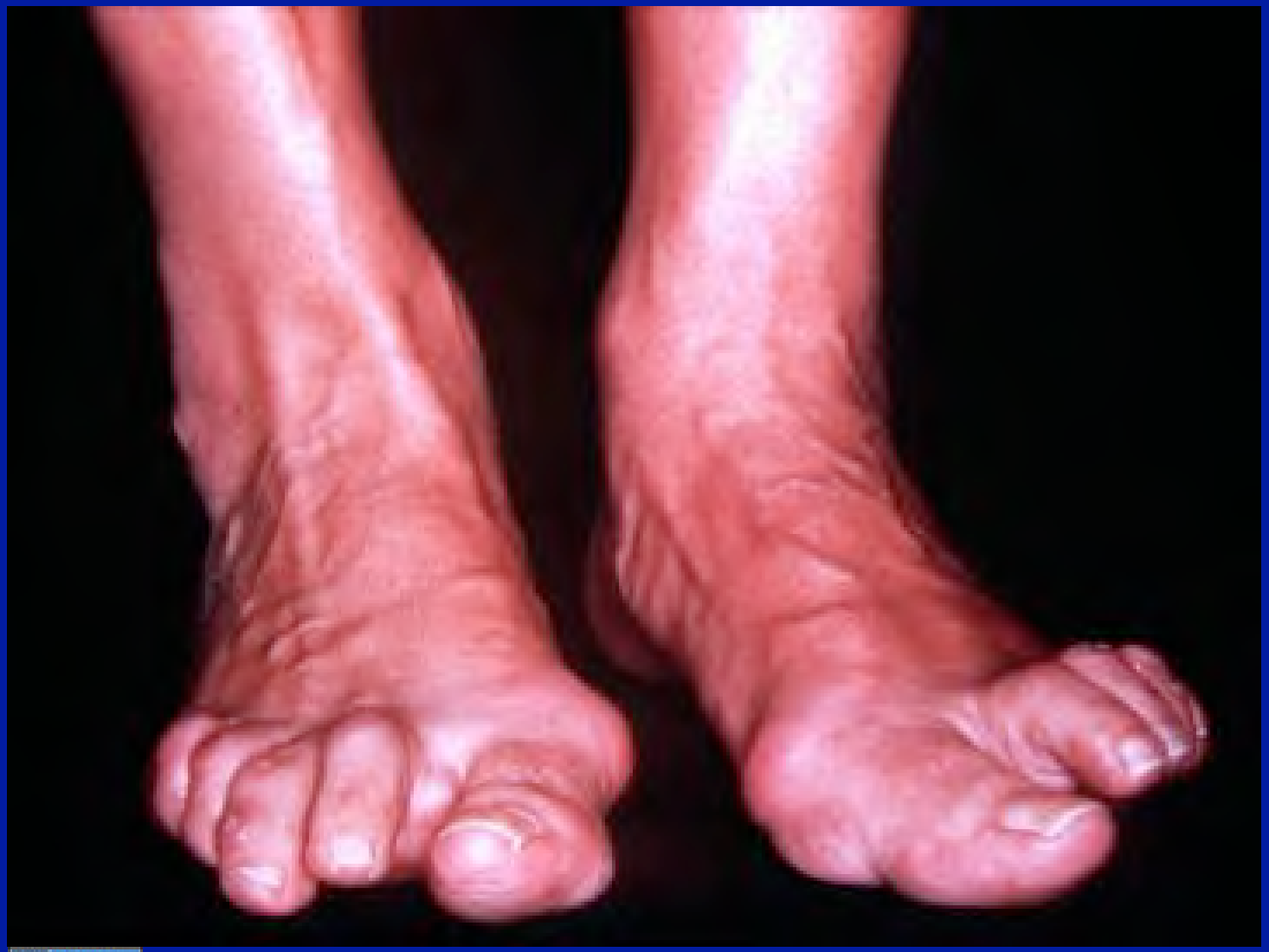
Extensor tendon synovitis leading to rupture of extensor tendons



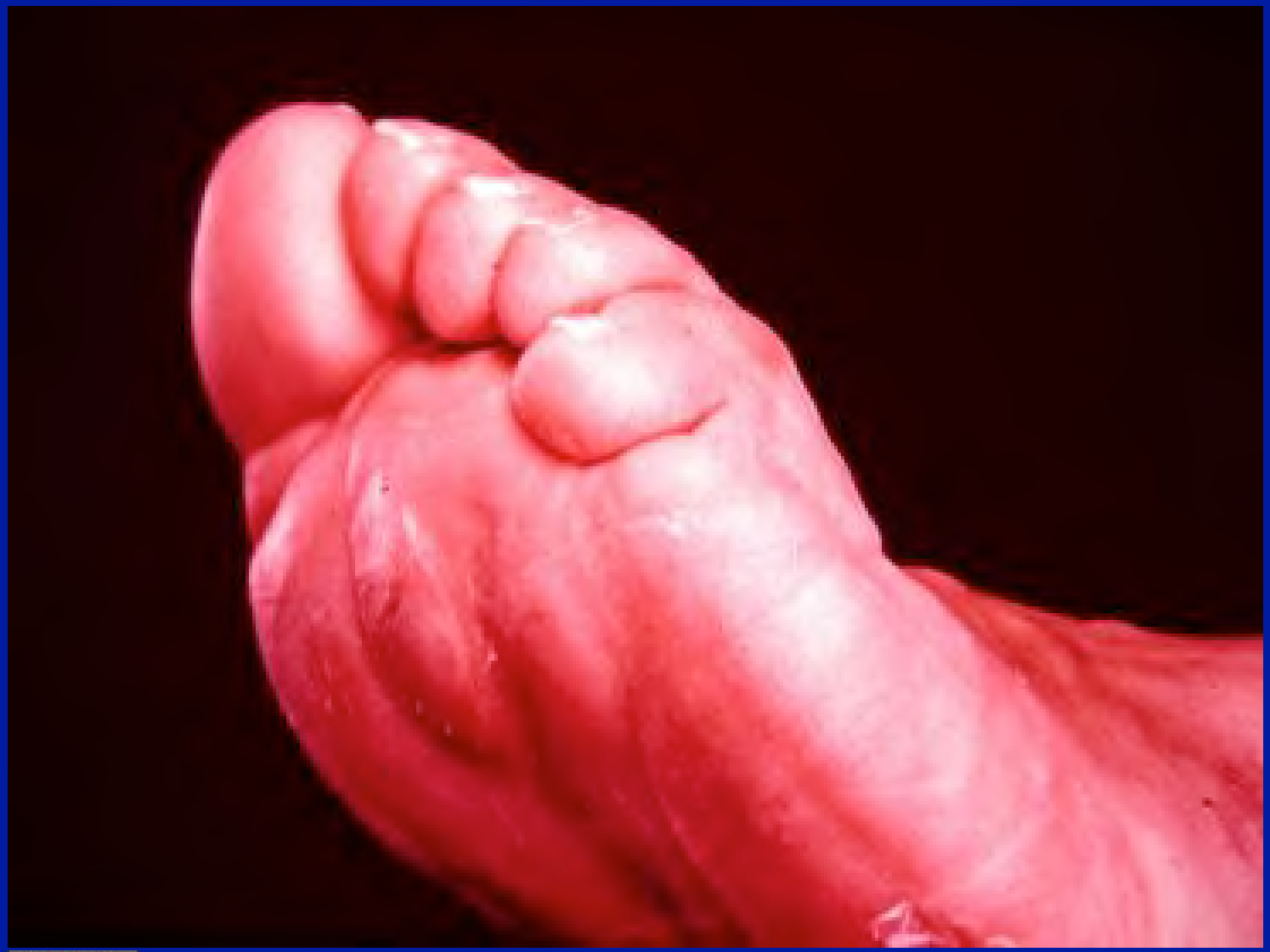
Thenar atrophy from wrist synovitis and median nerve compression



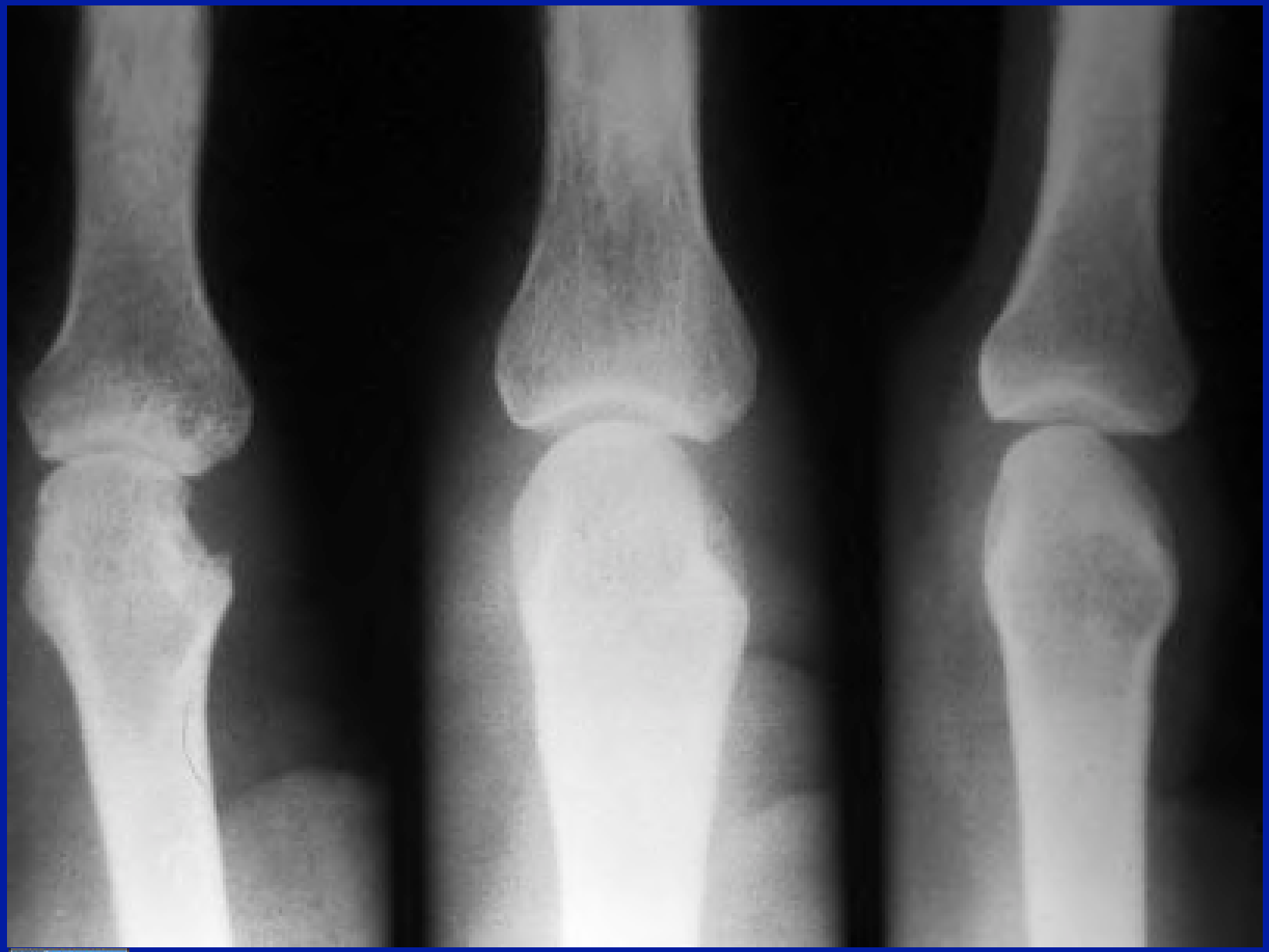
MTP deformities



MTP subluxation with plantar ulceration



Development of bone erosion



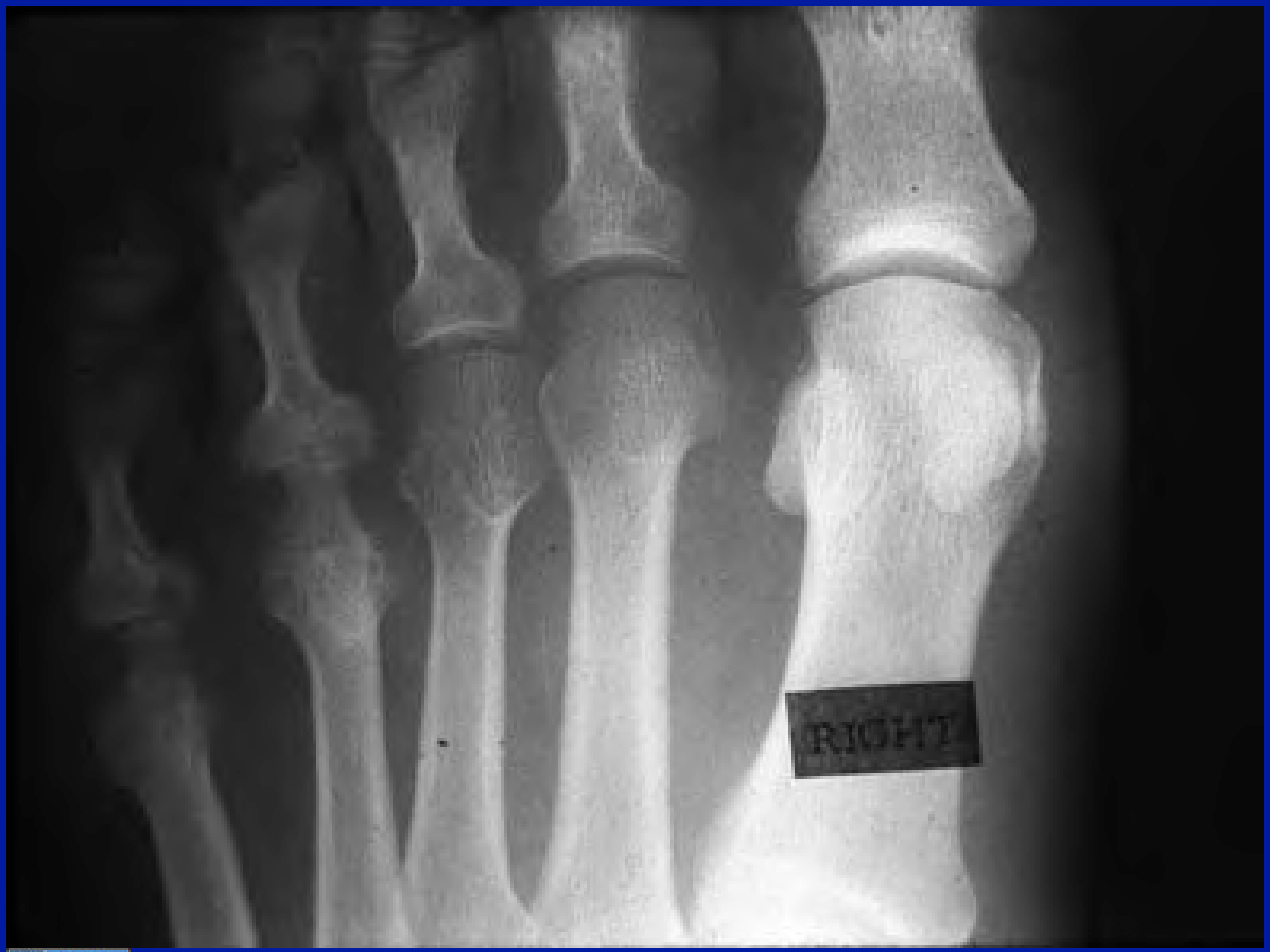
Radiographic Evaluation of Arthritis

1. Soft tissue swelling
2. Periarticular demineralization
3. Articular erosions
4. Reactive bone formation
5. Joint narrowing
6. Joint deformity
7. Distribution of involvement

Radiographic Features of Rheumatoid Arthritis and Osteoarthritis in the Hand

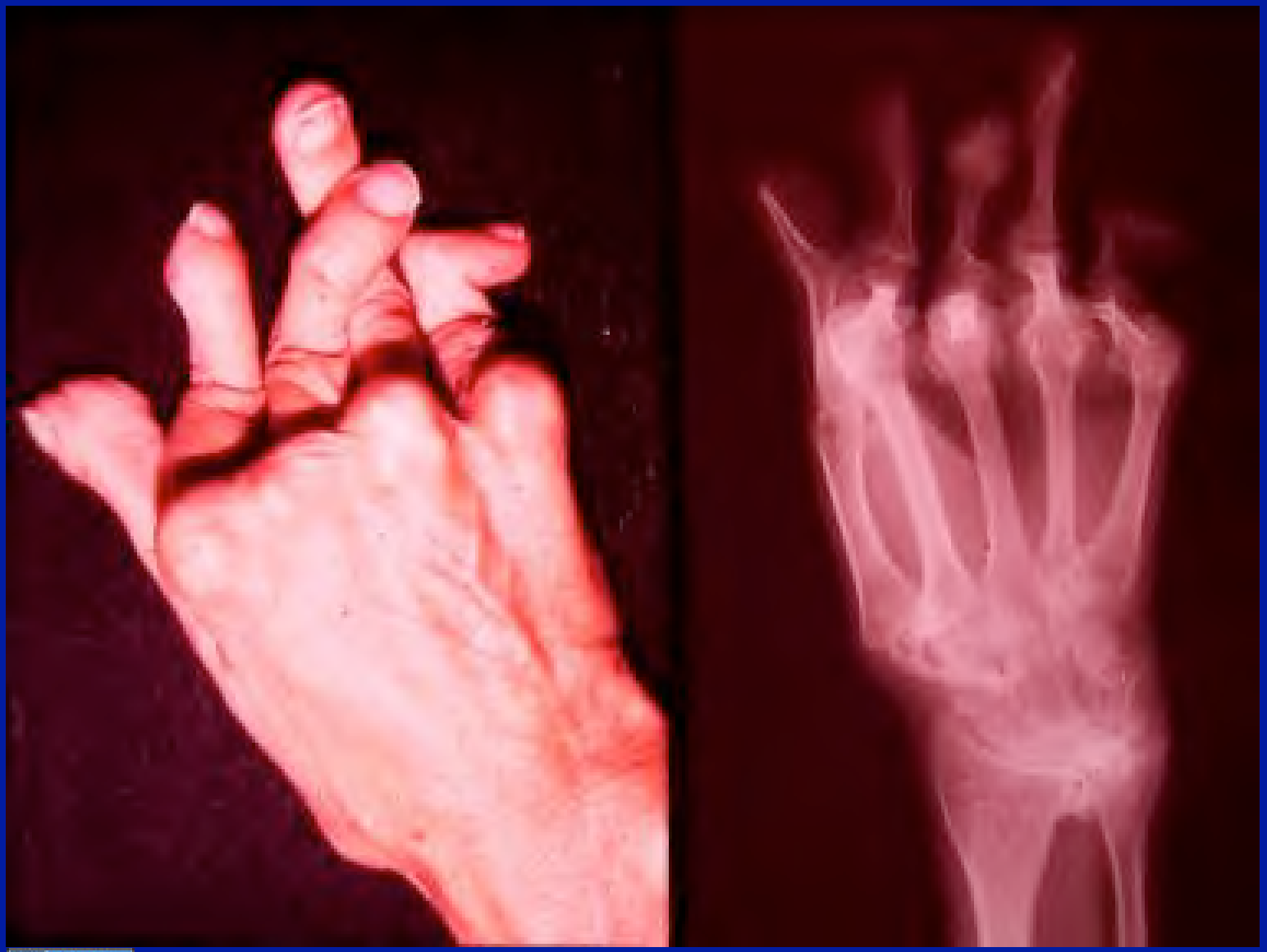
Rheumatoid Arthritis	Radiograhic Findings	Osteoarthritis
prominent, fusiform	soft tissue swelling	mild, focal
prominent, early	periarticular demineralization	not present
surface, pocketed or cystic	articular erosions	occasionally, cystic
minimal	reactive bone formation	prominent osteophytosis and subchondral sclerosis
mid to late, uniform	joint narrowing	early, irregular
late, subluxations an ddislocations	joint deformity	early, mild subluxation
wrists, metacarpophalangeal and proximal interphalangeal joints	distribution of involvement	distal interphalangeal, proximal interphalangeal and 1st carpometacarpal joints
early, asymmetric and non-uniform late, symmetric and uniform		asymetric and non-uniform

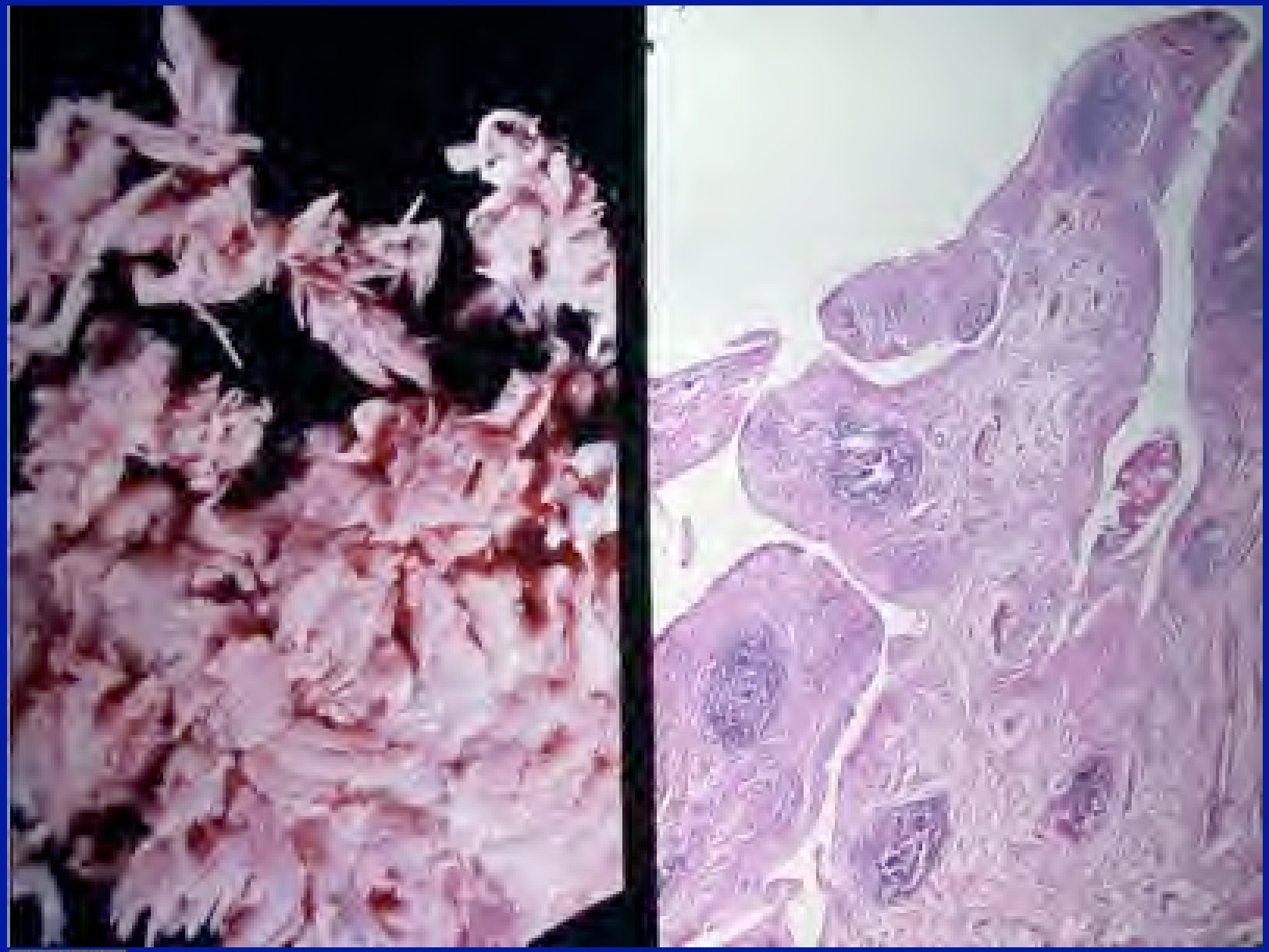
MTP erosions

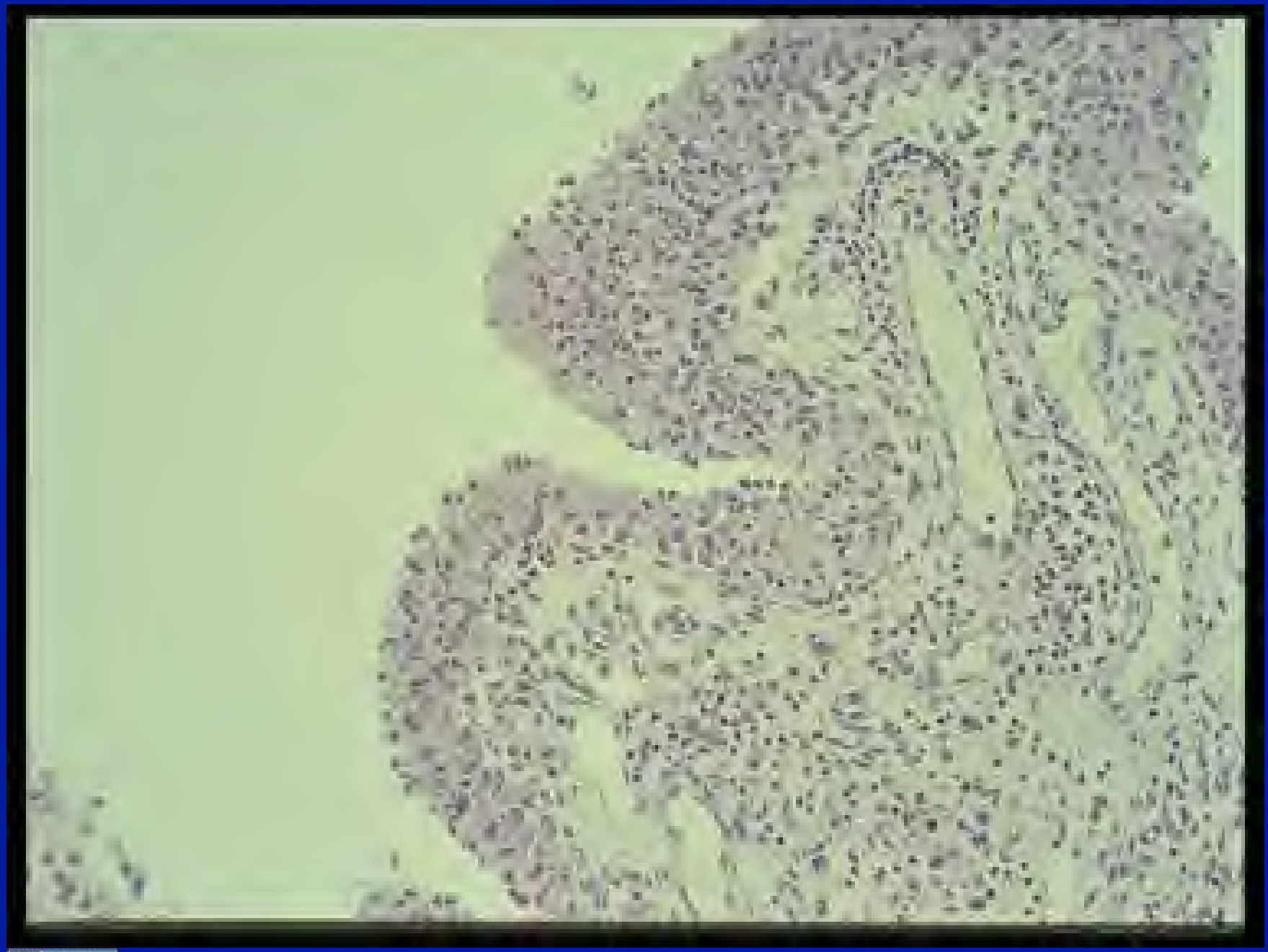


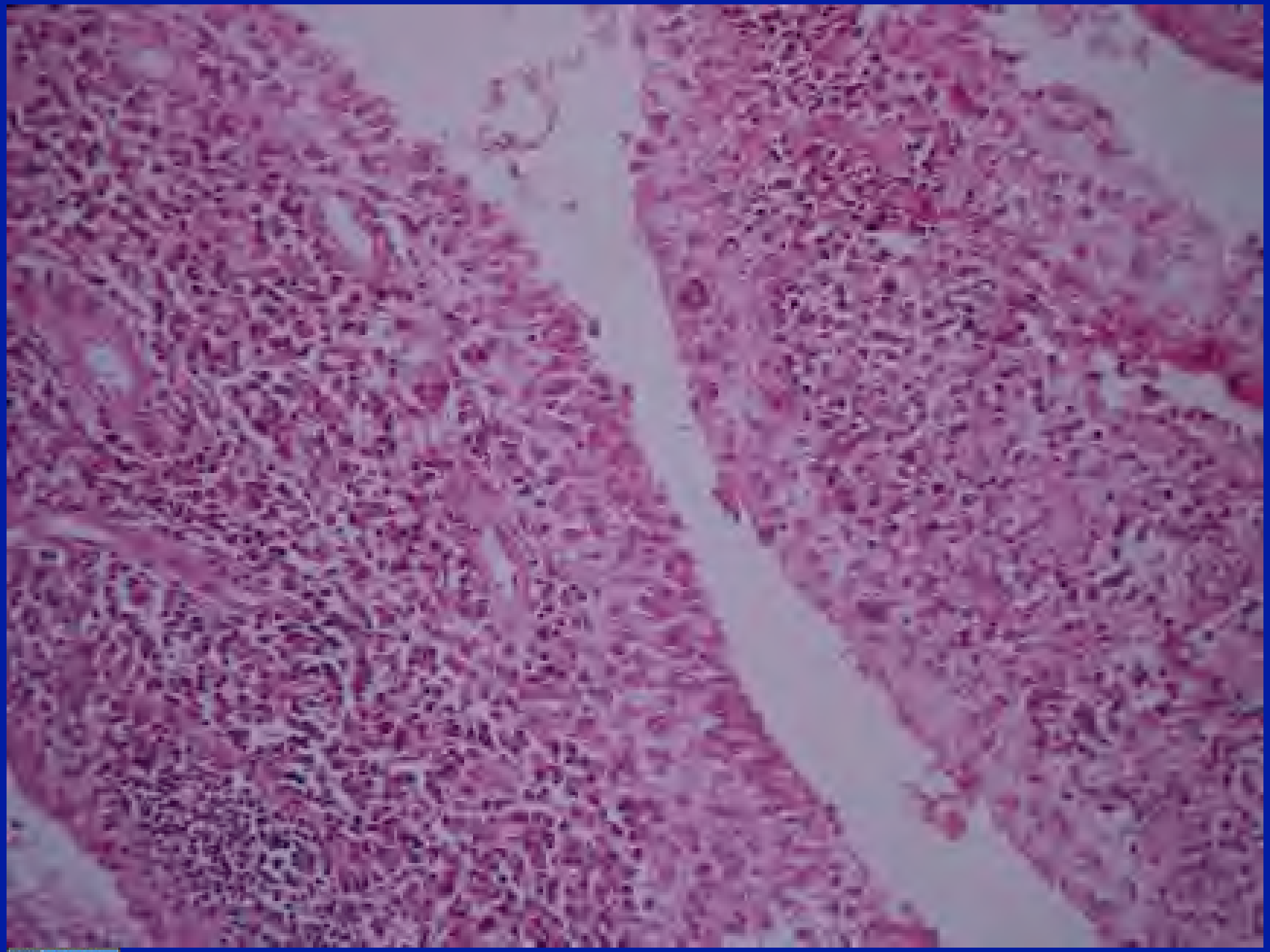
PD-INEL Source Undetermined

End-stage RA

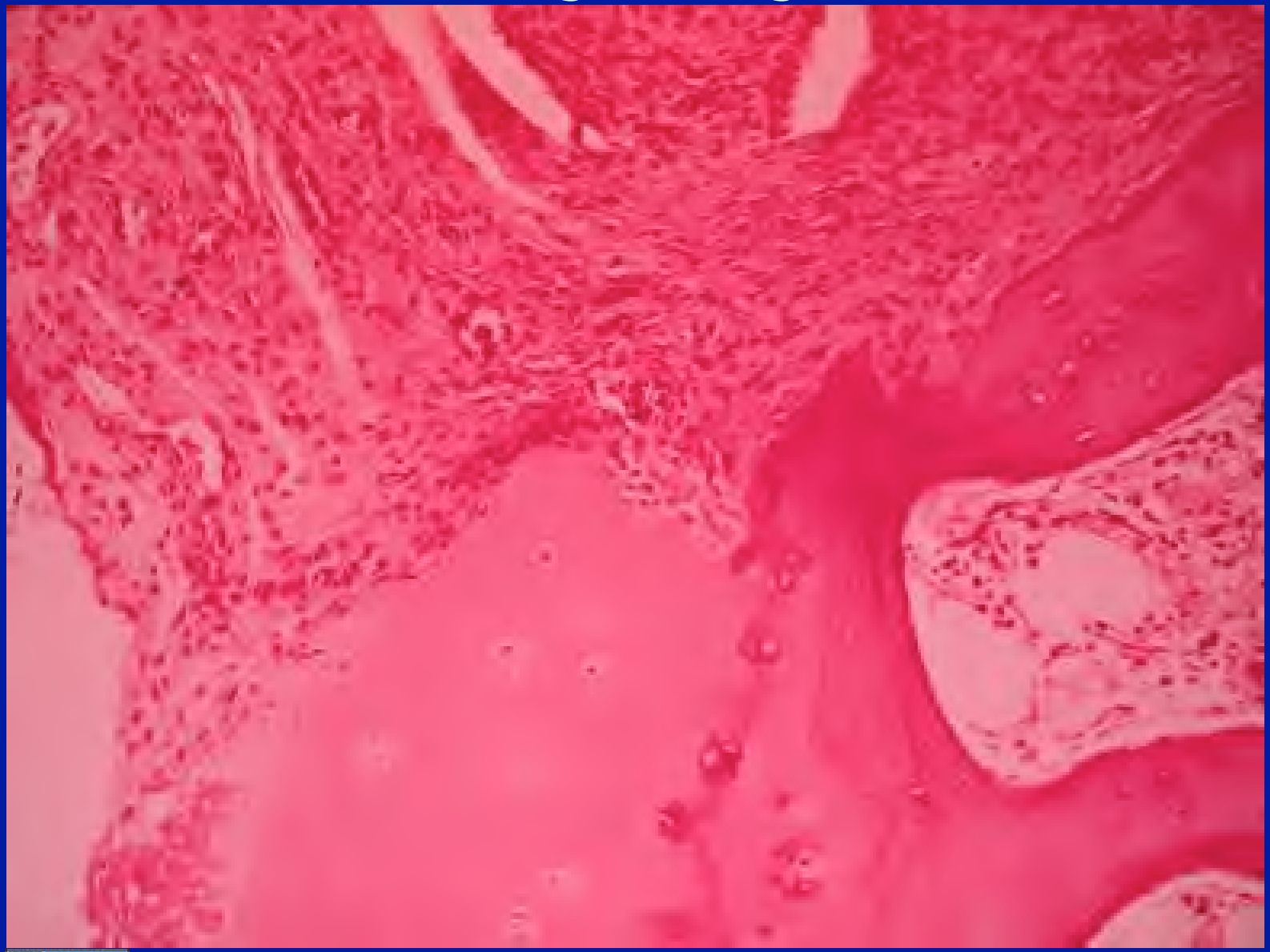








Pannus eroding cartilage and bone



Hypothesis for the Cause of RA

Synoviocyte transformation, synoviocyte interaction with macrophages, cartilage and bone

Cellular immune mechanisms (T cells, cytokines, monocytes

Humoral immune mechanisms (RF, immune complexes, complement)

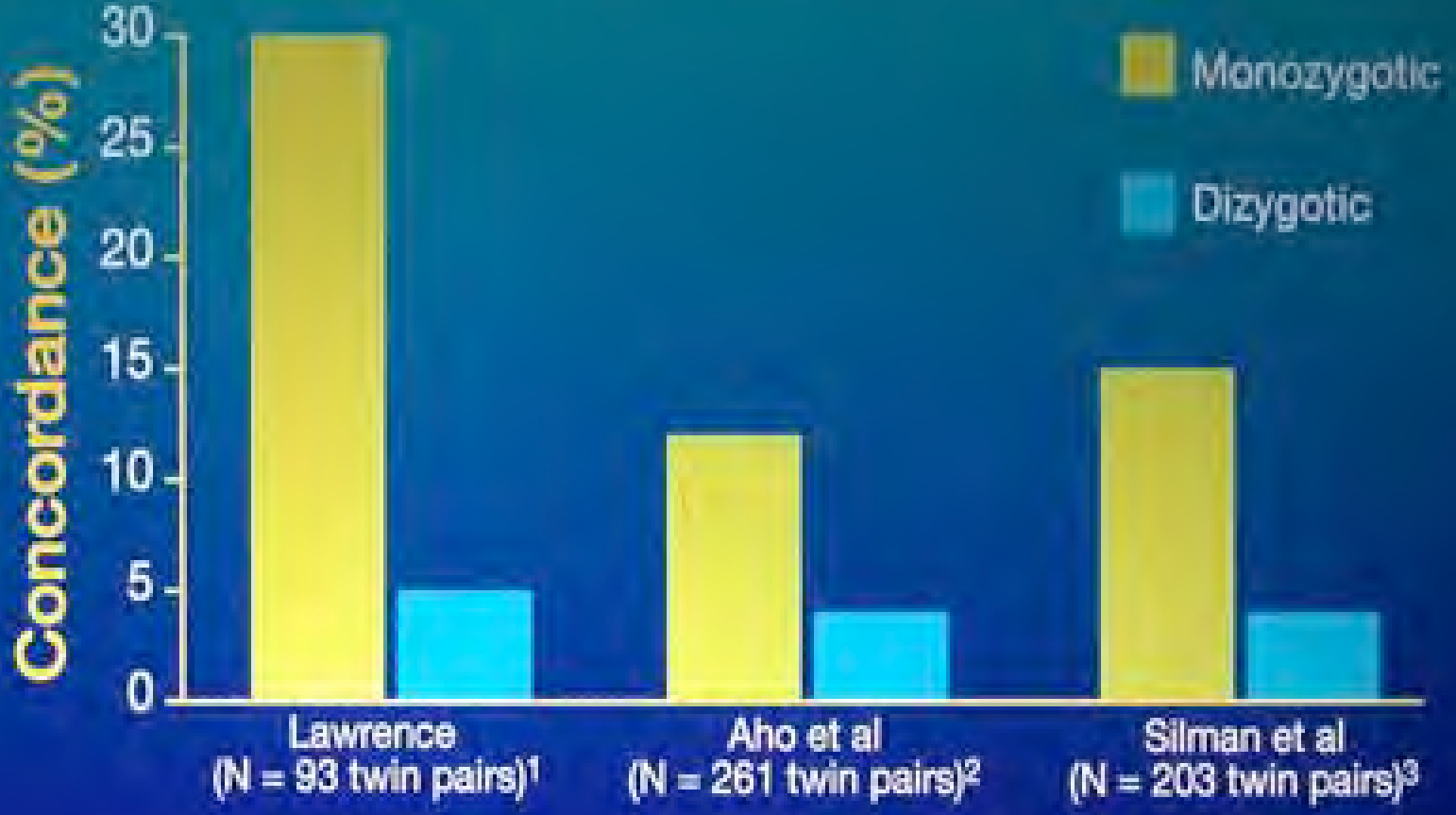
Infection

1920 1940 1960 1980 2000

Microbial Organisms Proposed as Possible Triggers for RA

Bacterial	gram positive cocci
	mycobacteria
	proteus
	E. coli
	mycoplasma
Viral	Epstein-Barr virus
	parvovirus
	retroviruses
	cytomegalovirus
	rubella
	human herpes virus 6

Twin Studies in RA



1. Lawrence JS. *Ann Rheum Dis*. 1970;28:357-379.
2. Aho K et al. *J Rheumatol*. 1986;13:899-902.
3. Silman AJ et al. *Br J Rheumatol*. 1993;32:903-907.

Genetic Susceptibility

- Familial aggregation and twin studies suggest that genetics may play a role in the development of RA
- Multiple genes involved
- In many populations (excluding most southern Europeans), approximately 80% of patients with RA share a common amino acid sequence in HLA-DR4 molecules (QKRAA) (shared epitope hypothesis)
- The presence of multiple copies of QKRAA may also predict disease severity
- Several non-MHC loci identified, all related to cellular immune responses

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Autoantibodies in Rheumatoid Arthritis

- **rheumatoid factor (RF)**
- anti-nuclear antibodiesanti-type II collagen
- anti-type IX collagen
- anti-cardiolipin
- anti-neutrophil cytoplasmic antibodies
- anti-keratin antibodies
- anti-perinuclear factor
- anti-calpastatin
- **anti-citrullinated peptides (anti-CCP)**

RHEUMATOID FACTOR

Rheumatoid Factor-
Evidence for a Role in the Pathogenesis of RA

- Most patients with RA have elevated levels of rheumatoid factor
- High titers of rheumatoid factor correlate with severe articular disease and with development of extra-articular manifestations.
- Pre-existing elevations of rheumatoid factor predict subsequent development of RA.
- Rheumatoid factor production is prominent in RA synovial tissue, and such rheumatoid factors show evidence of antigen-driven affinity maturation.
- Rheumatoid factor can enhance formation of pathogenic immune complexes.
- B cells bearing surface rheumatoid factor can trap antigens contained in immune complexes and present them to primed T cells.

Occurrence of Rheumatoid Factor in Various Diseases

IgM Rheumatoid Factor Frequently Present

Rheumatic diseases

Rheumatoid arthritis
Sjogren's syndrome (with or with arthritis)
Systemic lupus erythematosus
Progressive systemic sclerosis
Polymyositis/dermatomyositis
Cryoglobulinemia

Infectious diseases

Bacterial endocarditis
Tuberculosis
Syphillis
Infectious hepatitis
Leprosy
Schistosomiasis

Rheumatoid Factor Usually Absent

Osteoarthritis
Ankylosing spondylitis
Gout
Chondrocalcinosis
Suppurative arthritis
Psoriatic arthritis
Enteropathic arthritis
Reiter's syndrome

IgM Rheumatoid Factor Frequently Present

Noninfectious diseases

Normal aged individuals
Diffuse interstitial pulmonary fibrosis
Cirrhosis of liver, chronic active hepatitis
Sarcoidosis
Waldenstrom's macroglobulinemia

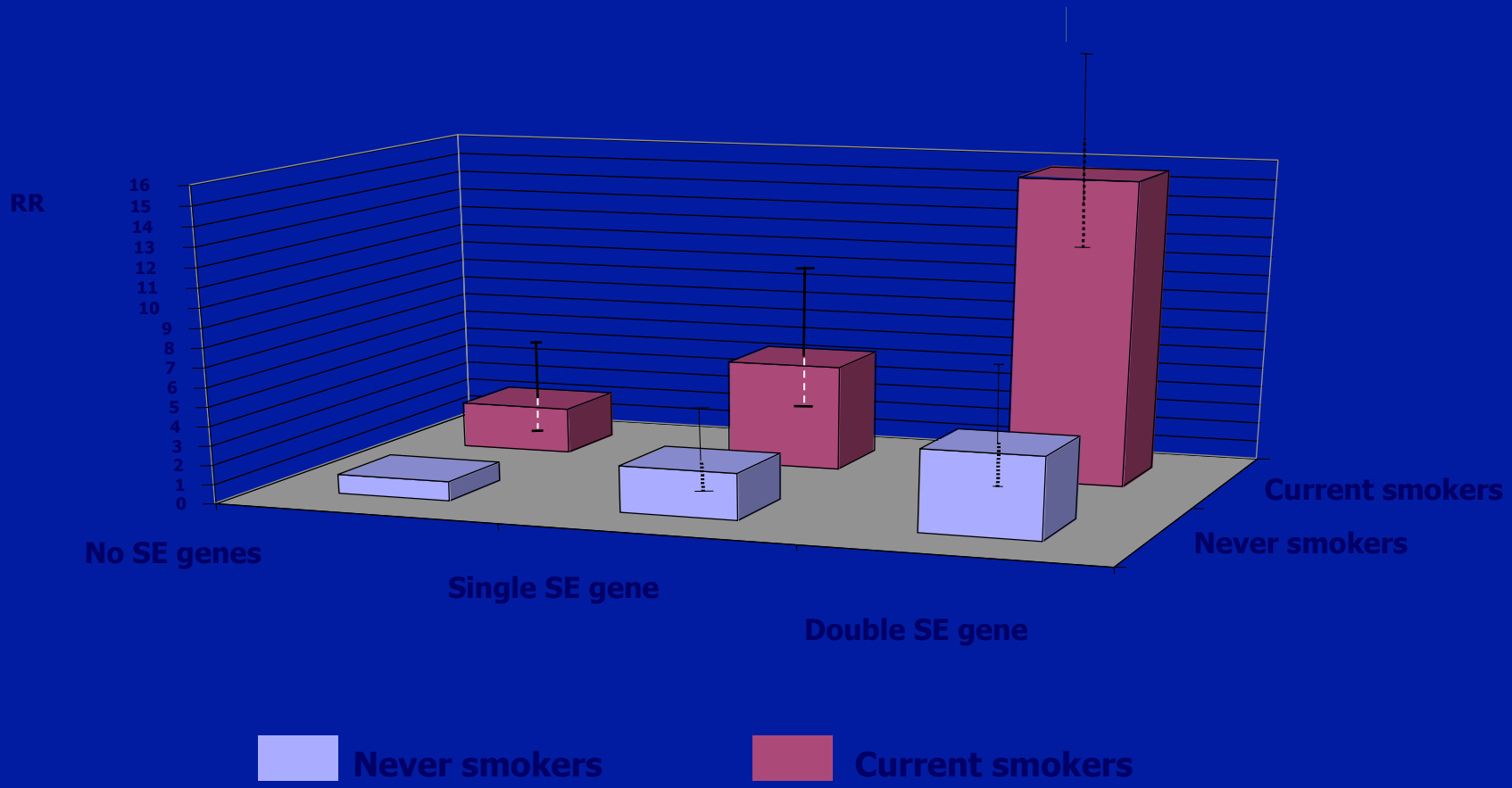
Anti-CCP and RA

- CCP = cyclic citrullinated peptides
- Arginine $\xrightarrow[\text{PADI}]{}$ citrulline
- PADI = peptidyl arginine deiminase
- Citrullinated proteins abundant in inflamed synovium
- Smoking $\longrightarrow$ citrullination of proteins in the lung

Risk Factors for RA

- Genetic
  - MHC Class II alleles
  - Multiple other genes
- Environmental
  - ? infection
  - smoking

Relative Risk of seropositive RA in Individuals with Different SE Genotype



Source: Padyukov, Silva, Stolt, Alfredsson, Klareskog; A&R 2004;50:3085-92

Predicting RA Before its Clinical Onset

- Genes
- Smoking
- Anti-CCP

Hypothesis for the Cause of RA

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1920 1940 1960 1980 2000

Evidence for a Central Role for T cells in RA

1. Large numbers of T cells an antigen-presenting cells are present in synovial tissue and fluid.
2. Synovial T cells express activation and memory makers.
3. T cell subsets and possibly clonal T cell populations, accumulate in RA joints in a non-random manner.
4. RA is associated with specific MHC class II alleles (DR and/or DQ).
5. RA is associated with a polymorphism at PTPN22, a tyrosine phosphatase that regulates signaling through the T cell receptor.
6. T cell-directed therapeutic interventions may be effective in RA, and are clearly effective in animal models.
7. T cell cytokines, such as IL-17, that are present in RA joints, mediate biologic effects highly relevant to the pathogenesis of joint inflammation and damage.

Proposed Antigenic Targets for T cells in RA

Microbial antigens

Superantigens, such as staphylococcal toxins
Epstein-Barr virus antigens
Heat shock proteins
Mycobacterial antigens
Parvovirus antigens
Peptidoglycan from gram+ bacteria

Autoantigens

Collagen (Type II and other types)
gp39
Cartilage link protein
Cartilage proteoglycan
205kDa synovial fluid antigens
Immunoglobulin binding protein (BiP)
Heat shock proteins
Class II MHC (shared epitope)
IgG (Fc portion)
RA33 (heterogeneous nuclear ribonucleoprotein A2)
Filaggrin
Glycosaminoglycans

RA a Th-17 disease?

- IL-17 is found in abundance in arthritic joints and serum
- Administration of IL-17 worsens CIA (collagen-induced arthritis, an animal model of RA)
- IL-17 R and IL-17 knockout mice develop less severe arthritis
- Neutralizing antibody to IL-17 reduces severity of CIA
- IL-23 deficient mice develop less severe arthritis
- Recent human study shows IL-17 and TNF mRNA in RA synovium predict aggressive disease

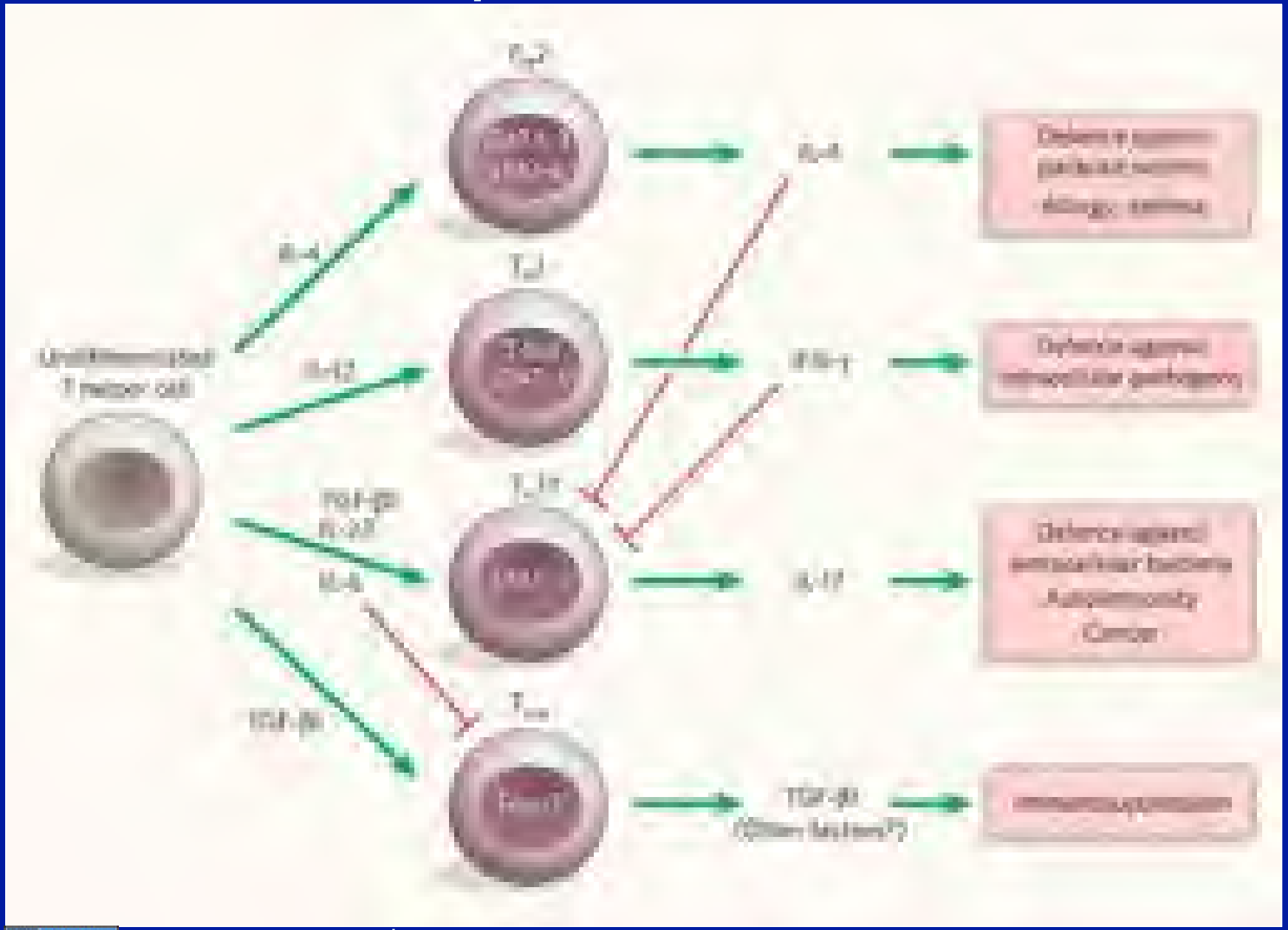
IL-17

- 17 kD cytokine
- Secreted by activated and memory T cells, recently defined as a distinct Th subset
- Six isoforms, termed IL-17 A-F
- “IL-17” = IL-17A
- Induced by IL-6 and TGF β

IL-23 and IL-17

- IL-23 is a cytokine made by APC's
- IL-23 and IL-12 are both heterodimers
- IL-23 and IL-12 share an identical p40 subunit
- IL-23 also contains a p19 subunit, IL-12 a p35 subunit
- IL-12 induces gamma-interferon
- IL-23 induces IL-17
- Co-stimulatory signals can also induce IL-17 when TCR is triggered

T-Helper Cell Differentiation



 Christina M Tato an dJohn J. O' Shea, Nature 441, 11 May 2006

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Image of cell-cell interactions in rheumatoid arthritis removed

Cell-cell Interactions in RA Synovium

Leukocyte–endothelial

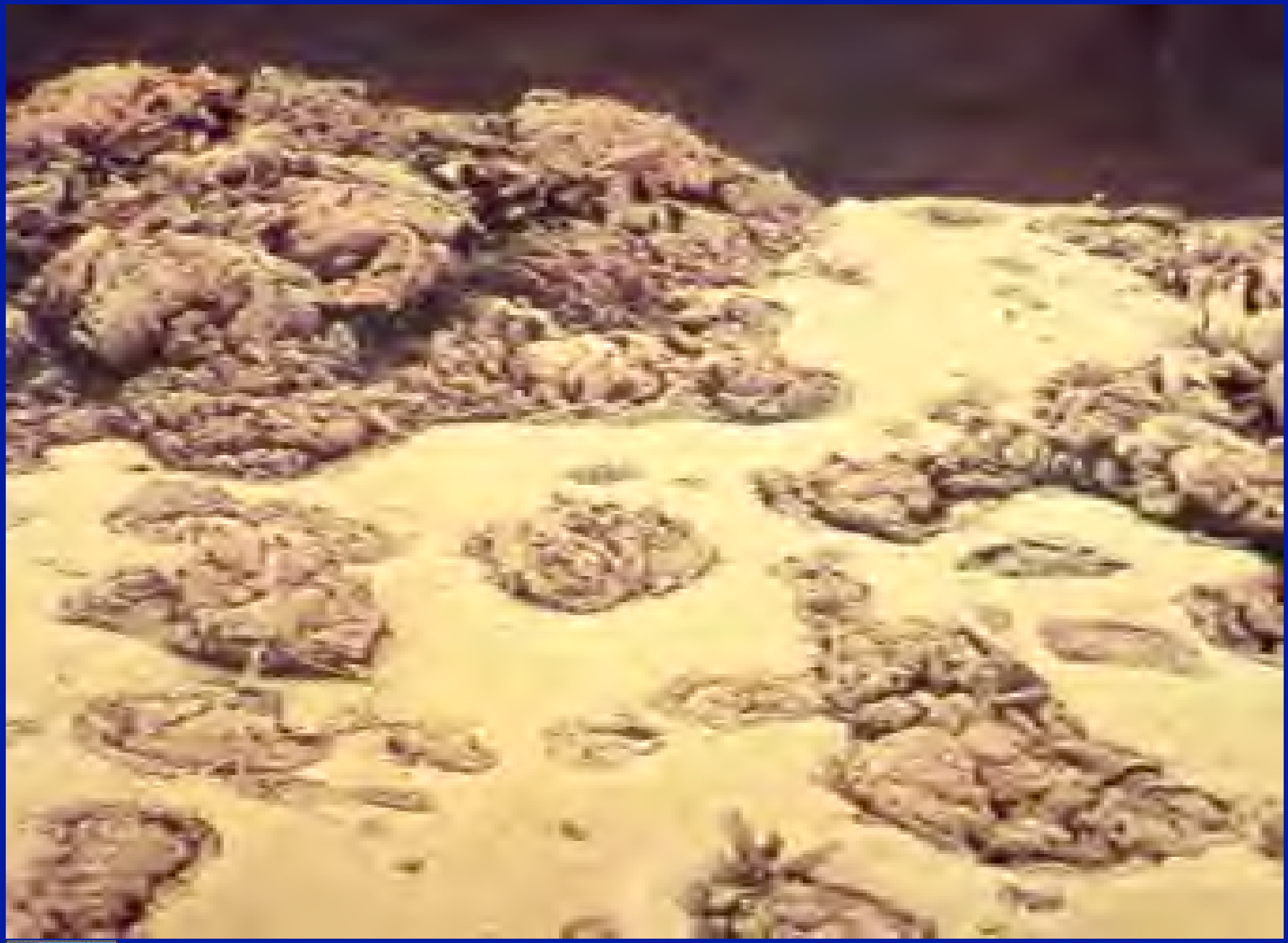
T cell–dendritic cell

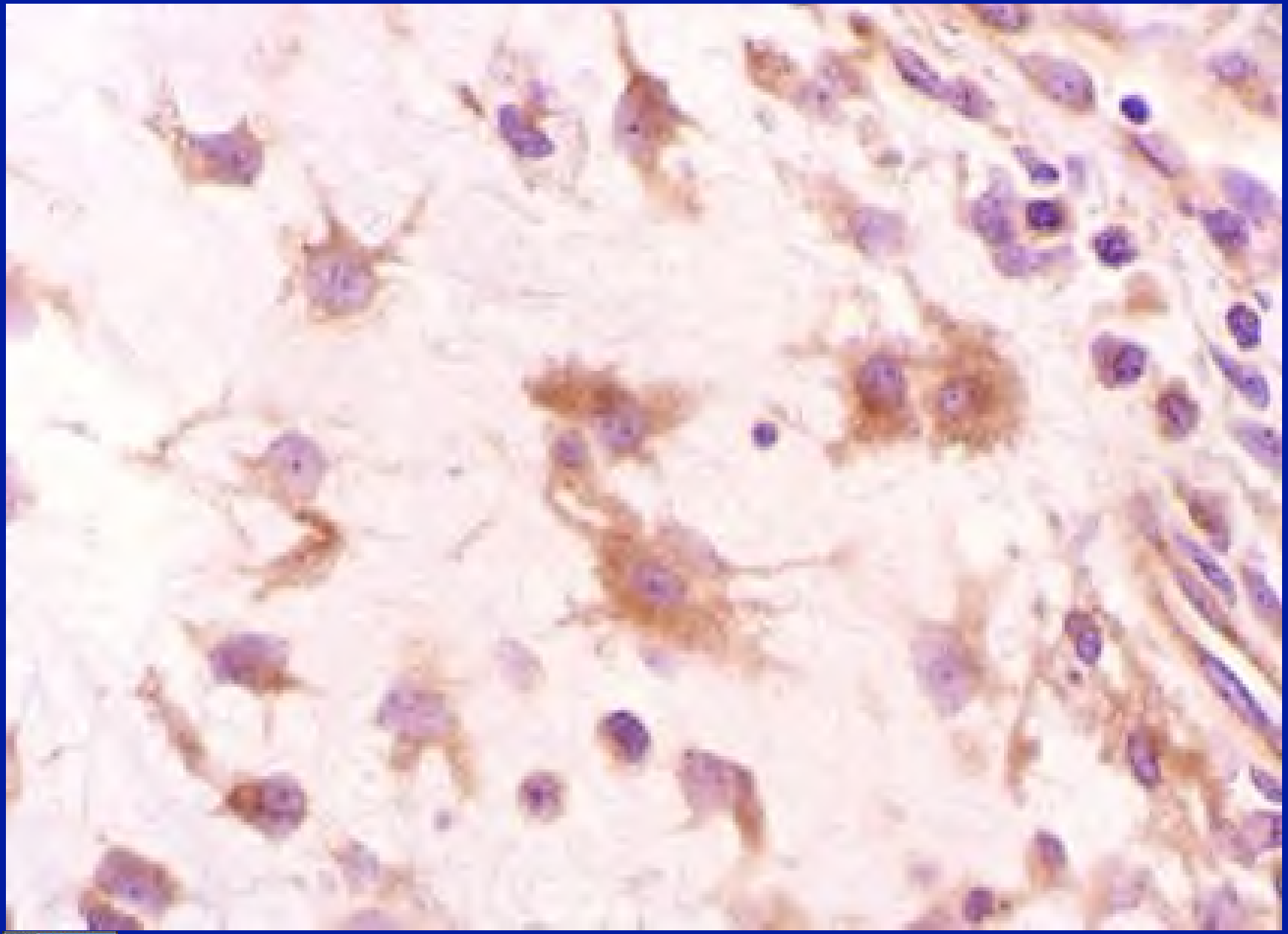
T cell–macrophage

Macrophage–fibroblast

T cell–fibroblast

B cell–fibroblast

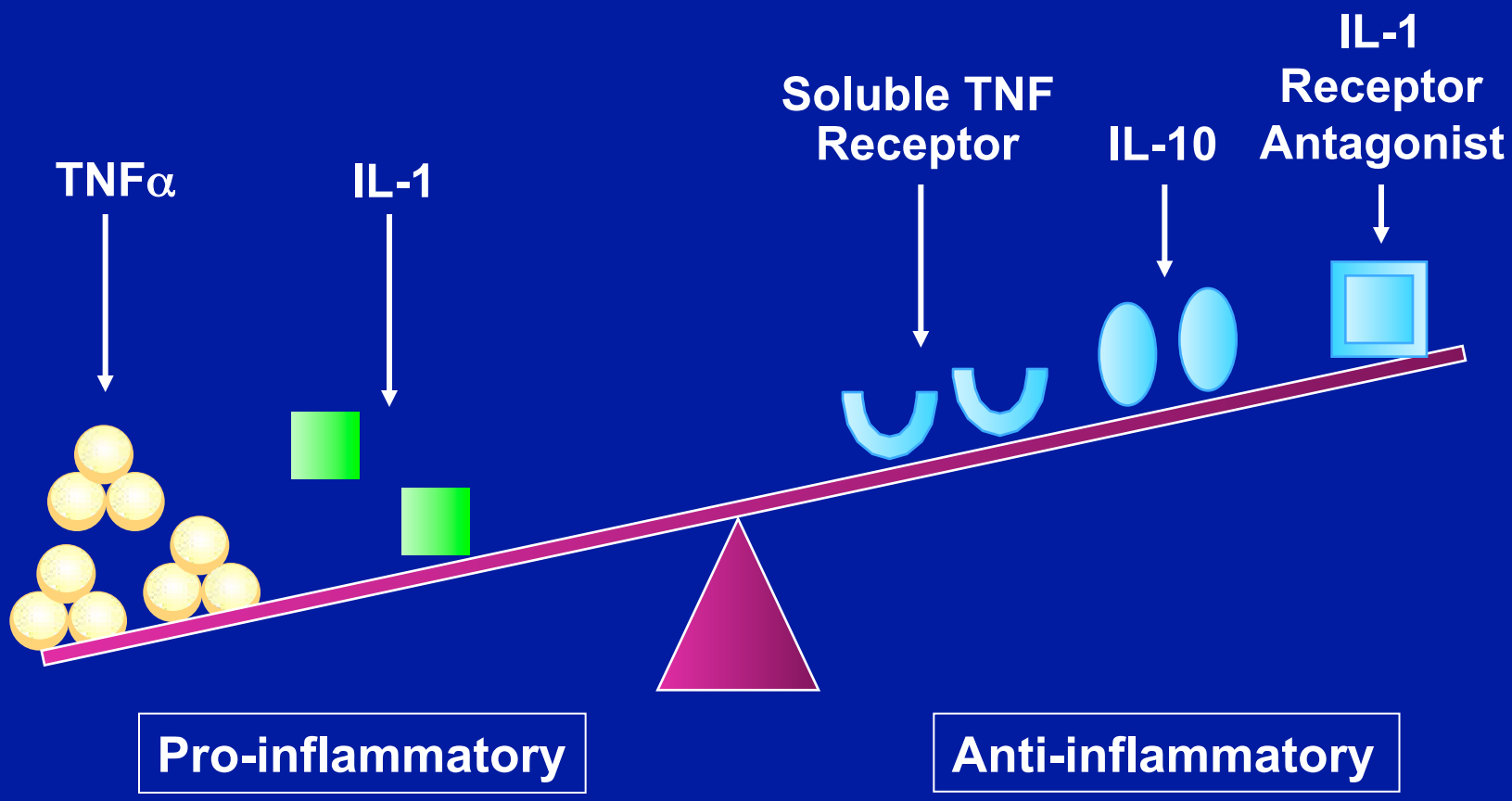




Cytokines

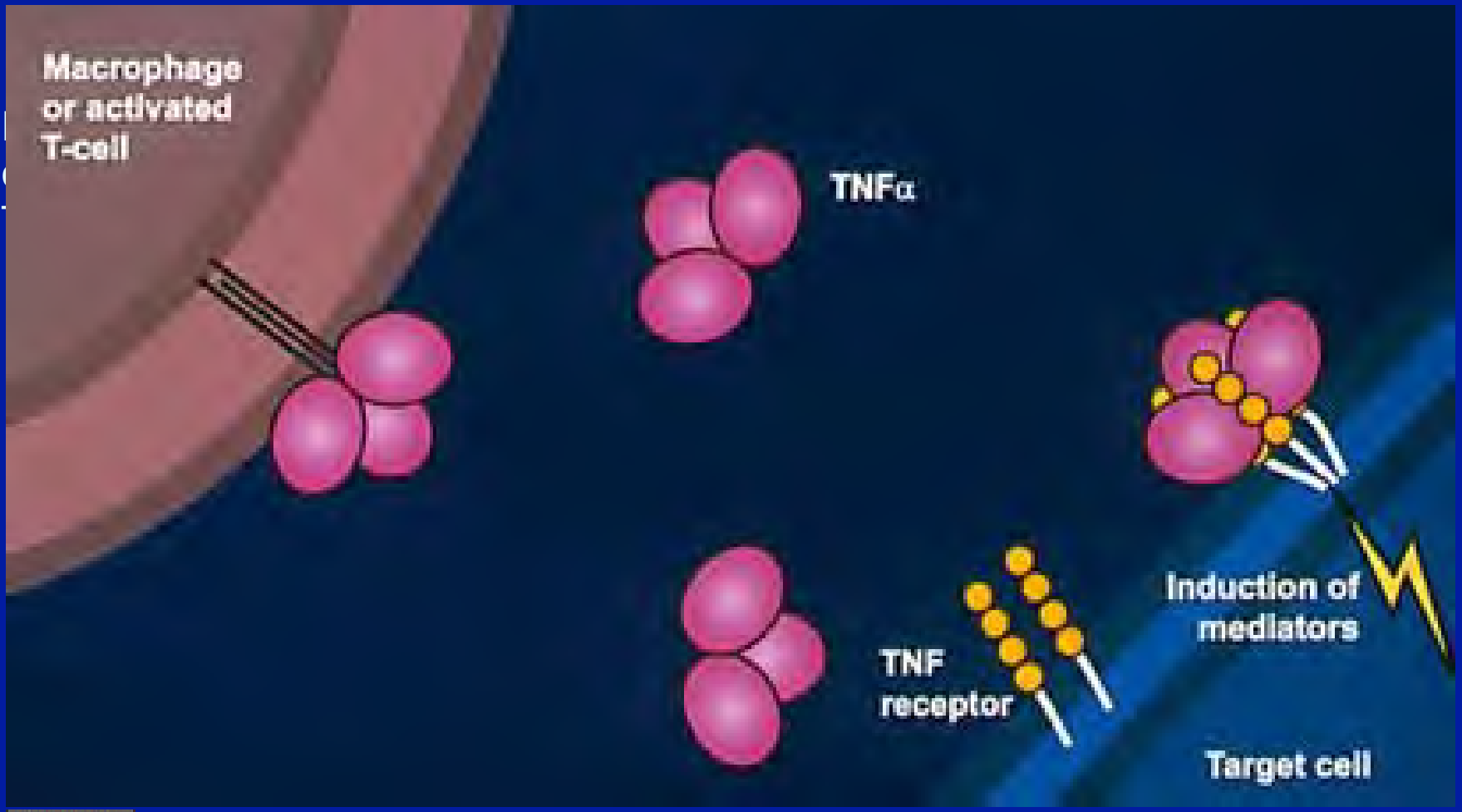
- Intercellular messenger molecules
- Synthesis
  - Heterogeneity of cell types
  - Inducible
- Effects
  - Primarily local (systemic when produced in abundance)
  - Mediated through
    - Cell-associated receptors on target cells
    - Intracellular signaling and gene transcription
- Regulation controlled at many steps
    - Message induction
    - Soluble receptors
    - Soluble receptor antagonists

Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



 Adapted with permission from Feldmann M et al. *Cell.* 1996:85:307-310.

Synthesis and Actions of TNF



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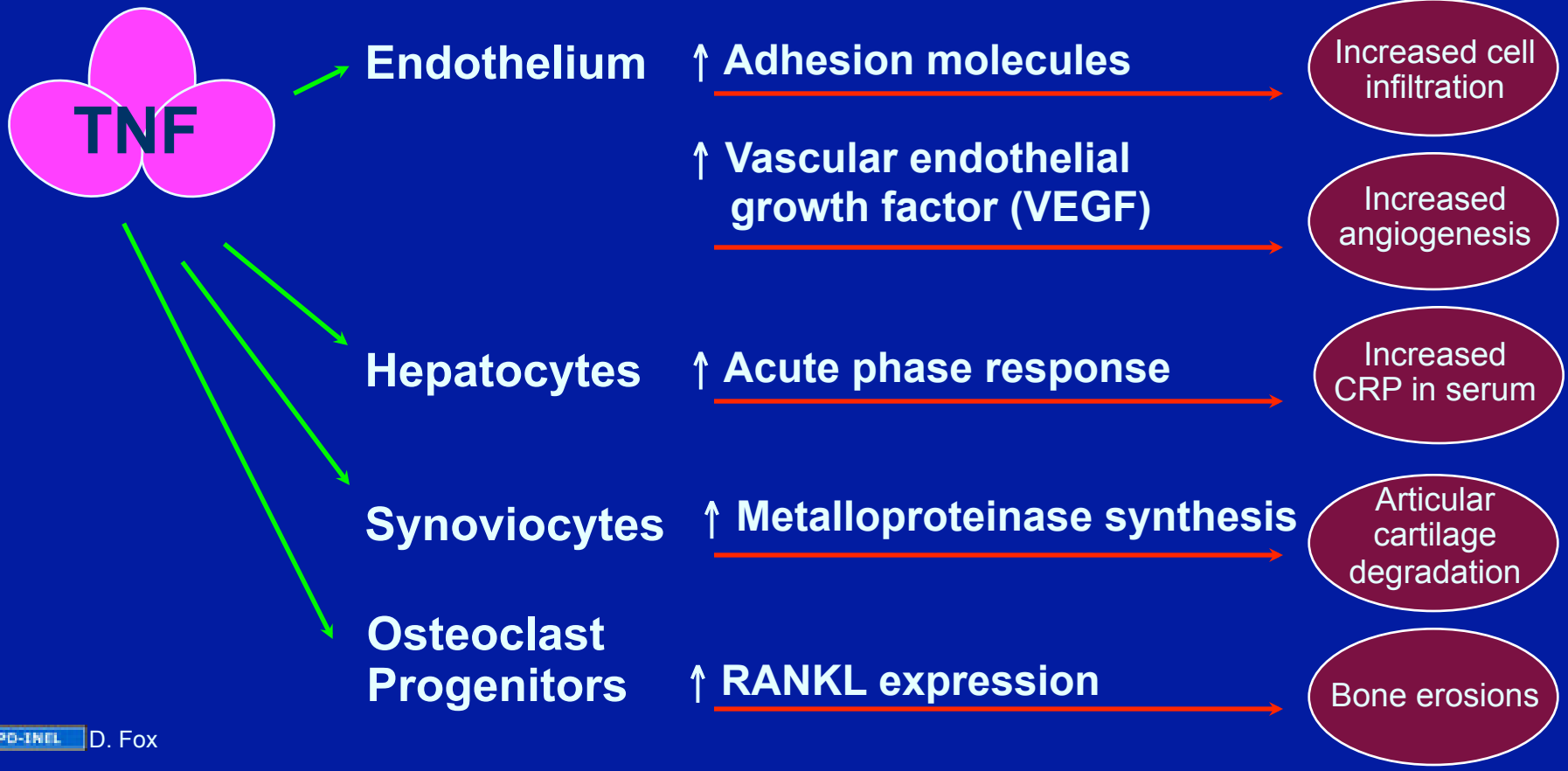
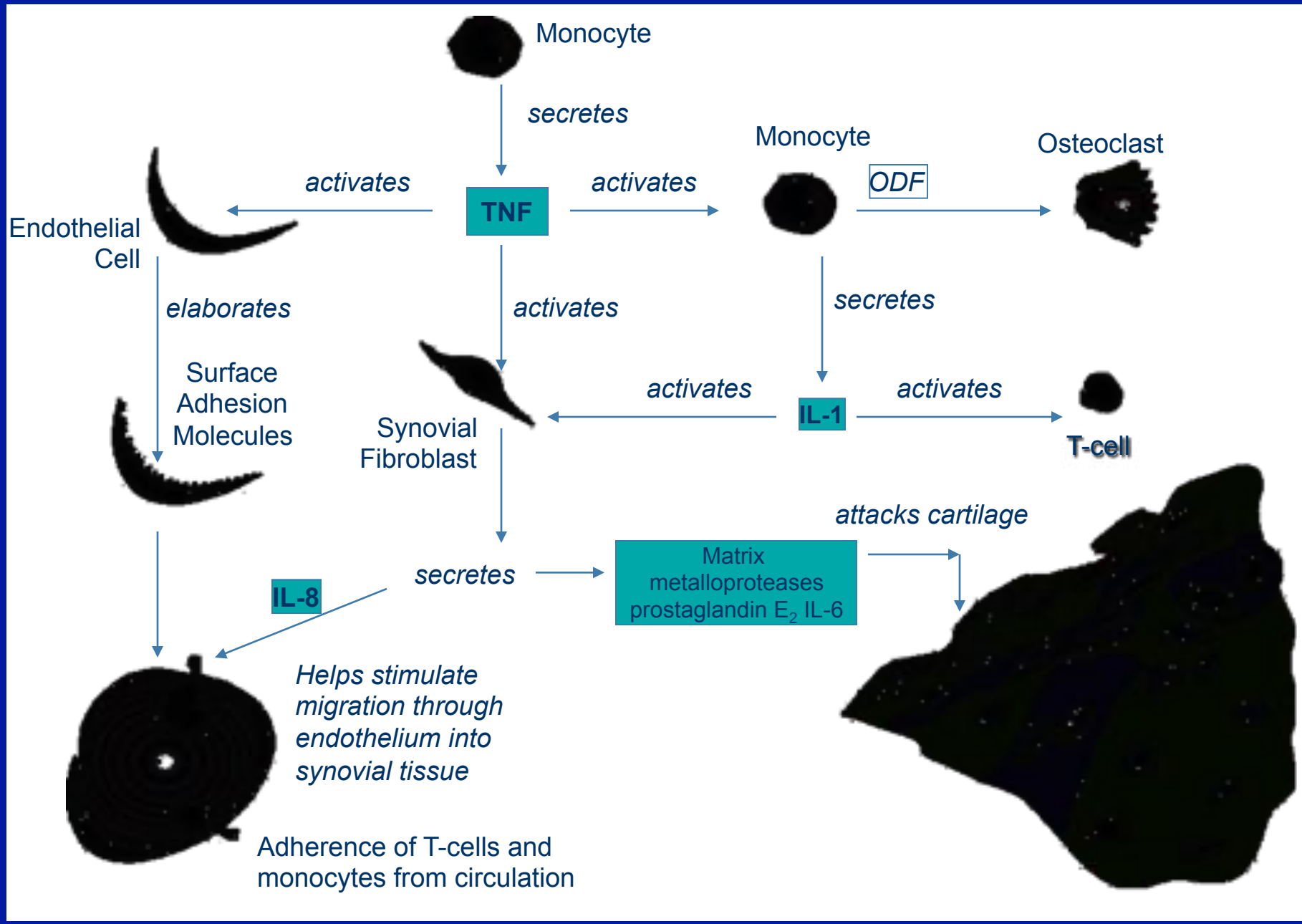
Key Actions Attributed to TNF





Actions of IL–1 and Endogenous IL–1Ra

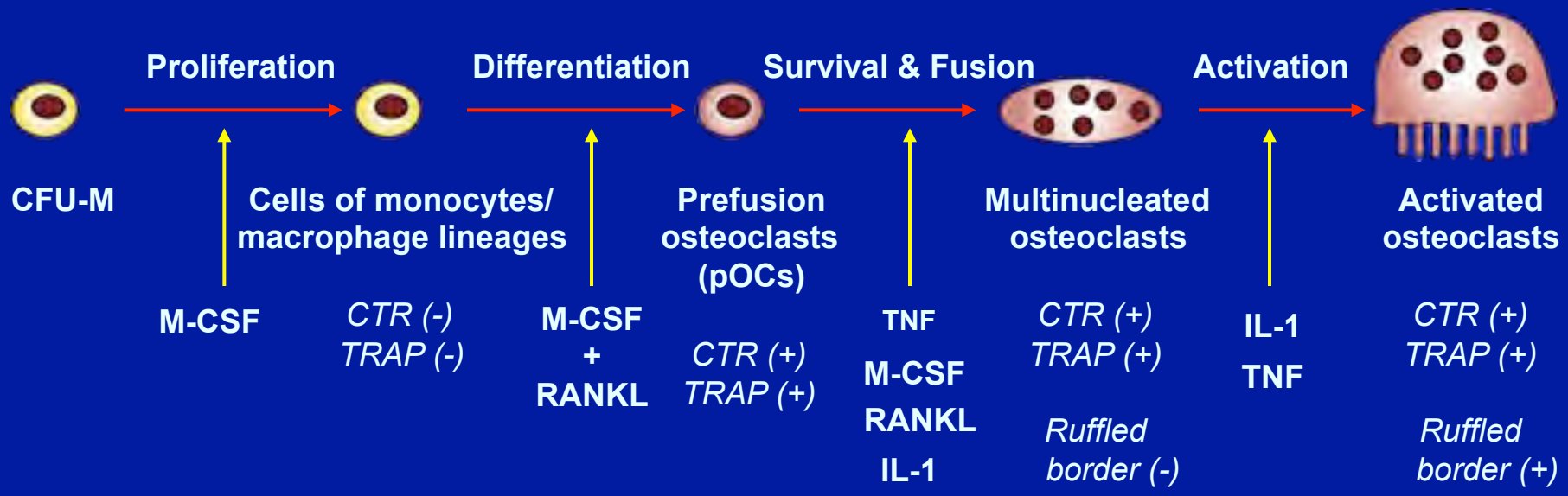
Source of original image:
Dinarello CA. *N Engl J Med*. 2000;343:733.

Role of Interleukin–1 in RA

- Pro-inflammatory cytokine
- Triggers production of other proinflammatory cytokines, including TNF
- Causes T cell/neutrophil accumulation in synovium by inducing expression of endothelial adhesion molecules
- Stimulates production of collagenase and stromelysin
- Stimulates osteoclast differentiation through intermediary TNF family cytokine, RANKL

Source: Bresnihan and Cunnane. *Rheum Dis Clin North Am.* 1998;24:615-628.

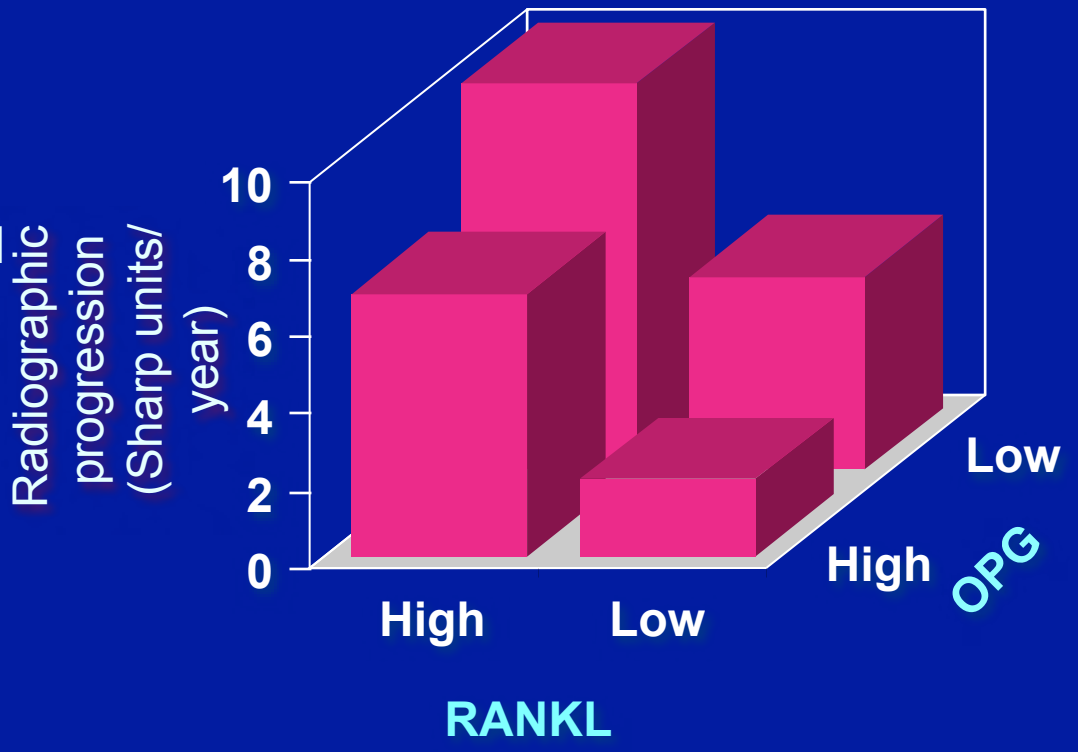
TNF and IL–1 Play a Critical Role in Osteoclast Differentiation



 D. Fox

RANKL:OPG and the Rate of Progression of Joint Destruction in RA

- RANKL promotes joint destruction
- OPG ameliorates RANKL-induced destruction of joints
- The RANKL:OPG ratio correlates well with the rate of joint destruction
- In RA osteoclasts destroy bone while synovial fibroblasts destroy cartilage



Geusens P, et al. *Arthritis Rheum*. 2003;48(suppl):5458 [Abstract 1145].

Role of Cytokines in Rheumatoid Arthritis Synovium

	Producing Cells		*Target Cells*		
Cytokine	**T cells**	**Synovial Macrophages and/or Fibroblasts**	**T cells**	**Synovial Macrophages and/or Fibroblasts**	**Other**
IL-1 β	+	++	+	+	osteoclast
TNFα	+ endothelium	++	+	+	
IL-6	+/-	+	+	-	hepatocyte, chondrocyte
IL-8	+/-	+	+/-	-	neutrophil
IL-15	-	+	+	-	-
IL-17	+	-	-	+	-

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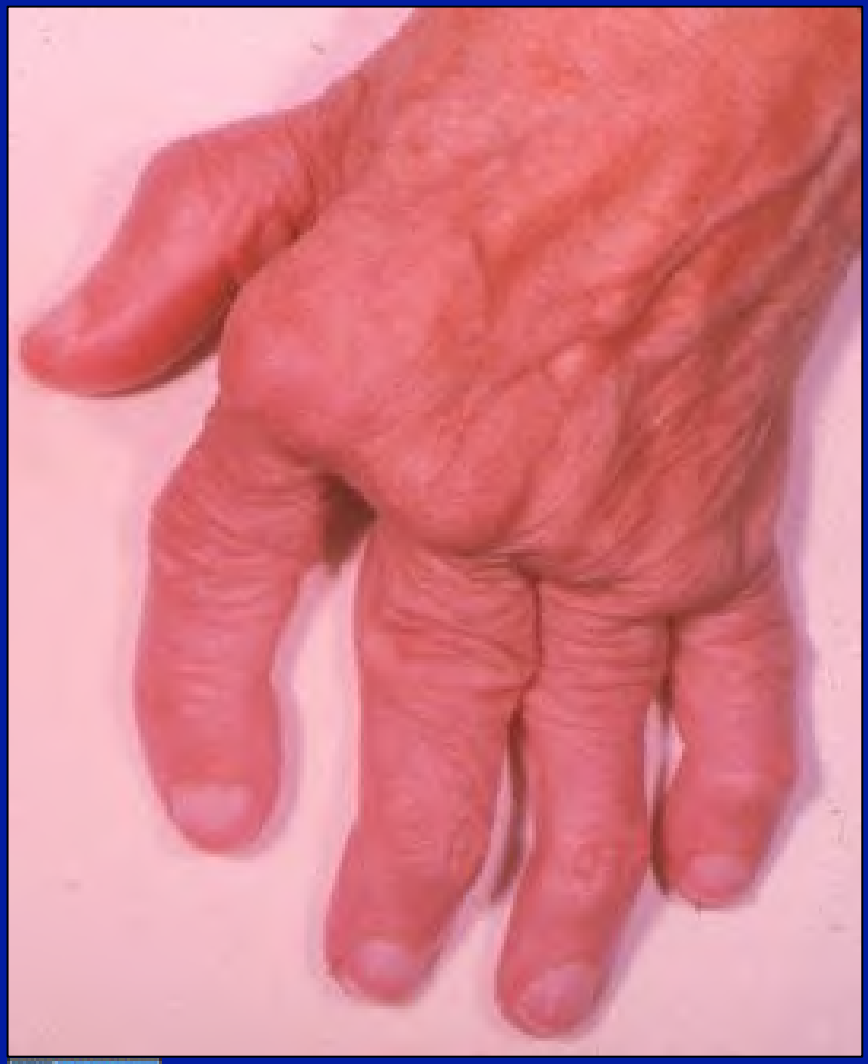

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