Rheumatoid arthritis

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Overview: Rheumatoid arthritis

- Epidemiology
- Pathology
- Clinical picture
- Differential diagnosis
- Burden of disease
- Treatment
- Conclusions

What is rheumatoid arthritis (RA) ?

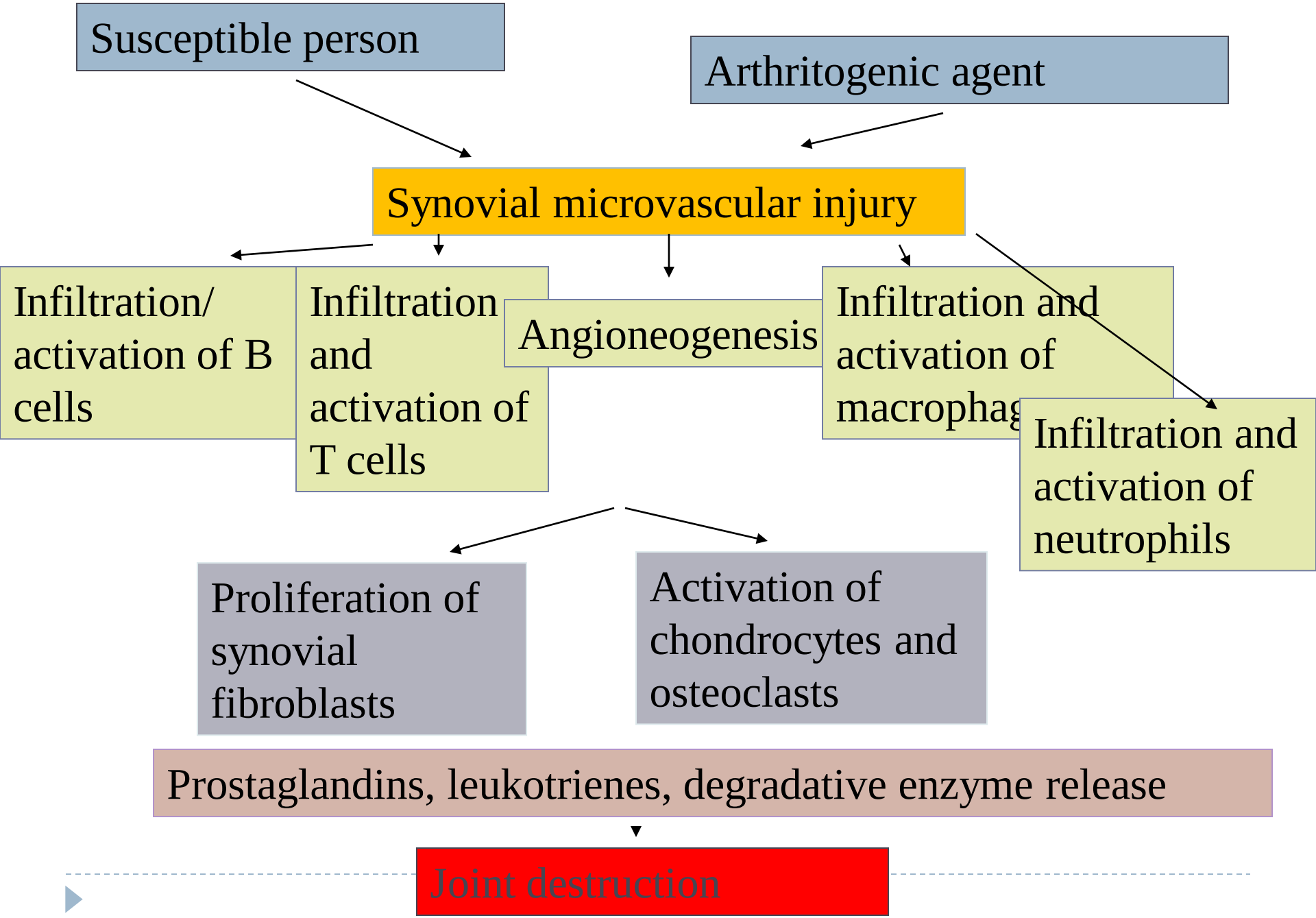
- Chronic, systemic, inflammatory disease
- Unknown etiology
- Causes progressive damage of the joints
- Symptoms: pain, deformity and loss of function
- In addition: systemic and extra-articular involvement
- High burden of disease
- Outcome improved with early diagnosis and treatment

Epidemiology

- World wide distribution
- All races
- Incidence 1-2 %
- 3:1 women:men
- Peak incidence in the 4th to 6th decades, but can occur at any age
- Familial tendency, HLA-DR 4 related

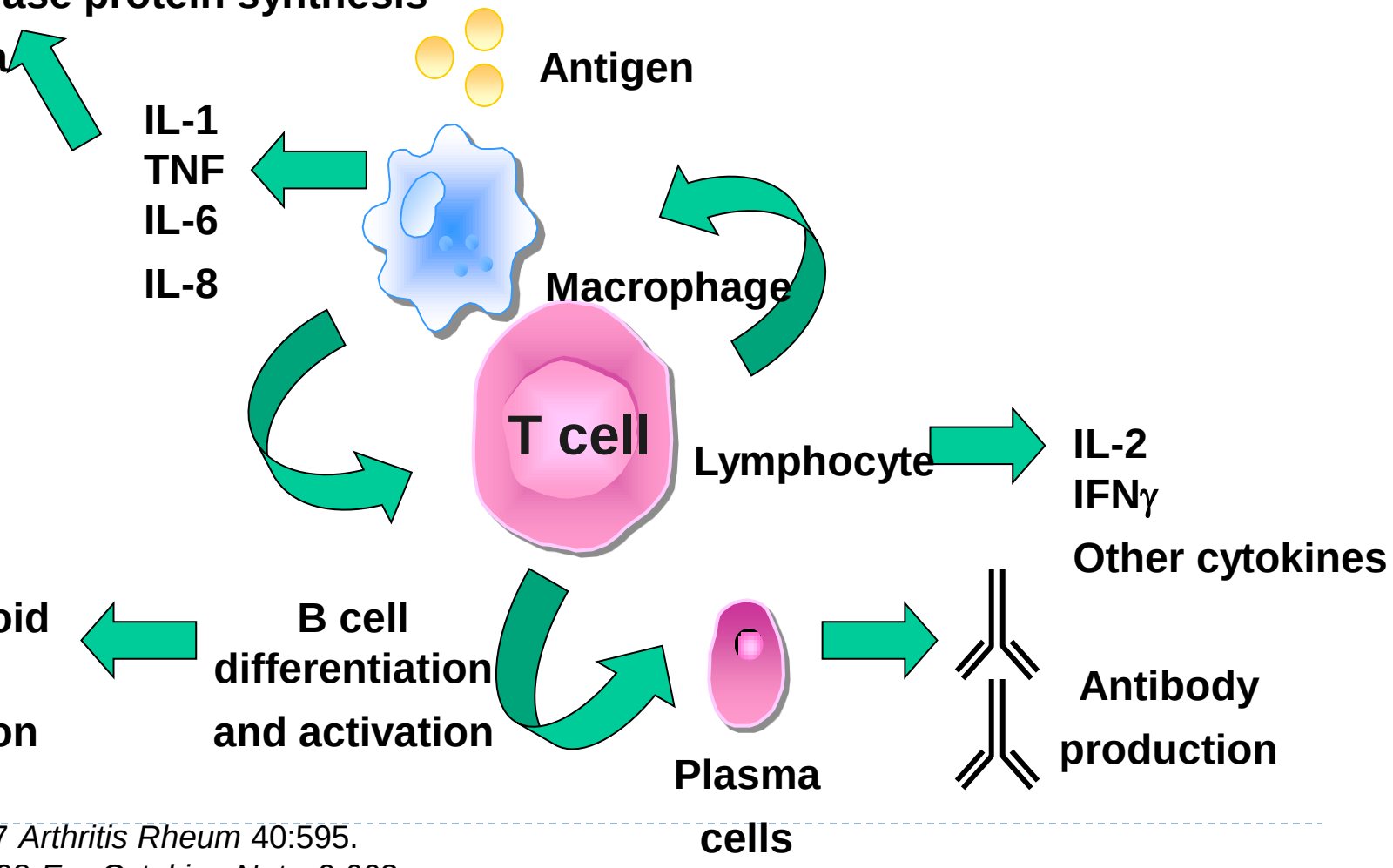
Pathogenesis of RA

- Auto-immune disease of serosal membranes
- Phases of the disease:
  - Initiation
  - Perpetuation
  - Destruction


Susceptible person
Arthritogenic agent
Synovial microvascular injury
Infiltration/ activation of B cells
Infiltration and activation of T cells
Angioneogenesis
Infiltration and activation of macrophag
Infiltration and activation of neutrophils
Proliferation of synovial fibroblasts
Activation of chondrocytes and osteoclasts
Prostaglandins, leukotrienes, degradative enzyme release
Joint destruction

Cellular Interactions RA

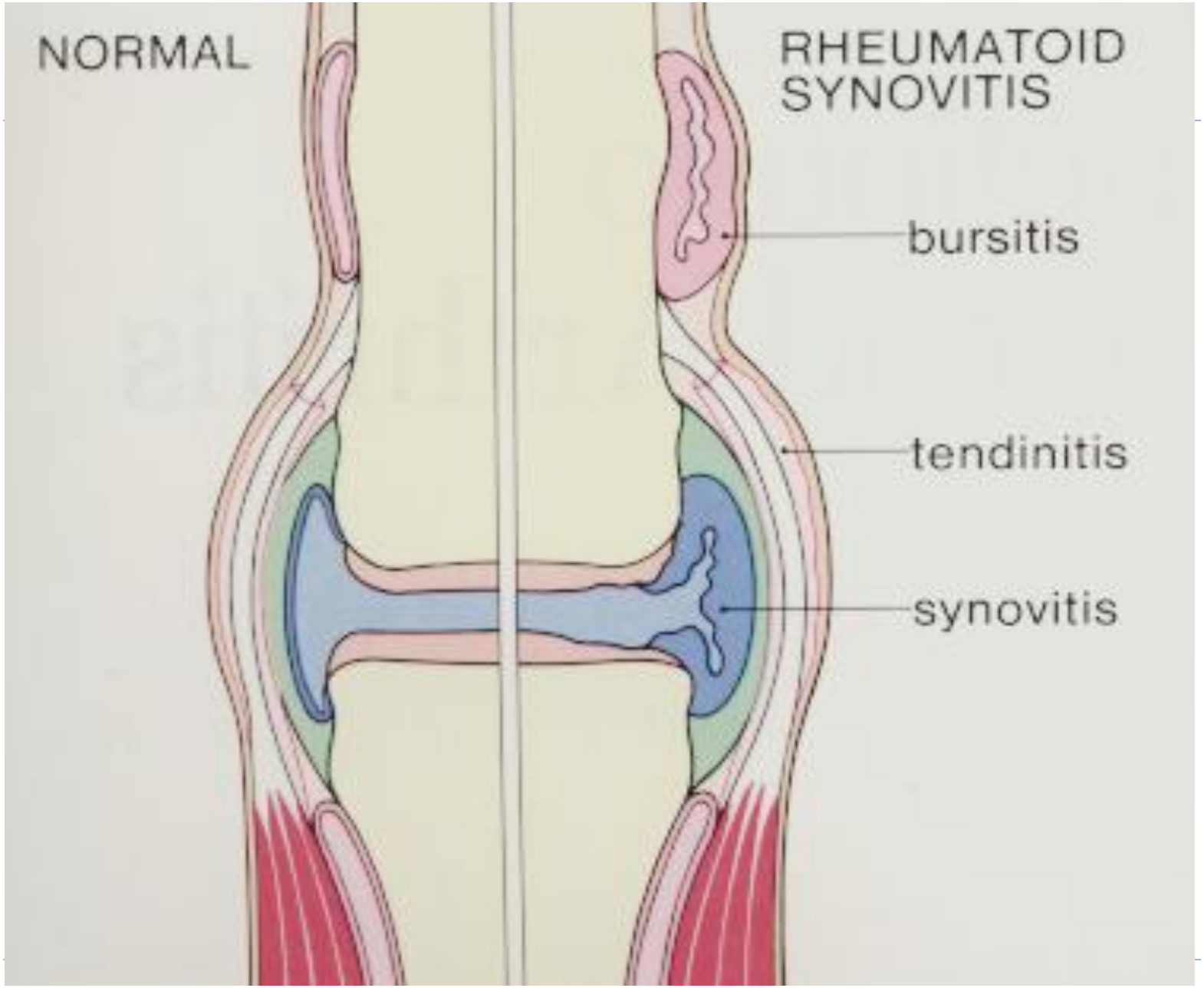
- **Inflammation**
- **Acute phase protein synthesis**
- **Cachexia**



Arend WP. 1997 *Arthritis Rheum* 40:595.
Deage et al. 1998 *Eur Cytokine Netw* 9:663.

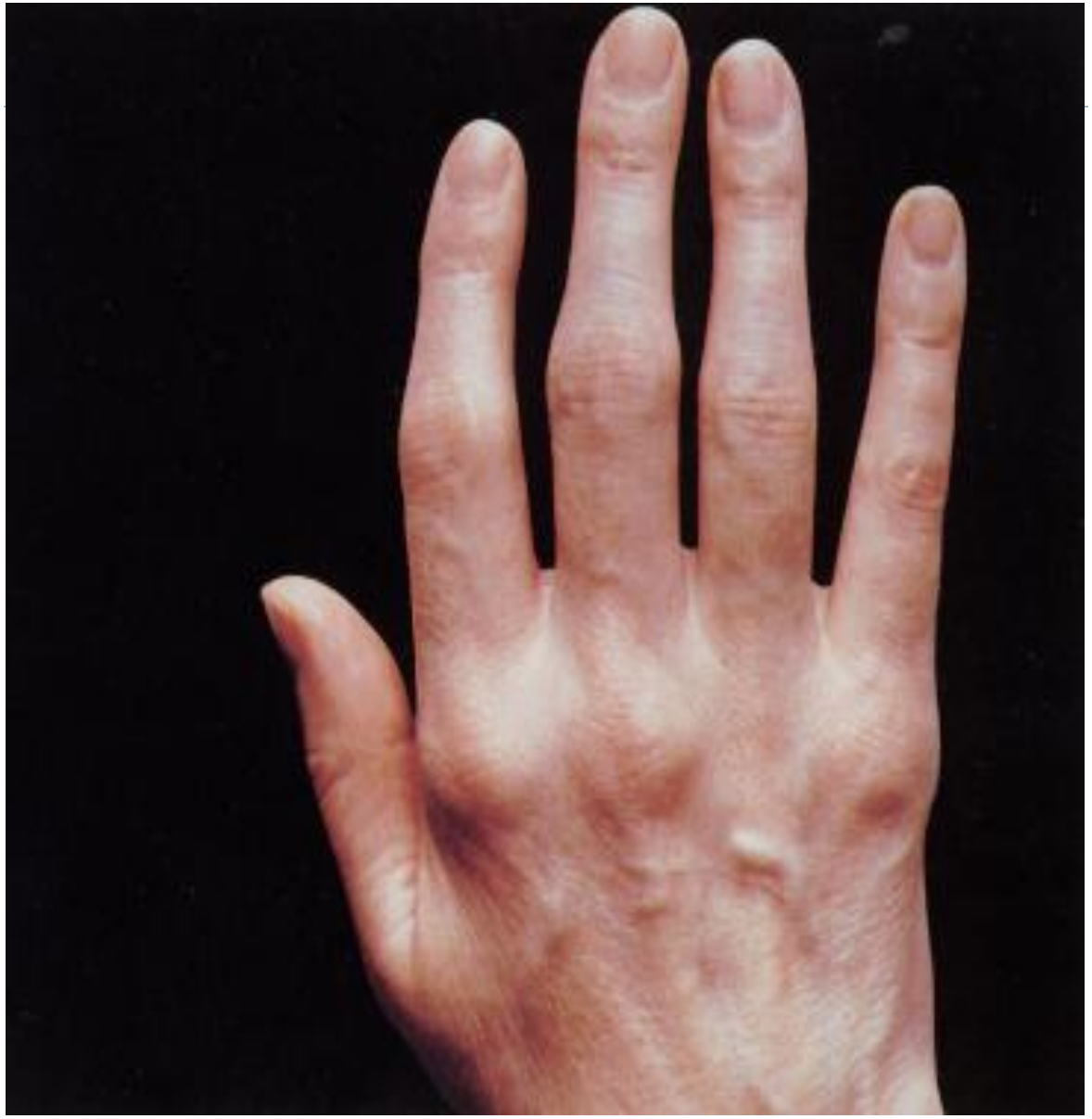
Pathology

- Serositis
  - Synovitis
    - Joints
    - Tendon sheaths
    - Bursae
  - Pericarditis
  - Pleuritis
- Nodules
- Vasculitis


NORMAL
RHEUMATOID SYNOVITIS
bursitis
tendinitis
synovitis

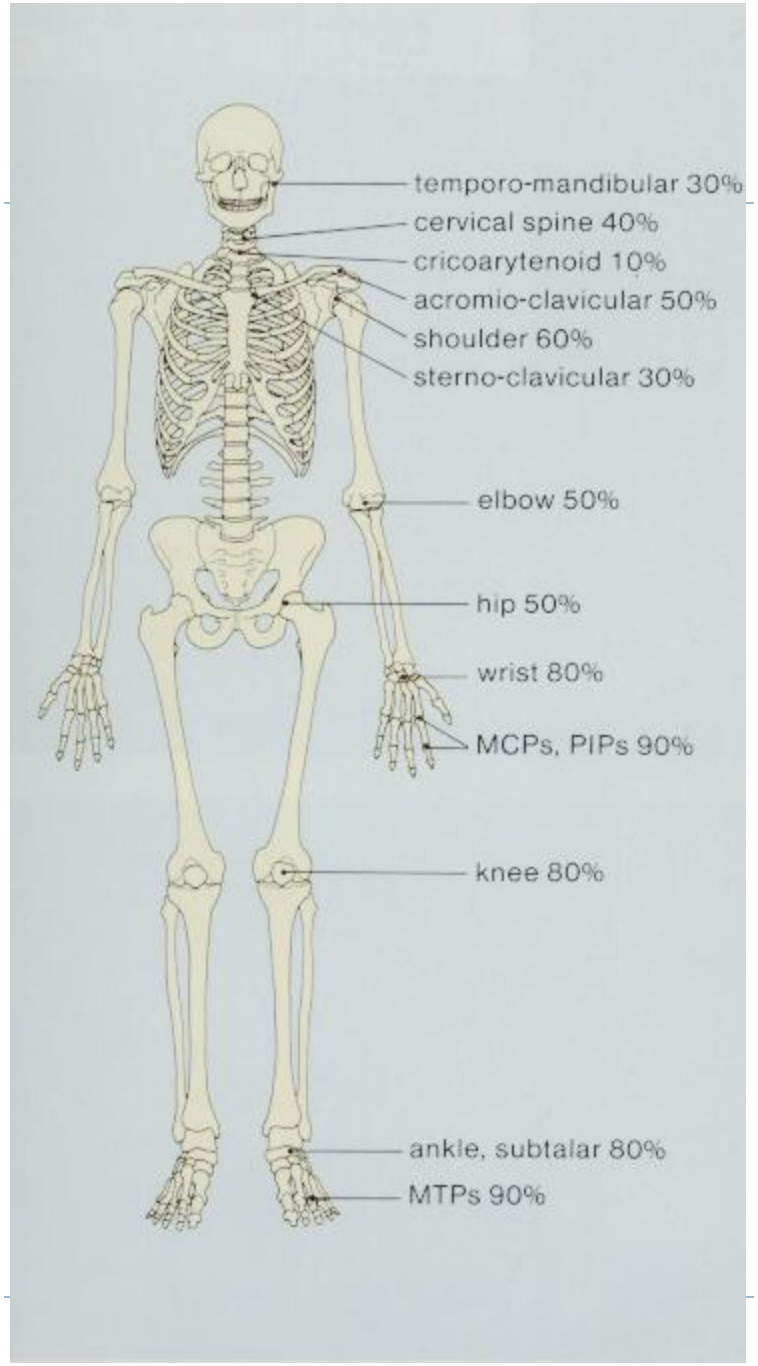
Clinical picture of RA

- Arthritis of synovial joints
  - Can present with only a few joints involved
  - Polyarthritis
  - Small and large joints involved
  - Symmetric arthritis
  - Onset can be acute or over time

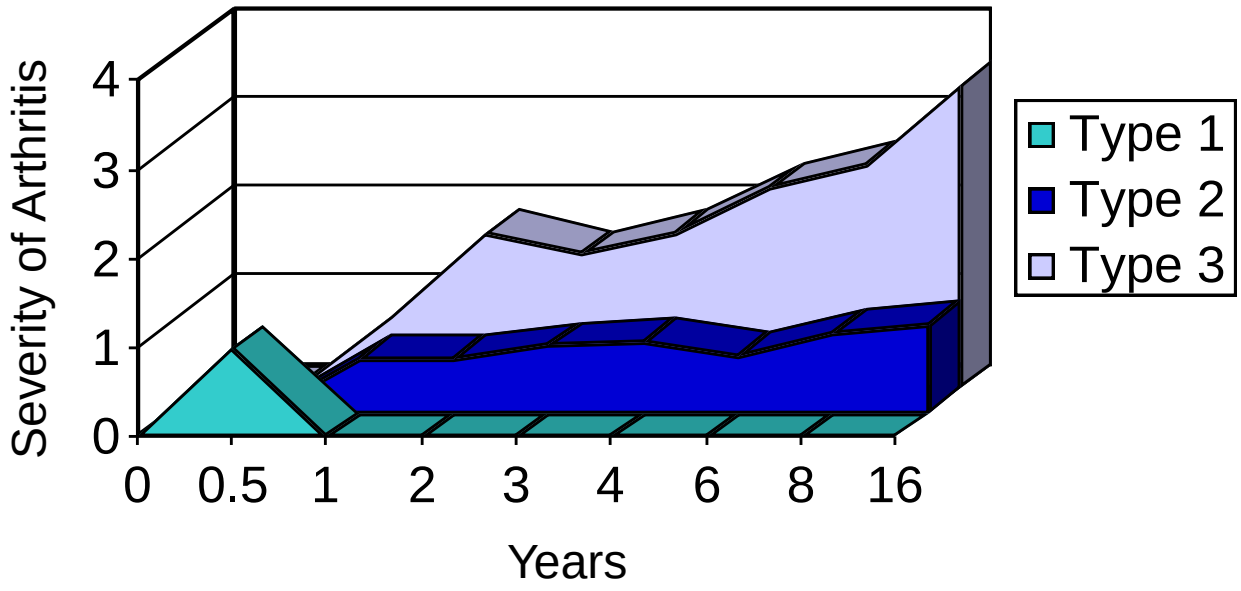


Rheumatoid Arthritis: PIP Swelling

- Swelling is confined to the area of the joint capsule
- Synovial thickening feels like a firm sponge


temporo-mandibular 30%
cervical spine 40%
cricoarytenoid 10%
acromio-clavicular 50%
shoulder 60%
sterno-clavicular 30%
elbow 50%
hip 50%
wrist 80%
MCPs, PIPs 90%
knee 80%
ankle, subtalar 80%
MTPs 90%

Clinical Course of RA



Type 1 = Self-limited—5% to 20%
Type 2 = Minimally progressive—5% to 20%
Type 3 = Progressive—60% to 90%

Pincus. *Rheum Dis Clin North Am*. 1995;21:619.

Diagnosis of RA

- No one specific diagnostic feature
  - Clinical picture
  - Blood tests to add to information
    - Rheumatoid factor
      - 45% positive in first 6 months
      - 85% positive with established disease
      - Not specific for RA, high titer early is a bad sign
    - Anti cyclic citrullinated peptide antibodies (ACPA)
      - AntiCCP more specific for RA
      - Predicts progressive disease
  - Use classification criteria

2010 ACR /EULAR RA Classification criteria

- Joint involvement

0-5 points according to number of joints

- Serology

0-3 points for low or high positive ACPA, RF

- Acute phase reactants

0-1points for elevated CRP or ESR

- Duration of symptoms < or > 6 weeks

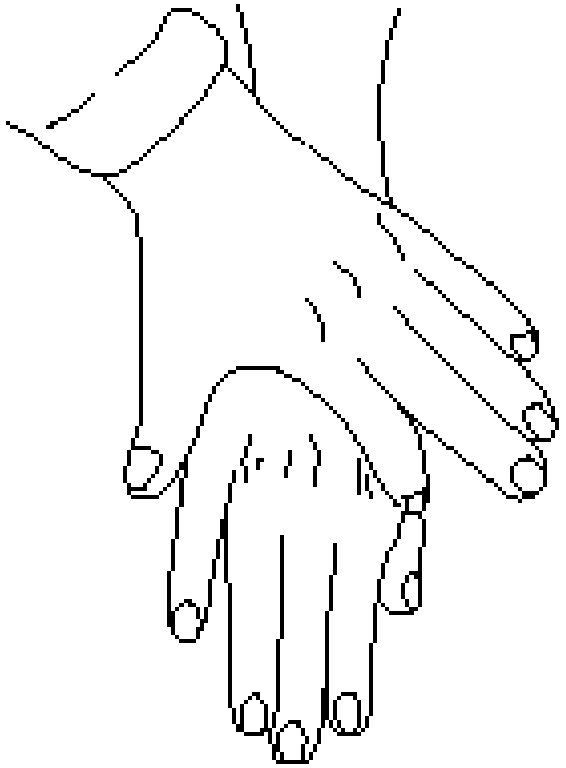
0-1 points

6 points = Definite RA

Which symptoms/signs? Early Referral Recommendations for *Potential RA*

Alarm signals

- **≥ 3 swollen joints**
- **MTP/MCP involvement**
- **(Squeeze Test positive)**
- **Morning stiffness ≥ 30 minutes**



Emery et al. 2002

Differential diagnosis of RA

- Non-articular rheumatism
- Osteoarthritis
- Other inflammatory arthritis
- Gout and crystal arthropathy
- Viral and other infective arthritis
- Medication:
  - Oral contraception
  - Aromatase inhibitors
  - Bisphosphonates
- Thyroid disease
- Malignancy

Consequence of RA: Damage and deformity

- Joint damage and deformity
- **Joint damage occurs early and progresses at rapid rate**
  - In first 2 years 50% have joint space narrowing/ erosions
- **~75% early RA patients have radiological joint erosions**
  - Erosions represent permanent structural damage
  - Erosions occur within 2 years
  - MRI changes at onset in >80%

Deformities of the hands

- Subluxation of MCP joints

Boutonniere and swan neck deformity

Tenosynovitis of the extensor tendons

Extensor tendon rupture

Flexor tendon rupture

Early foot involvement

Deviation of toes

Prominence of MTP heads

Subtalar joint subluxation

RA knee

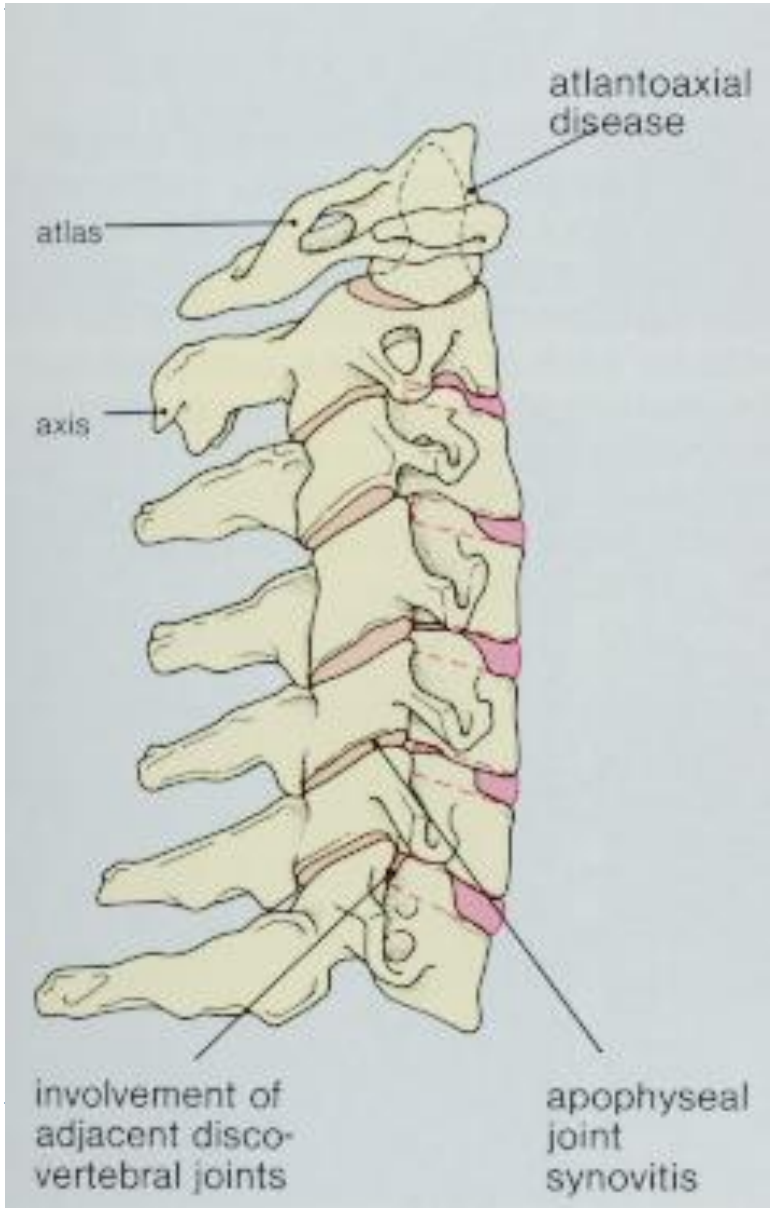
Early X-ray changes: peri –articular osteopaenia

Joint space narrowing and erosion

Joi

Se

RA involvement of the neck



Consequences of RA: Disability

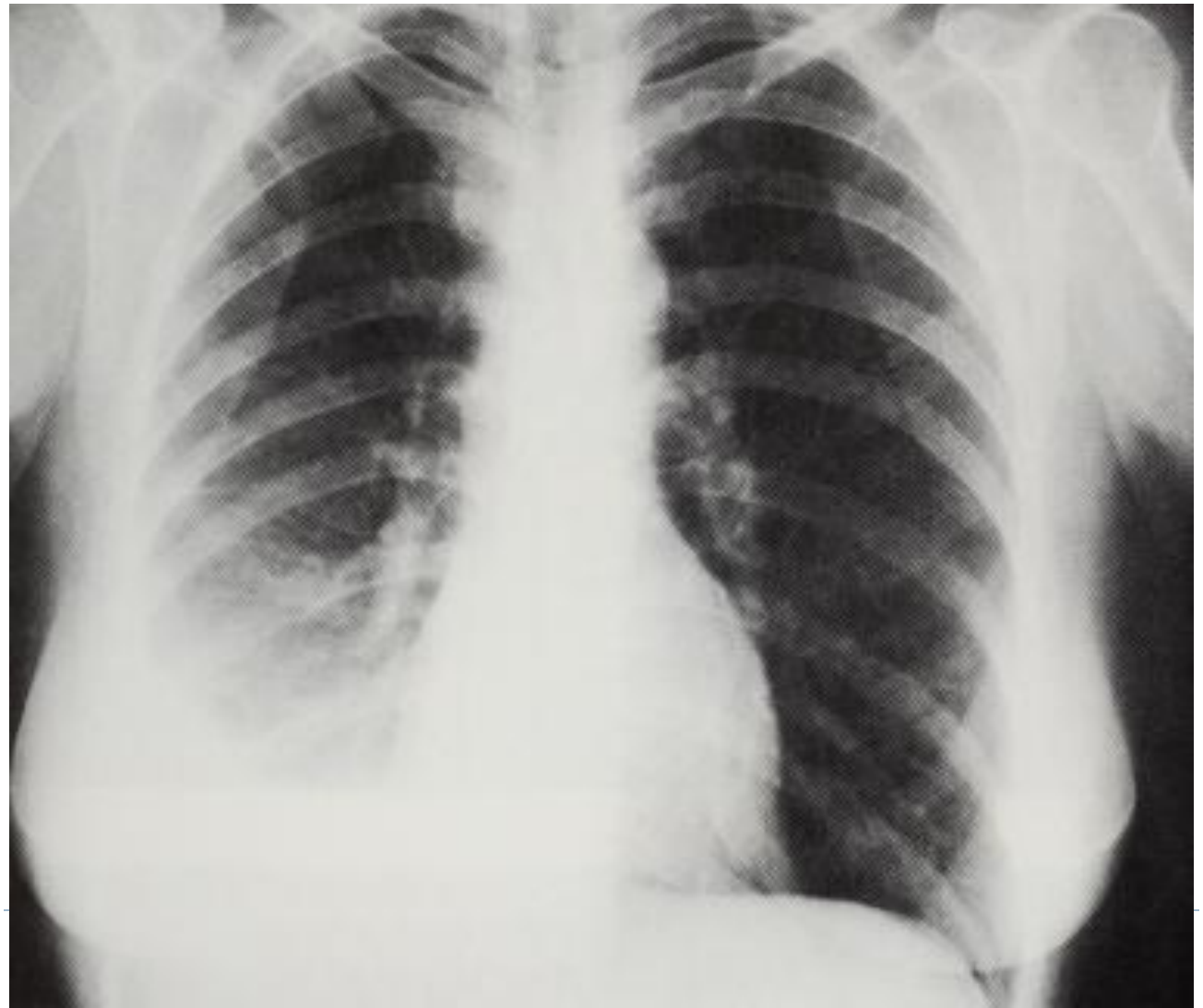
- In UK 85% of people with RA experienced difficulty with employment or had contemplated stopping work
- By 10 years, 50% of young working patients are disabled

- WHO report 1996: In the top 10 list of major causes of disease burden in women

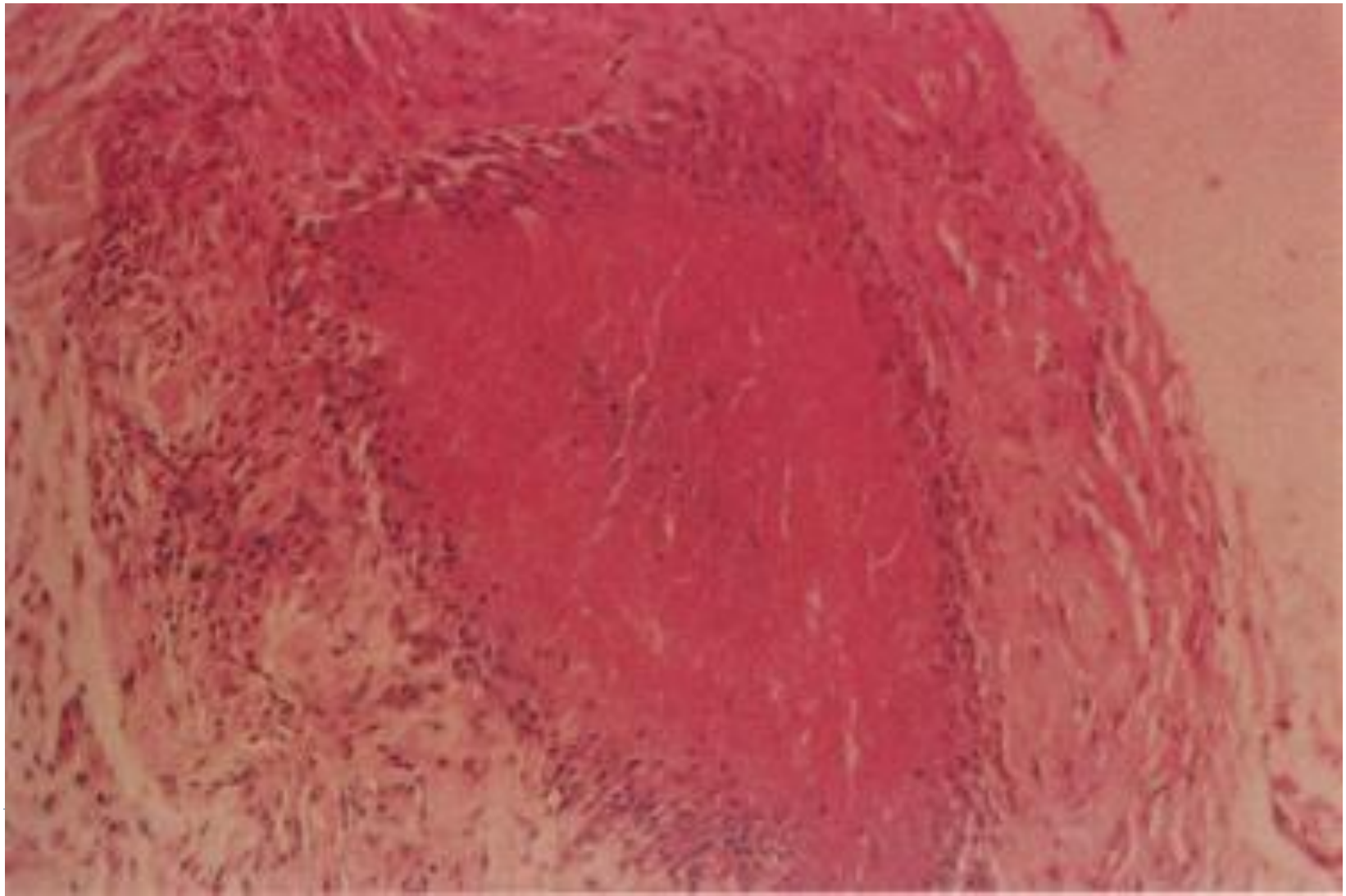
Consequences of RA: Extra articular involvement

Bursitis

Serositis



Rheumatoid nodules



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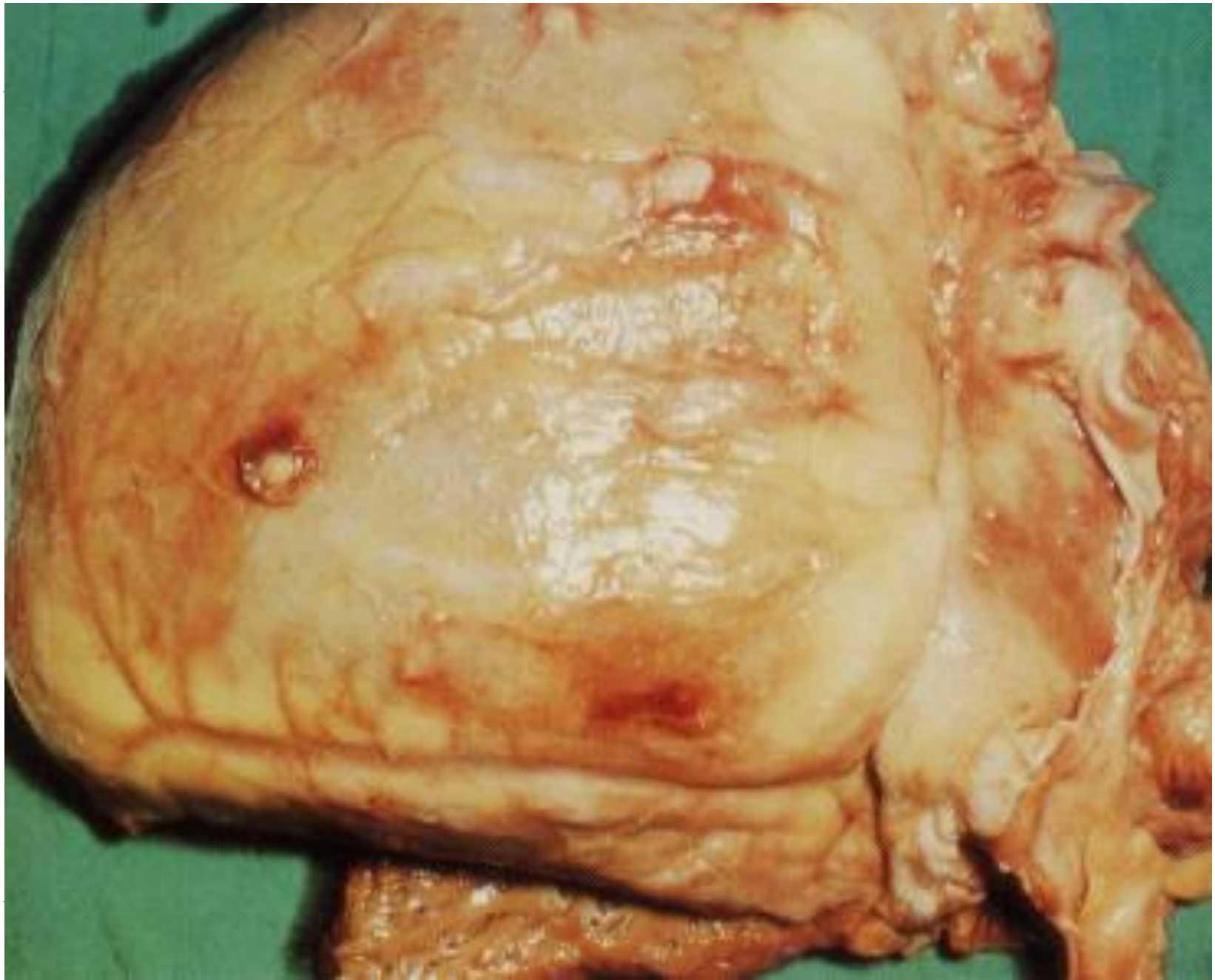
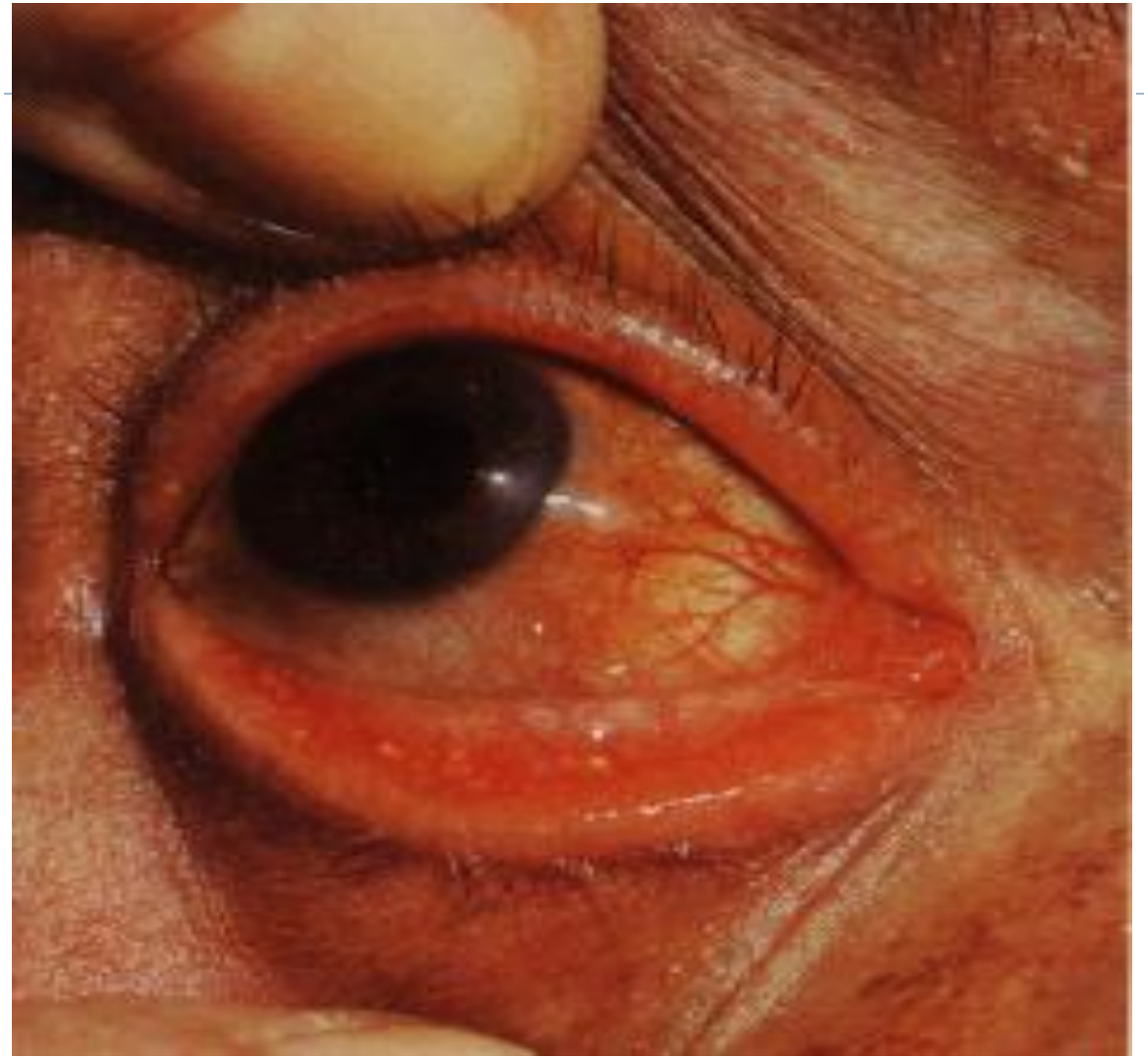


Vasculitis

Kerato-conjunctivitis sicca

Scleritis



Scleritis with scleromalacia

Consequences of RA: co-morbidities

- Serious and considerable co-morbidities
  - Cardiovascular

Cardiovascular disease in RA

- Similar histology in RA synovium and artherosclerotic plaques:
- Several of the same cells
- Similar cytokines

- Incidence of IHD 49% in RA pts
  - 33 – 50% of deaths in RA pts due to CVD

- Incidence of IHD 27% in OA pts

Consequences of RA: Death

- Increased mortality amongst RA patients

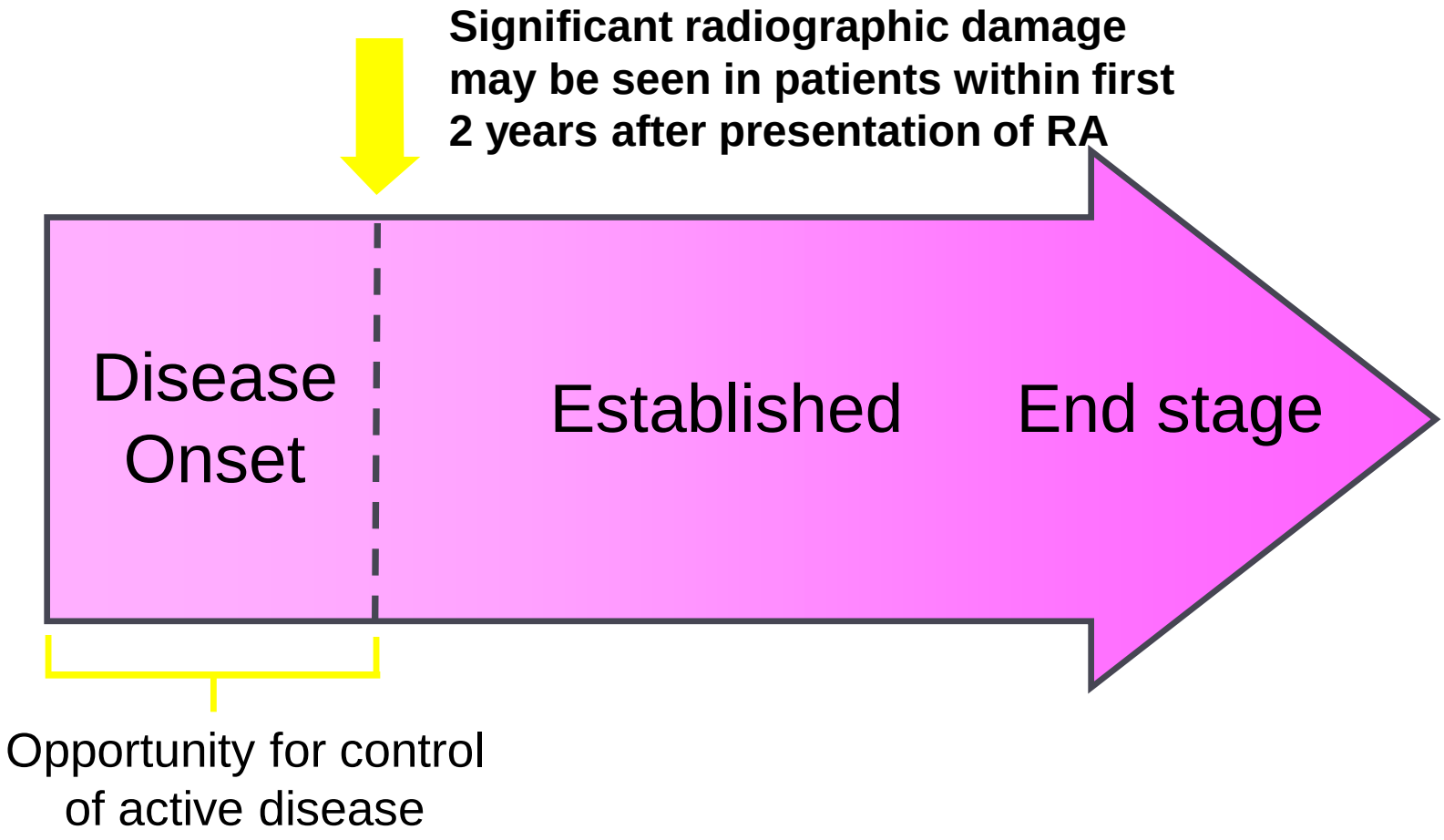
Death

- Death comes early
- The higher the disability scores, the greater the risk of mortality
- Mortality comparable to that of 3 -vessel coronary artery disease
- Multiple causes: Co-morbidities
- Compared to general population
  - Women lose 10 years
  - Men lose 4 years

RA treatment 2011

- **Establish the diagnosis early**
  - New RA criteria
- **Assess disease activity and define treatment goals:**
  - Tender and swollen joint count
  - HAQ, patient global assessment
  - CRP, ESR
  - Composite scores DAS, SDAI and CDAI
- **Treat to target**
- ***Remission is our ultimate target !!***

Importance of early, aggressive treatment of RA



Fuchs H et al. *J Rheumatol*. 1989 May;16(5):585-91.

Assessing disease activity and severity

Measuring disease activity and outcome

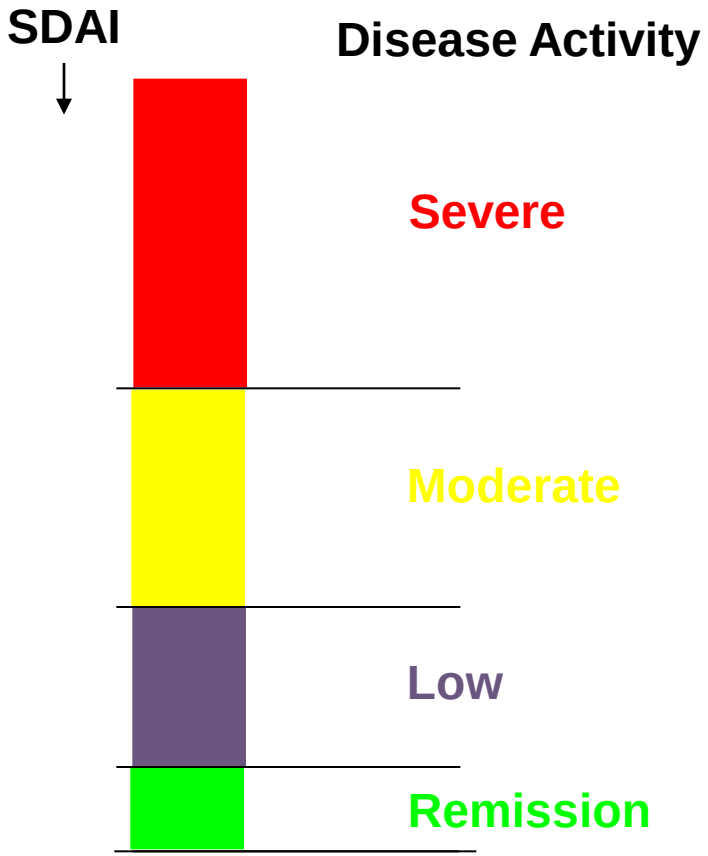
- Signs and symptoms
  - **Disease Activity Score (DAS) / DAS 28**
  - **ACR20/50/70**
  - **SDAI**
- Functional disability and QOL
  - **Stanford Health Assessment Questionnaire (HAQ)**
  - **Short Form-36 Health Survey (SF-36)**
- Radiographic progression and structural damage
  - **Sharp/Modified Sharp score**

ACR Ad Hoc Committee on Clinical Guidelines. *Arthritis Rheum.* 1996;39:713-722.
Grassi W et al. *Eur J Radiol.* 1998;27(suppl 1):S18-S24.
van Riel PLCM, van Gestel AM. *Ann Rheum Dis.* 2000;59(suppl 1):128-131.
Smolen JS, Breedveld FC, Emery P, et al. *Rheumatology*. 2003;42:244-257.

Simplified Disease Activity Index: SDAI

SDAI =

Tender joint count (0-28)
+ Swollen joint count (0-28)
+ Patient Global* (0-10 cm)
+ Physician Global*(0-10 cm)
+ CRP (mg/dL)



Improvement:
Major: > 20 points
Minor: 10-20 points
No: < 10 points

Smolen JS, Breedveld FC, Emery P, et al. *Rheumatology*. 2003;42:244-257.

Health Assessment Questionnaire – Disability Index (HAQ)

- 8 categories
- 20 questions
- Each ranges from 0 to 3
  - **0 = no difficulty, 1 = some difficulty, 2 = much difficulty or with assistance, 3 = unable**
- Score 2 for item that uses devices &/or another person
- HAQ score is average of worst score in each of 8 categories
- The total score ranges from 0 to 3
- MCID = .22

Buchbinder R et al. *Arthritis Rheum*. 1995;38:1568-1580.
Sullivan FM et al. *Ann Rheum Dis*. 1987;46:598-600.

Assessing disease severity: Prognostic factors

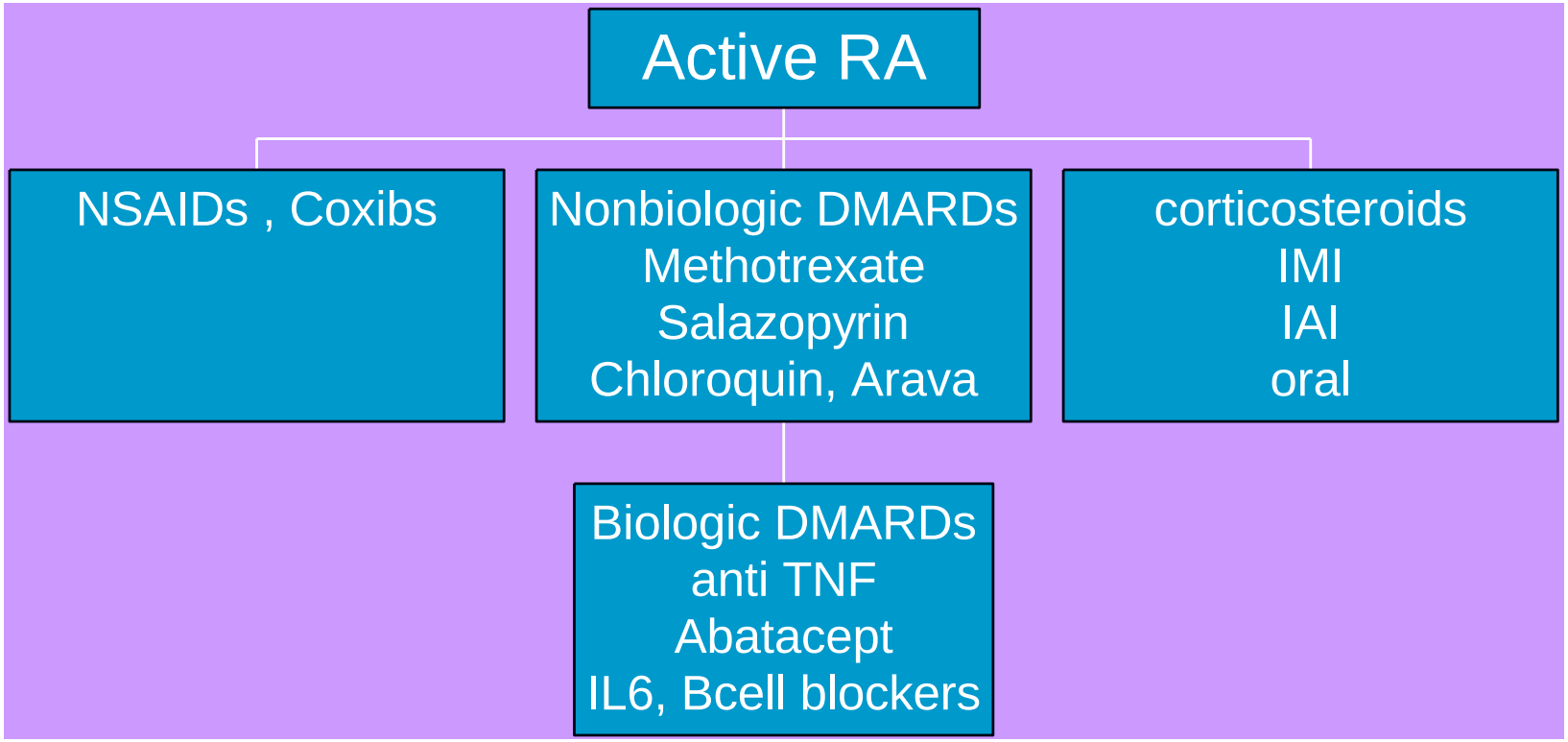
- RF and Anti cyclic citrillunated protein antibody (ACPA) positive
- Functional limitation (HAQ)
- Extraarticular disease
- Bony erosions on Xray
- Others -comorbid conditions
  - -smoking
  - -lack of education
  - - low socioeconomic status

Treat to Target principles of treatment of RA 2010

1. Treatment is a shared decision between Rheumatologist and patient
2. Maximise quality of life through control of symptoms, prevention of structural damage, maintain function and social participation
3. Abrogation of inflammation to achieve 2
4. Treating to target by measuring disease activity and adjusting therapy optimises outcomes
5. Early treatment increases chance of remission

1. Clinical remission: absence of signs and symptoms of clinical disease activity
2. Residual disease activity is realistic in longstanding disease
3. Targets must include low disease activity
4. Until target is reached: therapy adjusted every 1-3 months
5. Validated composite scores include joint counts and laboratory monitoring

Algorithm for Treatment of RA



Options for RA treatment

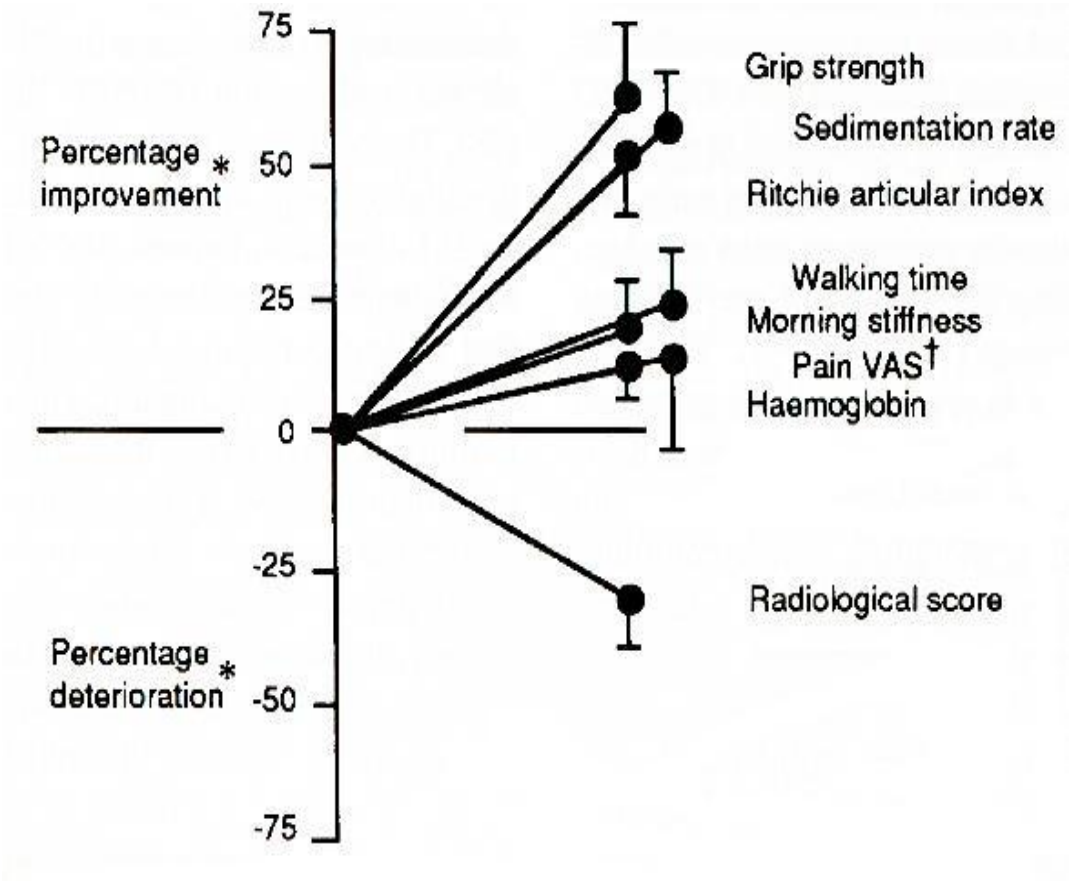
- Non-pharmacologic
- Pharmocologic
  - NSAIDs and analgesics etc
  - Corticosteroids
  - Synthetic DMARDs
  - Biologic DMARDs

Traditional DMARD Selection

Agent	Time to Benefit	Potential for Toxicity	Comments
MTX	1–2 mo	Moderate	Most effective single DMARD Good benefit-to-risk ratio
HCQ	2–6 mo	Low	Moderate effect, low cost
LEF	4–12 wk	Low	Similar to MTX, hepatotoxicity
SSZ	1–3 mo	Low	Moderate effect, low cost
Azathioprine	2–3 mo	Moderate	Slow onset, reasonably effective
Gold, parenteral	3–6 mo	Moderate	Slow onset, decreases progression, rare remission Requires close monitoring

ACR Subcommittee on Rheumatoid Arthritis Guidelines. Arthritis Rheum 2002;46:328-46

Relationship of clinical symptoms to damage:

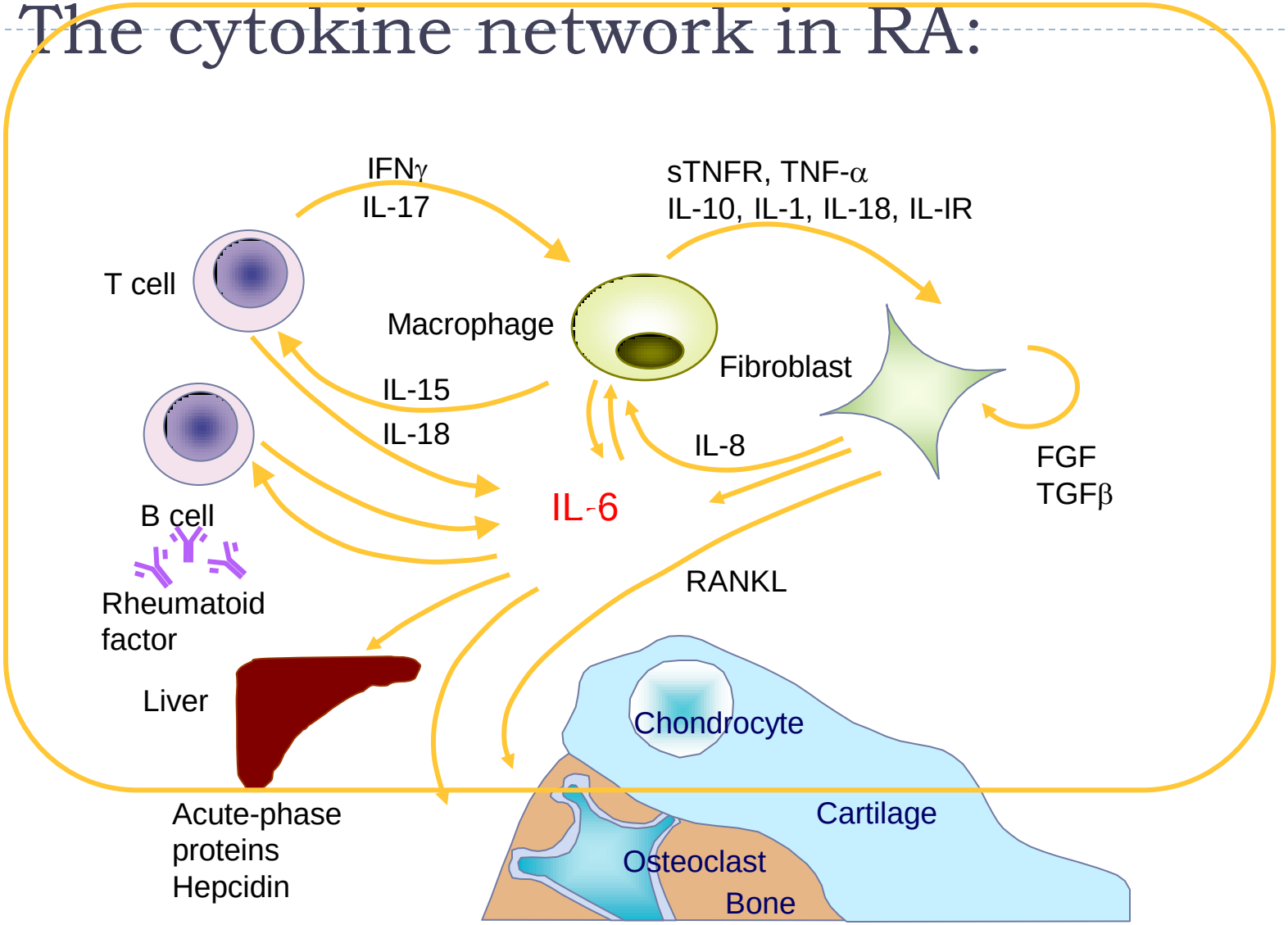


Mulherin et al, Br J Rheumatol 1996

Development of the biologic DMARDs

- Targeted therapy

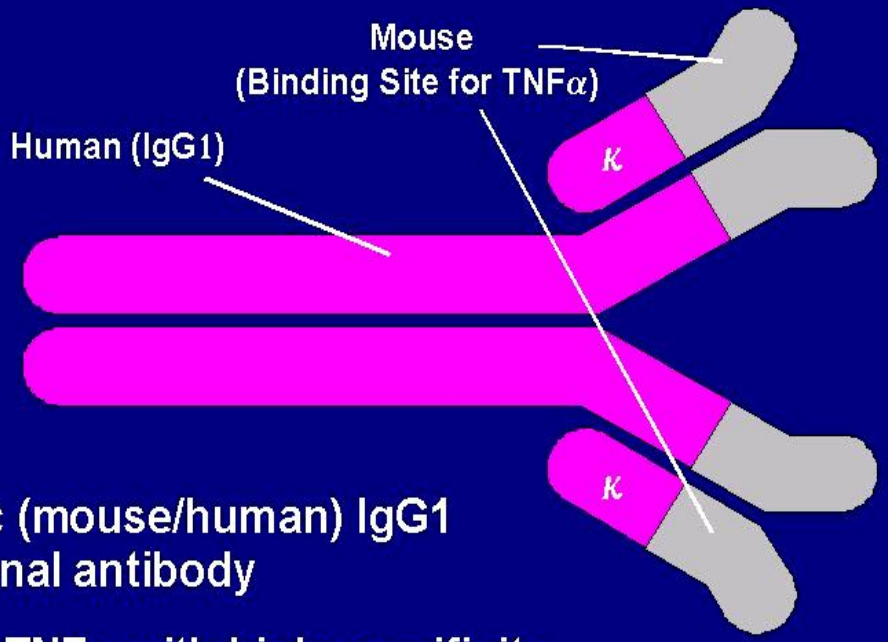
The cytokine network in RA:



Firestein GS. *Nature* 2003; 423:356–361; Smolen JS and Steiner G. *Nat Rev Drug Disc* 2003; 2:473–488.

The TNF blockers

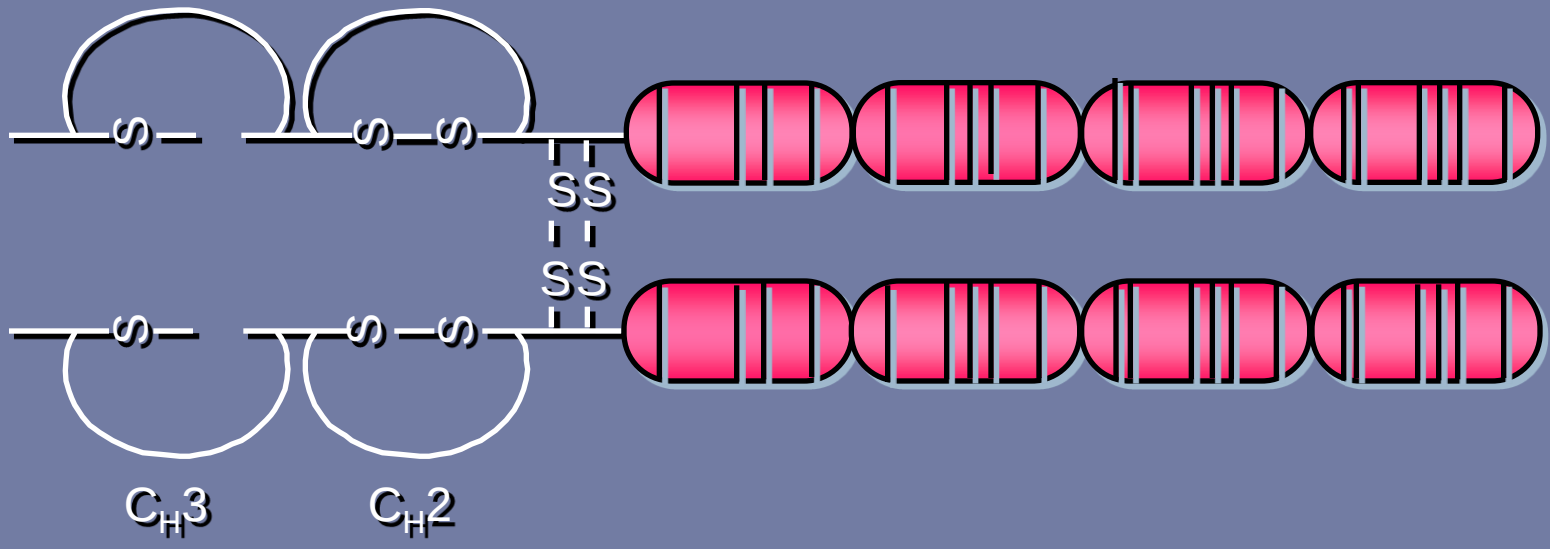
Structure of Infliximab



- Chimeric (mouse/human) IgG1 monoclonal antibody
- Binds to TNFα with high specificity, high affinity, and high avidity

Knight DM, et al. *Mol Immunol.* 1993; 30(16):1443-53.

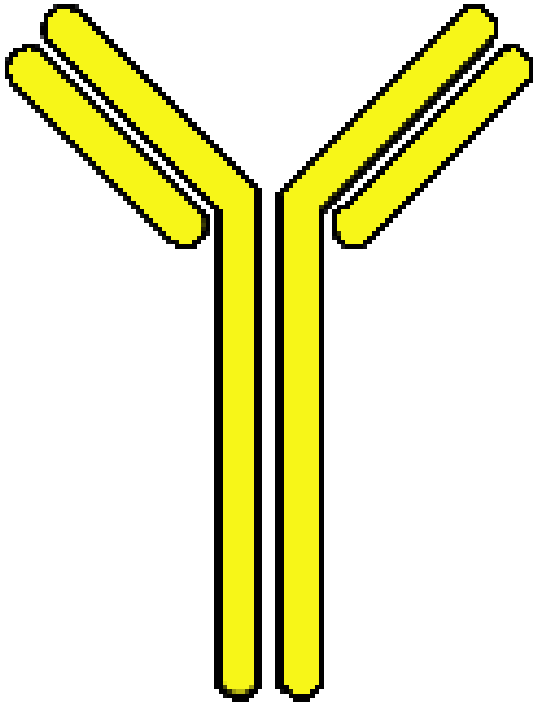
Etanercept: soluble TNF receptor



Fc Region of Human IgG1

Extracellular Domain of Human p75 TNF Receptor

Adalimumab (D2E7) Characteristics

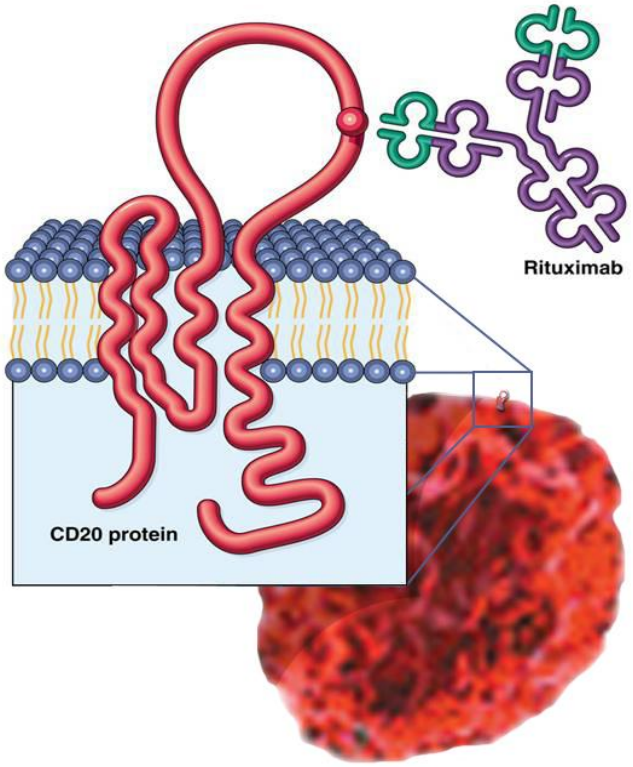


Fully Human Anti-TNFα Antibody

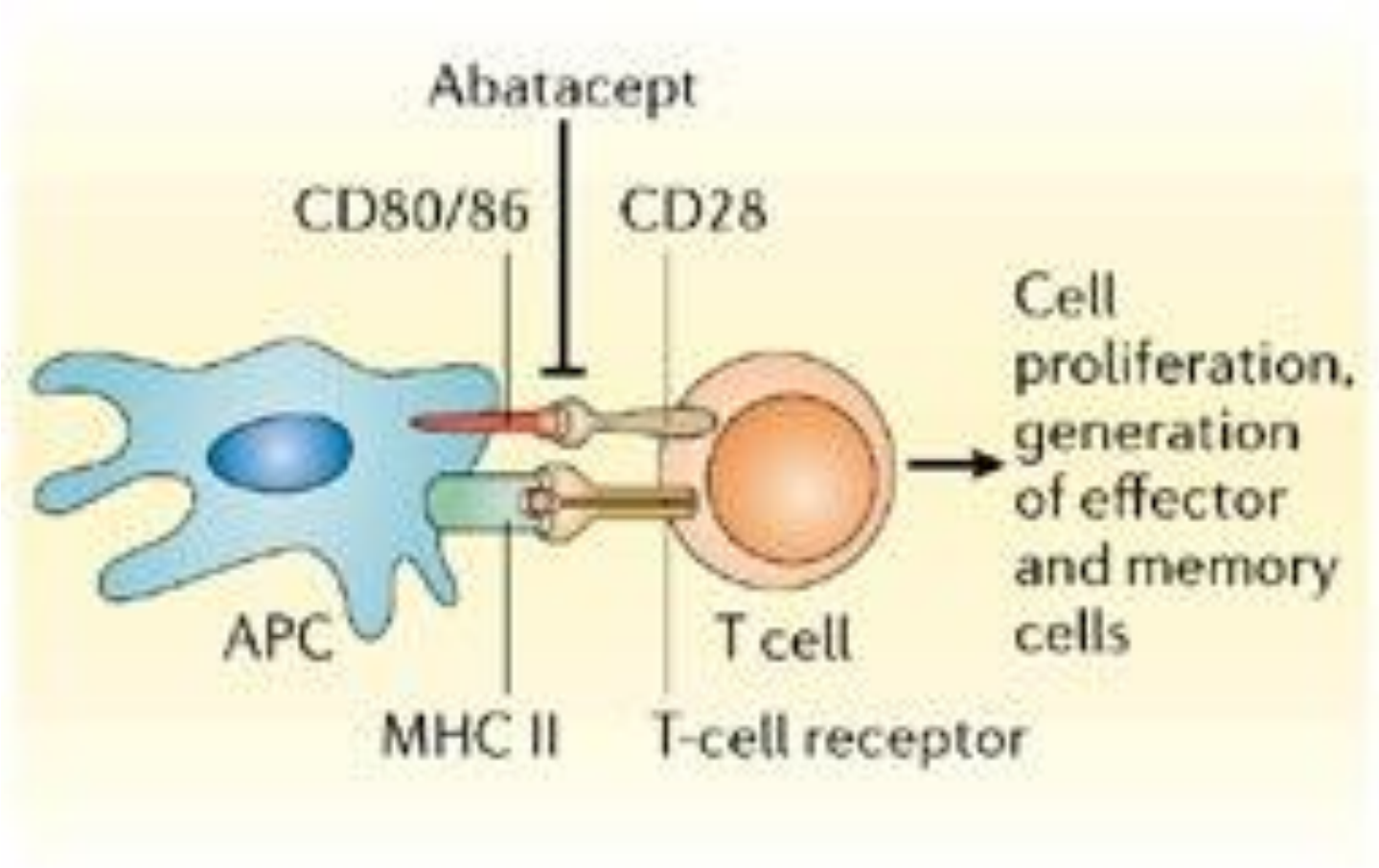
- With T½ ~ 2 weeks
- Binds only TNFα and not other TNF family members

Rituximab: a novel biological agent for RA

- Rituximab is a novel genetically engineered anti-CD20 therapeutic monoclonal antibody that *selectively* targets CD20-positive B cells

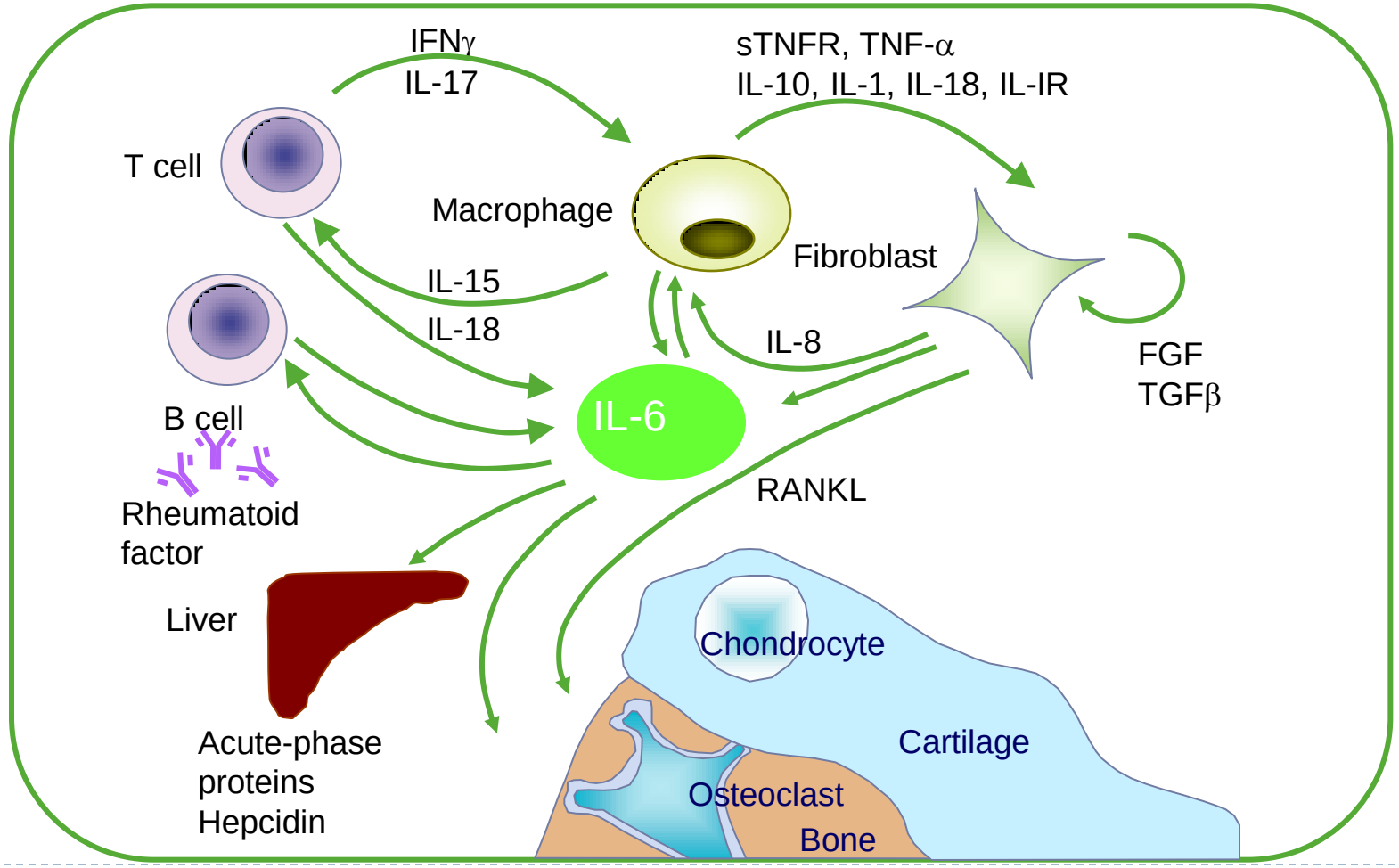


(Shaw et al, 2003; Silverman & Weisman, 2003)



Nature Reviews | Drug Discovery

IL-6 is a key regulator of the inflammatory response



Firestein GS. *Nature* 2003; 423:356–361; Smolen JS and Steiner G. *Nat Rev Drug Disc* 2003; 2:473–488.

Summary:

- Rheumatoid arthritis is a common, sometimes devastating disease
- Important to treat as early as possible and as effectively as possible
- Remission is the target of treatment

Core principles of RA management:

- Detect and refer patients early even if the diagnosis is uncertain
- Treat RA immediately
- Tight control of inflammation in RA improves outcomes and requires structured protocols and regular review
- Consider the risk-benefit ratio and tailor treatment to each patient