Rheumatoid Arthritis

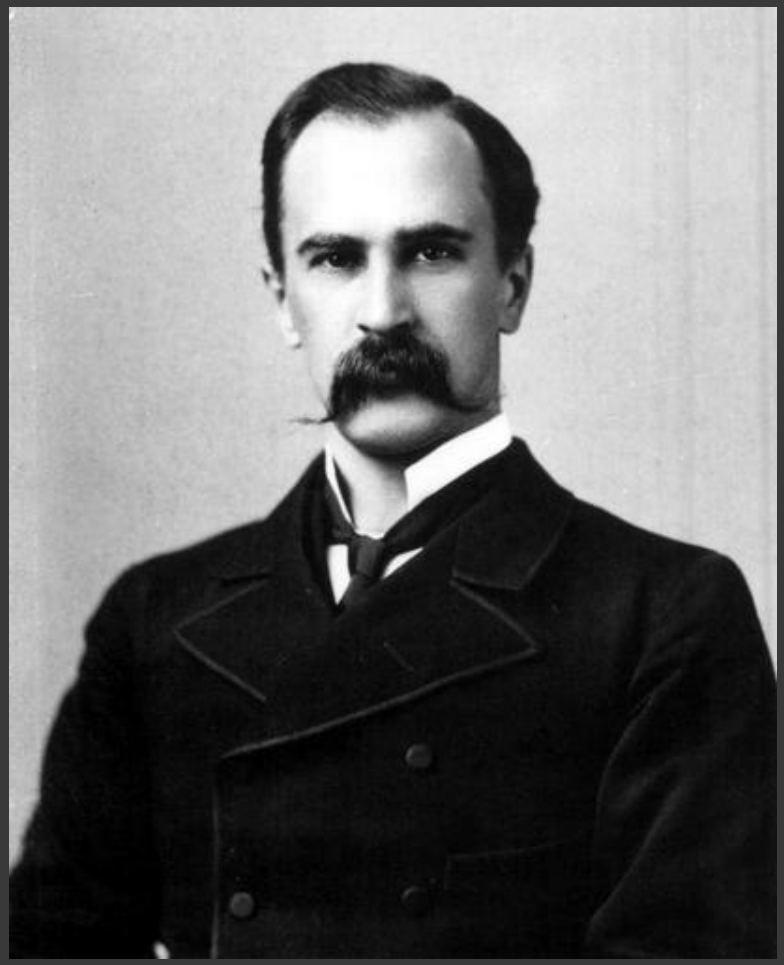
4th year MBBS

Marwan Adwan

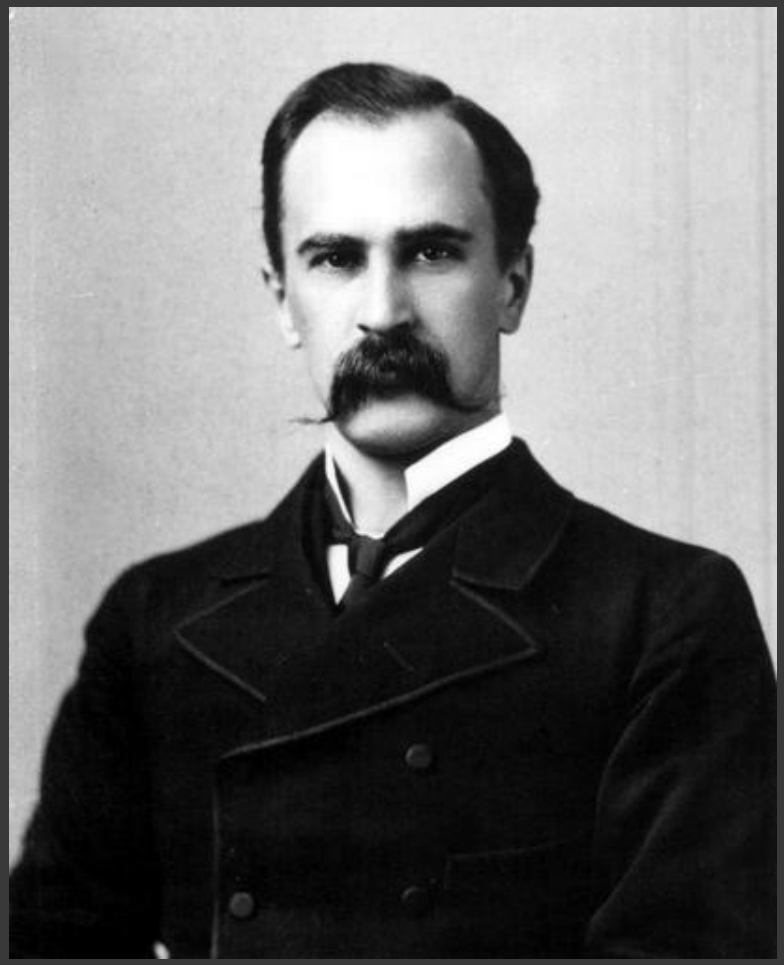
MBChB, MRCPI, MSc, SCE(rheum)

Consultant Rheumatologist

When a patient with arthritis comes in the front door, I try to go out the back door



When a patient with arthritis comes in the front door, I try to go out the back door



William Osler 1849 – 1919


الجامعة الأردنية
١٣٨٢هـ ١٩٦٢م

? ?

- A 42 YO lady presents with 6/12 Hx of progressively increasing pain, stiffness and swelling of small joints of hands & feet, elbows and knees. She denied any fever, hair loss, dry eyes, dry mouth, mouth ulcers, rash, raynaud's, pleurisy.
- She wakes at night with tingling in her R thumb, index & middle fingers.

- O/E: Antalgic gait
- Shoulders: restricted abduction & internal rotation
- Elbows: limited flexion to 85
- Wrists: swelling, warmth, tenderness, limited ROM
- Positive Tinel’s & phalan’s
- Hands: swelling, warmth, tenderness in MCPs & PIPs
- Knees: effusions
- Feet: positive MTP squeeze
- Spine: normal ROM, SIJs normal

Investigations

- Blood Tests:
  - Haemoglobin 10.5 ↓
  - Platelets 650 ↑
  - ESR 85 ↑
  - RF strongly positive
  - ANA negative
- X ray hands: soft tissue swelling, periarticular osteoporosis, erosions

DIAGNOSIS??

Objectives

- Definition
- Epidemiology
- Genetics
- Aetiology & pathology
- Clinical features
- Extra-articular manifestations
- Treatment

Definition

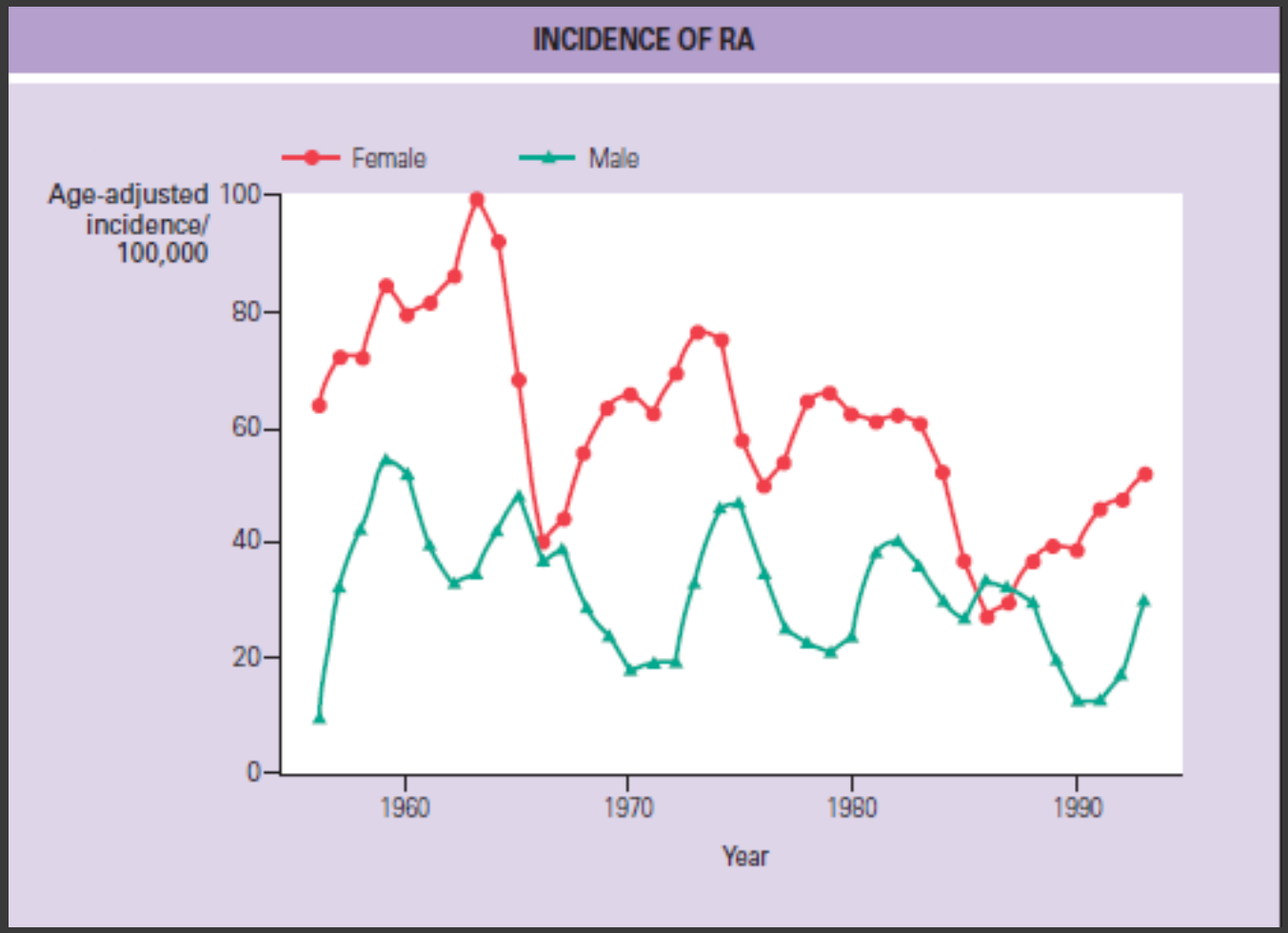
- Chronic multisystem disease of unknown aetiology
- Characterized by synovitis
- Involves peripheral joints
- Symmetrical
- Leads to cartilage damage and bone erosions and subsequent joint damage

Epidemiology

- Incidence: 30/100,000/yr
- Prevalence: 1% (increases with age)
- High prevalence in certain North American Indian tribes
- Rare in rural Africans and in Chinese
- Gender: F:M = 3:1
- Age: 80% between 35-50
- 4X expected rate in first-degree relatives
- 10% of patients with RA will have an affected first-degree relative

TIME TRENDS ??

Time trends


INCIDENCE OF RA
Female
Male
Age-adjusted incidence/ 100,000
100
80
60
40
20
0
1960
1970
1980
1990
Year

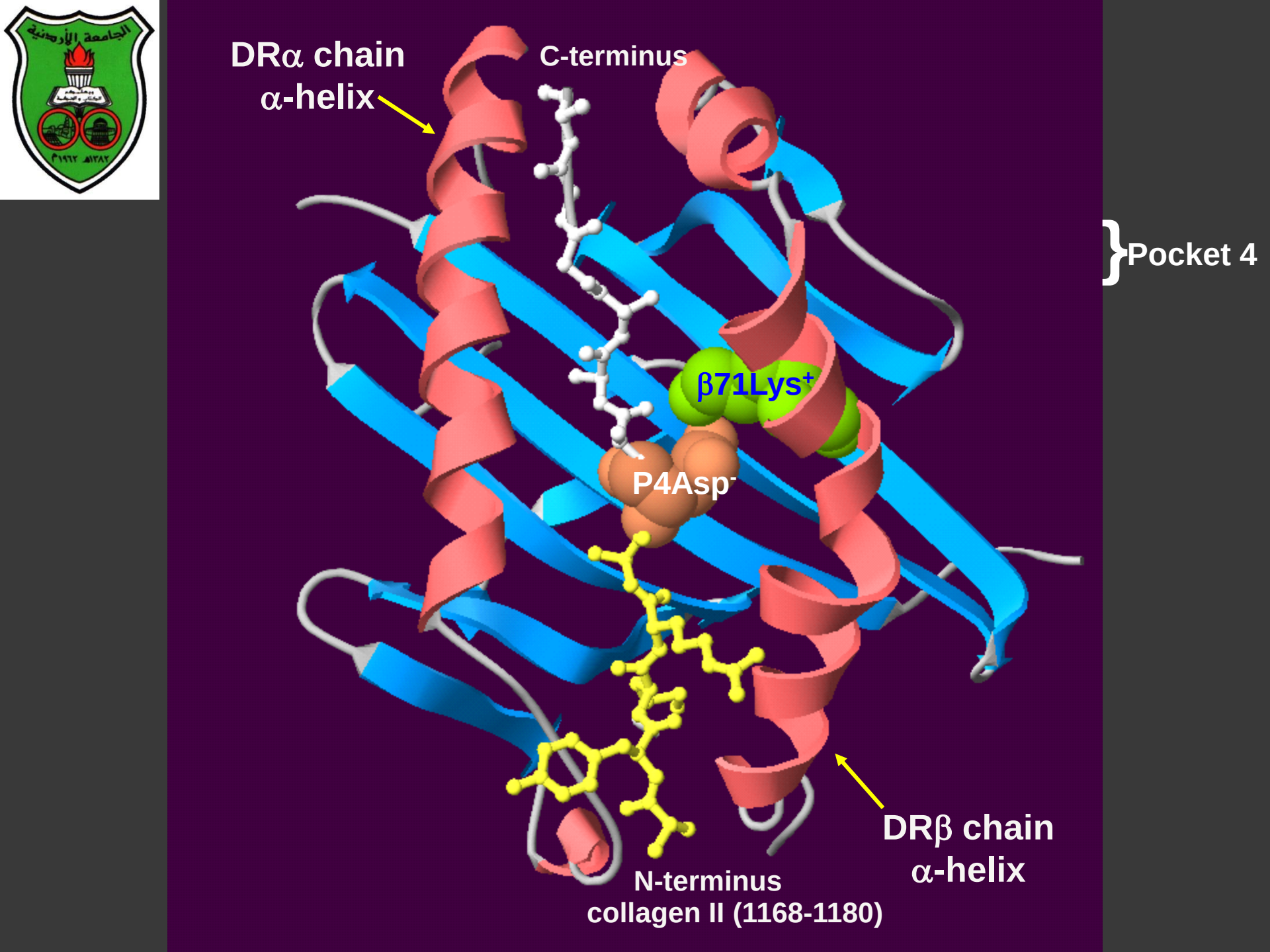
Genetics

- Monozygotic twins 4X more likely to be concordant for RA than dizygotic twins
- Concordance:
  - 15% in monozygotic twins
  - 4% in dizygotic twins
- Genetic factors explain ~60% of the disease susceptibility. 40% other
- The highest risk is HLA-DR4
- 70% of patients with RA express HLA-DR4
- Compared with 28% of control individuals
- HLA-DR3 (DRβ1∗0301) in Arab populations

- Patients with more severe RA, especially those with systemic complications such as vasculitis and Felty's syndrome, are more likely to have HLA–DR4 than patients with less aggressive disease

Shared epitope

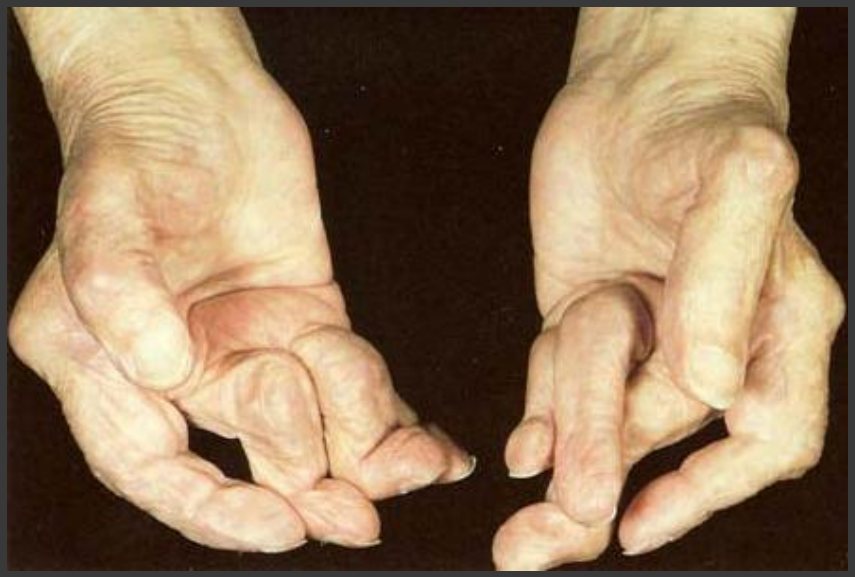
- The most common HLA-DRB1 susceptibility alleles: *0101, *0401, *0404 in individuals of European ancestry
- These alleles share similarities in a sequence of five amino acids at residues 70-74 in the third hypervariable region of the HLADRB1 gene
- QKRAA

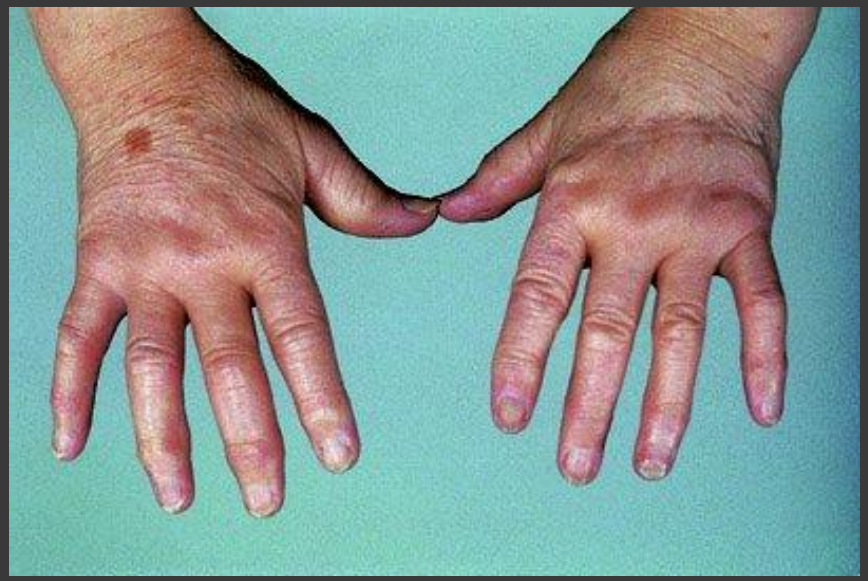

DRα chain
α-helix
C-terminus
β71Lys+
P4Asp-
Pocket 4
DRβ chain
α-helix
N-terminus
collagen II (1168-1180)

Genes outside MHC region

- HLA genes contribute 1/3 of the genetic susceptibility
- Other genes:
  - PTPN22
  - STAT4
  - FcRγ3
  - PADI4
  - CTLA4

Severity also declining over time





Autoantibodies

Anticitrullinated protein/peptide antibodies

Citrullinated proteins originate in the synovium

ACPAs :-produced in inflamed synovium by local plasma cells

HLA-DRB1 shared epitope alleles :-major genetic risk factor for RA associated with ACPA -positivity

Sensitivity :-around 68% goes to 82% with assays measuring Anti-Sa

Specificity :-over 96% when measured with second-generation ELISA

ACPAs are considered the most accurate serological marker for RA

Occasionally associated with psoriatic arthritis, tuberculosis, leprosy, and autoimmune hepatitis.

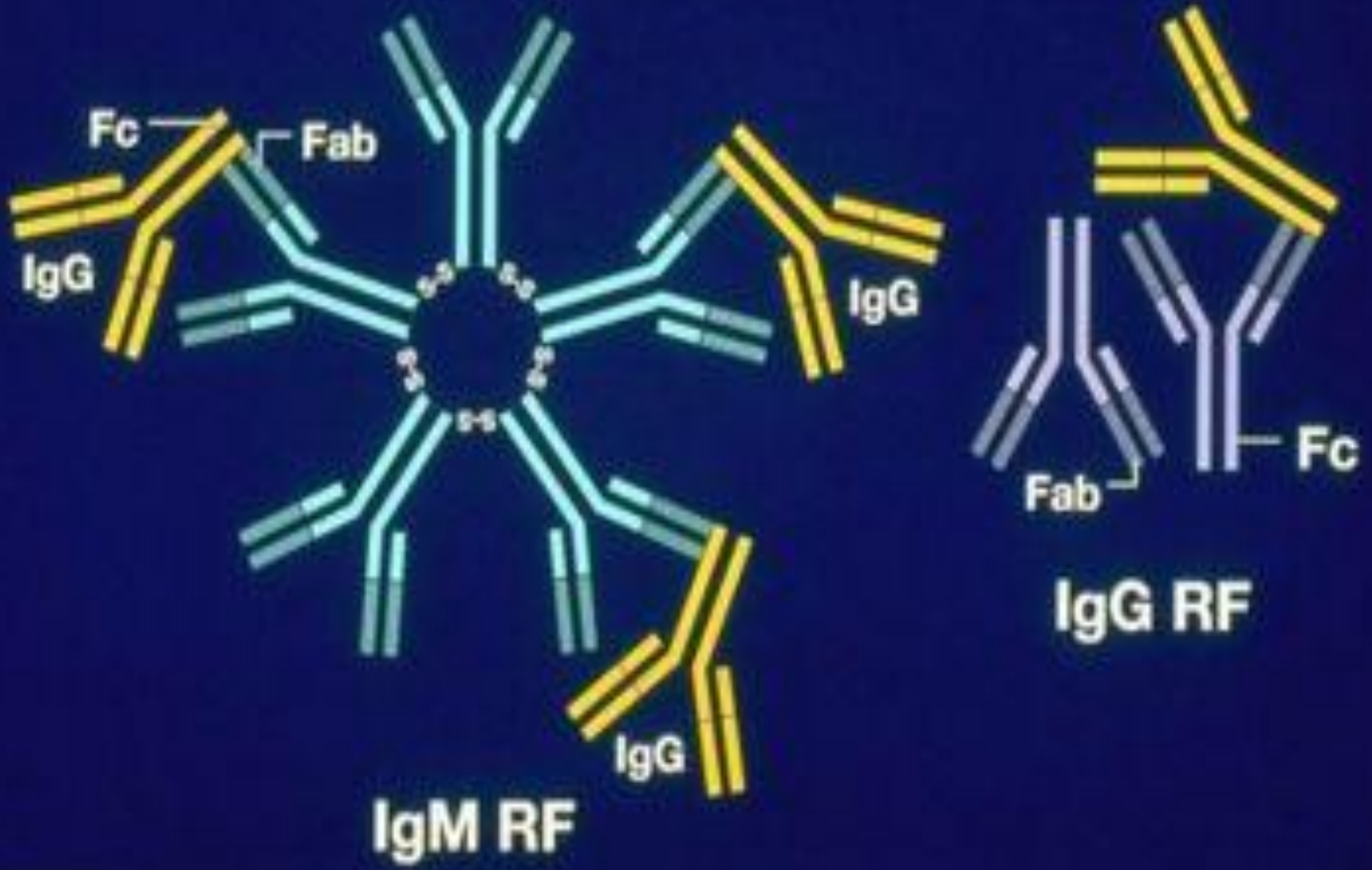
- predictor of radiographic progression in patients with early RA
- Disease-specific marker of RA detectable early in the preclinical phase of RA

Rheumatoid factor

Antibodies IgM directed against the Fc portion of IgG.

- **45% positive in first 6 months.**
- **85% positive with established disease.**
- Not **pathognomonic or** specific for RA.

Rheumatoid Factors



Diseases Commonly Associated With Rheumatoid Factor

- Rheumatoid Arthritis
- Lupus
- Scleroderma
- Overlap Syndromes
- Sjögren's Syndrome
- Sarcoidosis
- Acute Viral Infection and Vaccination
- Chronic Infections
- Malignancies
- Cryoglobulinemia
- Cirrhosis
- Chronic Pulmonary Disease

ETIOLOGY

Cause is unknown

ETIOLOGY

- ? Response to an infectious agent in a genetically susceptible host
- Possible causative agents: *Mycoplasma,* EBV, CMV, parvovirus, rubella virus
- No convincing evidence

Risk factors

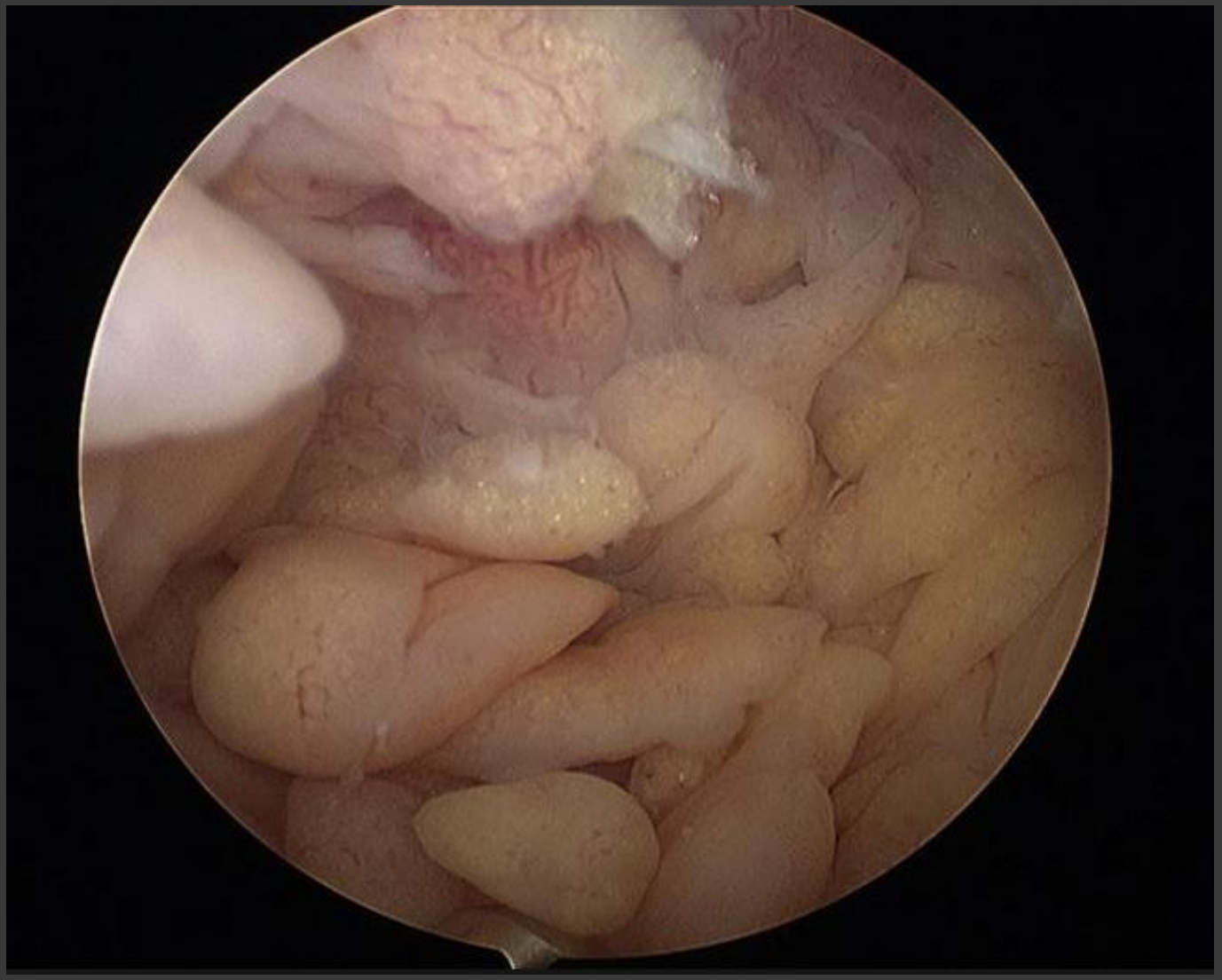
1. Environment:
   a) Smoking (in CCP-positive patients)
   b) low level of formal education
   c) Urban environment

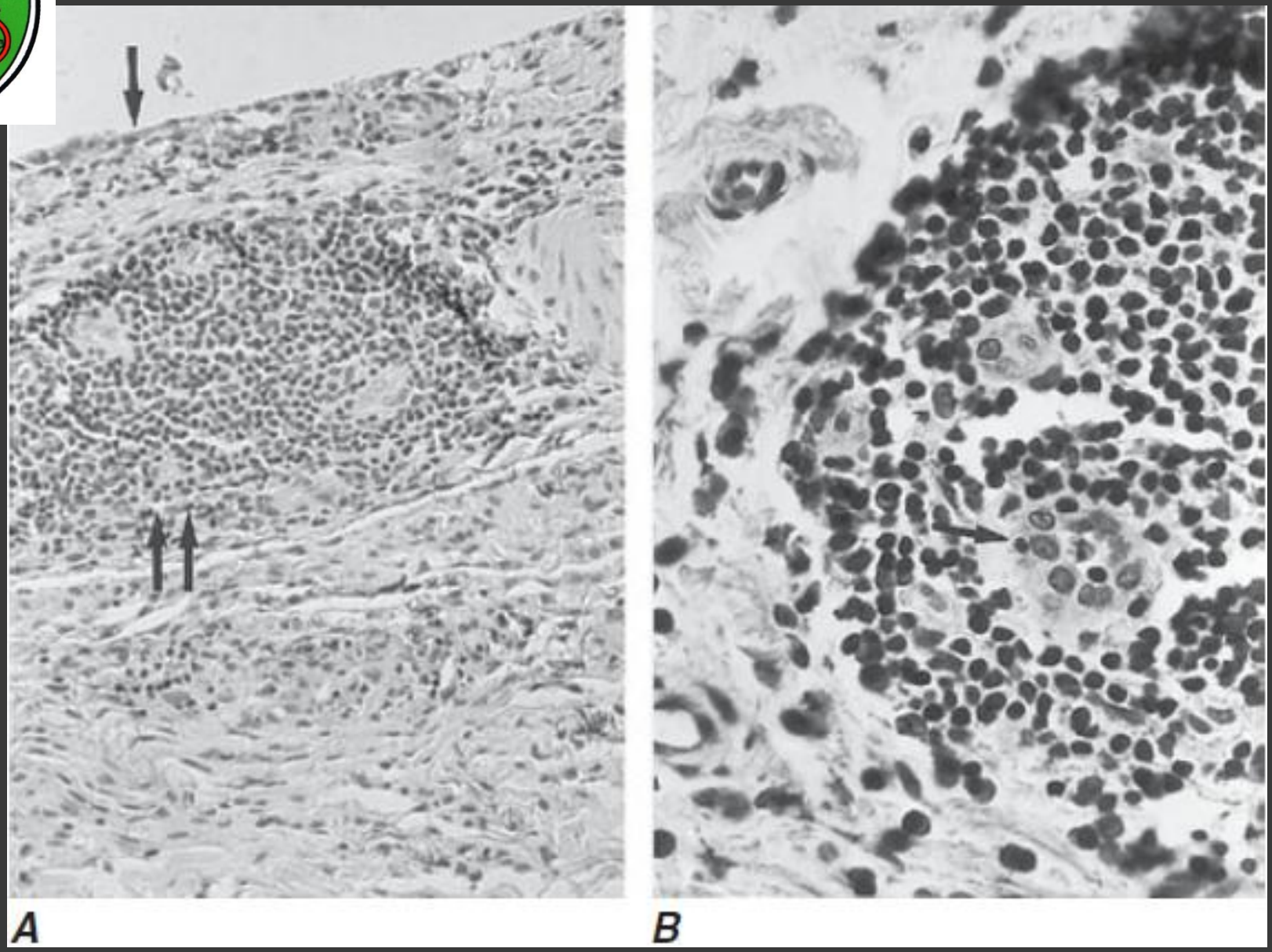
2. Hormones:
   a) Oestrogen
   b) Breast-feeding after 1st pregnancy
   c) Pregnancy has a favourable effect on RA

3. Genes:
   a) HLA–DR4, DR1
   b) PTPN22
   c) STAT4

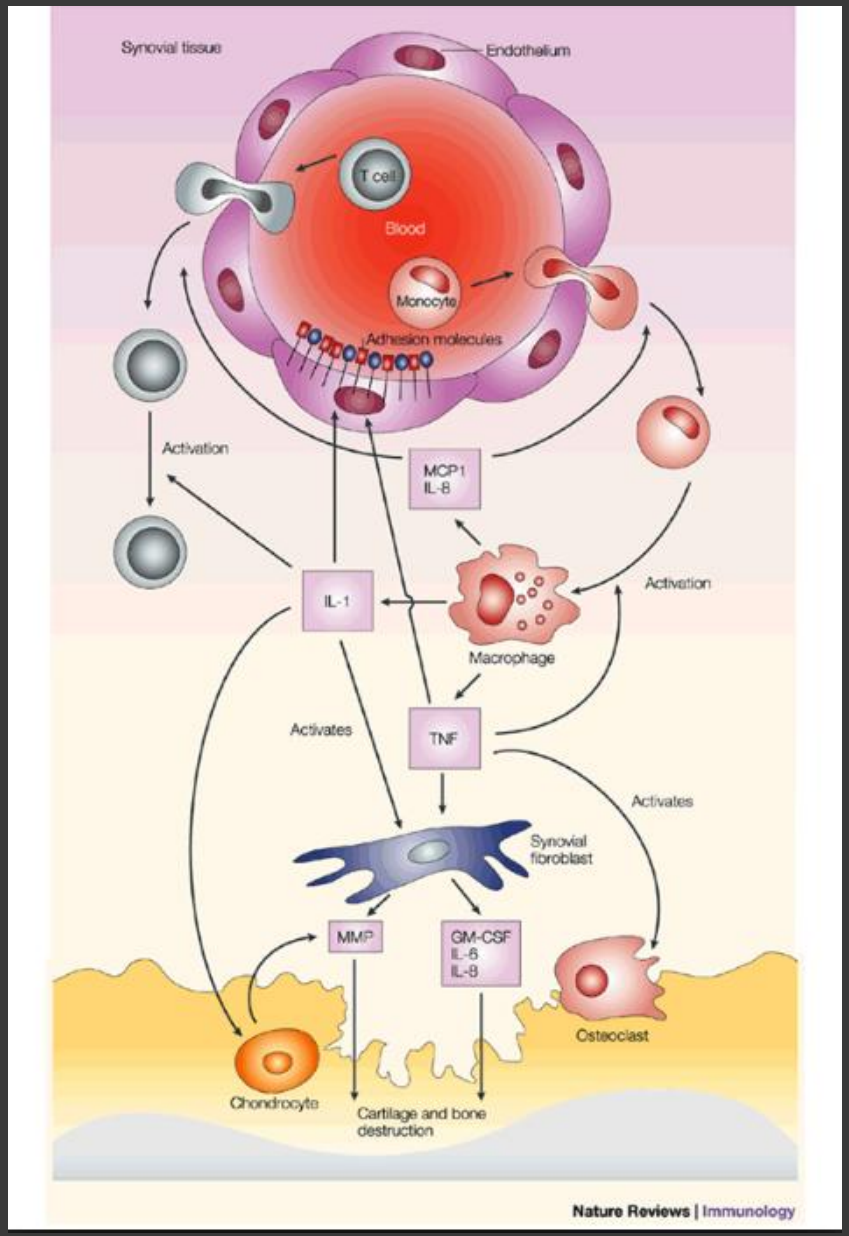
Pathology

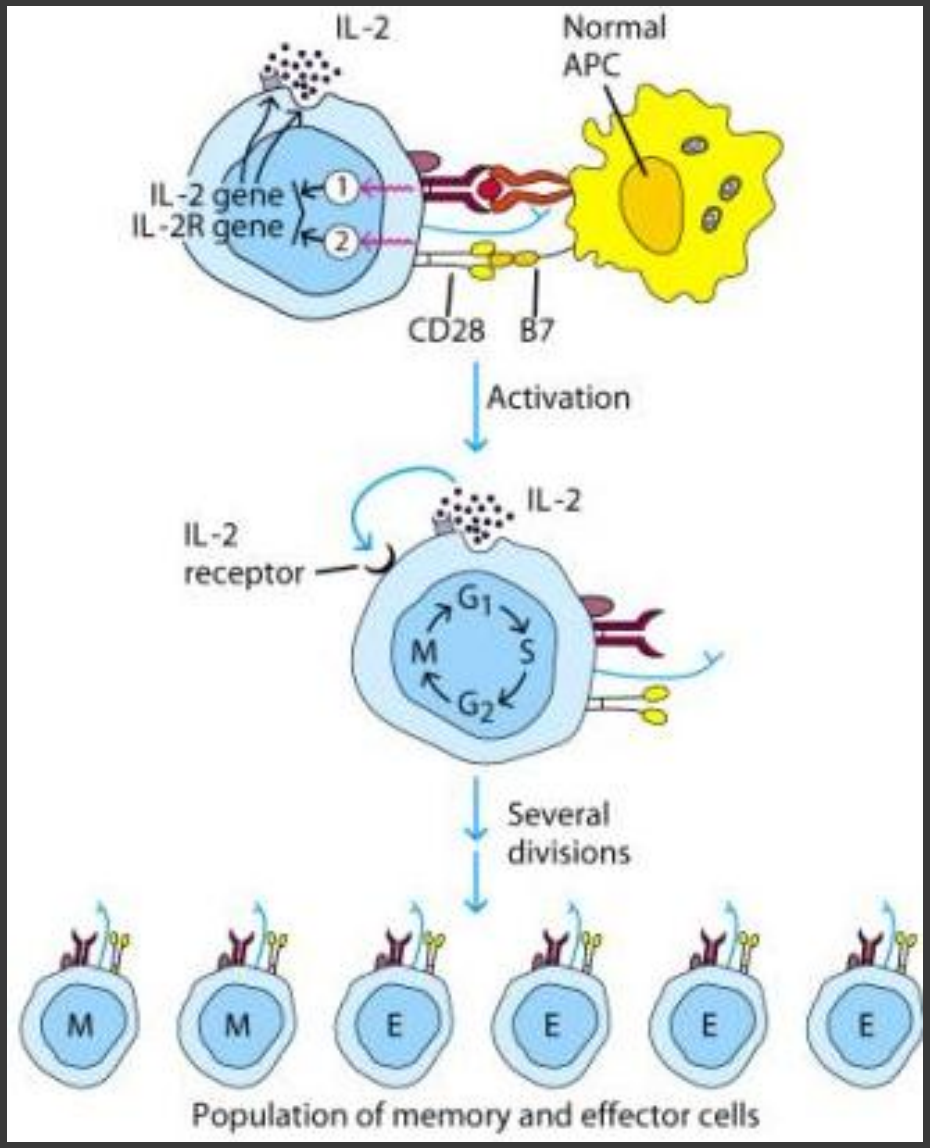
- Increased number of synovial lining cells
- Perivascular infiltration with mononuclear cells
- The synovium becomes oedematous and protrudes as villous projections.

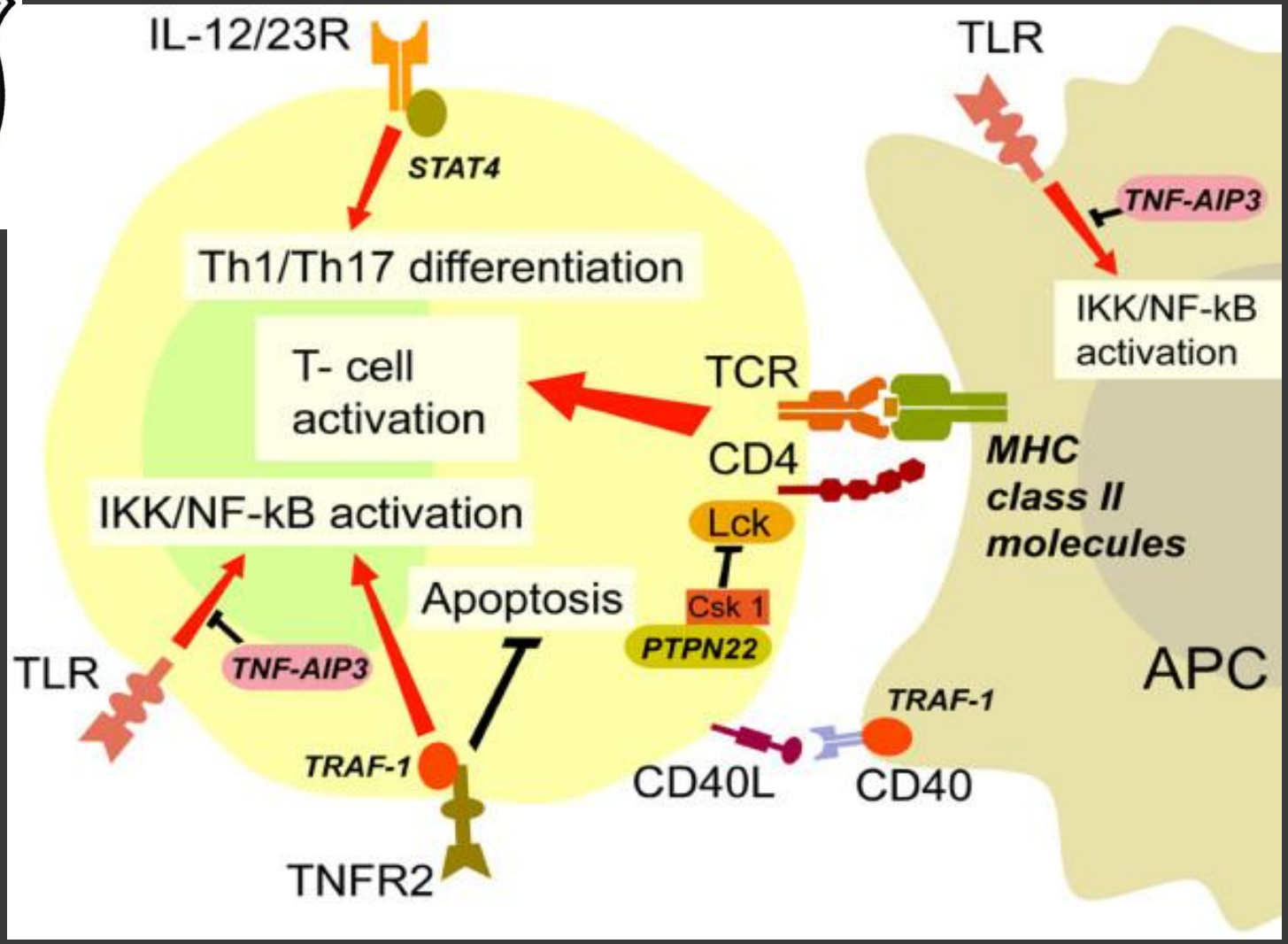



A
B

Pathogenesis


Synovial tissue
Endothelium
T cell
Blood
Monocyte
Adhesion molecules
Activation
MCP1
IL-8
IL-1
Macrophage
Activation
Activates
TNF
Activates
Synovial fibroblast
MMP
GM-CSF
IL-6
IL-8
Osteoclast
Chondrocyte
Cartilage and bone destruction
Nature Reviews | Immunology


IL-2
Normal
APC
IL-2 gene
IL-2R gene
1
2
CD28
B7
Activation
IL-2
IL-2
receptor
G1
S
G2
M
Several
divisions
M
M
E
E
E
E
Population of memory and effector cells



T cell-APC interaction to illustrate biologic pathways involving rheumatoid arthritis-associated genes (indicated in italics). APC, antigen-presenting cell; IKK, IκB kinase; MHC, major histocompatibility complex; NF-κB, nuclear factor-κB; TCR, T-cell receptor; Th, T-helper;

TLR, Toll-like receptor; TNFR2, type 2 TNF receptor.

Clinical features

ACR/EULAR (2010) Classification Criteria

ACR/EULAR (2009) Classification Criteria for Rheumatoid Arthritis

Symptom Duration (as reported by patient)	Points
< 6 weeks	0
> 6 weeks	1

Joint Distribution	Points
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	4
> 10 joints (at least 1 small joint)	5

Serology	Points
RF- and CCP-	0
Low RF+ or CCP+	2
High RF+ or CCP+	3

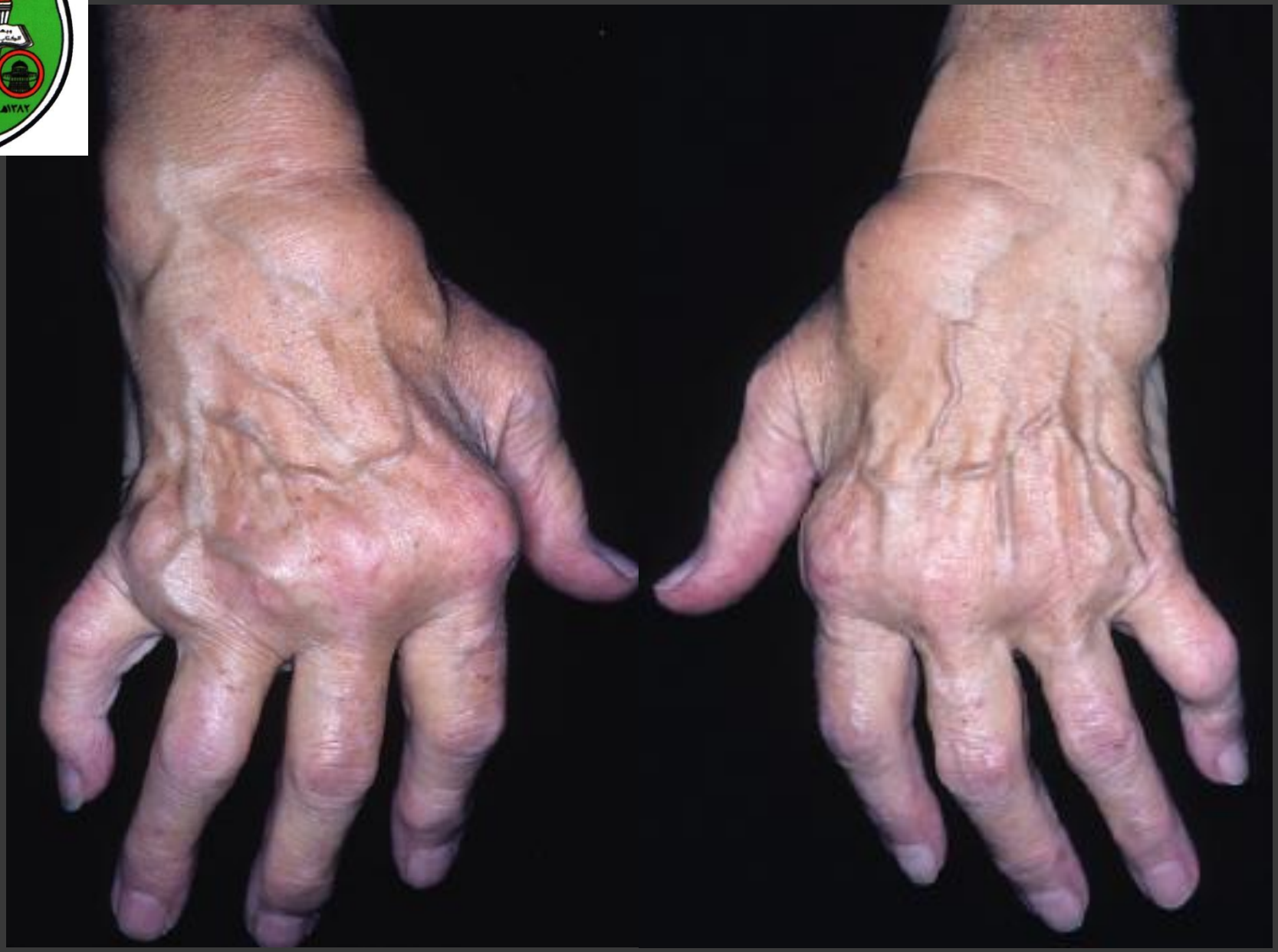
Acute Phase Reactants	Points
Normal ESR or CRP	0
Abnormal ESR or CRP	1

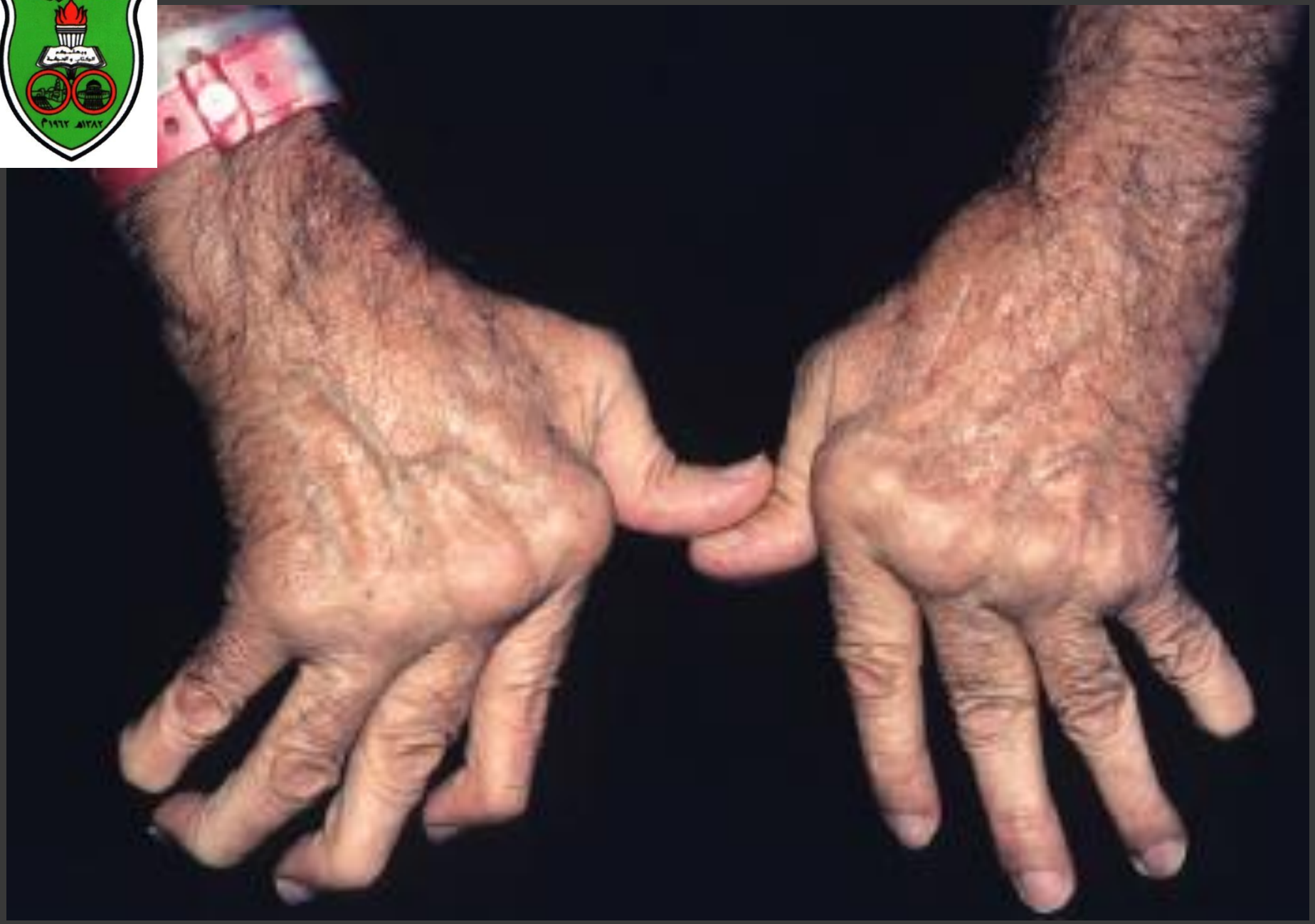
- Symptoms of RA develop gradually over weeks to months
- 15% present acutely over days (good prognosis)

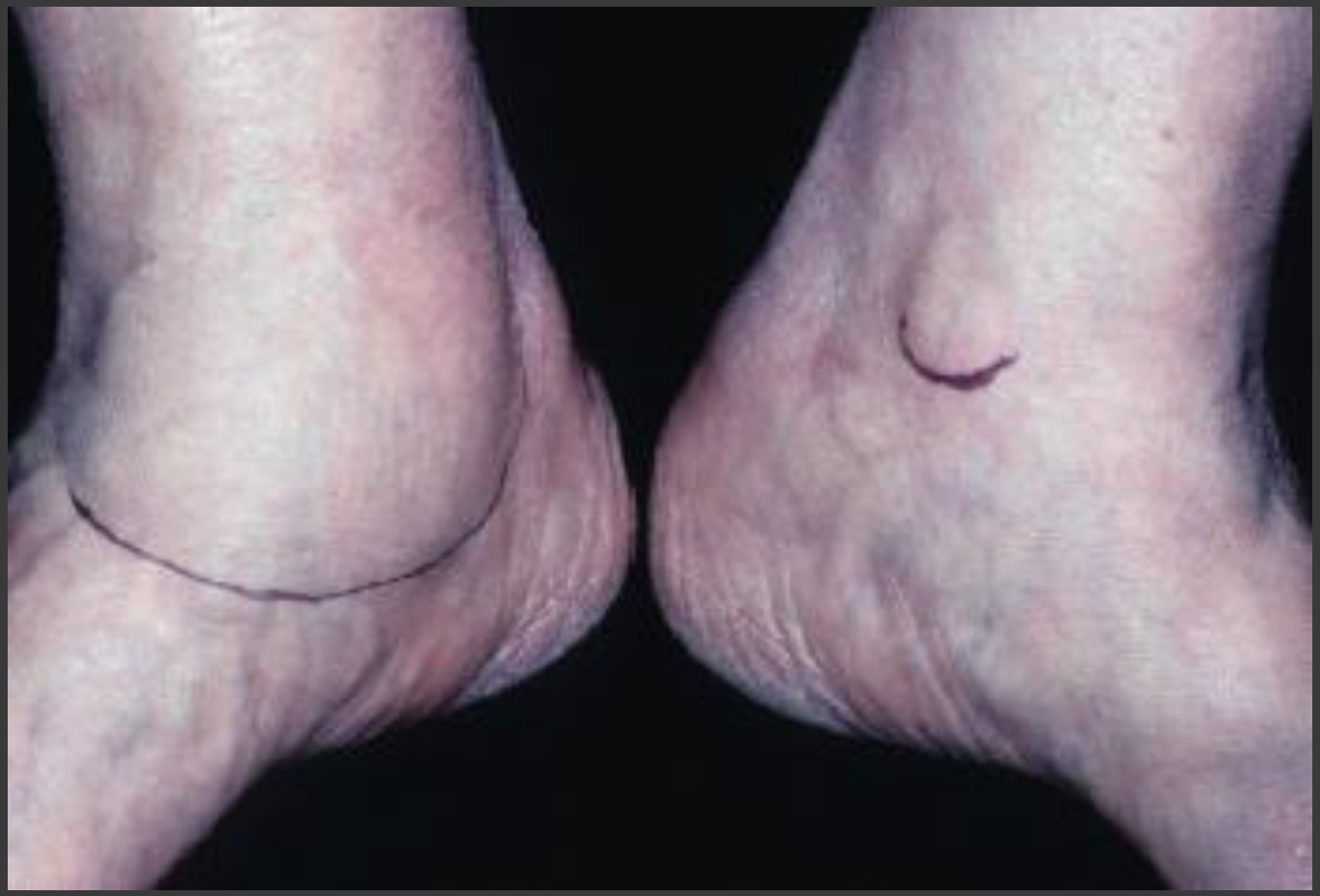
History

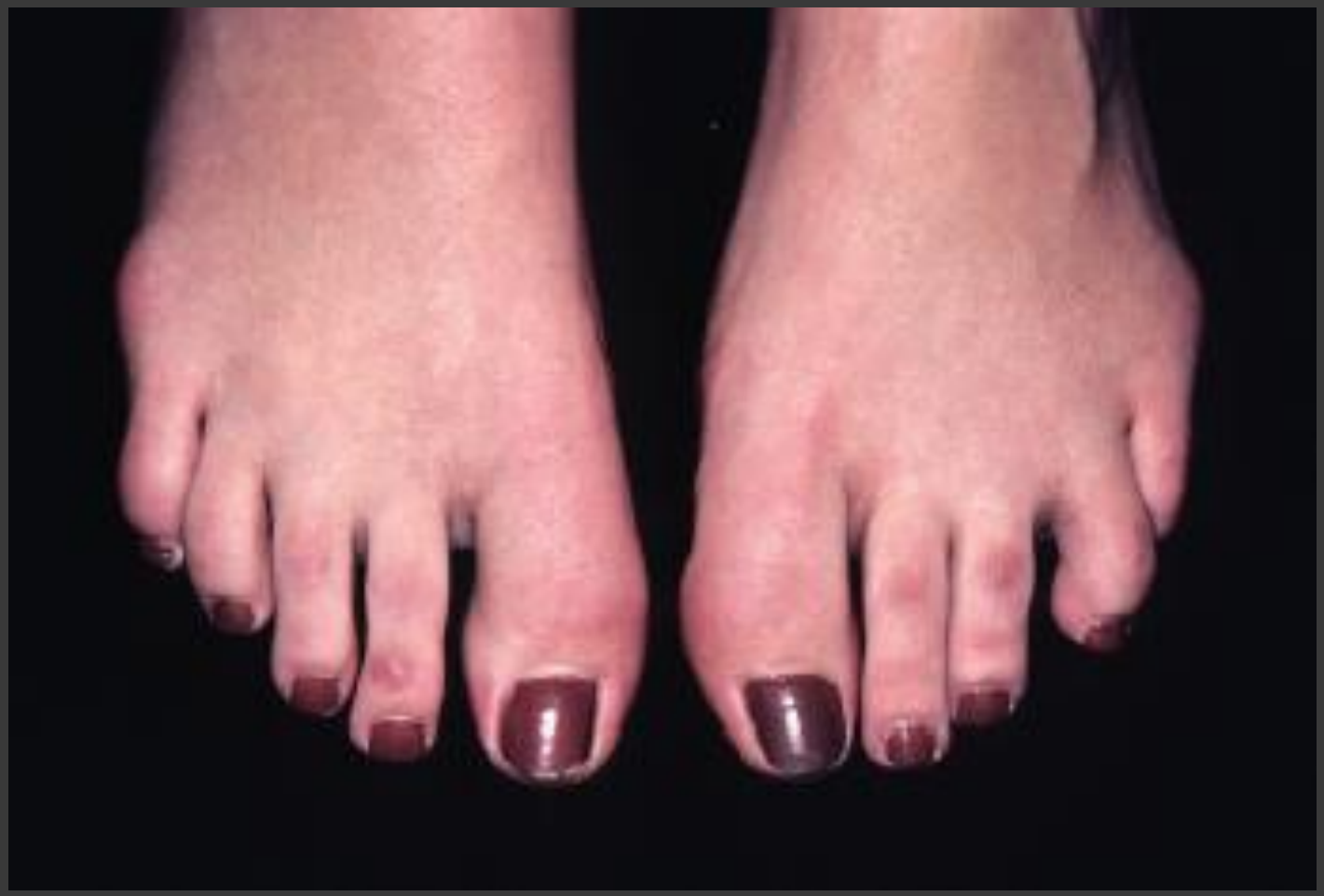
- Pain
  - Onset
  - Character
  - Aggravating & relieving factors
- Stiffness
- Deformity
- Impairment of function
- Constitutional: fever, anorexia, lassitude

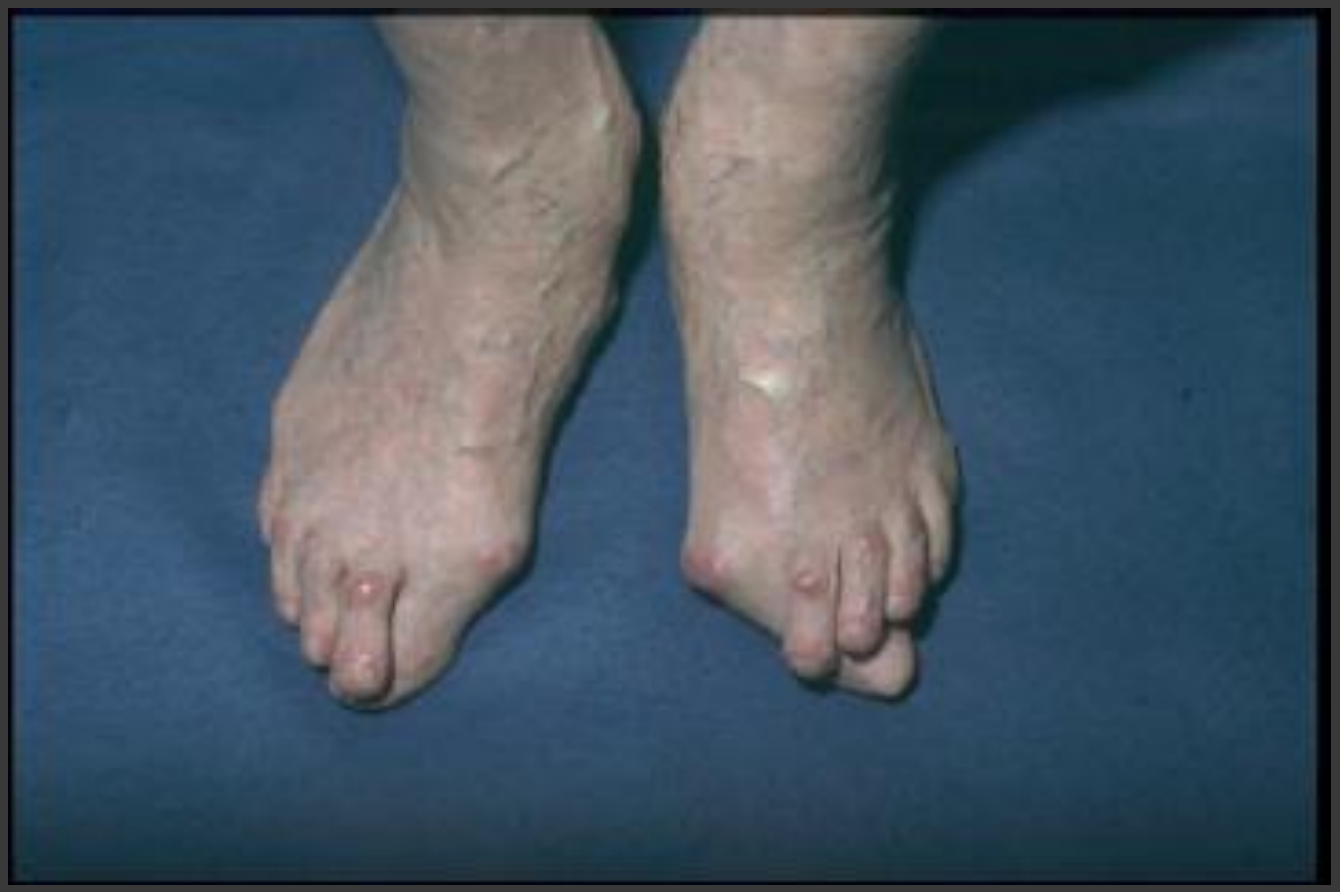
Examination

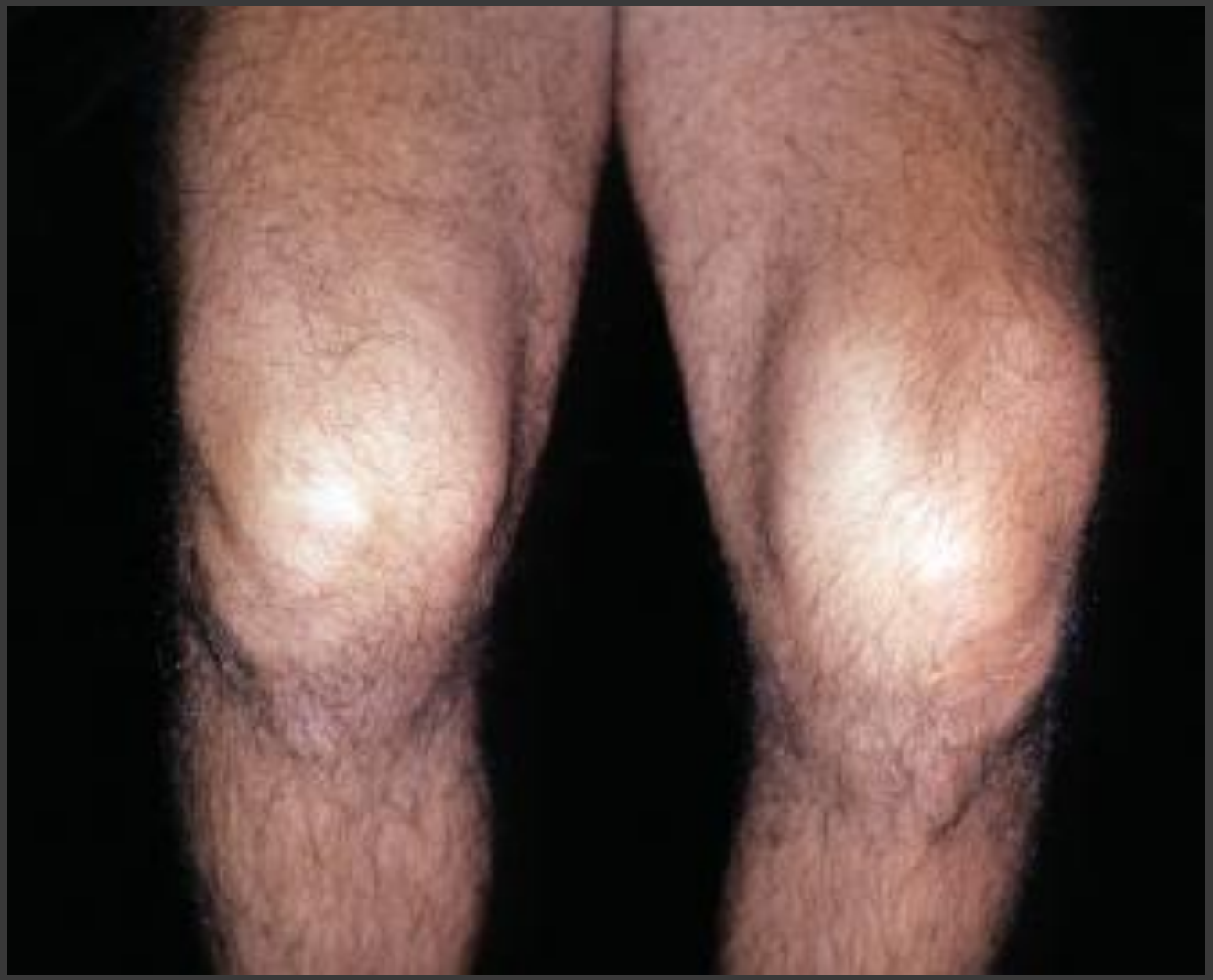


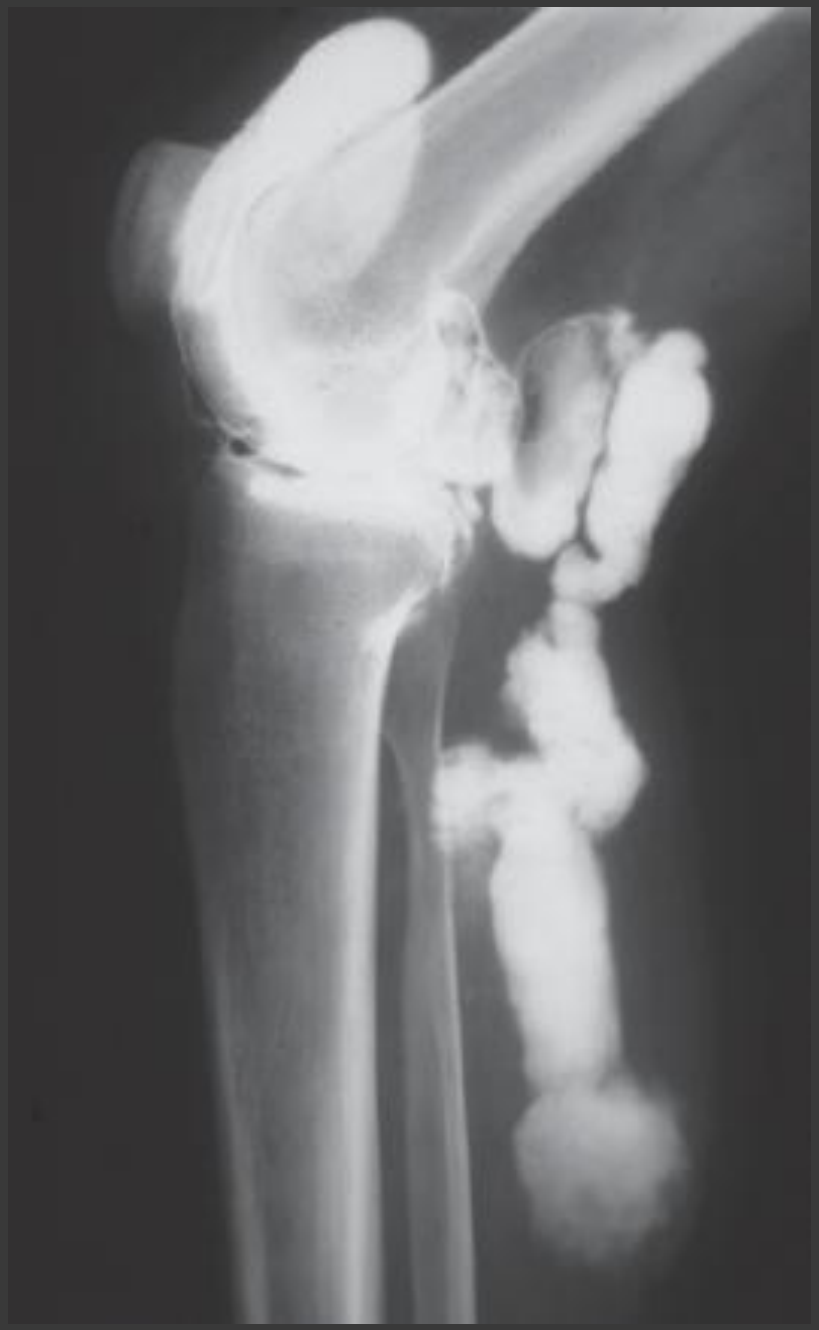


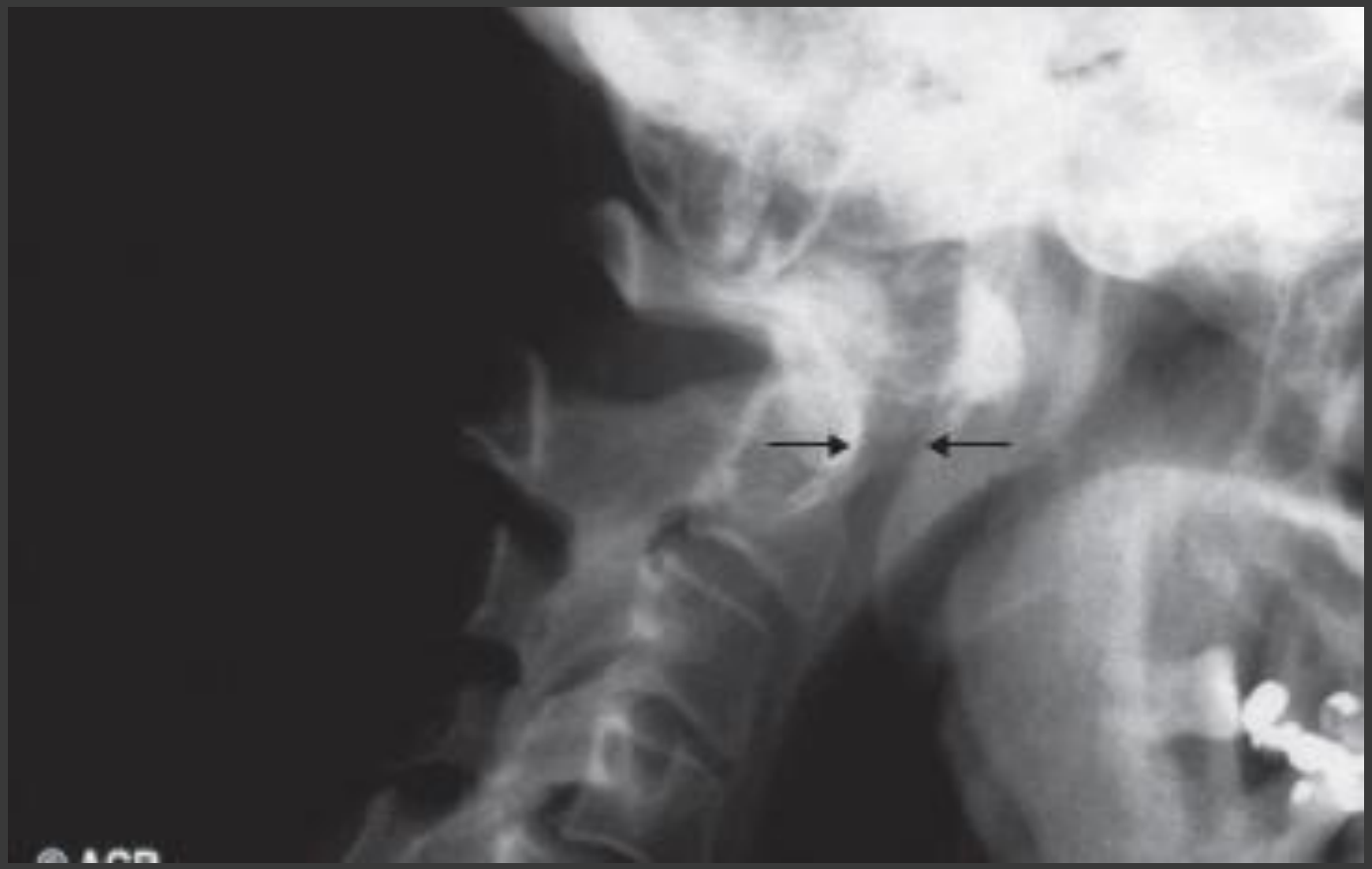




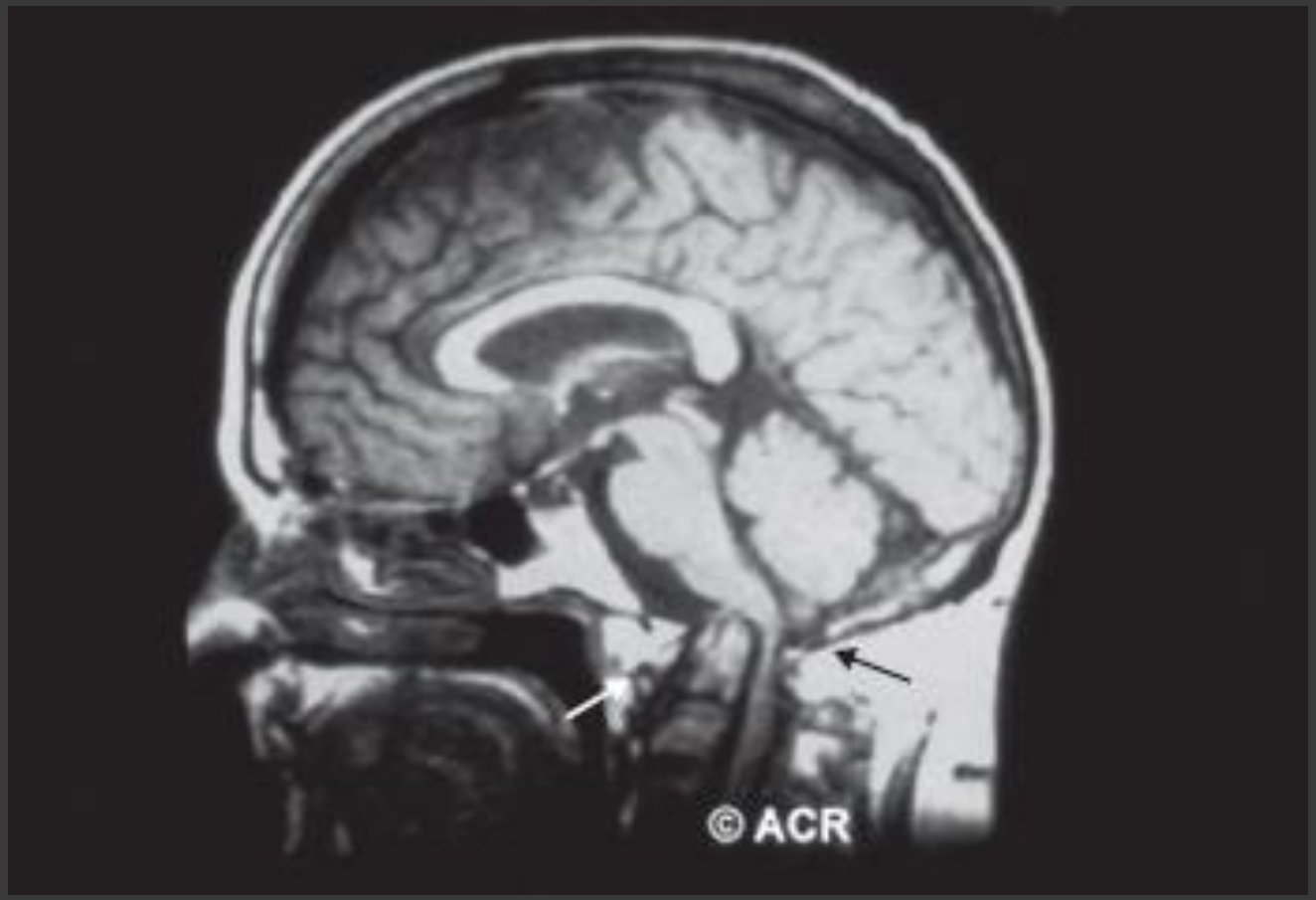


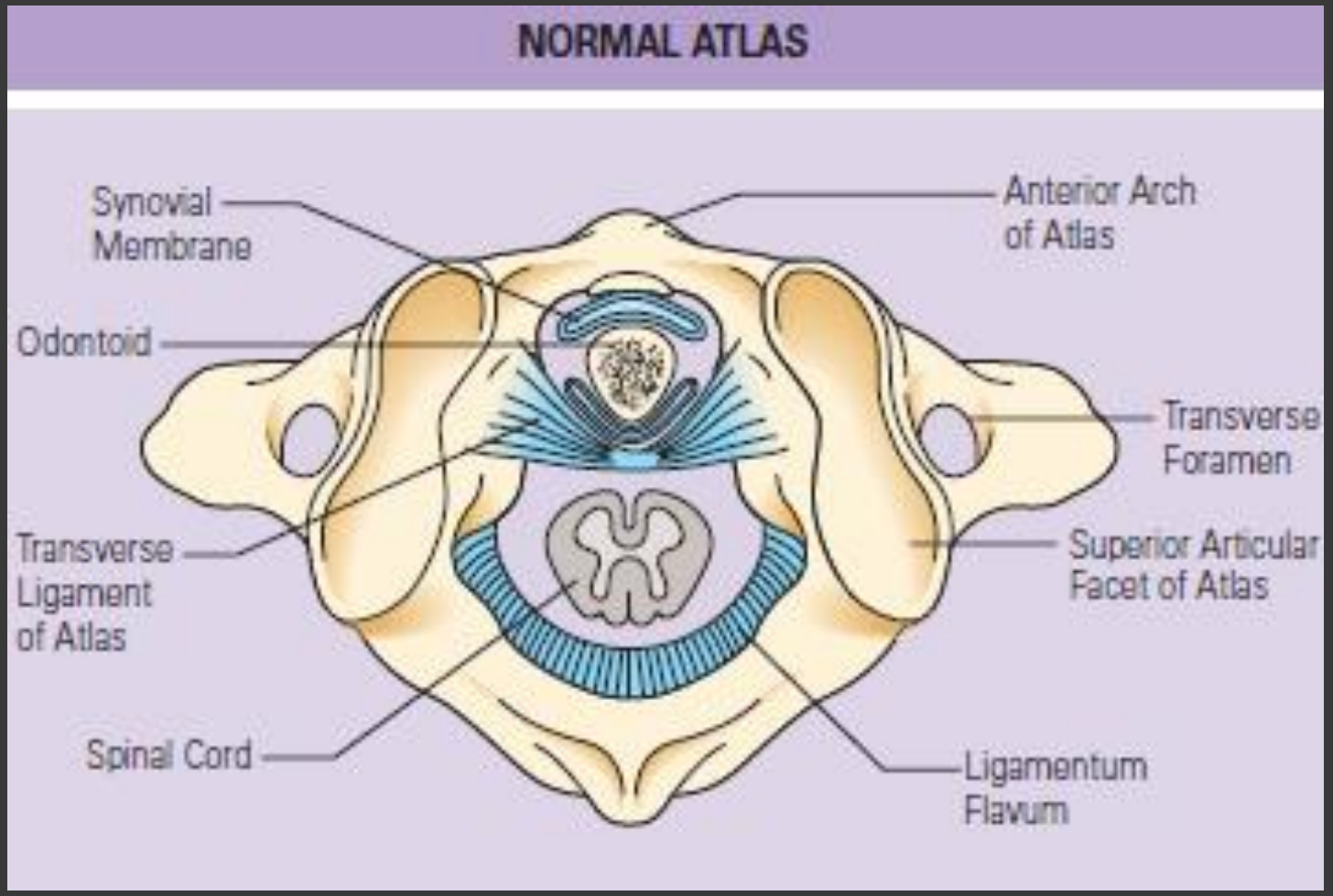






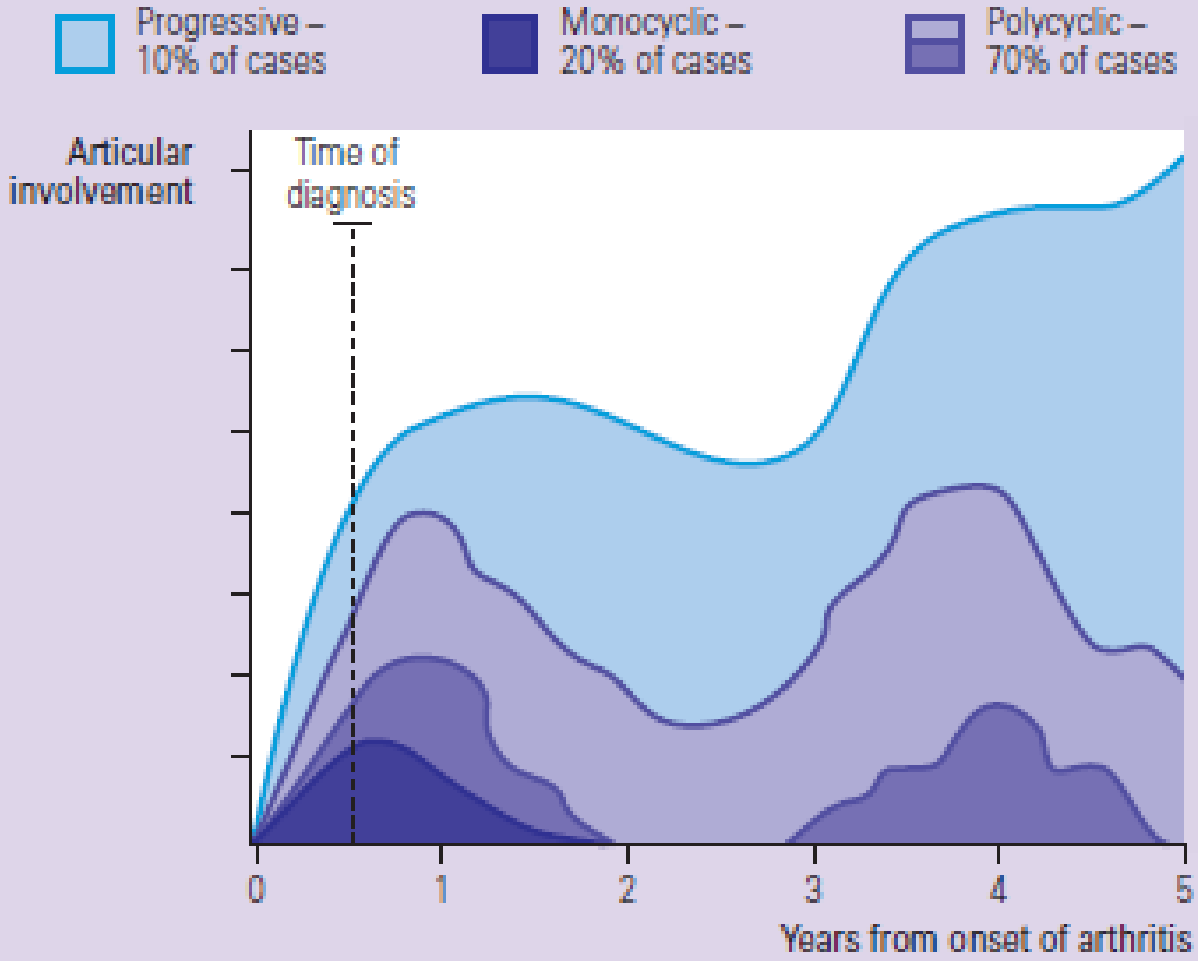
Atlantoaxial subluxation is defined as > 3 mm between the odontoid process of C-2 and the anterior arch of the atlas (C-1)


© ACR


NORMAL ATLAS
Synovial Membrane
Anterior Arch of Atlas
Odontoid
Transverse Foramen
Transverse Ligament of Atlas
Superior Articular Facet of Atlas
Spinal Cord
Ligamentum Flavum

Clinical course

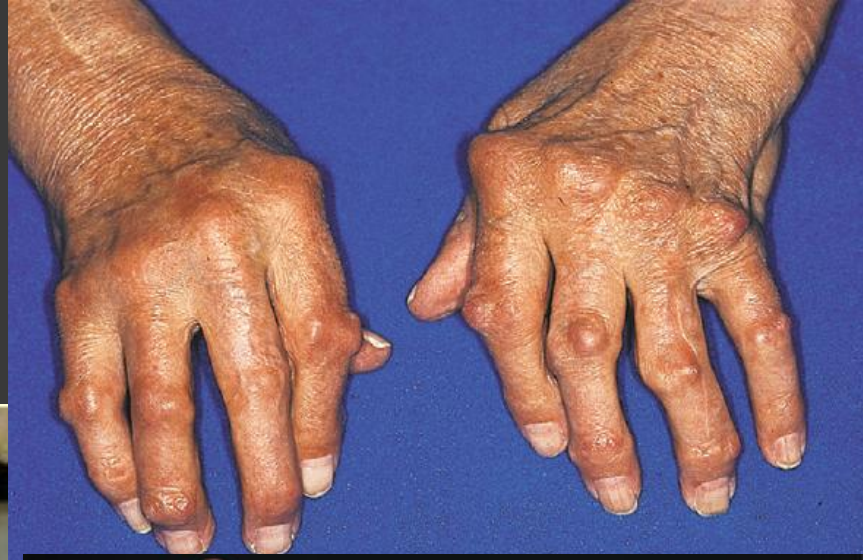
PATTERNS OF THE CLINICAL (ARTICULAR) COURSE OF RHEUMATOID ARTHRITIS

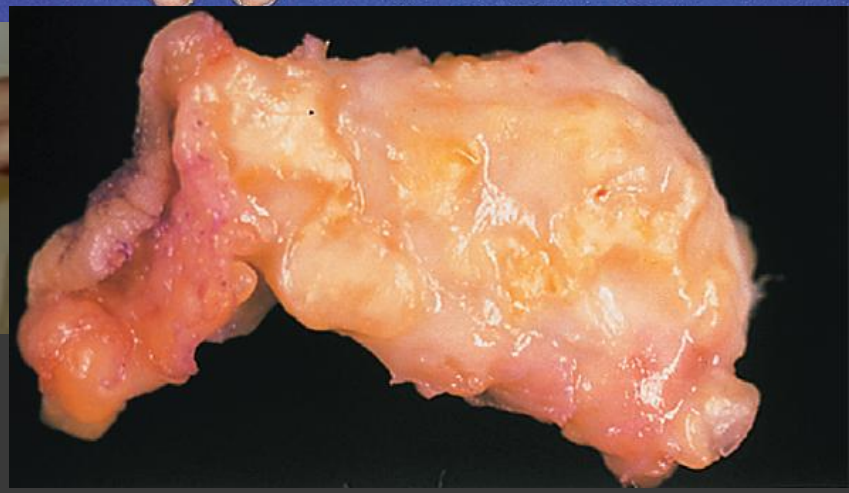


Extra-articular features

- Nodules
- Haematological
- Vasculitis
- Ocular
- Pulmonary
- Cardiac
- Renal
- Neurological

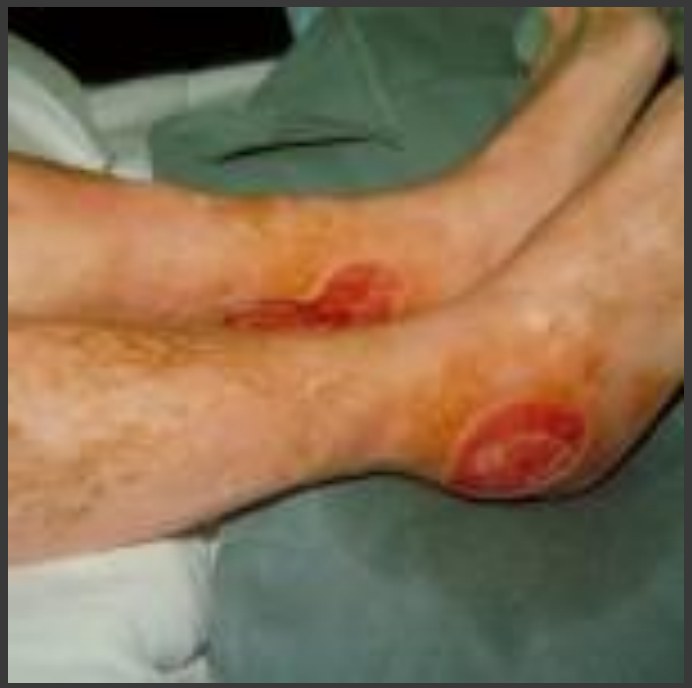
Nodules

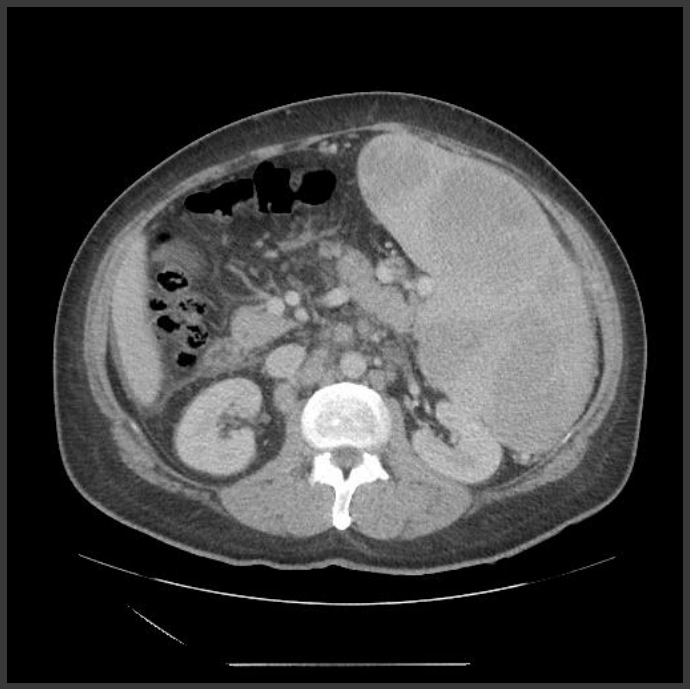




- occur in 20% of seropositive patients
- develop in areas of increased friction or pressure, such as the extensor aspects of the elbow, olecranon bursae, fingers, and Achilles tendons.
- may regress during DMARD treatment
- MTX causes increase

Felty’s syndrome

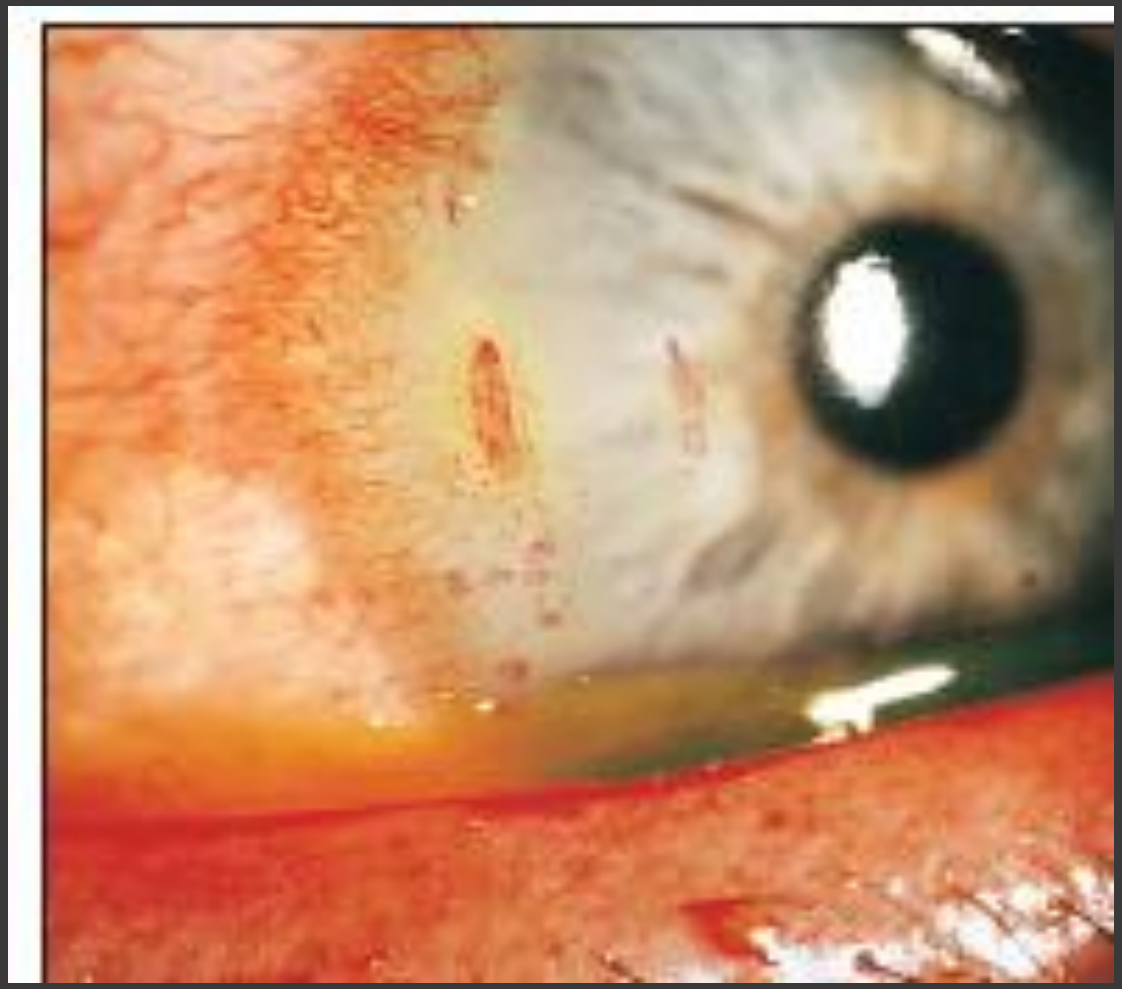




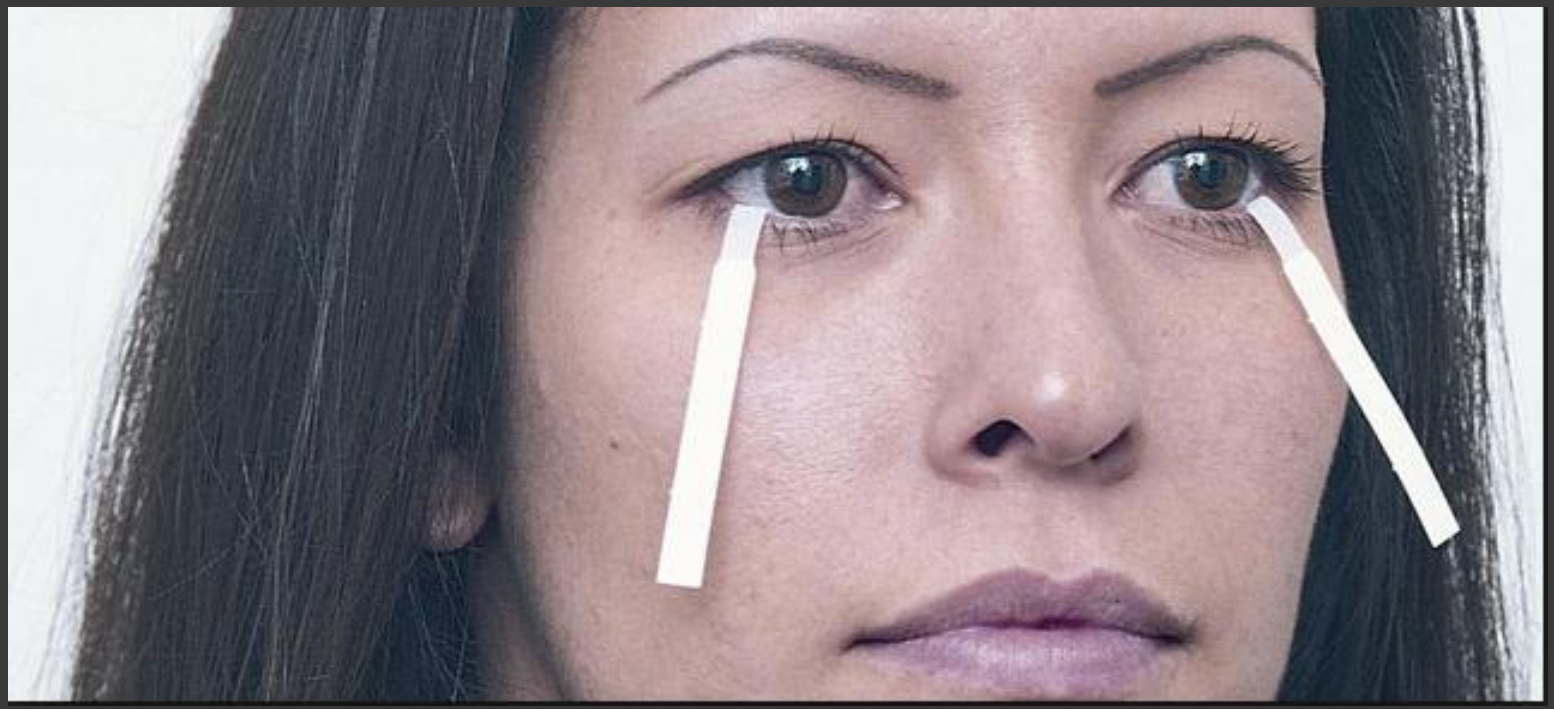
- RA
- Splenomegaly
- Neutropenia

Occurs in individuals with long-standing disease, high titers RF & nodules
increased frequency of infections

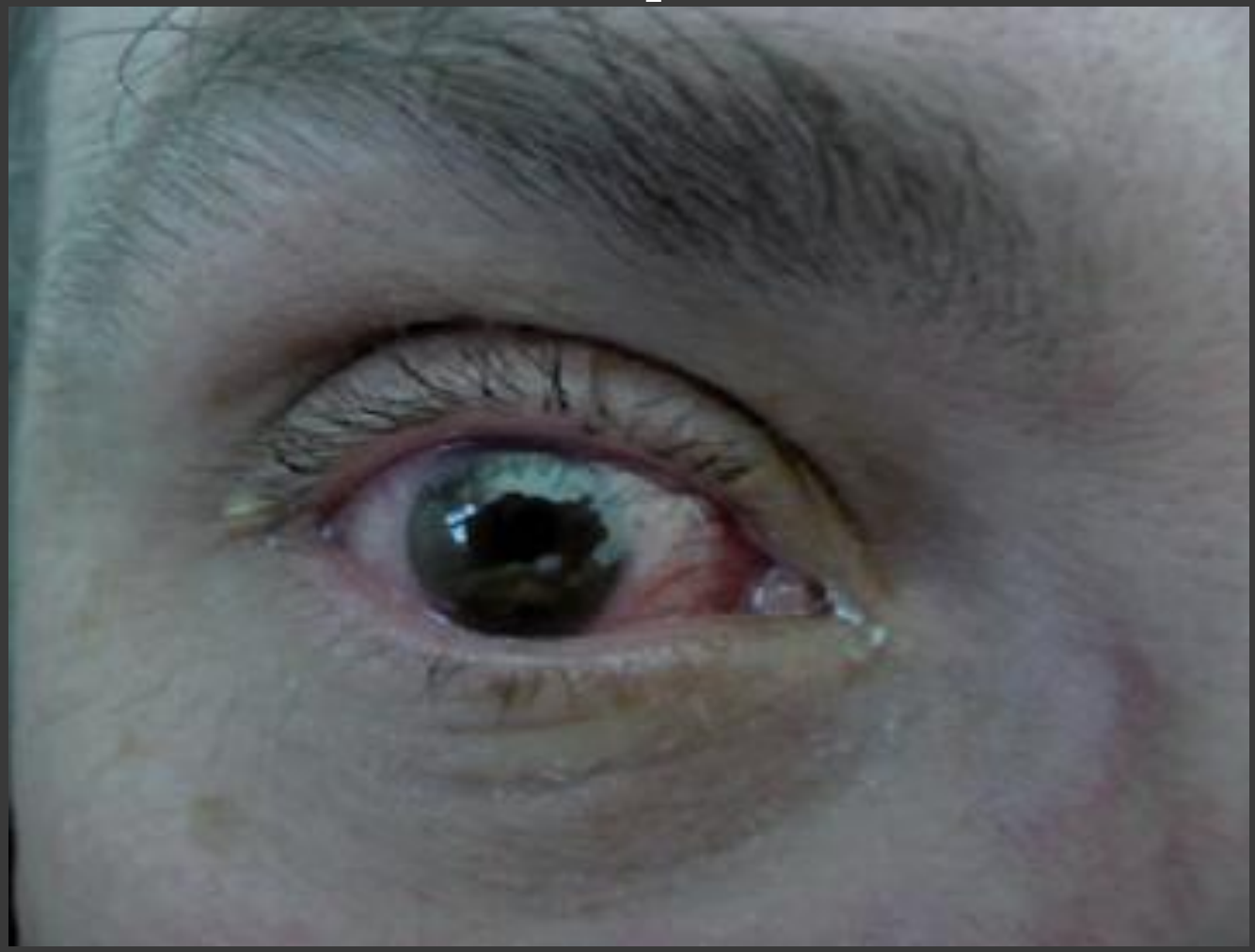
Keratoconjunctivitis sicca



Keratoconjunctivitis sicca



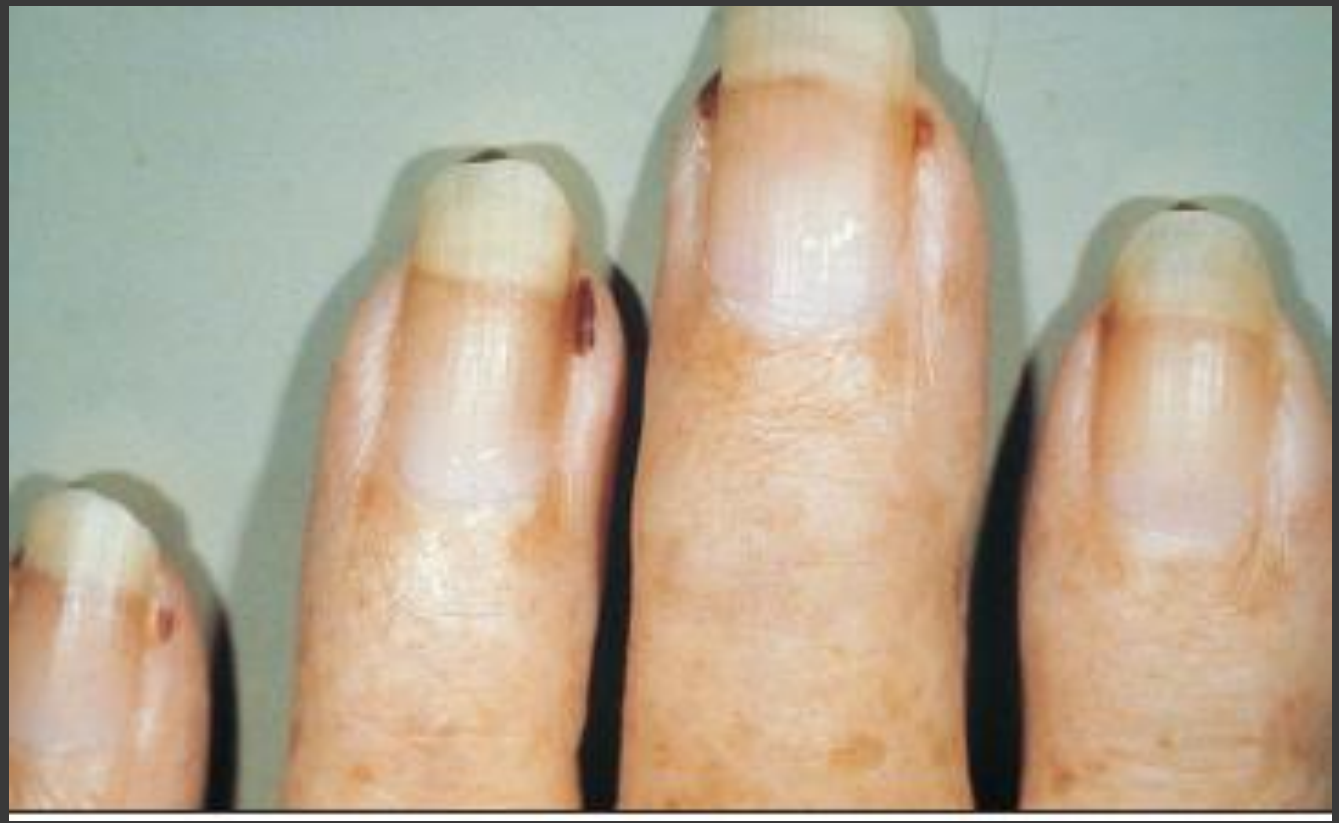
Scleritis/episcleritis



Scleromalacia

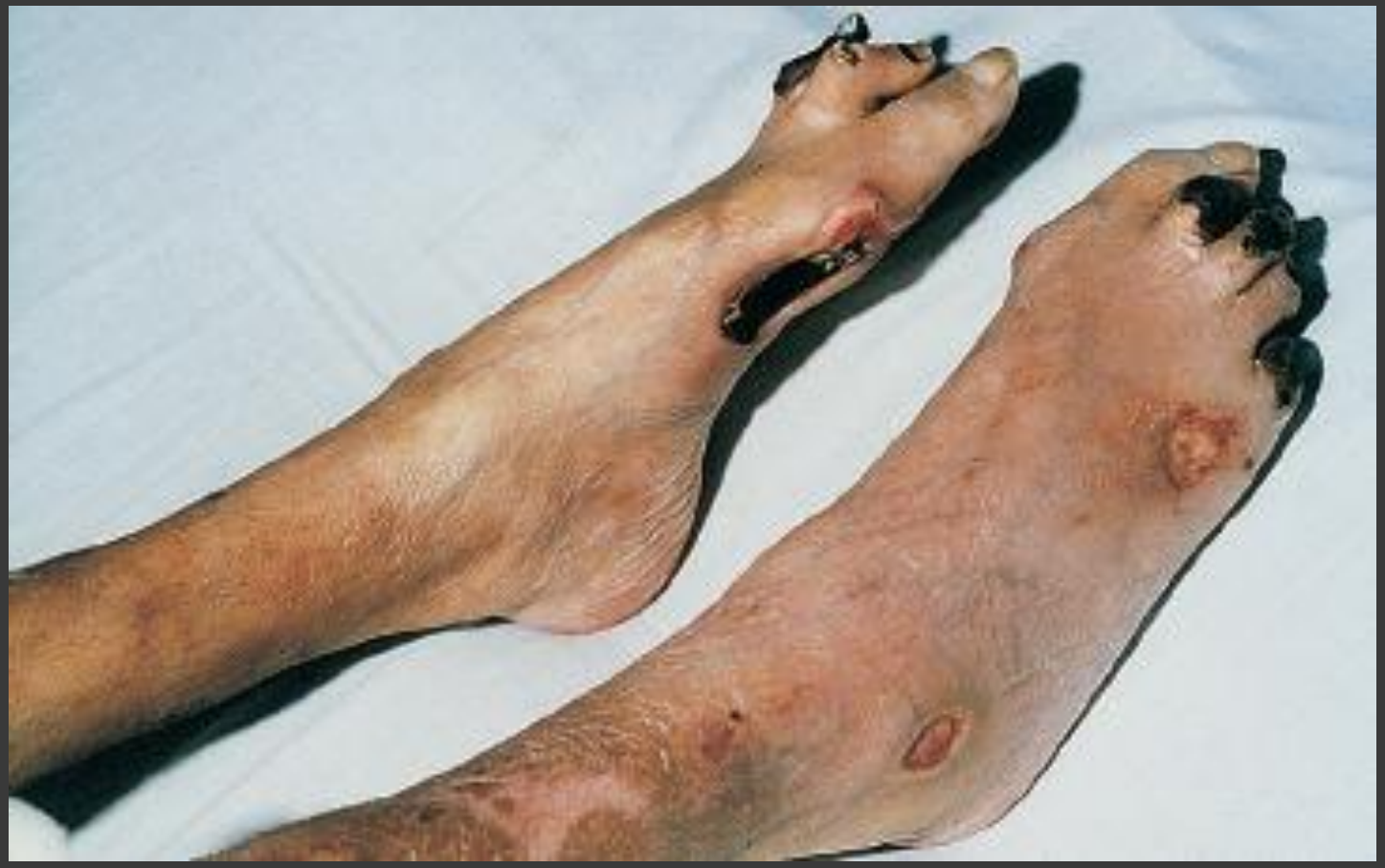
Risk of perforation of eyeball

Vasculitis

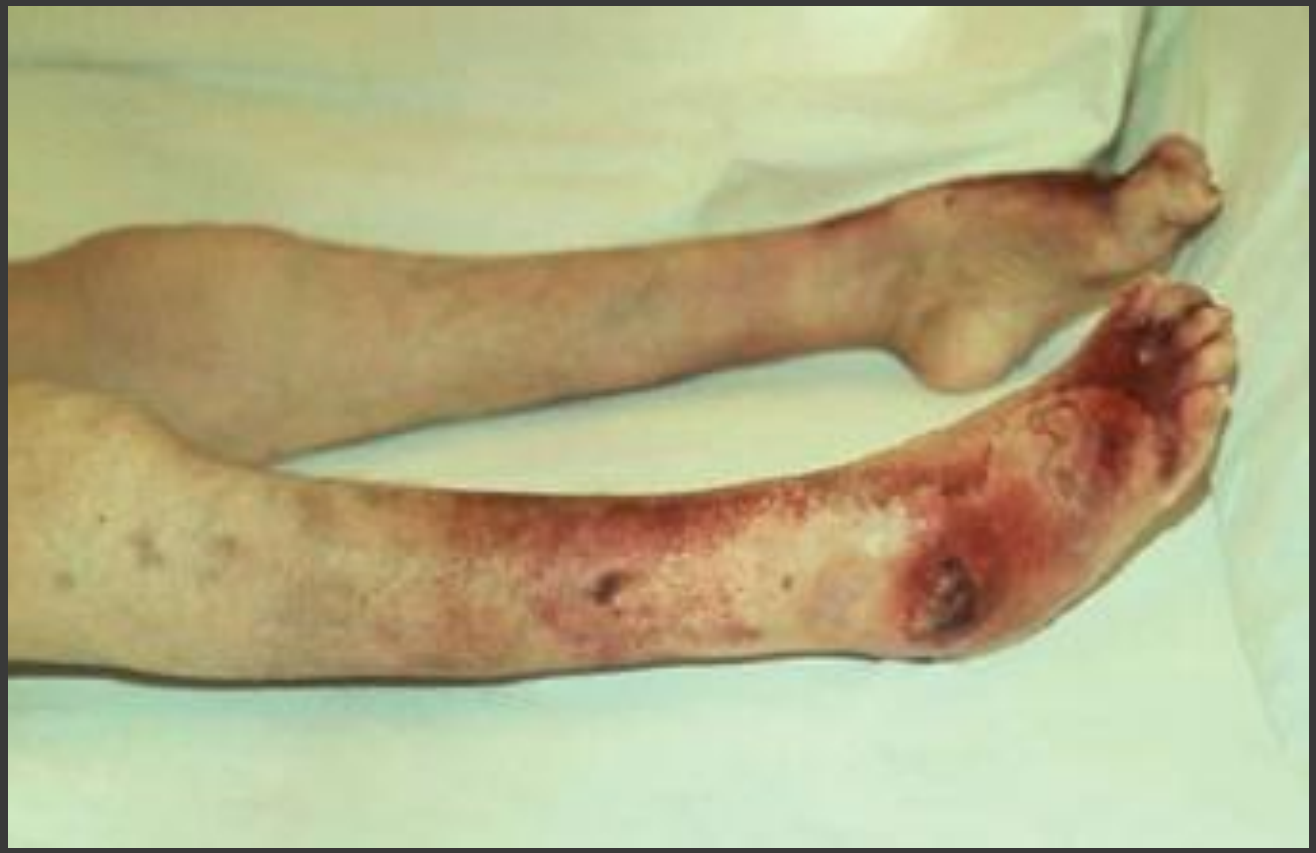


NOW RARE

Vasculitis

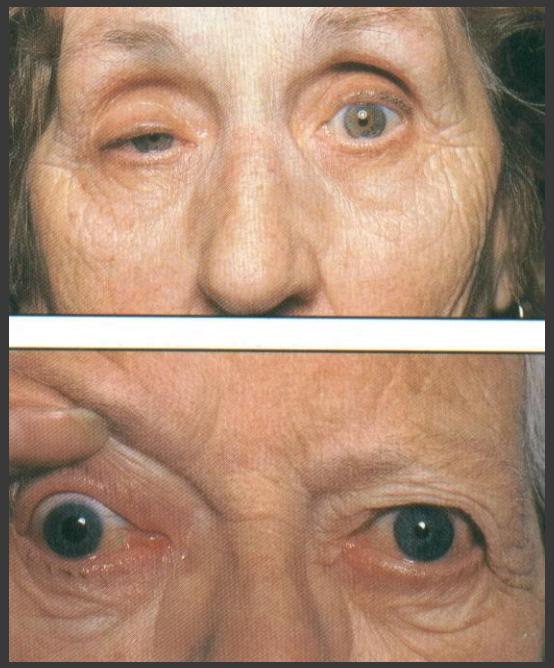


Vasculitis

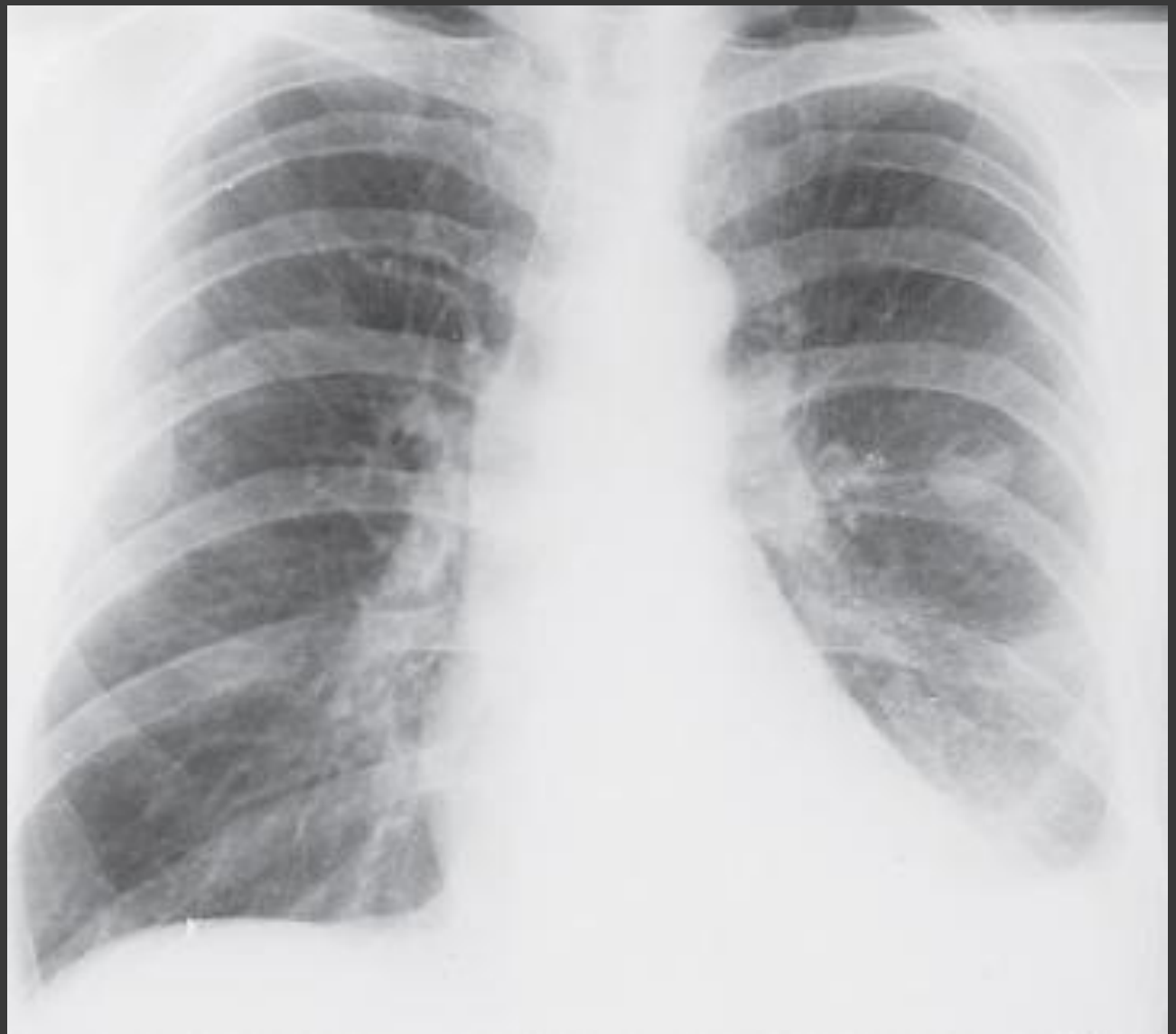


Third nerve palsy

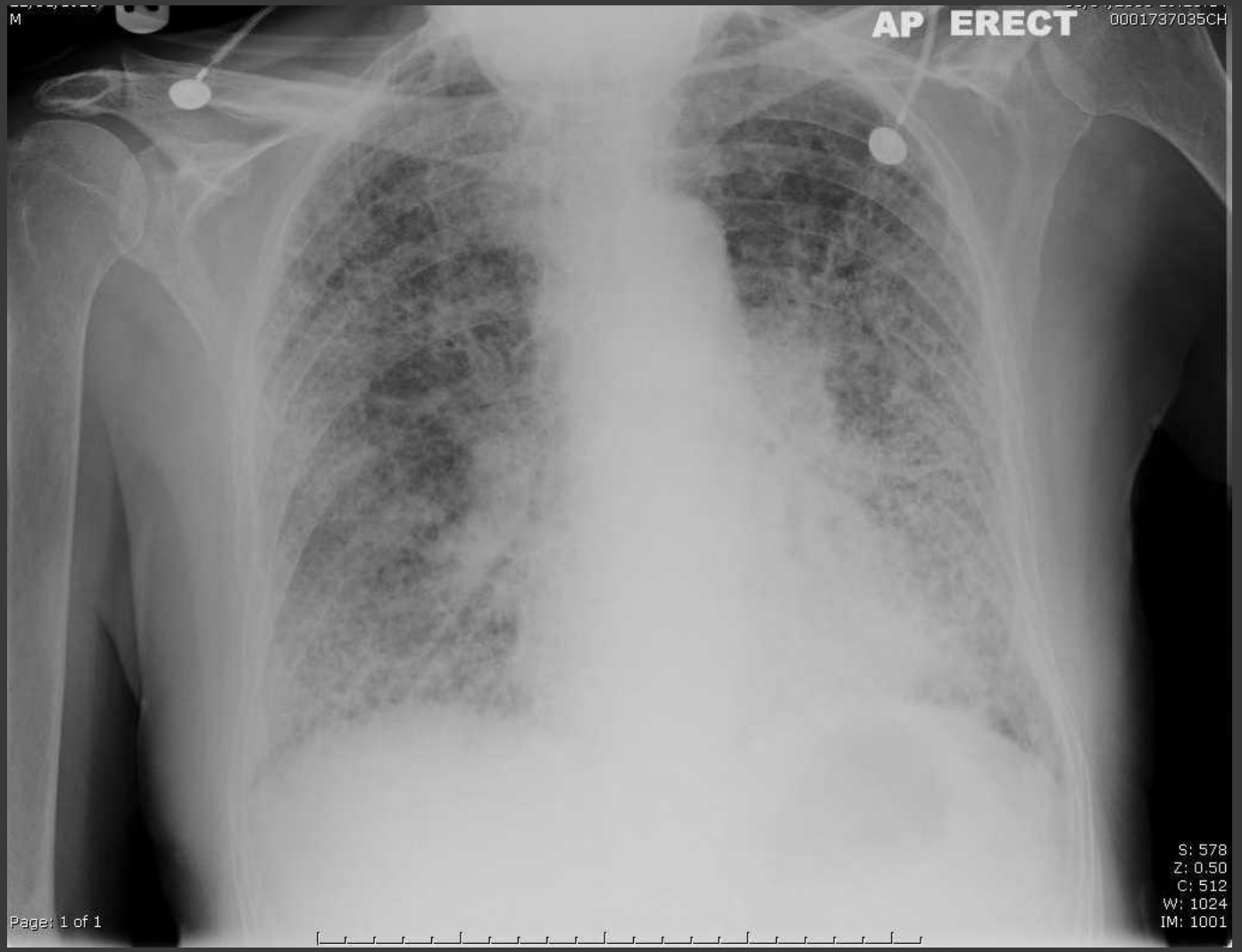
Part of mononeuritis multiplex



Nodules/Caplan’s

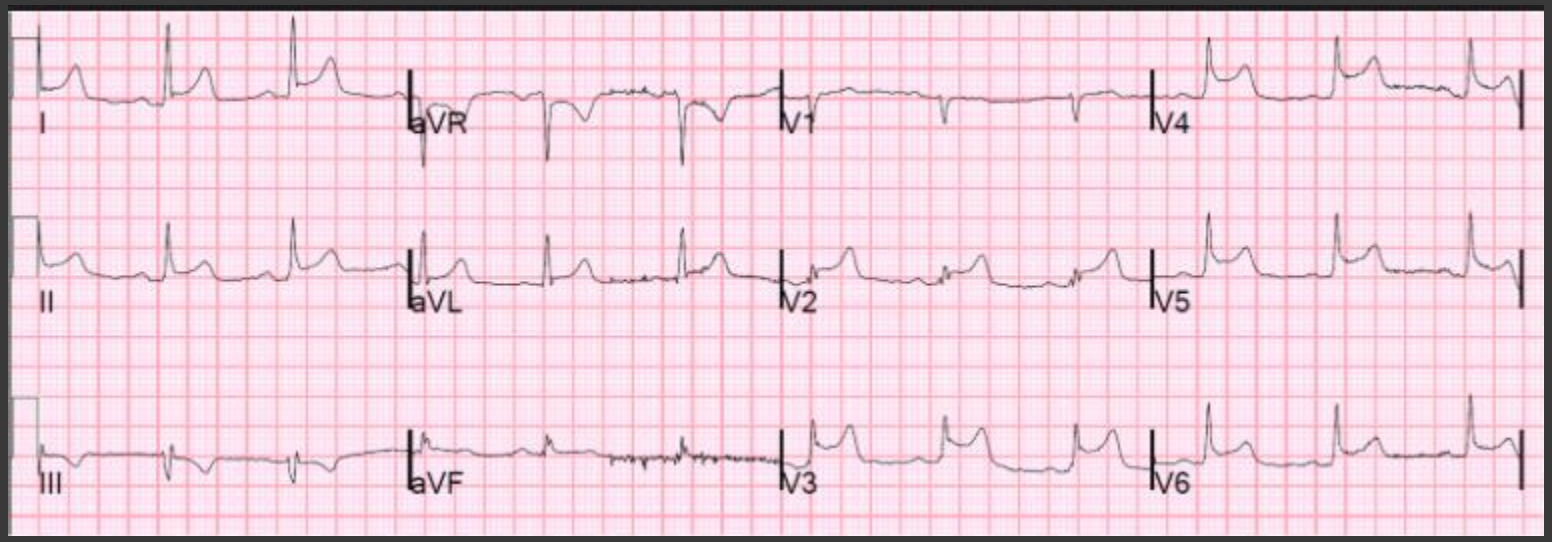


Iinterstitial lung disease



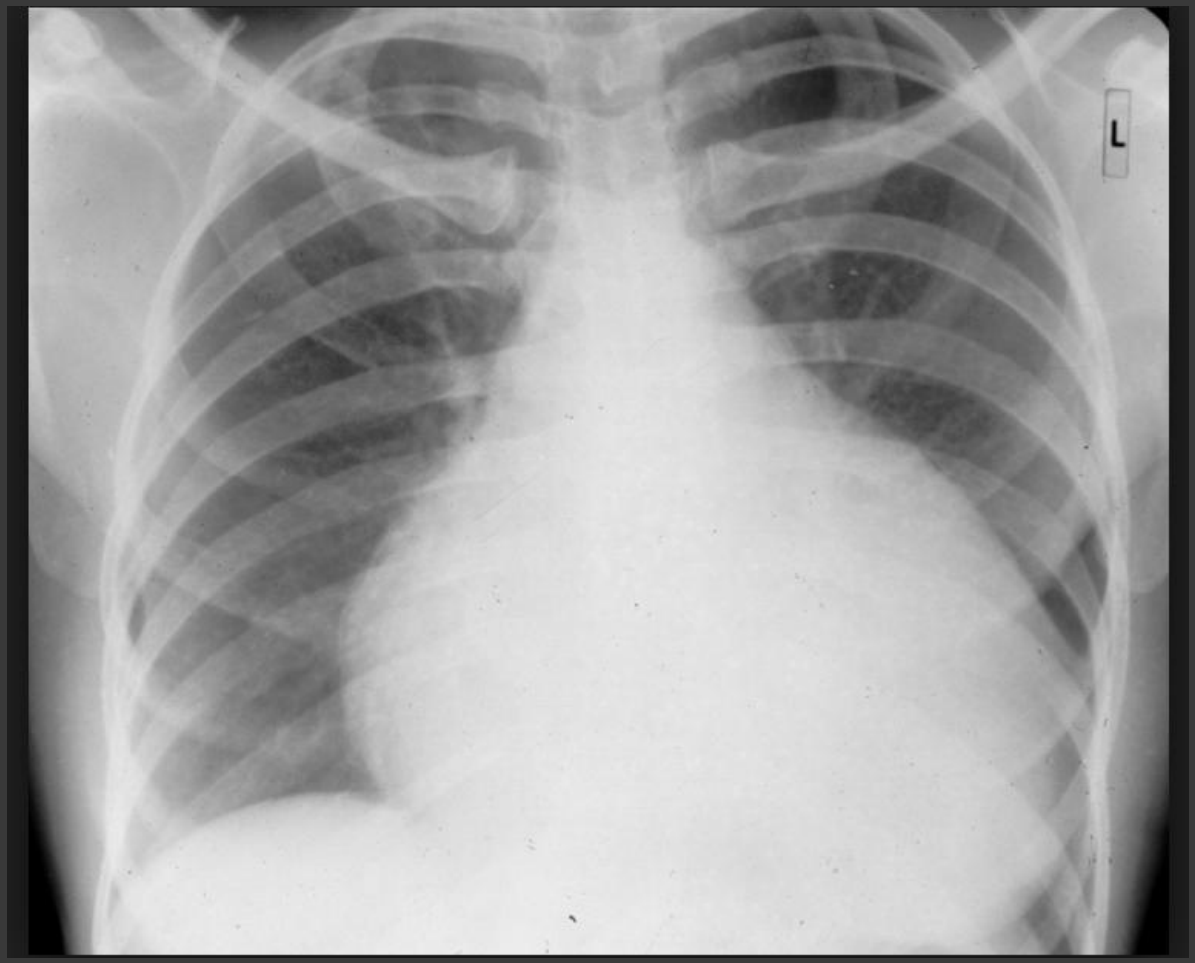
Restrictive lung defect

Pericarditis

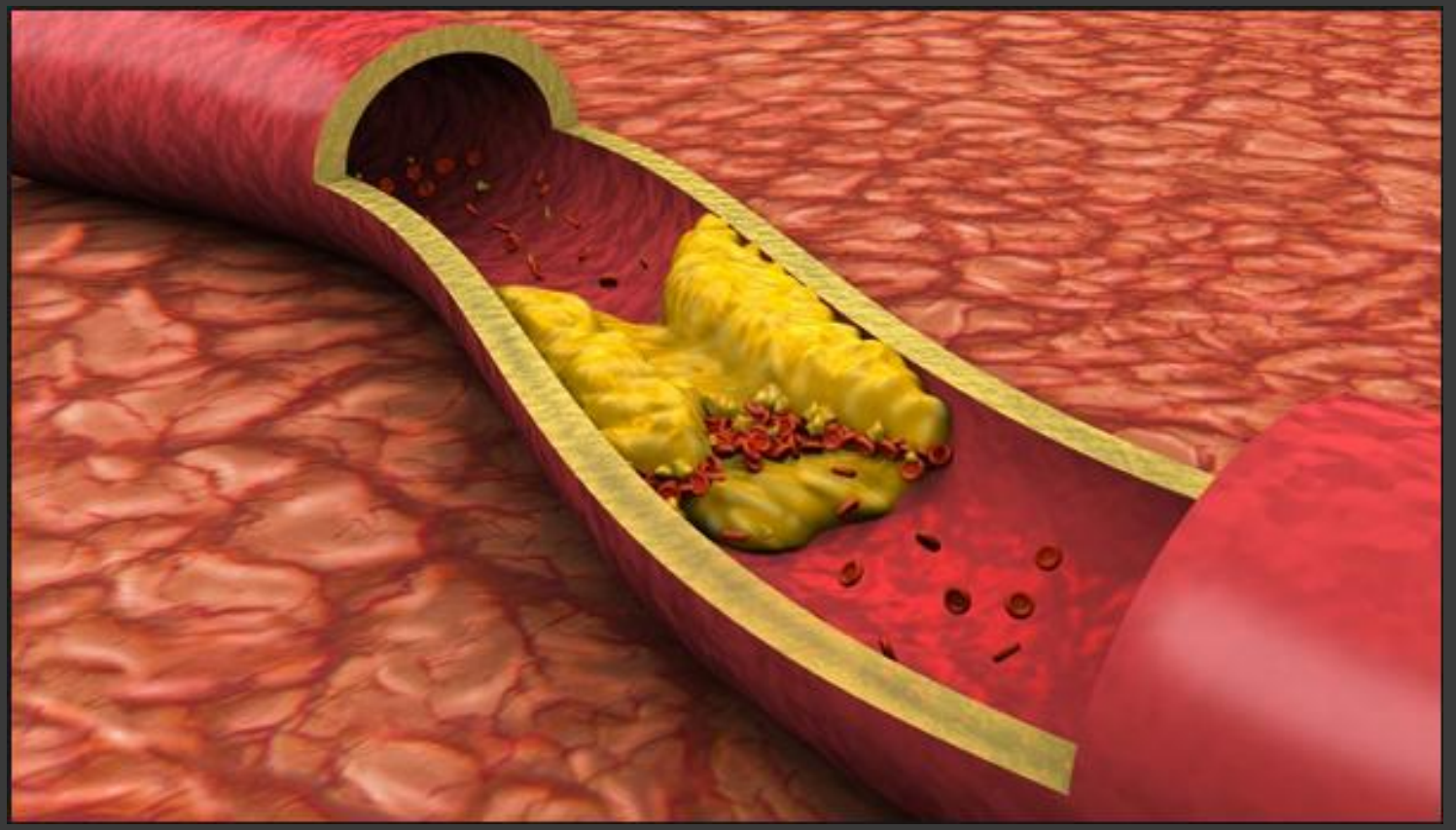


Sharp chest pain

Pericardial effusion

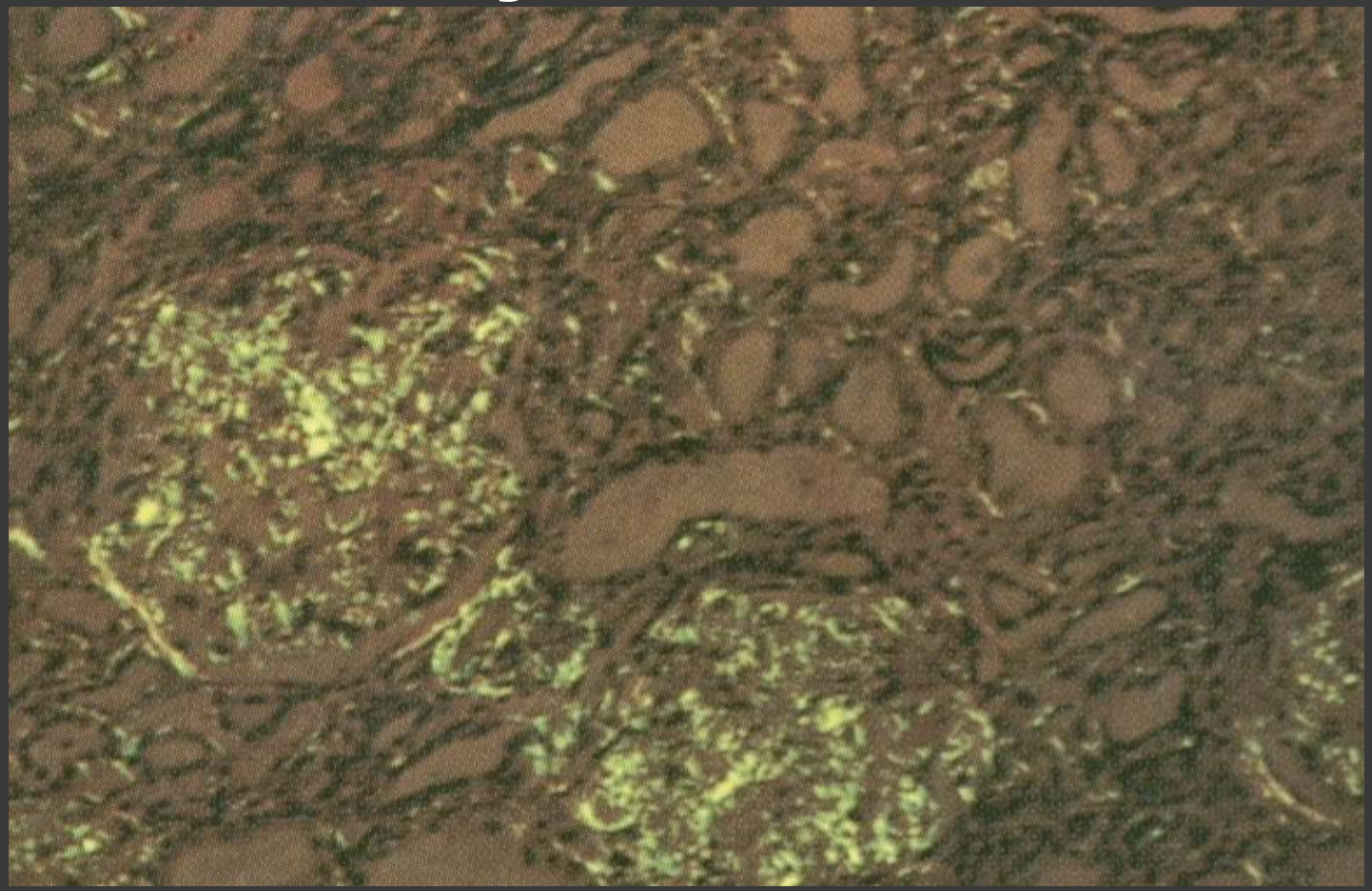


Atherosclerosis



CV disease is responsible for almost half of all deaths in RA

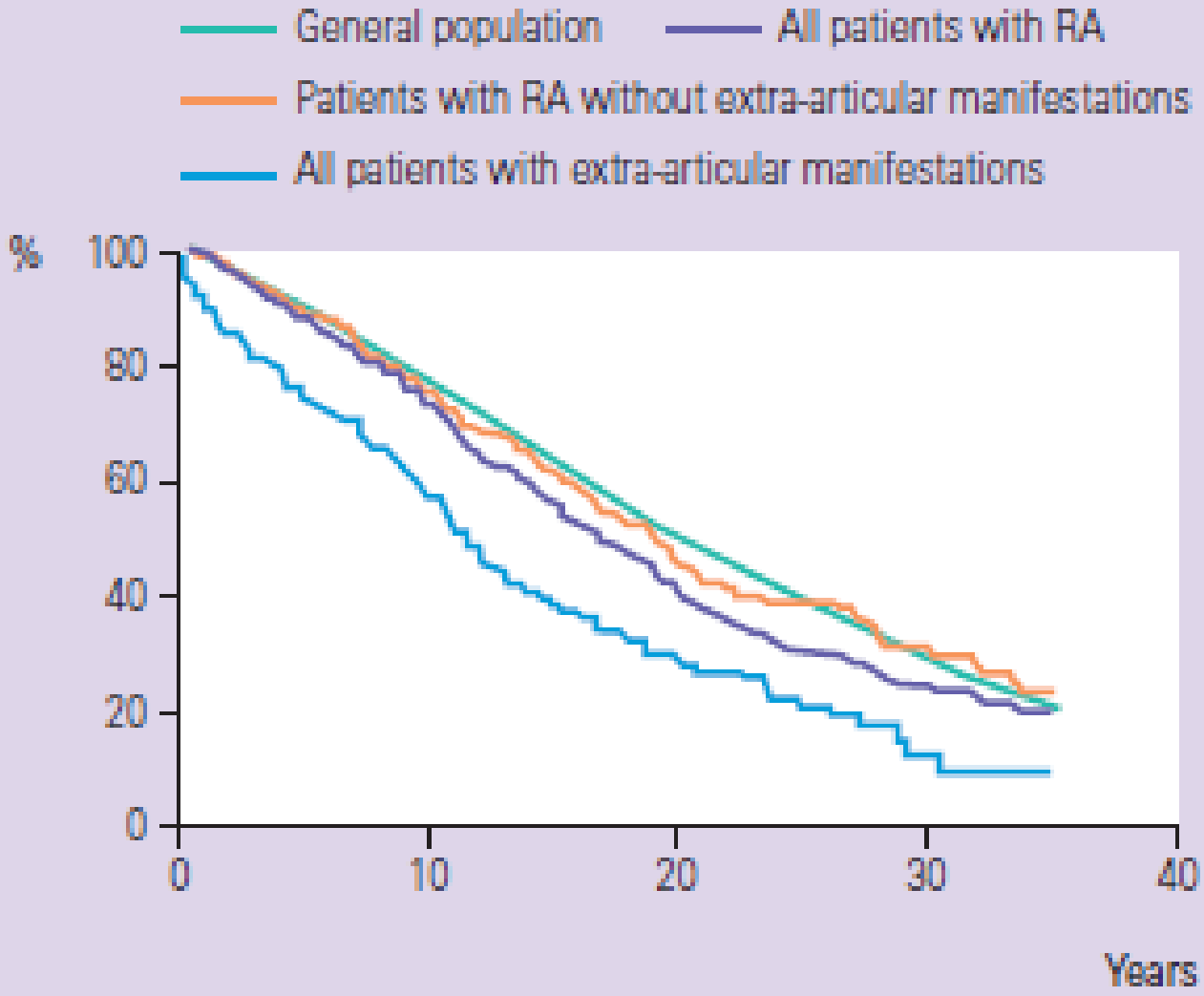
Amyloidodis



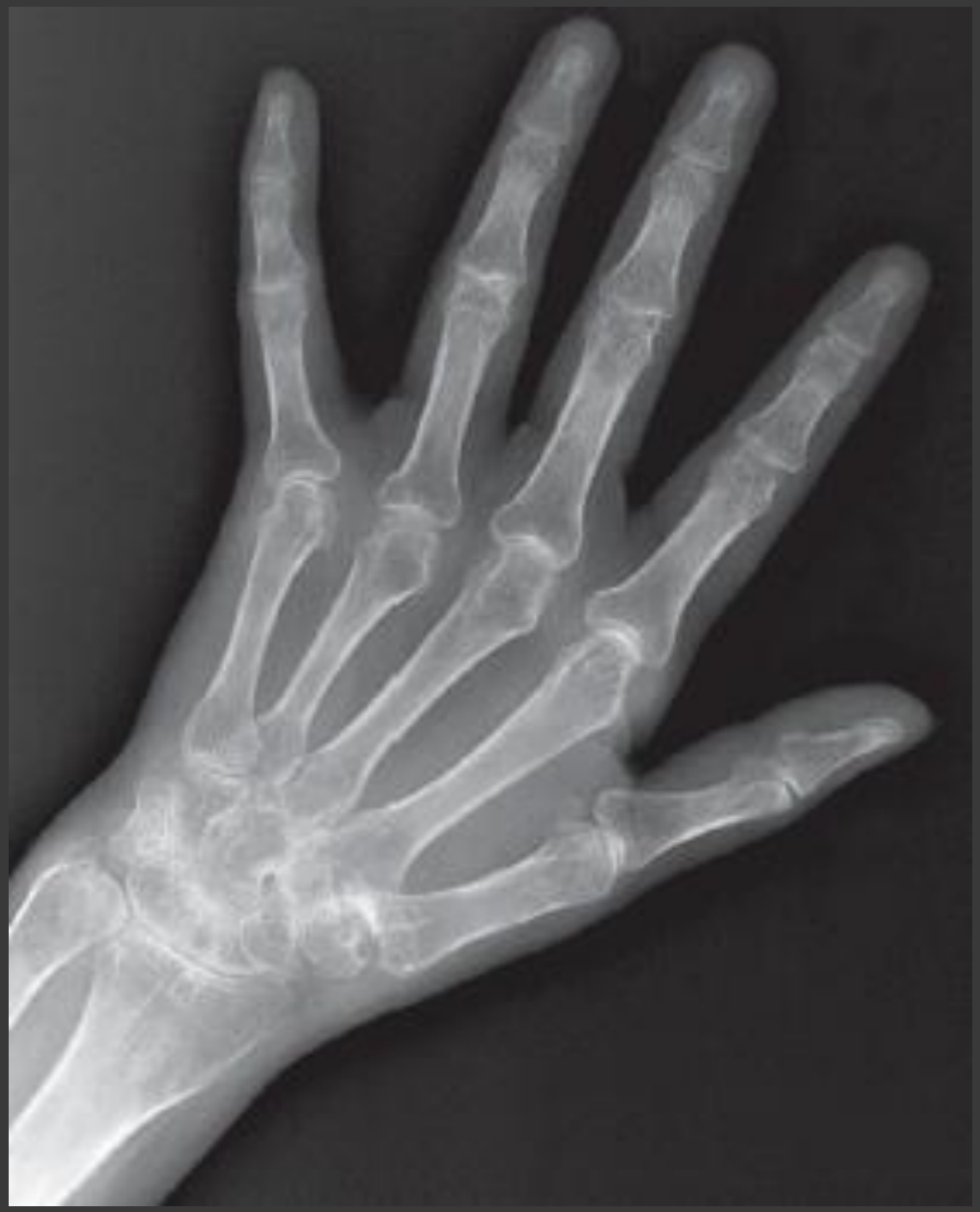
Suspect if proteinuria develops

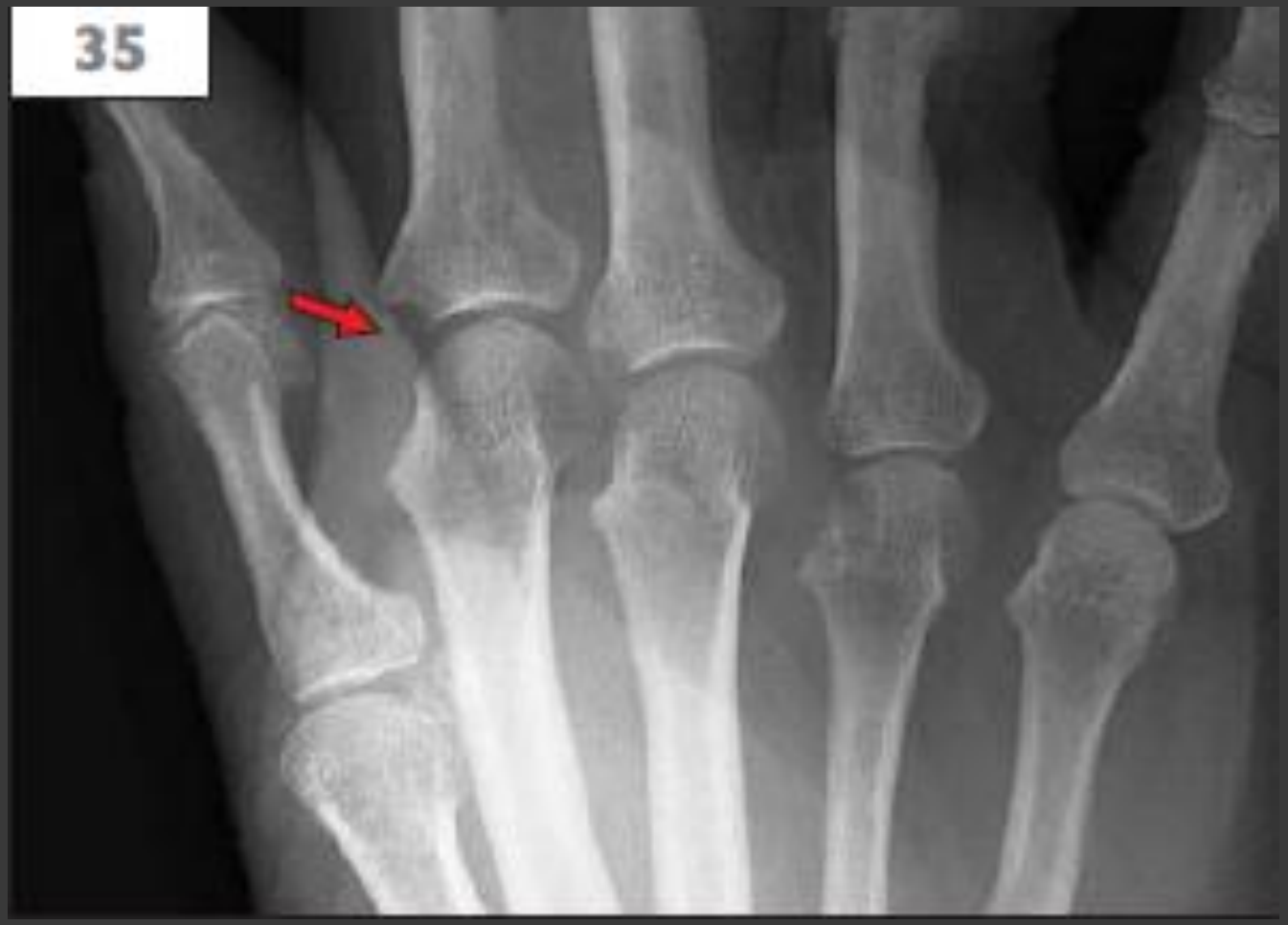
Survival in patients with extra-articular manifestations

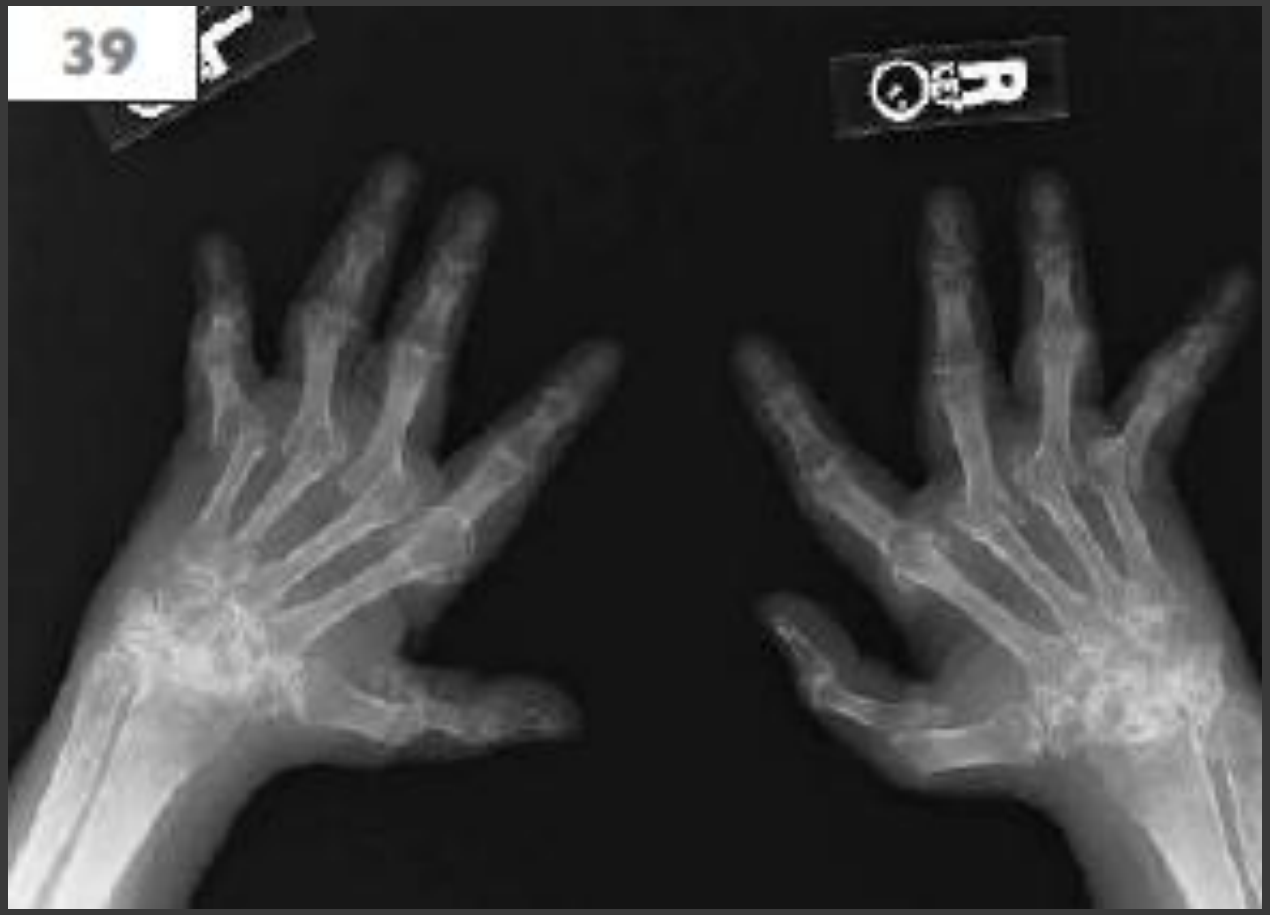
SURVIVAL OF PATIENTS WITH EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

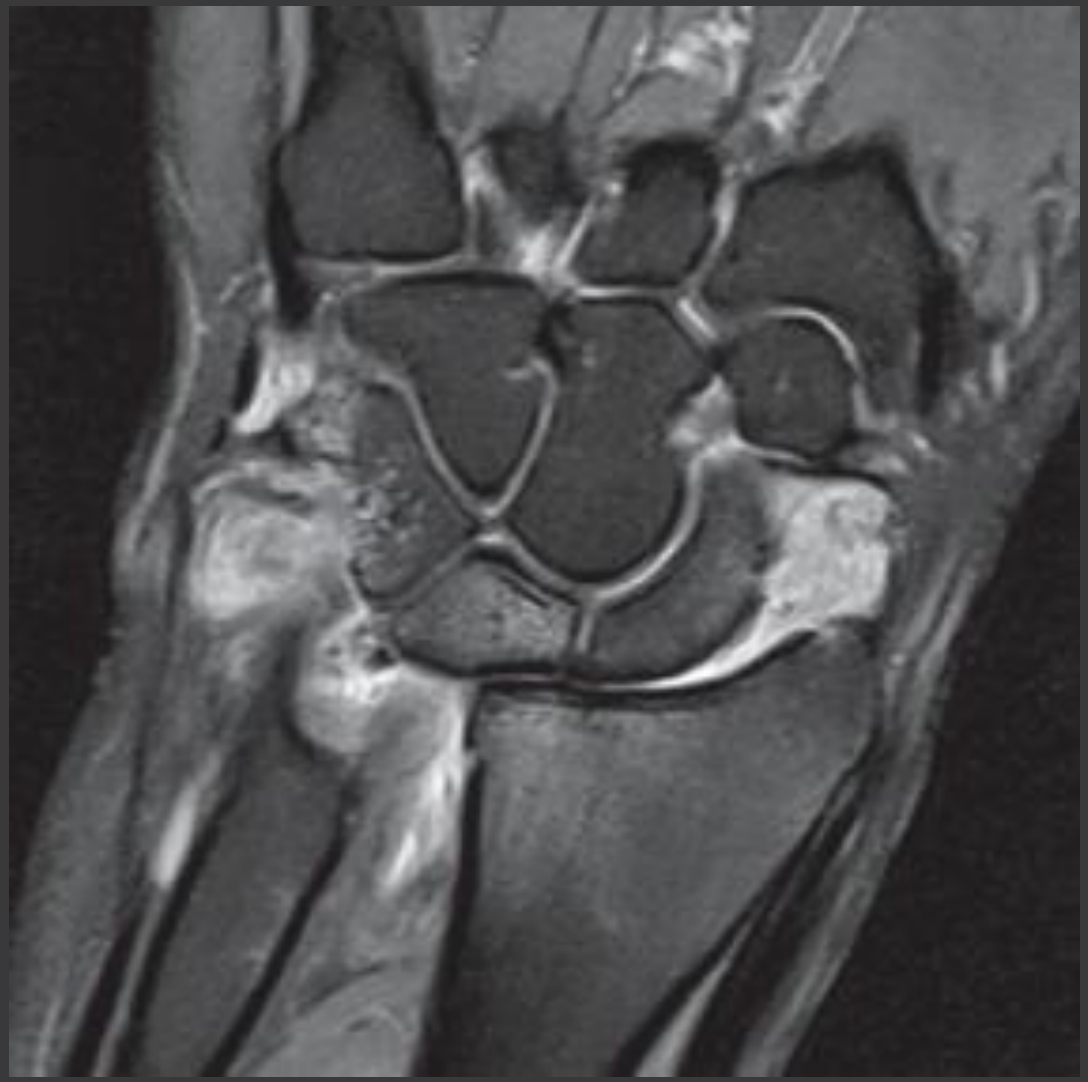


Radiological features




35


39



Treatment

Disease Modifying Drugs (DMARDs)

Disease-modifying antirheumatic drugs (DMARDs).

- These agents are characterised by their capacity to reduce or reverse:
  - Signs and symptoms
  - Disability
  - Impairment of quality of life
  - Inability to work
  - Progression of joint damage

Disease-modifying antirheumatic drugs (DMARDs).

- Over the last 15 years, care of patients with RA has improved considerably.

- New drugs with novel modes of action have led to improvements in signs and symptoms, as well as in long-term outcomes, including joint destruction and disability.

Two major classes DMARDs

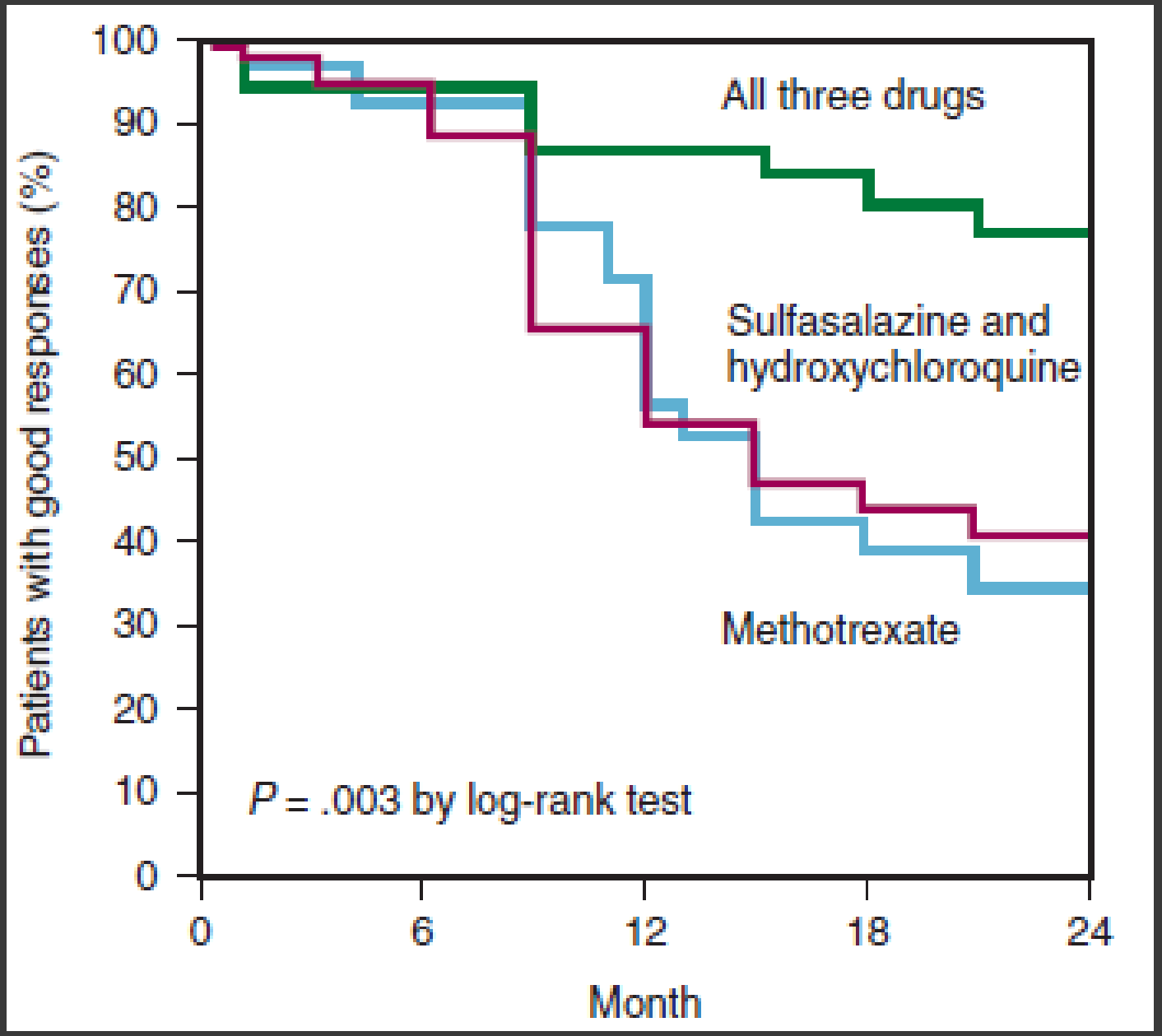
- Synthetic chemical compounds (sDMARDs)

- Biological agents (bDMARDs)

sDMARDs:

- Conventional (csDMARDs):
  - methotrexate (MTX)
  - sulfasalazine
  - Leflunomide
  - HCQ

- Targeted (tsDMARD):
  - tofacitinib


Patients with good responses (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
Month
All three drugs
Sulfasalazine and hydroxychloroquine
Methotrexate
P = .003 by log-rank test

bDMARDs

1) TNF inhibitors:
    1) (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab)

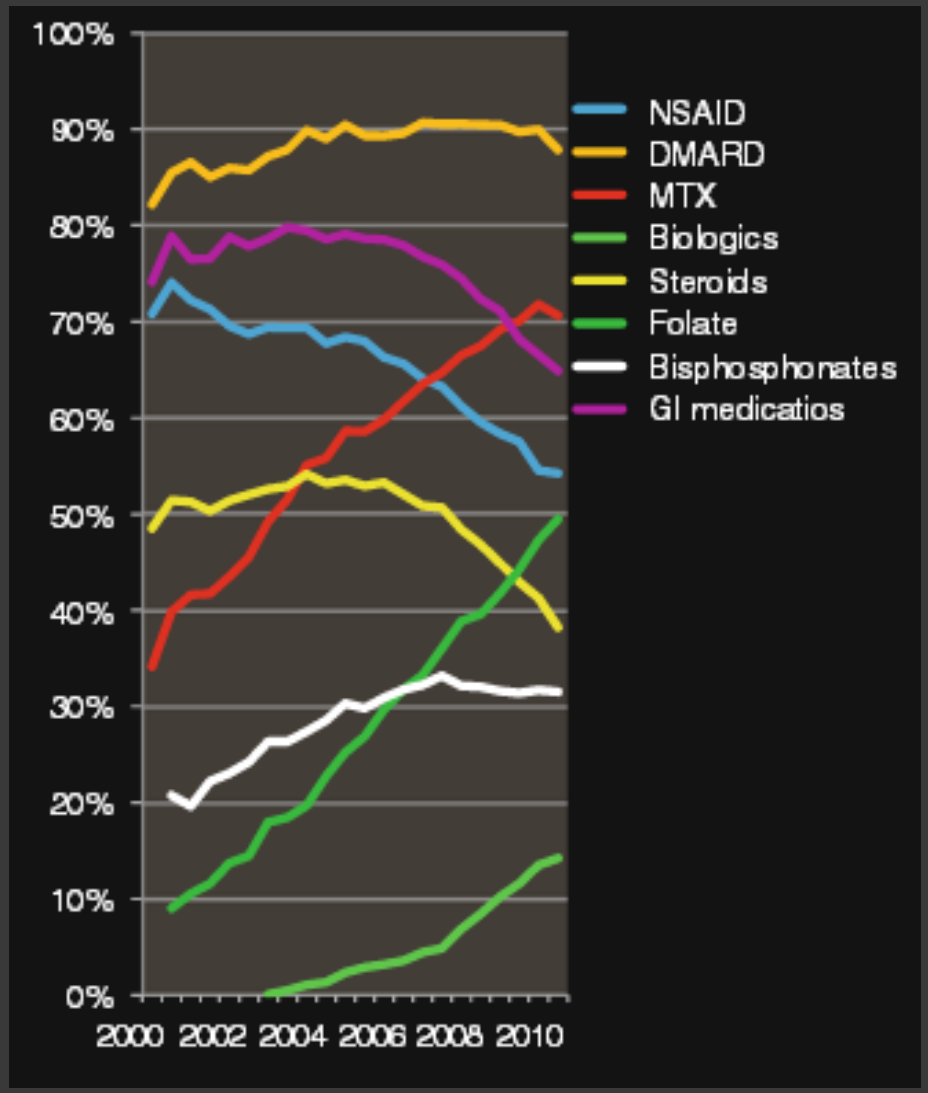
2) T cell costimulation inhibitor:
    1) abatacept

3) anti-B cell agent:
    1) rituximab

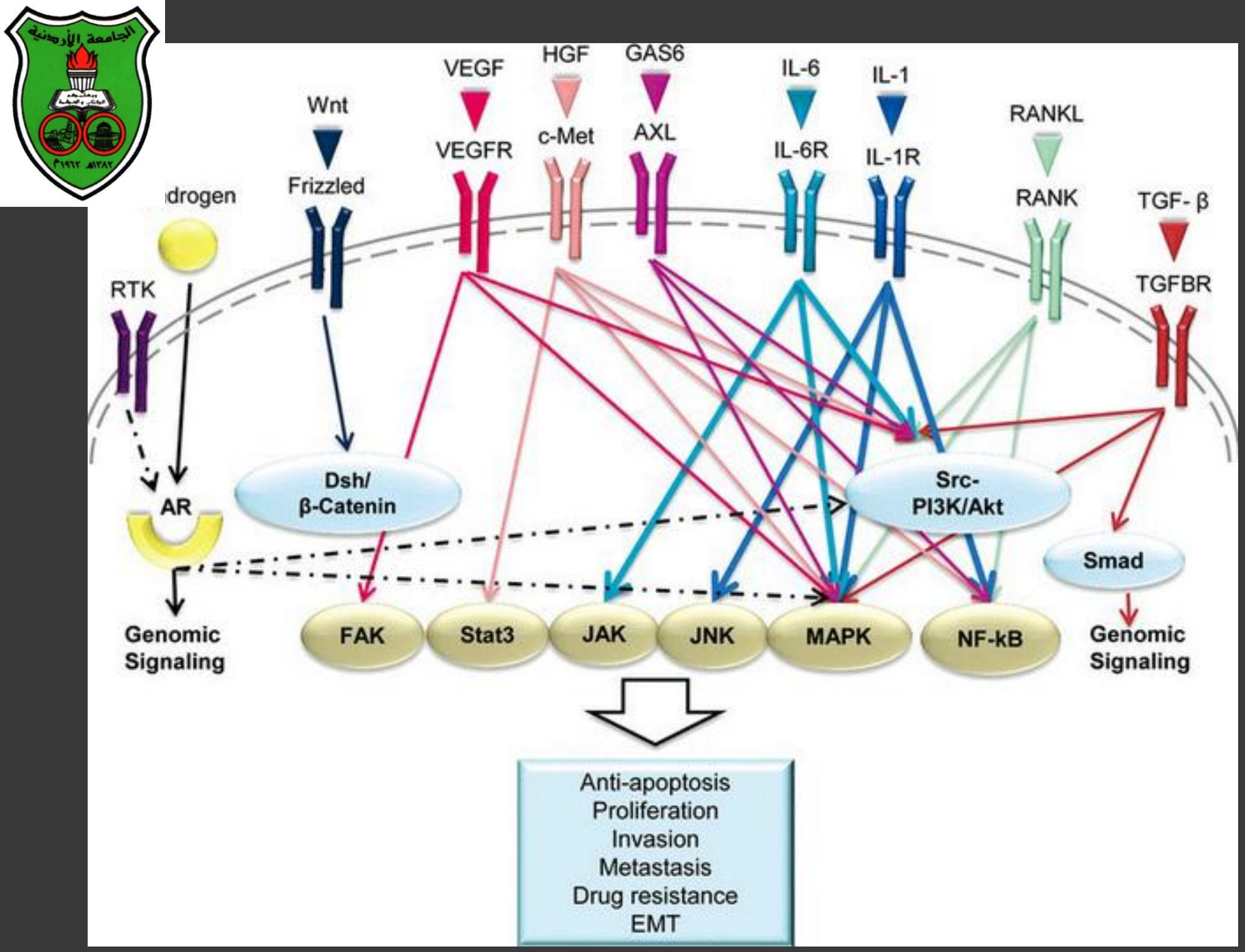
4) interleukin (IL)-6 receptor (IL-6R)-blocking monoclonal antibody:
    1) tocilizumab

5) biosimilars (bs)
    1) bs-infliximab

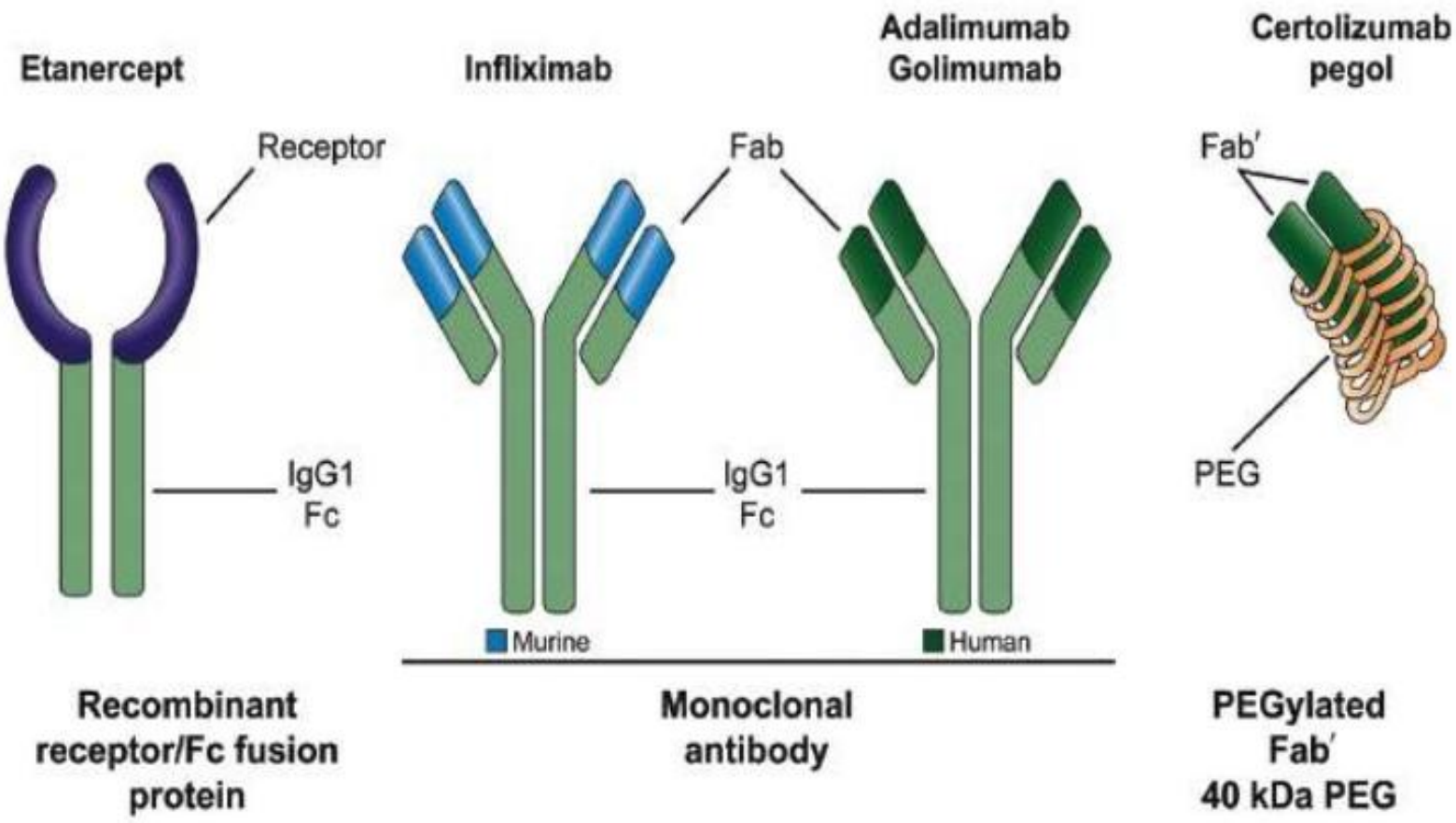
Changes of drugs from 2000-2011



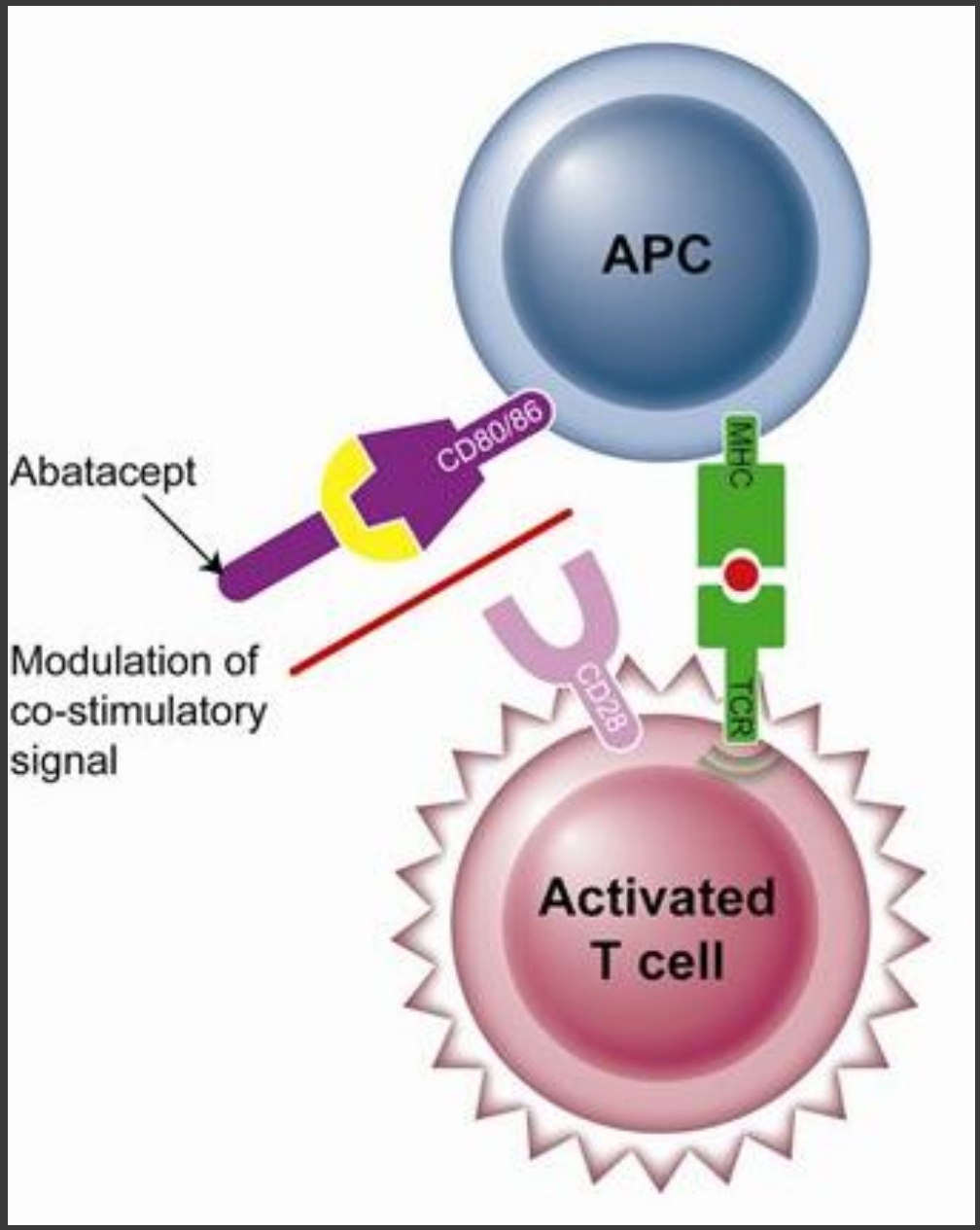
Yamanaka et al


VEGF
HGF
GAS6
IL-6
IL-1
Wnt
VEGFR
c-Met
AXL
IL-6R
IL-1R
RANKL
RANK
TGF- β
Frizzled
TGFBR
RTK
AR
Dsh/
β-Catenin
Src-
PI3K/Akt
Smad
Genomic
Signaling
FAK
Stat3
JAK
JNK
MAPK
NF-kB
Genomic
Signaling
Anti-apoptosis
Proliferation
Invasion
Metastasis
Drug resistance
EMT

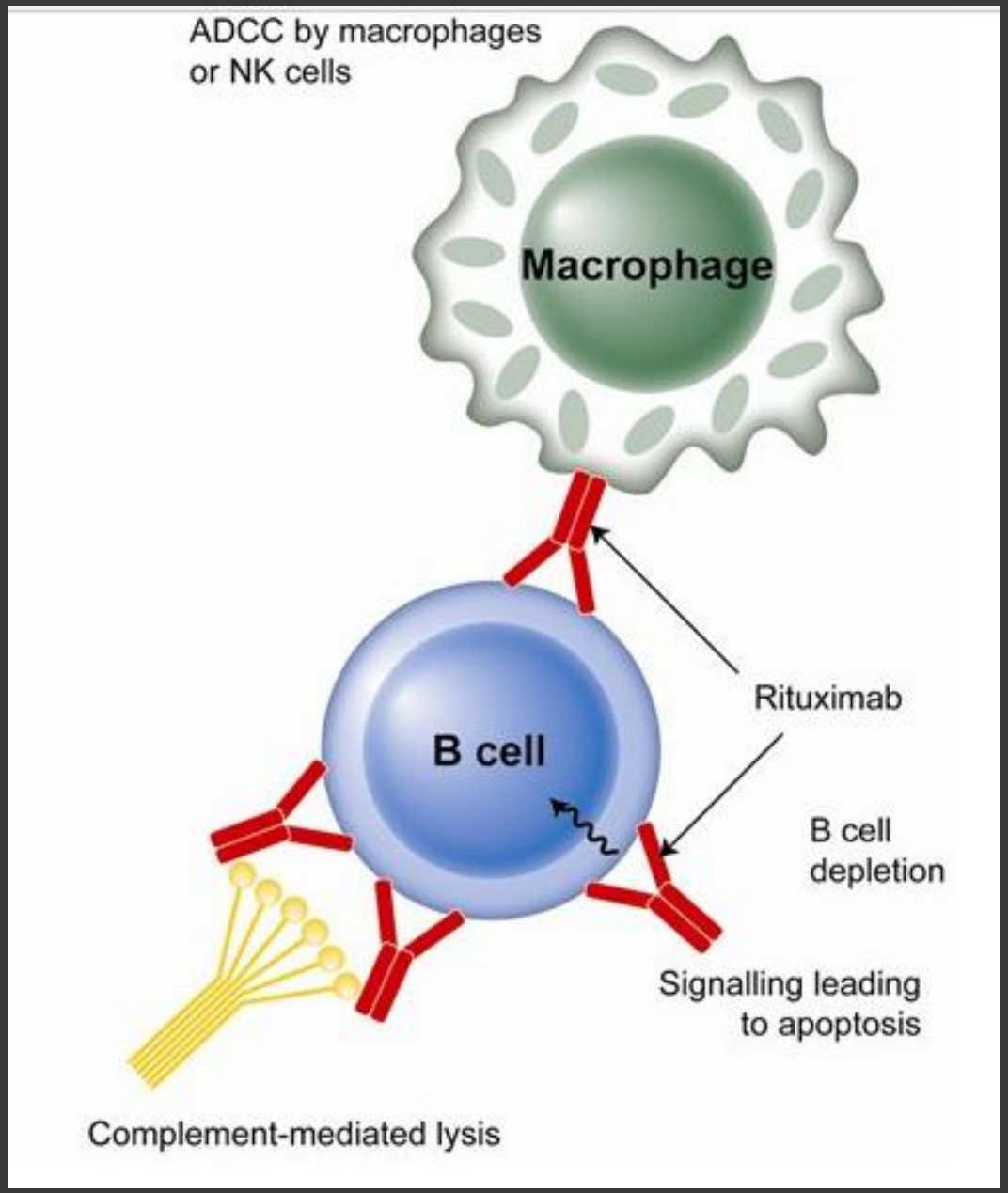
Anti-TNF antibodies



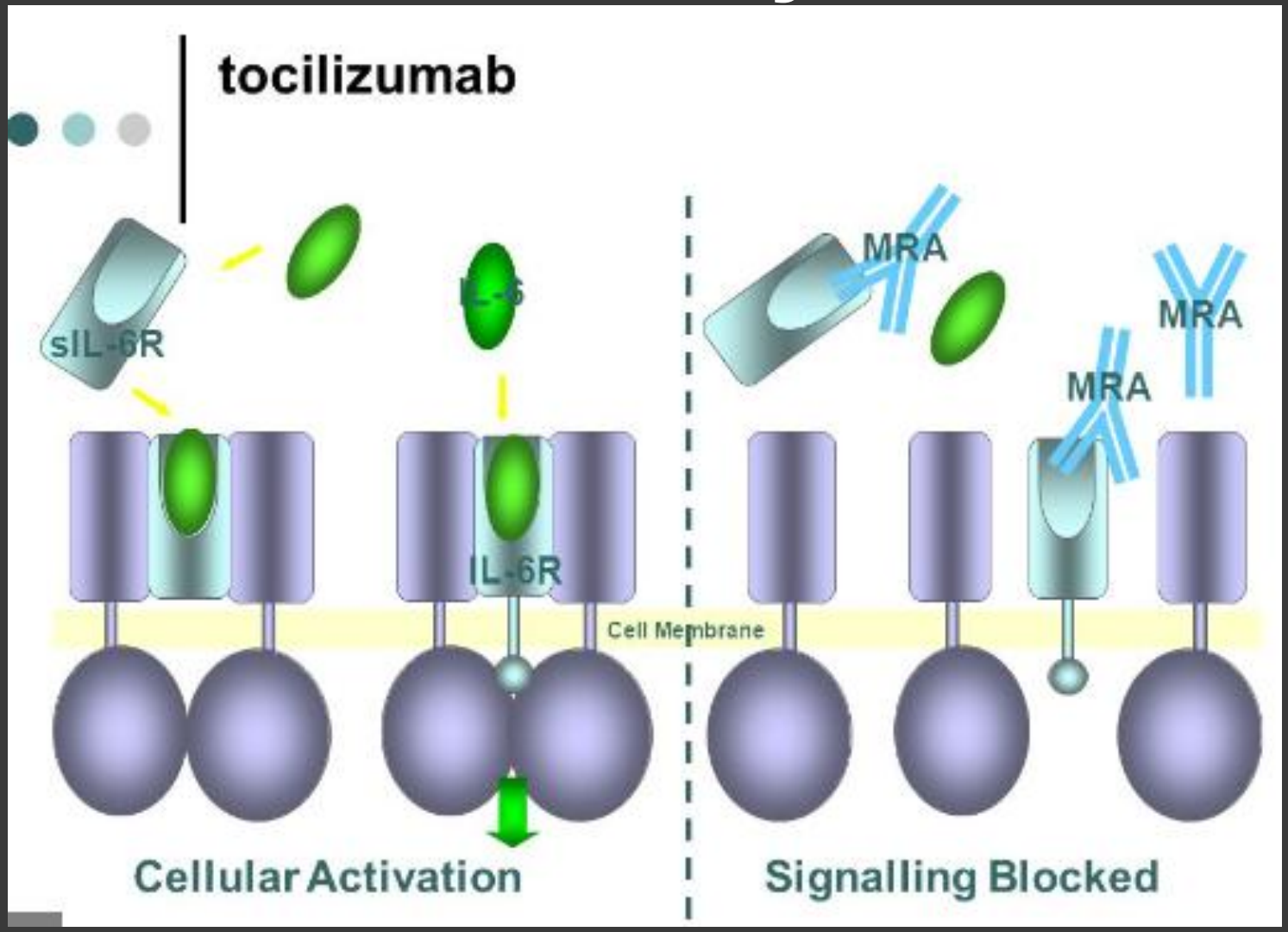
T cell costimulation inhibitor



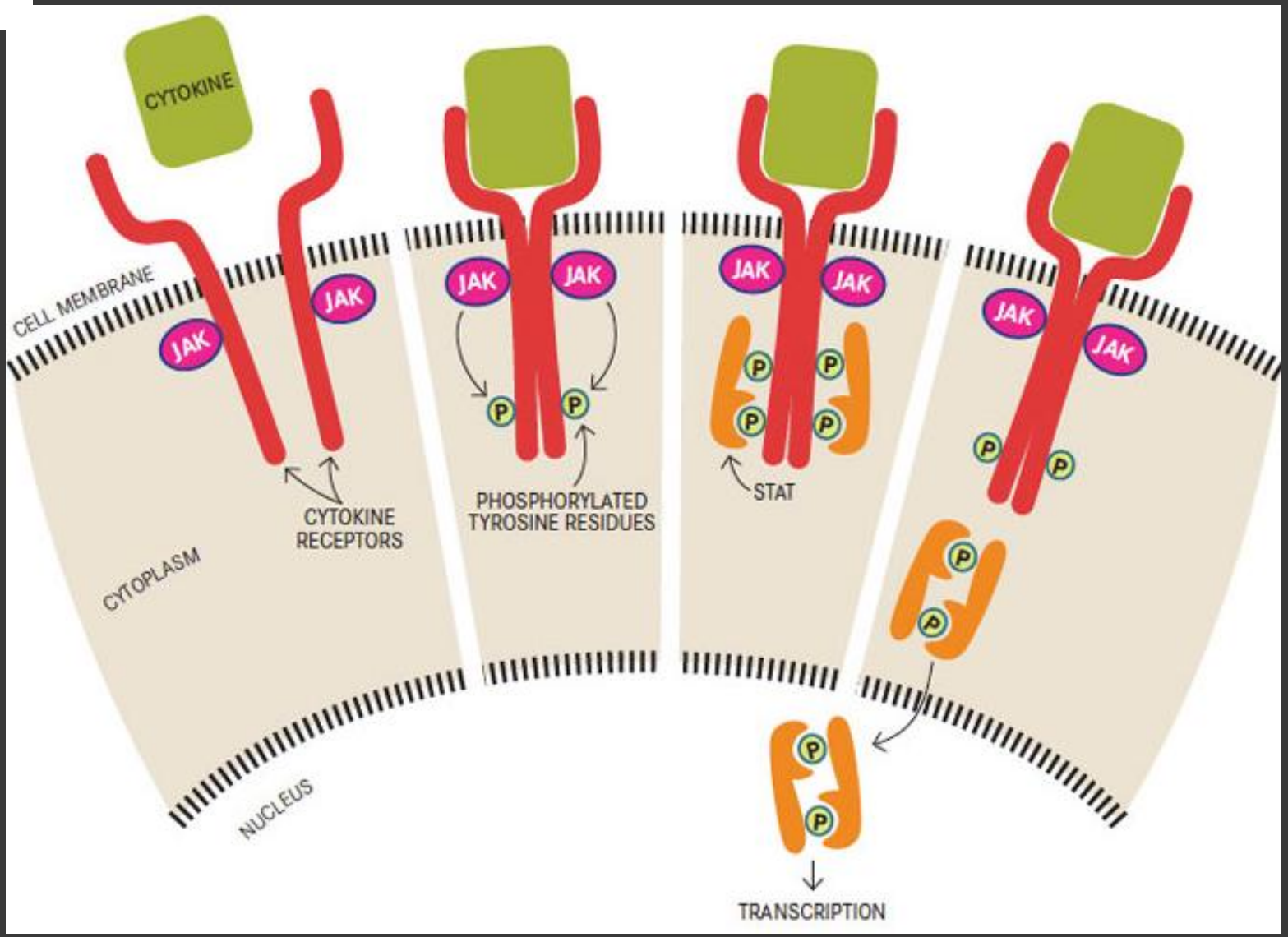
Anti-B cell antibodies



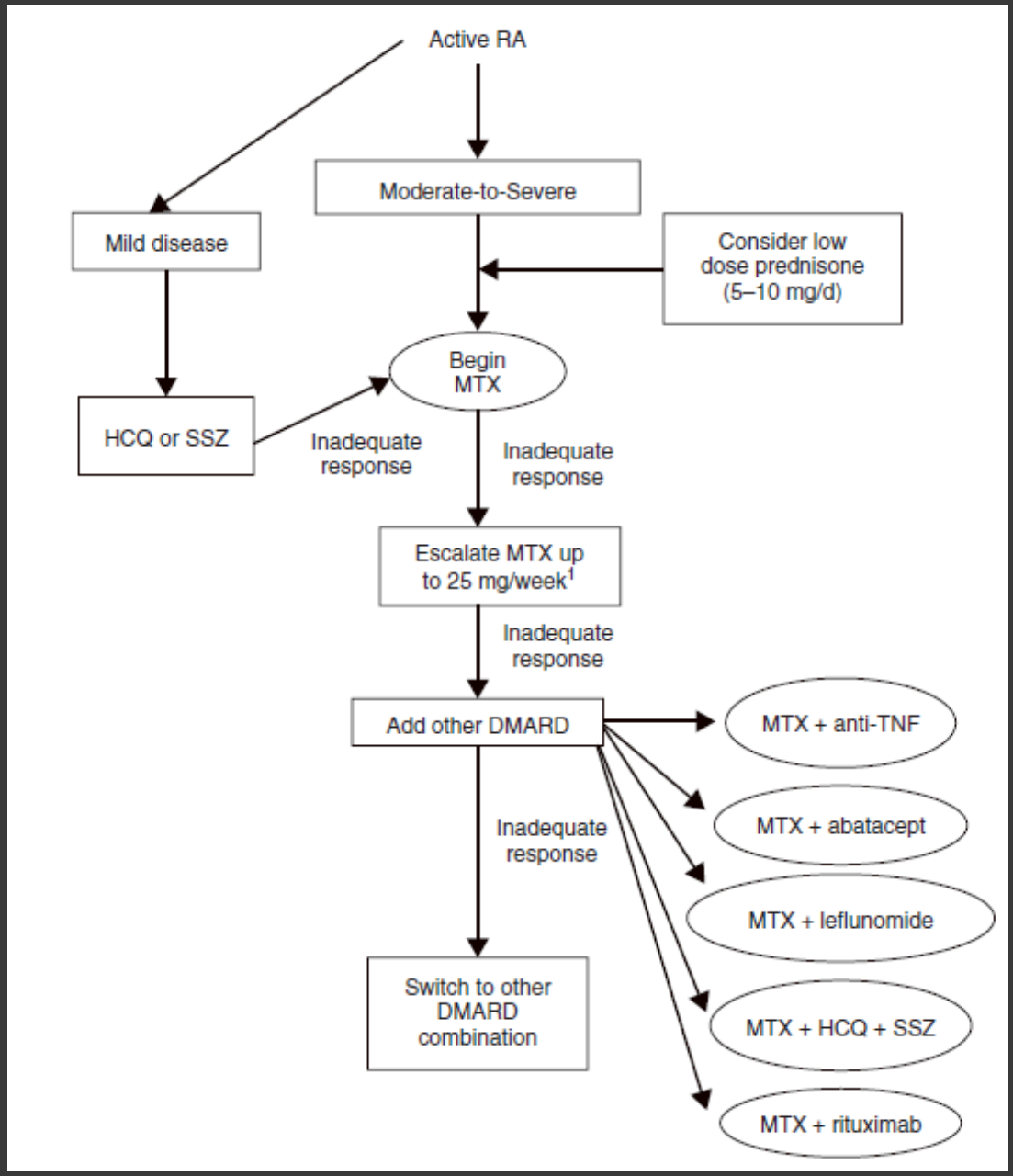
IL-6 receptor monoclonal antibody

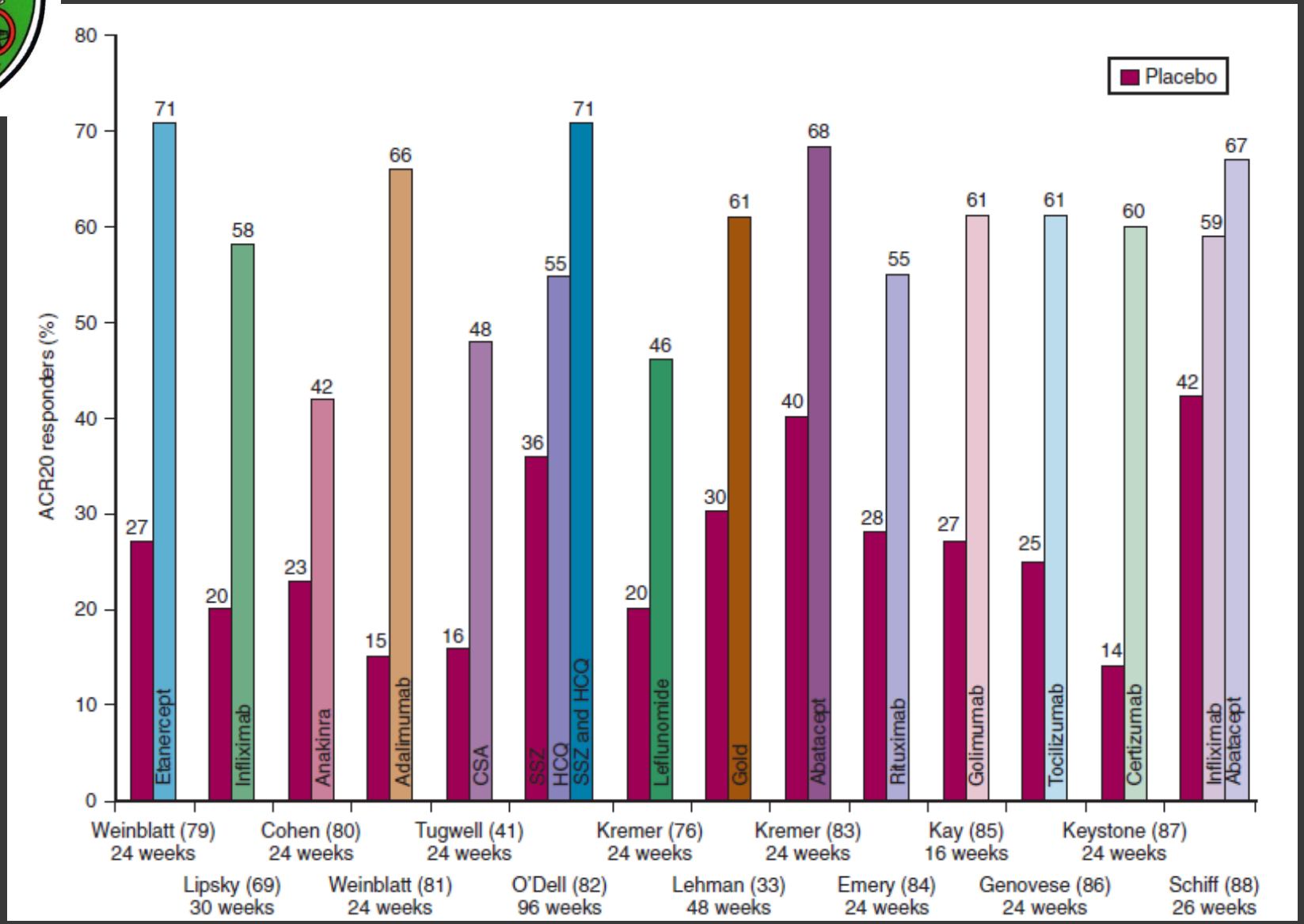


JAK inhibitors



- If therapy is delayed more than 2 years, functional impairment is likely to be permanent
- Start DMARD early
- Patients with aggressive disease resistant to monotherapy may benefit from combination therapy.
- If no response after 3-6 month change to biologic


Active RA
Moderate-to-Severe
Mild disease
Consider low dose prednisone (5–10 mg/d)
Begin MTX
HCQ or SSZ
Inadequate response
Inadequate response
Escalate MTX up to 25 mg/week[1]
Inadequate response
Add other DMARD
MTX + anti-TNF
MTX + abatacept
MTX + leflunomide
MTX + HCQ + SSZ
MTX + rituximab
Inadequate response
Switch to other DMARD combination


ACR20 responders (%)
Placebo
Etanercept
Infliximab
Anakinra
Adalimumab
CSA
SSZ
HCQ
SSZ and HCQ
Leflunomide
Gold
Abatacept
Rituximab
Golimumab
Tocilizumab
Certizumab
Infliximab
Abatacept
Weinblatt (79) 24 weeks
Lipsky (69) 30 weeks
Cohen (80) 24 weeks
Weinblatt (81) 24 weeks
Tugwell (41) 24 weeks
O'Dell (82) 96 weeks
Kremer (76) 24 weeks
Lehman (33) 48 weeks
Kremer (83) 24 weeks
Emery (84) 24 weeks
Kay (85) 16 weeks
Genovese (86) 24 weeks
Keystone (87) 24 weeks
Schiff (88) 26 weeks

Any questions?