Approach Autoimmune Rheumatic diseases

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11 May 2019

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Faculty of
Health Sciences

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

Make today matter

Focus of presentation

- Degenerative – Osteoarthritis
- Metabolic disorders – Gout
- Autoimmune diseases – inflammatory arthritis
  - Connective tissue diseases

Spectrum of disorders

- **Localised soft tissue**

Multisystem disease

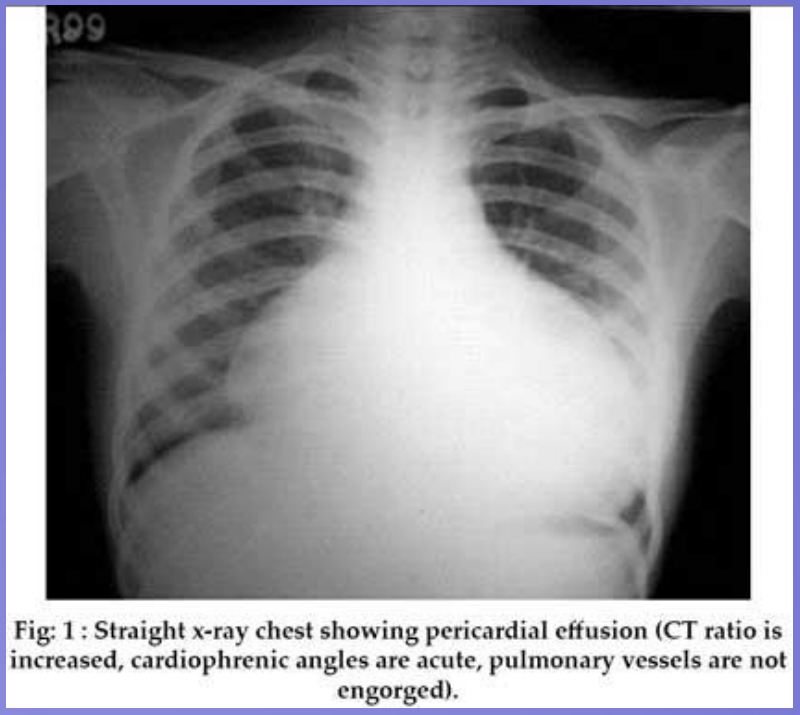


Fig: 1 : Straight x-ray chest showing pericardial effusion (CT ratio is increased, cardiophrenic angles are acute, pulmonary vessels are not engorged).

pathogenesis

- **Simple overuse**
- **Metabolic disorders**
- **Complex immune dysregulation/ auto-immunity**

Debilitating joint diseases

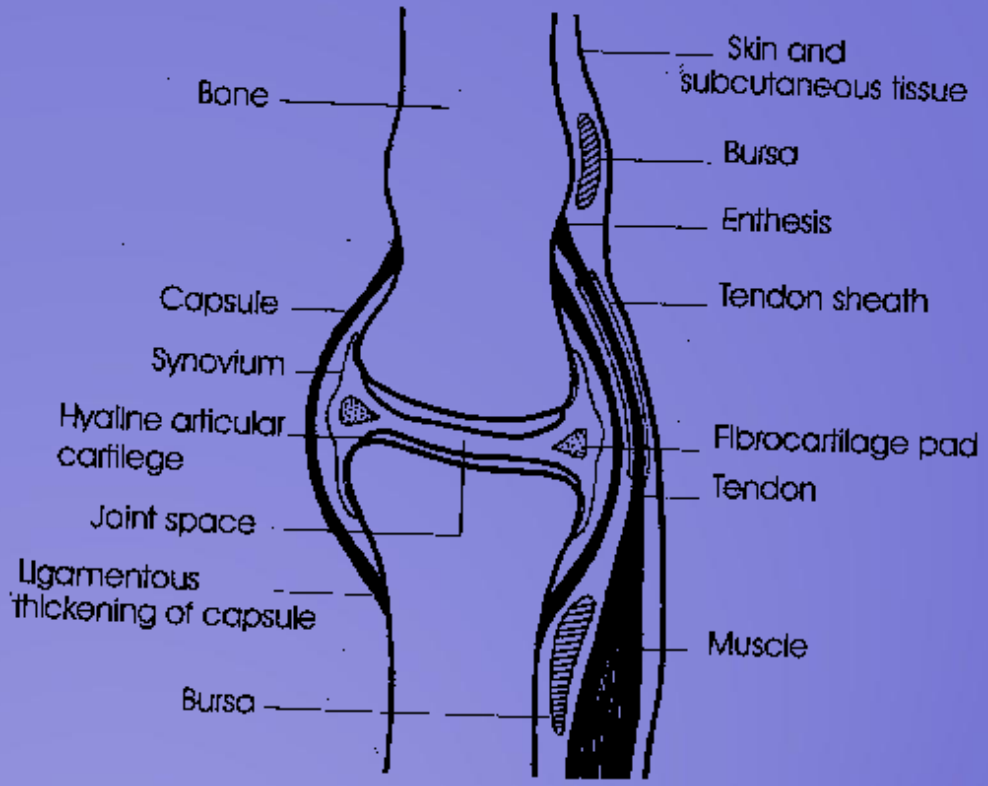
- **Osteoarthritis**
- **Gout**
- **Rheumatoid arthritis**

Osteoarthritis

- **Classic example of a degenerative arthritis**
- **Most common form of arthritis in patients > 50 years**
- **12% of patients > 65 years of age have symptomatic OA**

Etiological Factors

- **Joint to be viewed as a functional unit**
  - **Articular bones**
  - **Cartilage**
  - **Ligament**
  - **Capsule**
  - **Muscle**
  - **nerves**



Etiological Factors

- **Not simple wear and tear but multifactorial**
  - **Age**
  - **Genetic factors**
  - **Sex**
  - **Obesity**
  - **Nutrition**
  - **Trauma/Other forms of arthritis**

Other Factors

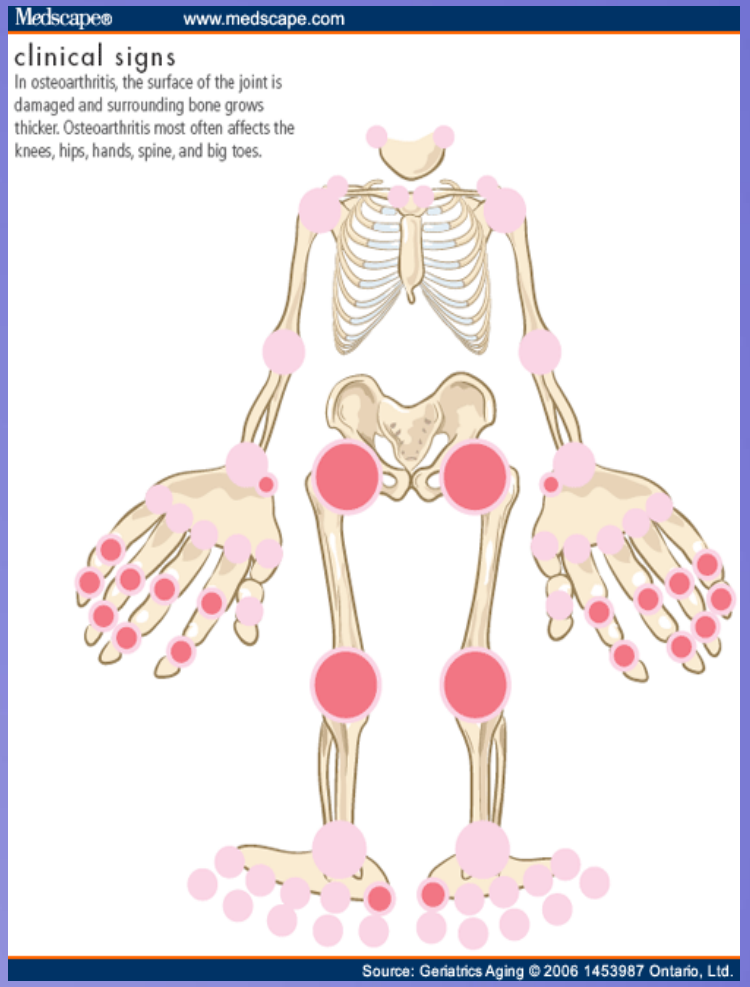
- **Genetic Factors**
  - **Siblings of patients undergoing hip surgery for OA – 5 fold increase risk of developing OA**
- **Weight**
  - **Increased load on weight bearing joints**

Other Factors

- **Muscles and nerves**
  - **Important sensory/motor function for maintaining joint stability**
  - **Shock absorption and coordinating movement ensuring minimal stress**
- **Crystal arthropathy**
  - **Amplifies cartilage degeneration**

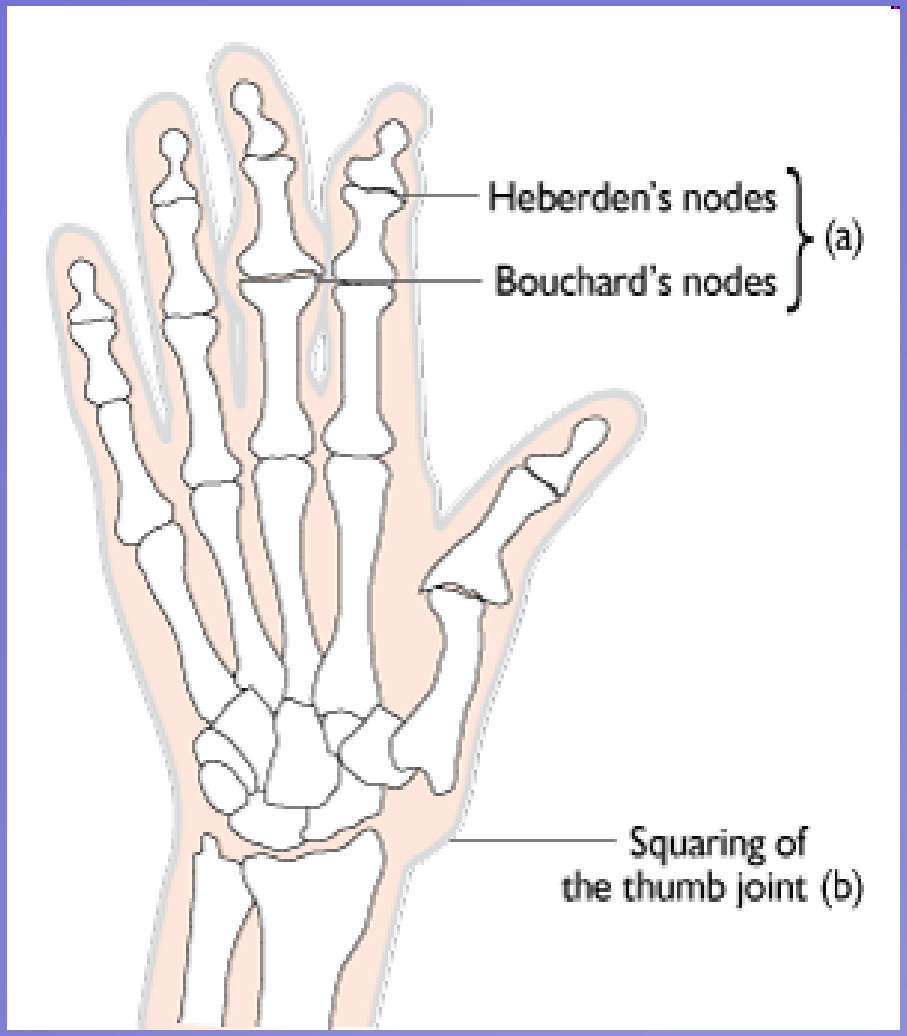
Clinical Features

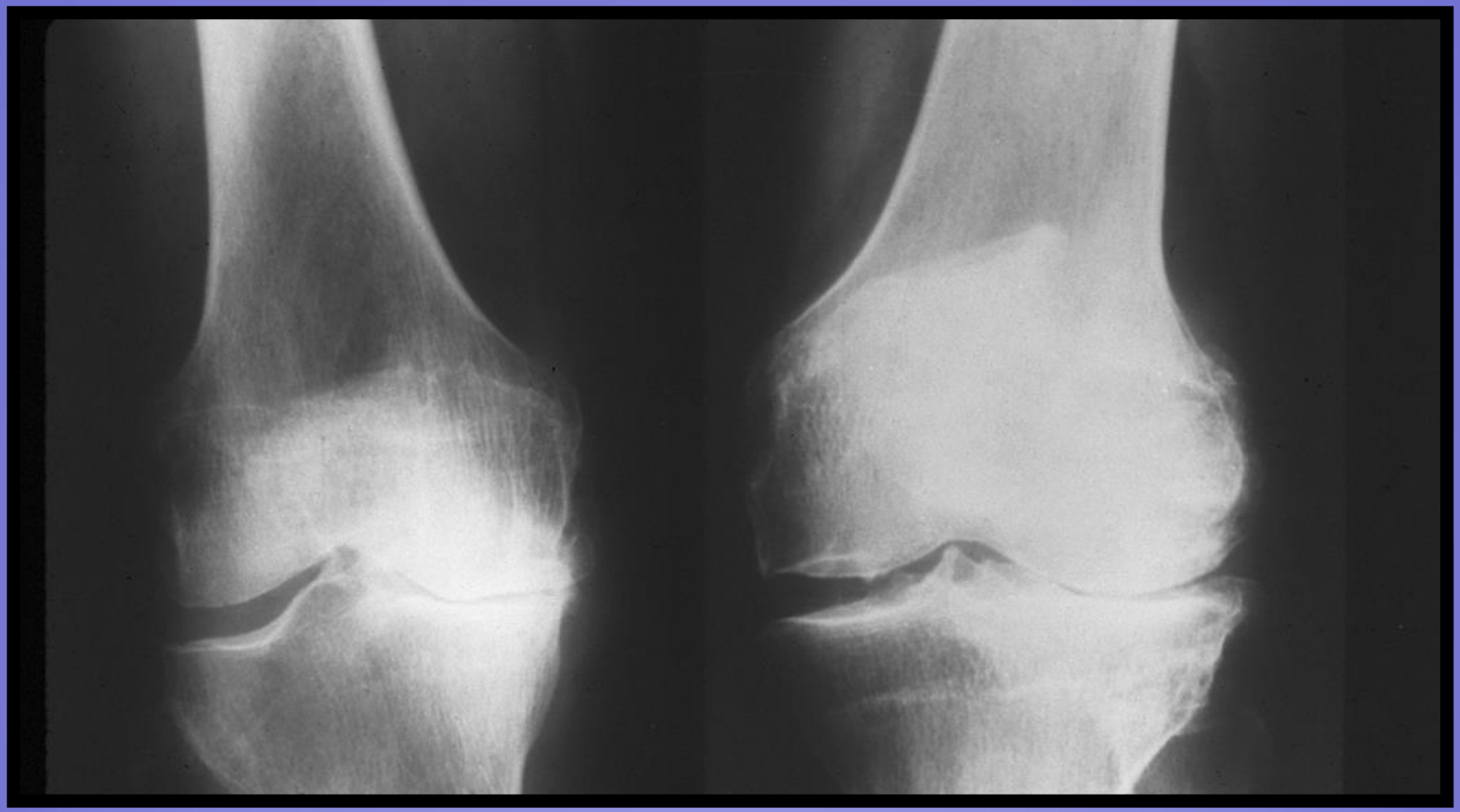
- > 50 years of age
- Weight bearing joints and hands including DIP
- Minimal morning stiffness
- Family history often positive
- Occupational risk factors
- Systemic symptoms absent
- Nocturnal/rest pain suggest advanced disease



Clinical Features

- Bony swelling at joint margins
  - Heberden's and Bouchard's nodes
- Crepitus
- R.O.M.
- Valgus or Varus
- deformities
- Muscle weakness


Heberden's nodes
Bouchard's nodes
(a)
Squaring of
the thumb joint (b)



Investigation

- **ESR negative**
- **Immunological test not necessary**
- **Uric acid**
- **X-ray – classic radiological features**

Note: Radiological features do not correlate with symptoms

Pharmacological Treatment

- **Simple analgesics**
- **NSAIDS**

<u>Factors determining the choice of agents</u>

- **Risk factors for upper GIT bleeding**
  - **Age > 65 years**
  - **History of peptic ulcer disease**
  - **Concomitant use of glucocorticoids or anticoagulants**
  - **Presence of co-morbid conditions**
- **Renal impairment**
- **Cost**
- **Patient tolerance/allergies**

Pharmacological Treatment

- New class of NSAIDS: COX II inhibitors
  - Similar efficacy
  - Less GI side effects

- Opiod and opiod like drugs
  - Codeine use should be discouraged
  - Paracetamol
  - Synthetic opiod : tramadol

- Topical treatment
  - NSAIDS

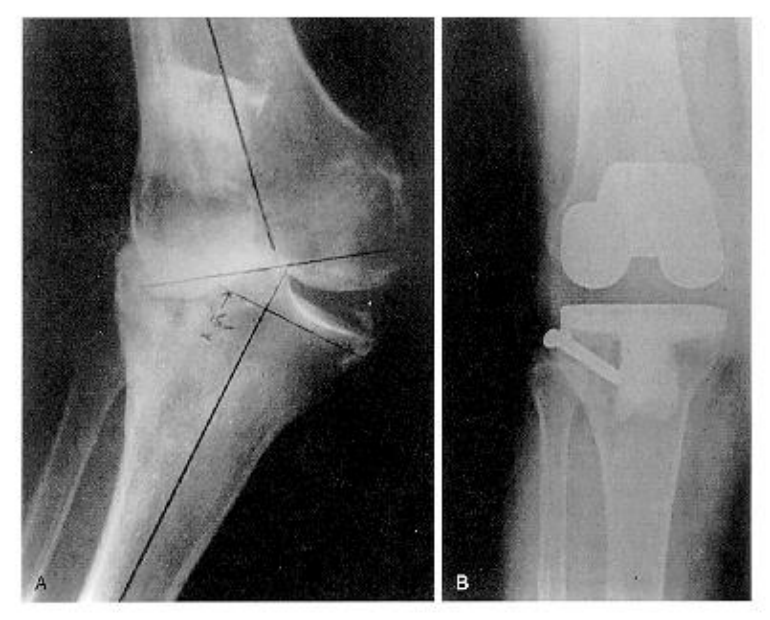
- Intra articular treatment
  - Steroids

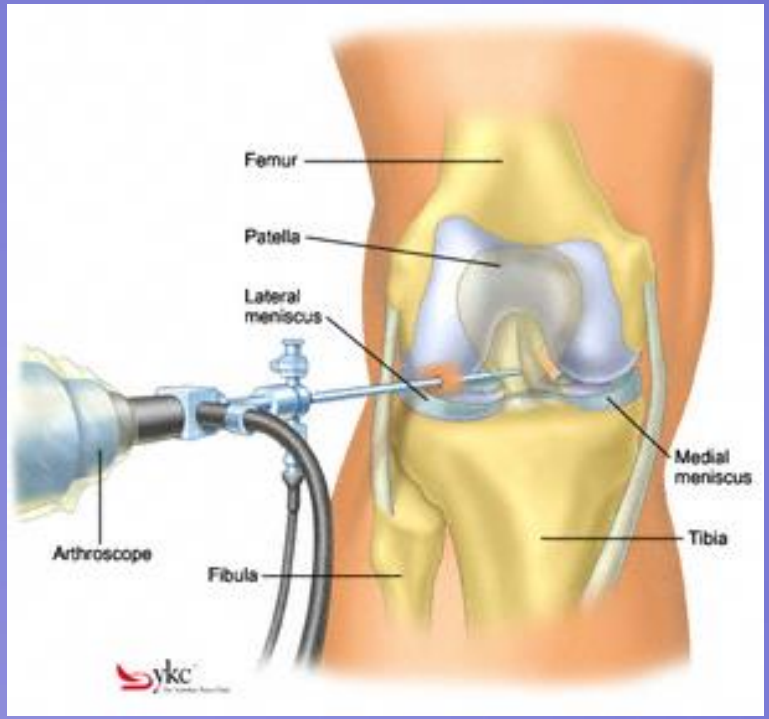
Non Pharmacological Treatment

- Education
- Physiotherapy and exercise
- Weight Loss
- Posture
- Assistive devices
- Podiatrist

Surgical

- **Arthroscopy**
- **Joint replacement**



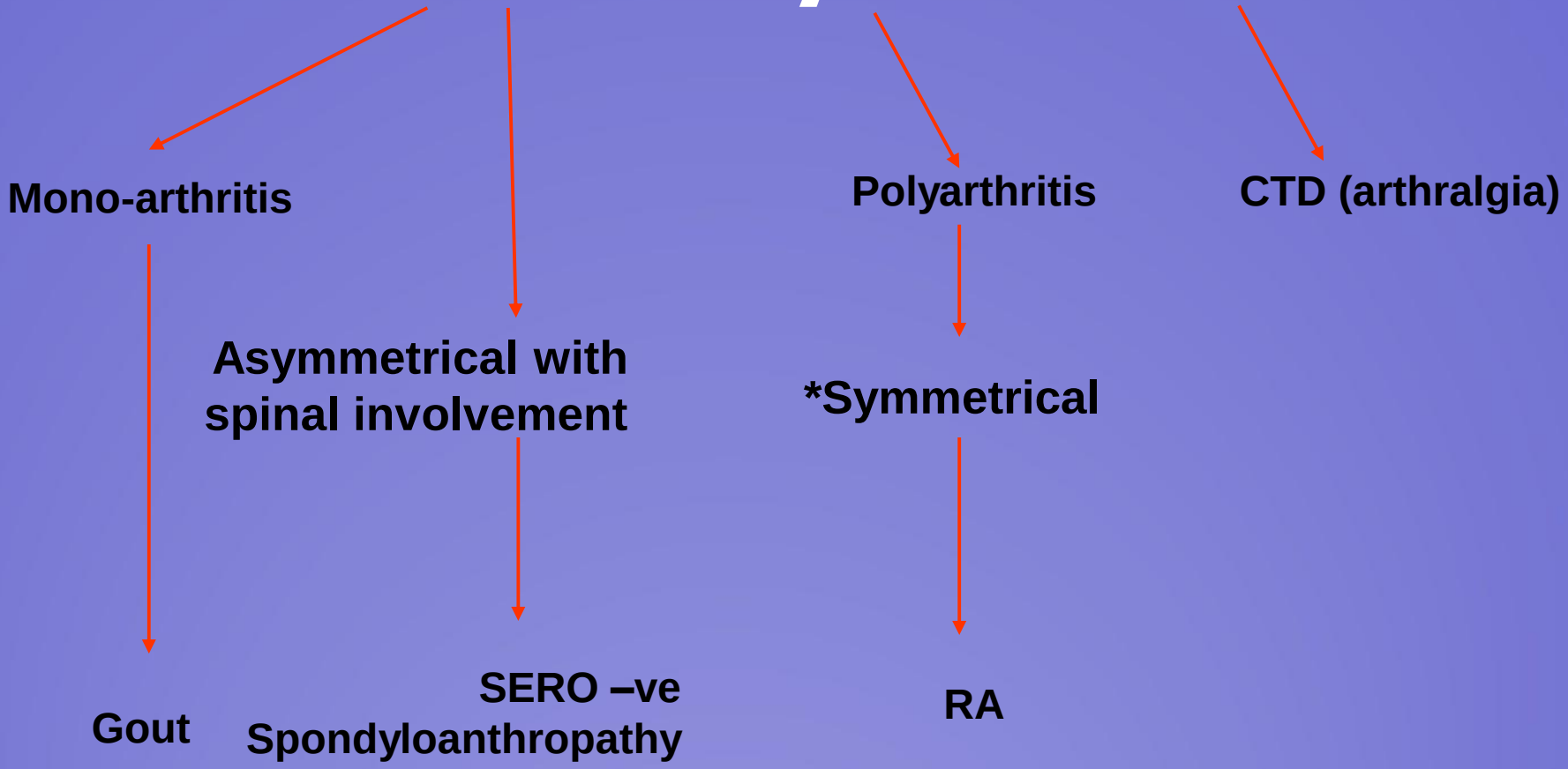


Features suggestive of inflammatory arthritis

- **Degenerative: >50 YRS**
  - **Worse with usage**
  - **Improves with rest**
  - **No systemic symptoms**
  - **Weight bearing joints**

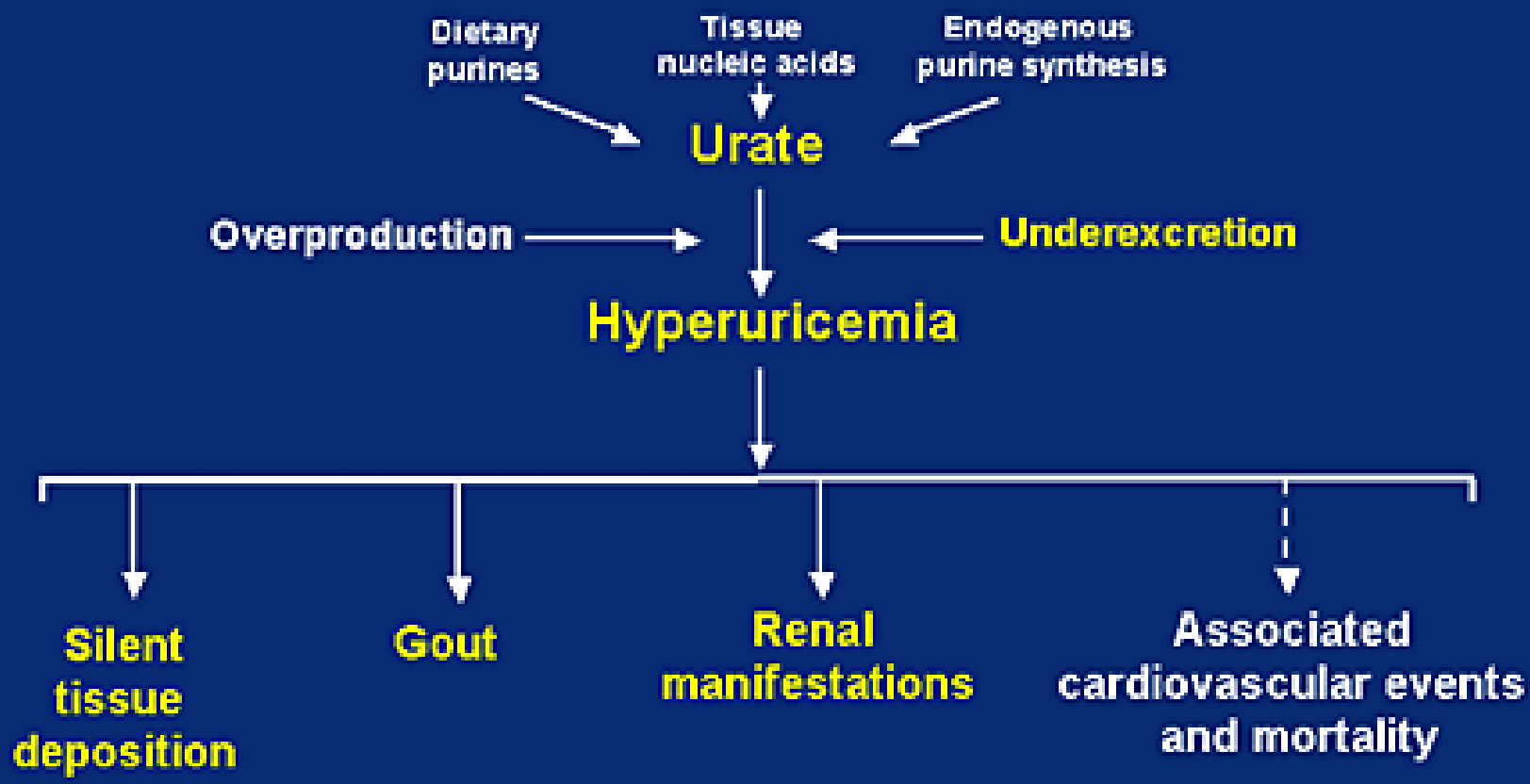
- **Inflammatory: ANY AGE GROUP**
  - **Marked morning stiffness/pain > 30 minutes**
  - **Improves with exercise**
  - **Worse with inactivity**
  - **Associated systemic symptoms**

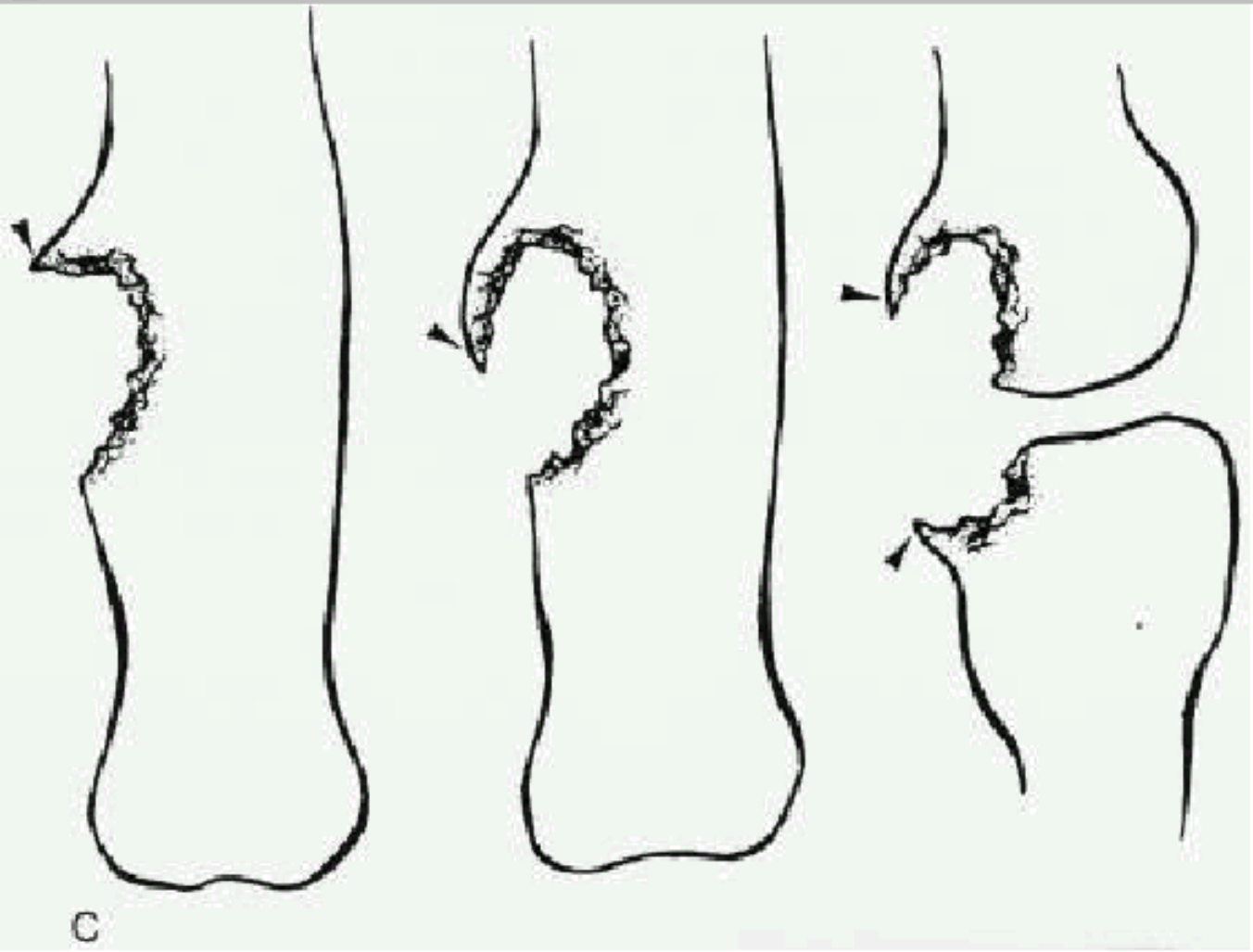
Inflammatory Arthritis



ACUTE GOUT

Review of the Hyperuricemia Cascade





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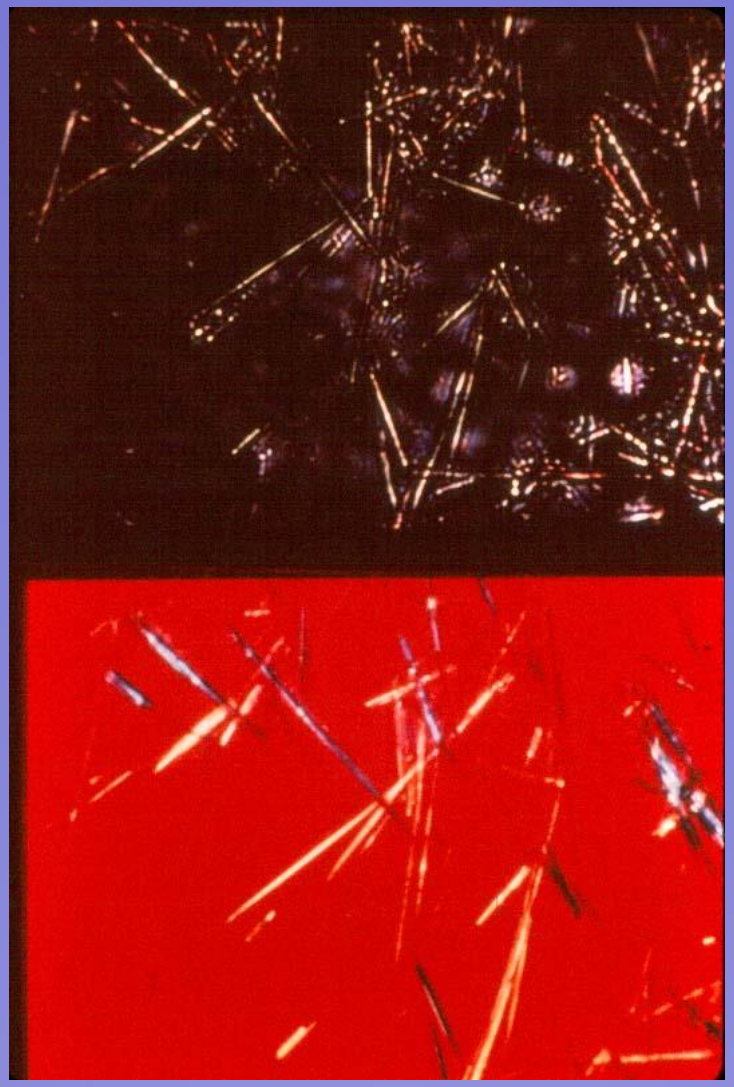
Definitive diagnosis is established by joint aspiration and identification of negatively birefringent intracellular crystals by polarized microscopy.



Correctable Factors Contributing to Hyperuricemia

- **Obesity**
- **ETOH**
- **Diuretic Therapy**
- **High purine consumption**
- **Decreased urine flow (<1 ml per minute)**

GOUT - TREATMENT

GOALS:

1. **terminate acute attack**
2. **provide rapid, safe pain/anti-inflammatory relief**
3. **prevent complications**
   - **destructive arthropathy**
   - **tophi**
   - **renal stones**

ACUTE GOUT TREATMENT

Agents:

1. **NSAIDS**

2. **Corticosteroids**

ACUTE GOUT - TREATMENT

NSAIDS

- **use in patients without contraindication**
- **use maximum dose/potent NSAID**

  e.g., Indomethacin 50 mg po t.i.d.

  Diclofenic 50 mg po t.i.d.
- **continue until pain/inflammation absent for 48 hours**

ACUTE GOUT - TREATMENT

Corticosteroid

- **use when • NSAIDS risky or contraindicated**

e.g.

renal impairment
liver impairment

- **NSAIDS ineffective**

ACUTE GOUT - TREATMENT

- **DO NOT START A URATE LOWERING DRUG (eg: allopurinol) DURING AN ACUTE ATTACK-(controversial)**

- **IF ON A URATE LOWERING DRUG, DO NOT STOP OR ADJUST DOSE.**

GOUT -PROPHYLAXIS

Colchicine (at low dose)

- **indications:**

  -until dose of urate lowering drug optimized

- **dose:**
  -0.5 mg b.i.d.

  -avoid in renal disease

URATE LOWERING TREATMENT

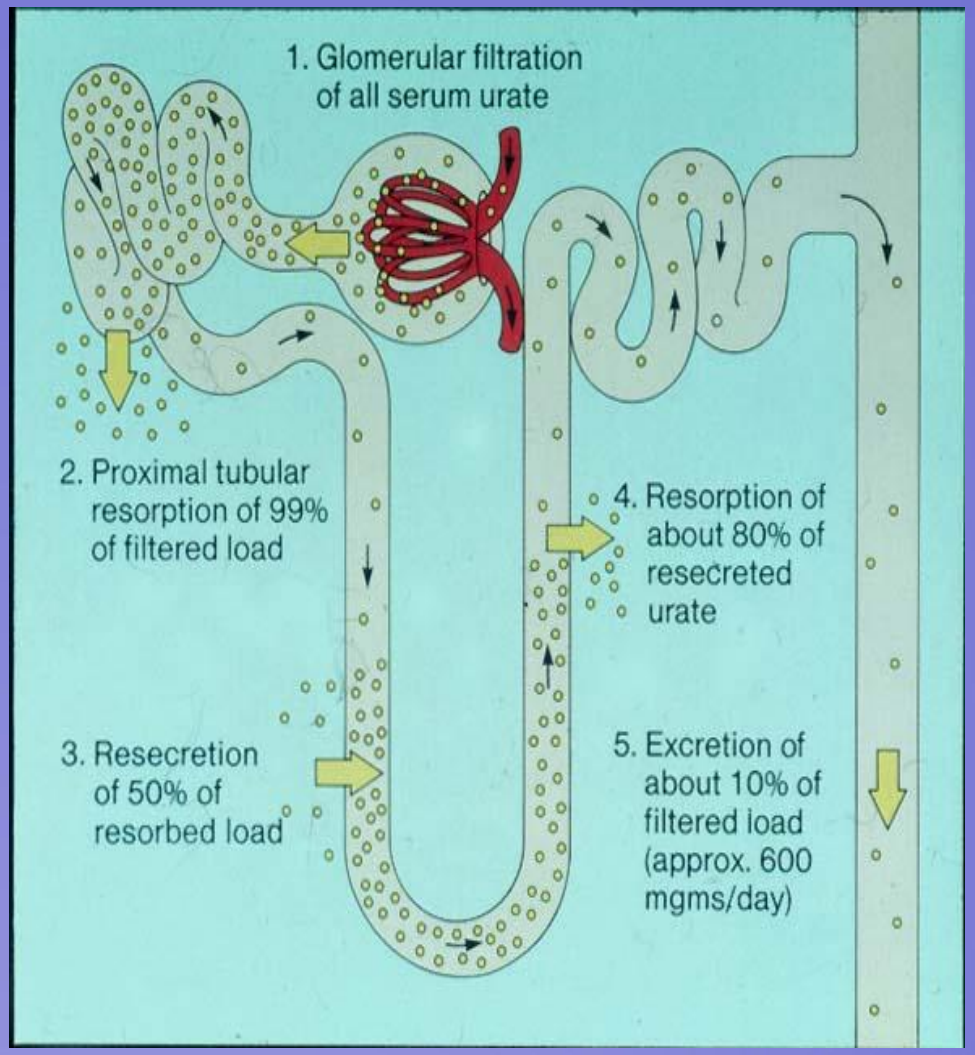
Who to treat?

1. **tophi**
2. **gouty athritis(>2 attacks per year)**
3. **radiographic changes of gout**
4. **multiple joint involvement**
5. **nephrolithiasis**

URATE LOWERING DRUGS

Uricosurics –

Probenecid



URATE LOWERING DRUGS

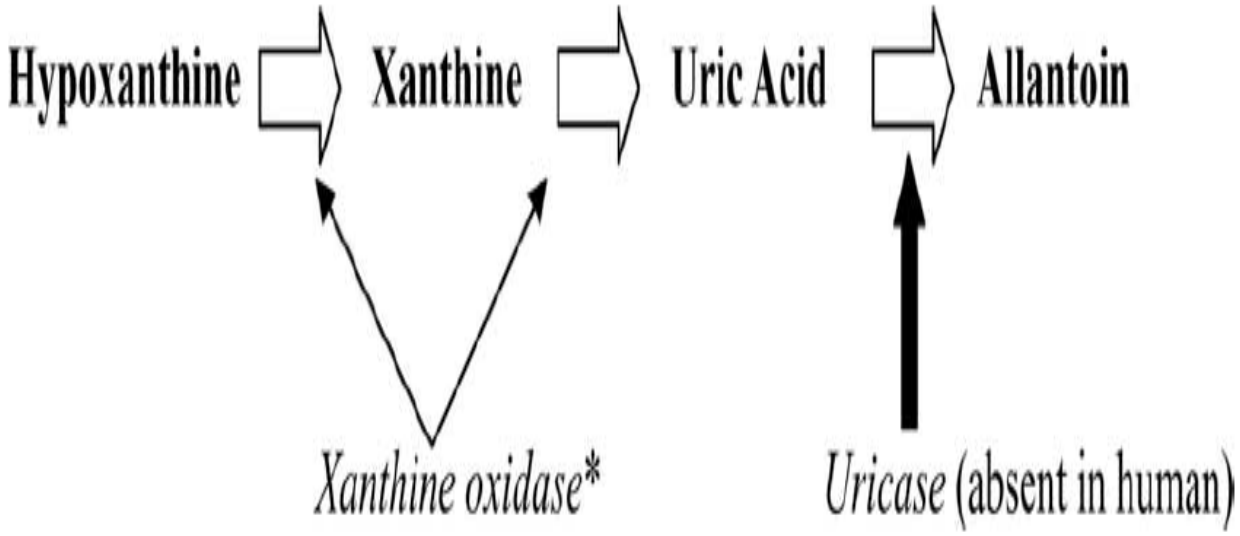


Fig. (1). Uric acid metabolism and sites of action of allopurinol and febuxostat (xanthine oxidase inhibitor*).

URATE LOWERING DRUGS

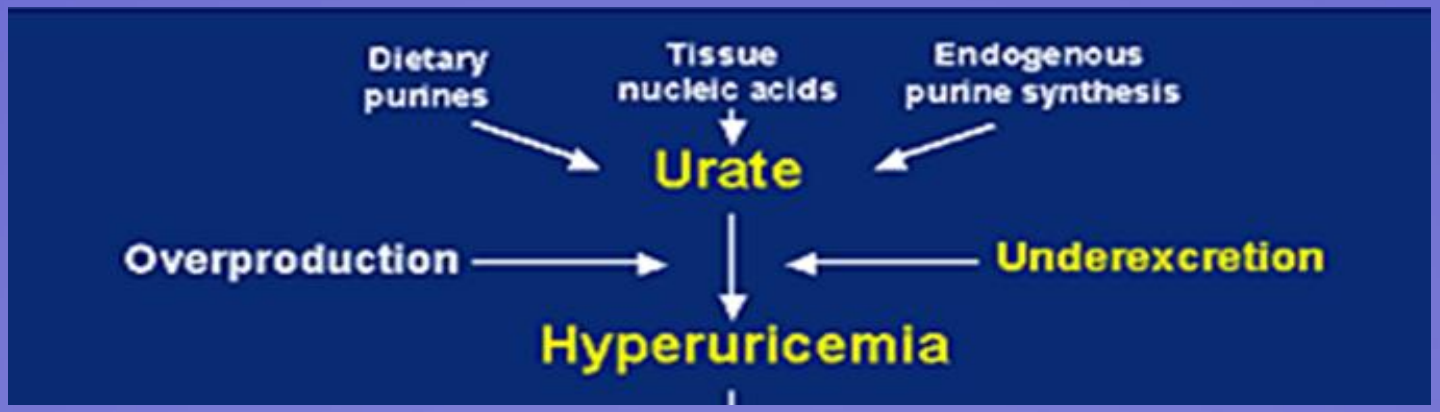
Allopurinol - an inhibitor of xanthine oxidase

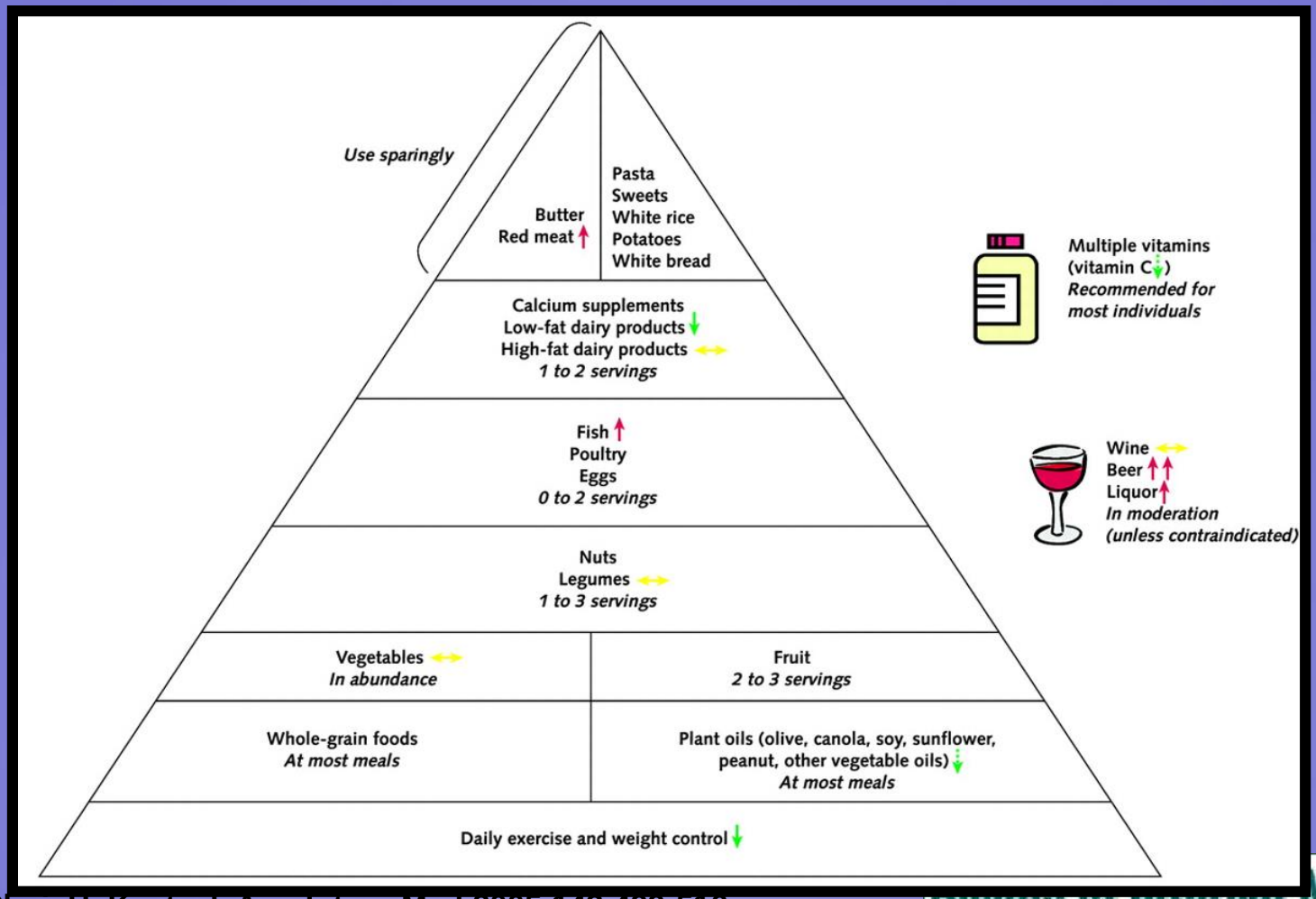
- **start low eg 50-100 mg qd**
  - **increase by 50-100mg every 2-3 weeks according to symptoms and measured SUA**

- **"average" dose 300 mg daily**
  – lower dose if renal/hepatic insufficiency

higher dose in non-responders(50% of cases)

- **prophylactic colchicine until allopurinol dose stable**



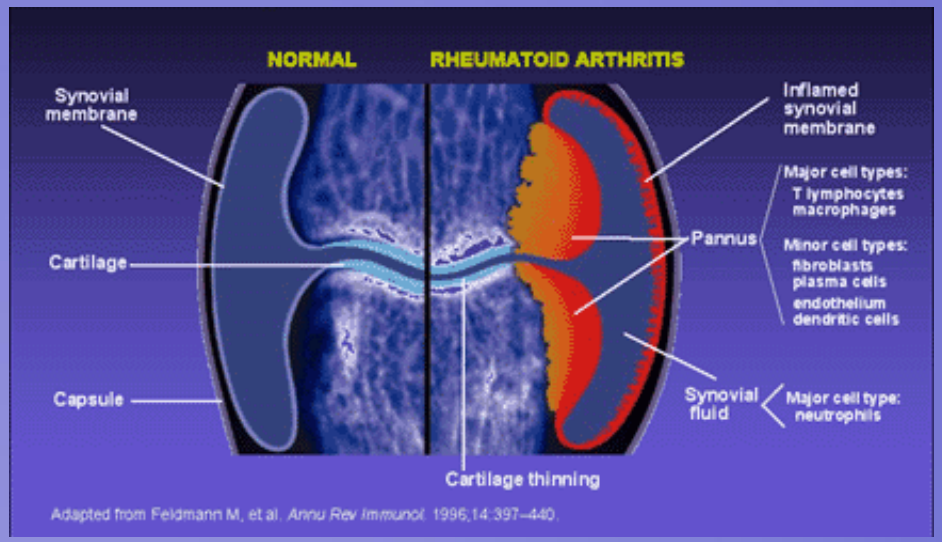


Choi, H. K. et. al. Ann Intern Med 2005;143:499-516


"I LIMIT MYSELF TO ONE GLASS OF WINE A DAY."

Autoimmune Rheumatic diseases

- **Inflammatory Arthritis – Spondyloarthropathy**
  - Rheumatoid arthritis
- **Connective Tissue Disorders**

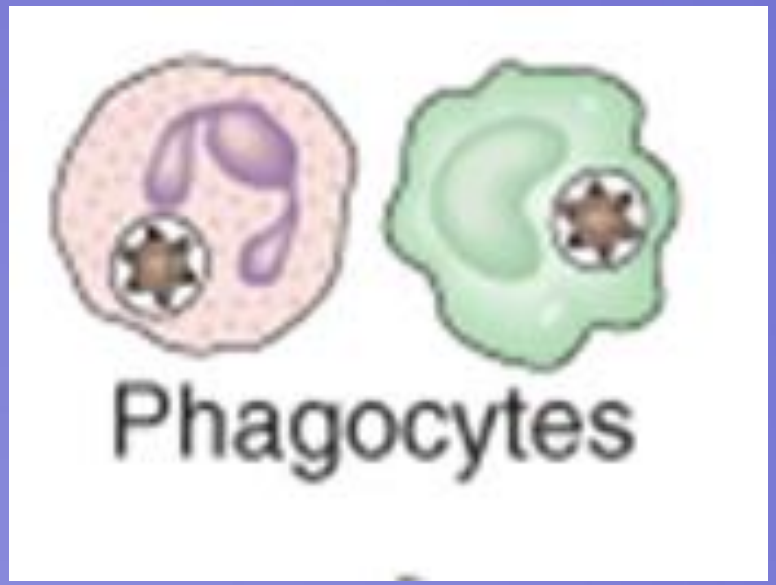


Immune system

- **Defence**
- **Infections**
- **malignancy**

THE INNATE IMMUNE RESPONSE

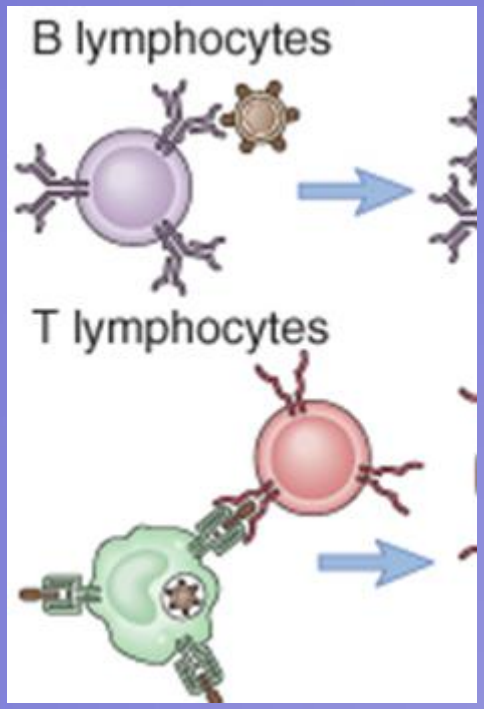
- **First line of defence/non specific**
- **Recognize common molecules of bacterial cell surface**
- **Phagocytes**
  - Cells specialized in the process of phagocytosis
    - Macrophages
      - Reside in tissues and recruit neutrophils
    - Neutrophils
      - Enter infected tissues in large numbers

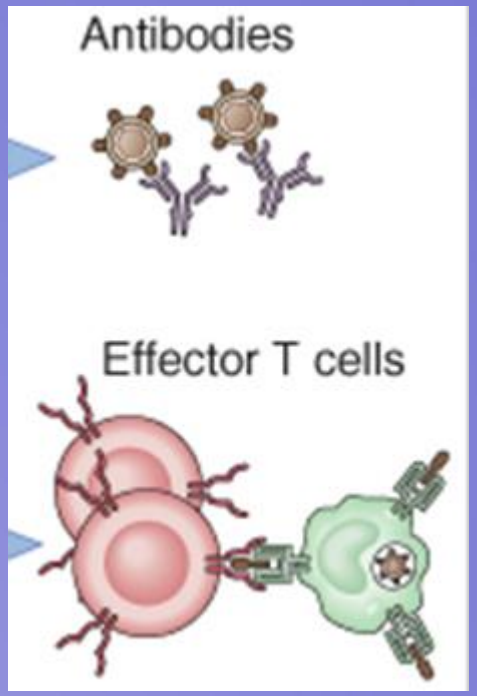


THE ADAPTIVE IMMUNE RESPONSE

- specific antibody-mediated and cell-mediated immunity

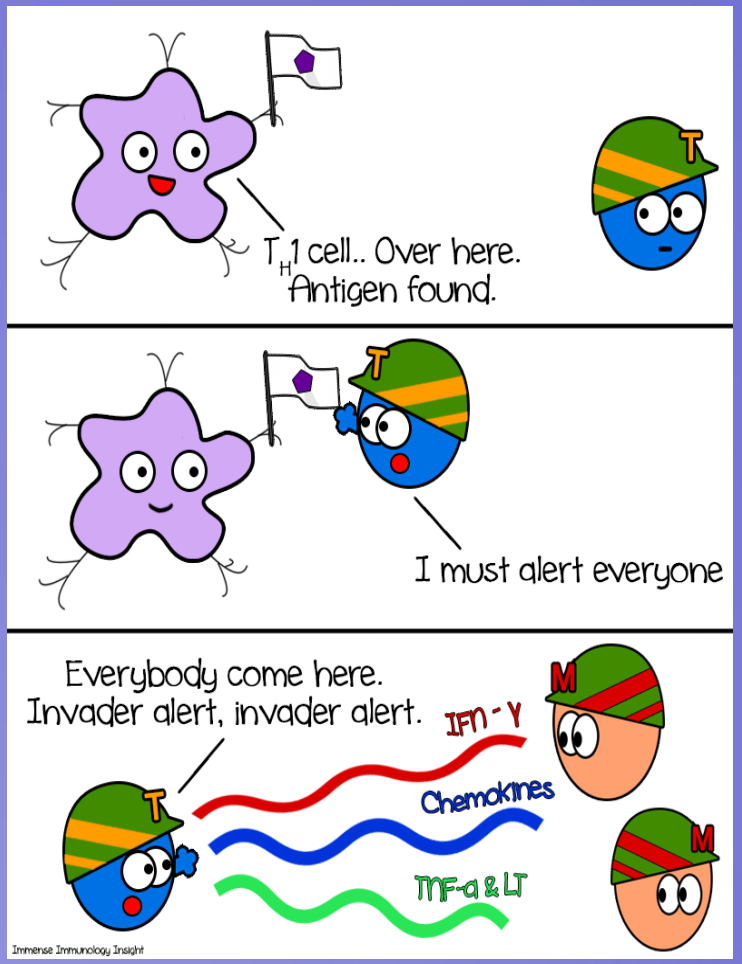
- Second line of defense
- Highly specific with memory

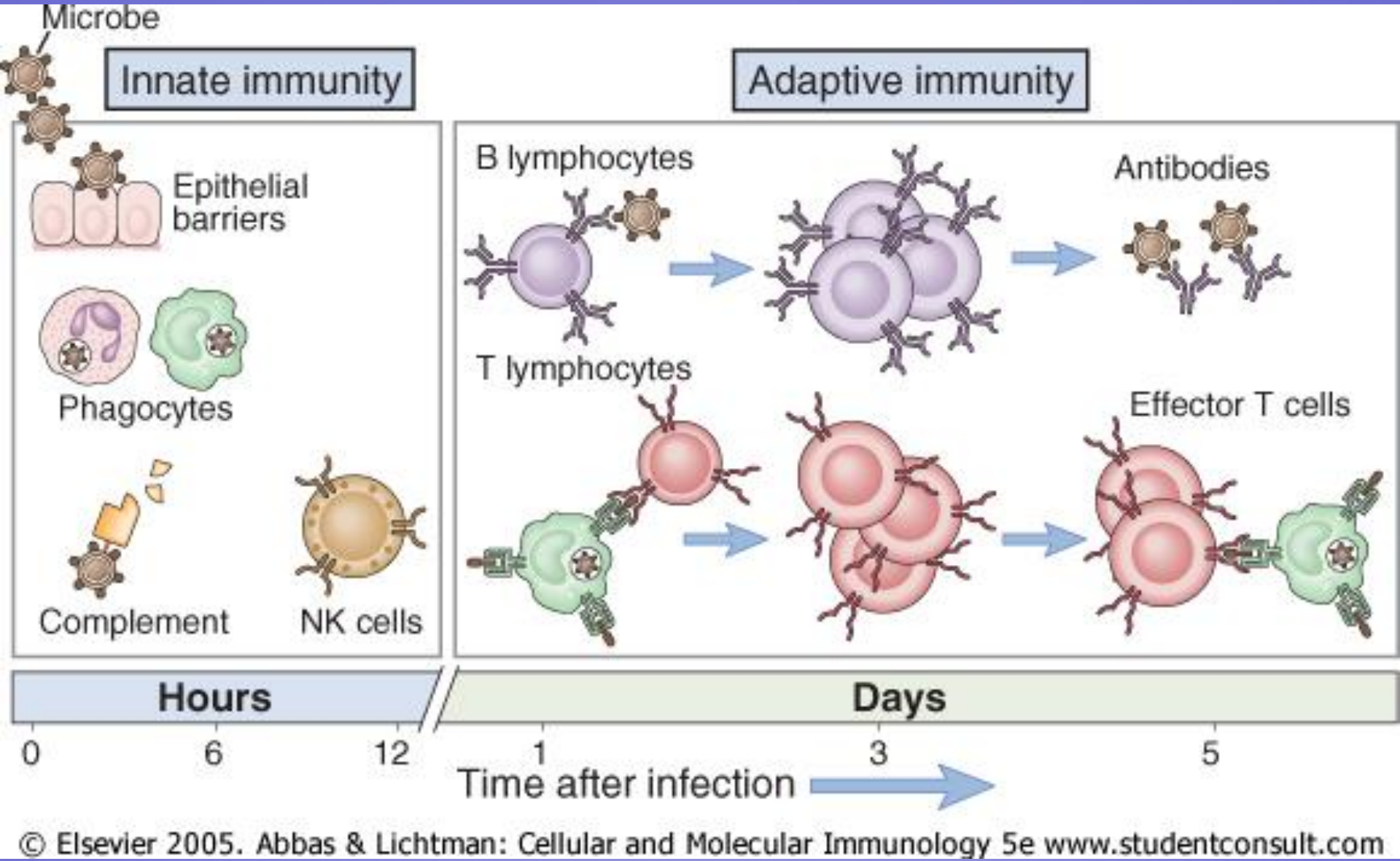




DEFENSE MECHANISMS OF THE HUMAN HOST

- **Innate Mechanisms (Innate immunity)**
- **Adaptive Mechanisms (Adaptive immunity)**
- **Co-operation between mechanisms require molecular messengers**





NATURALLY ACQUIRED IMMUNITY

- Active
  - **Antigens enter body naturally with response of the immune systems**
  - **Provides long term protection**

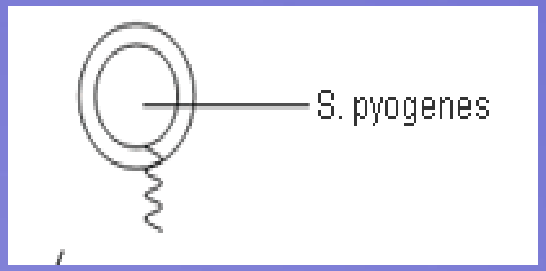
- Passive
  - **Antibodies pass from mother to**
    - **Fetus across placenta**
    - **Infant in breast milk**
  - **Provides immediate short term protection**

ARTIFICIALLY ACQUIRED IMMUNITY

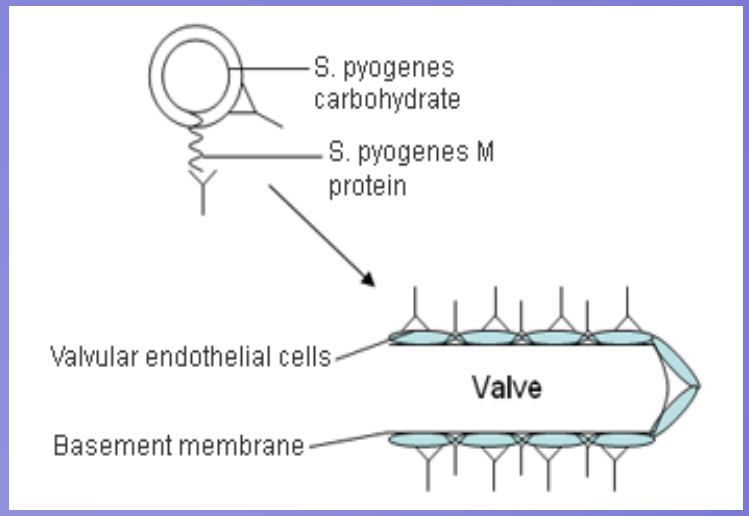
- **Antigens enter body through vaccination**
- **Provides long term protection**

DISORDERS OF THE IMMUNE SYSTEM

- Hypersensitivity Reactions
  - **Over-reaction of adaptive immune response to harmless antigens**



- Autoimmunity
  - **Misdirected immune response**
  - **? Why – Molecular mimicry**



Immune mediated Inflammatory Arthritis

Asymmetrical with spinal involvement

SERO –ve Spondyloanthropathy

Polyarthritis

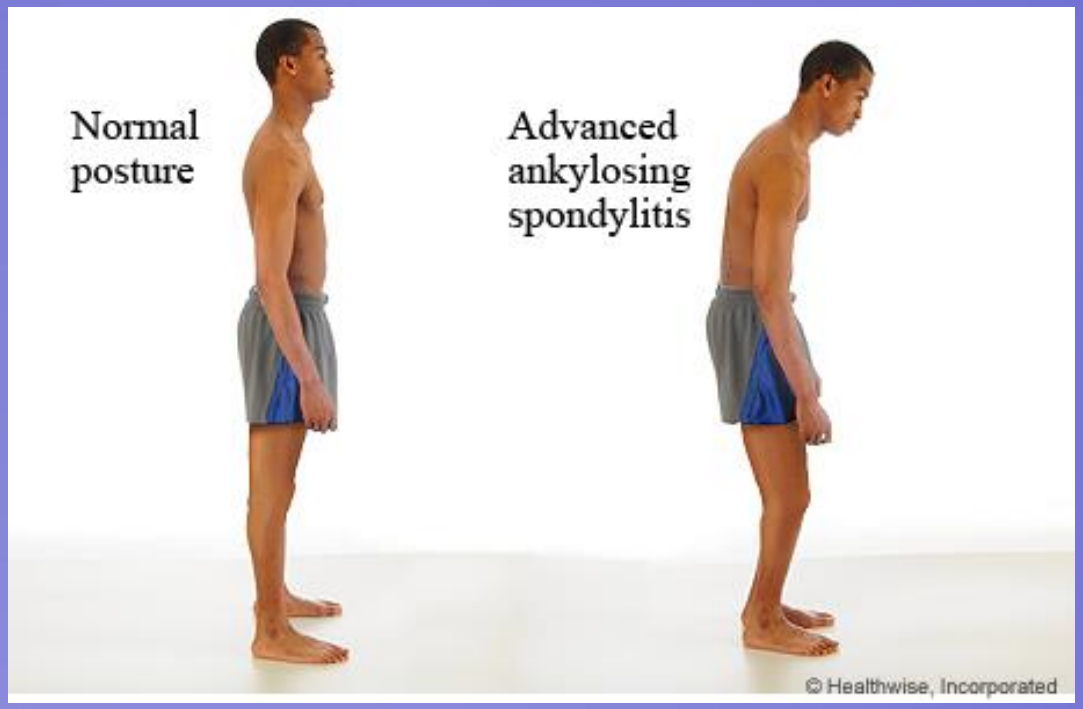
*Symmetrical

RA

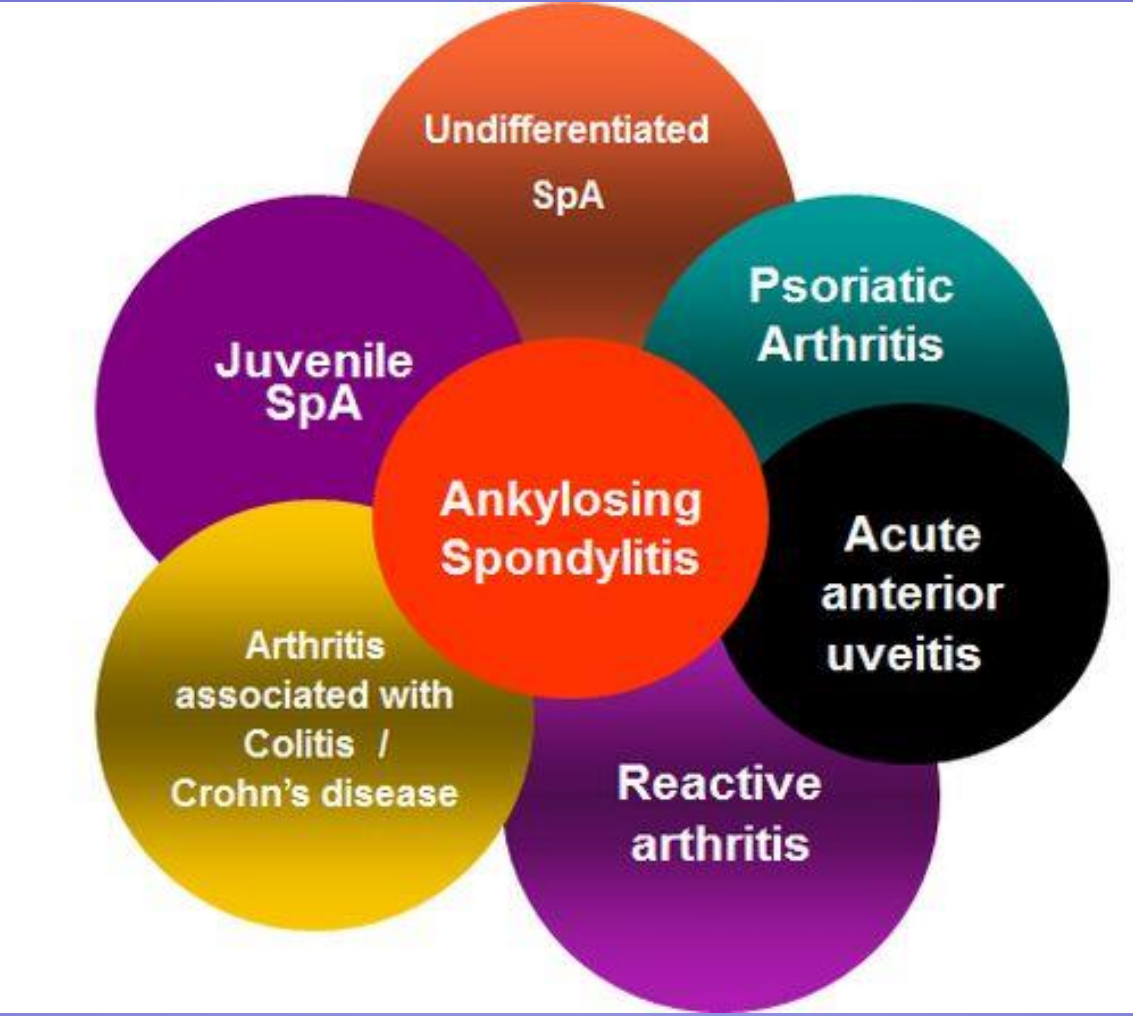
CTD (arthralgia)

Spondyloarthropathies

- **Vertebral**
- **Non vertebral**



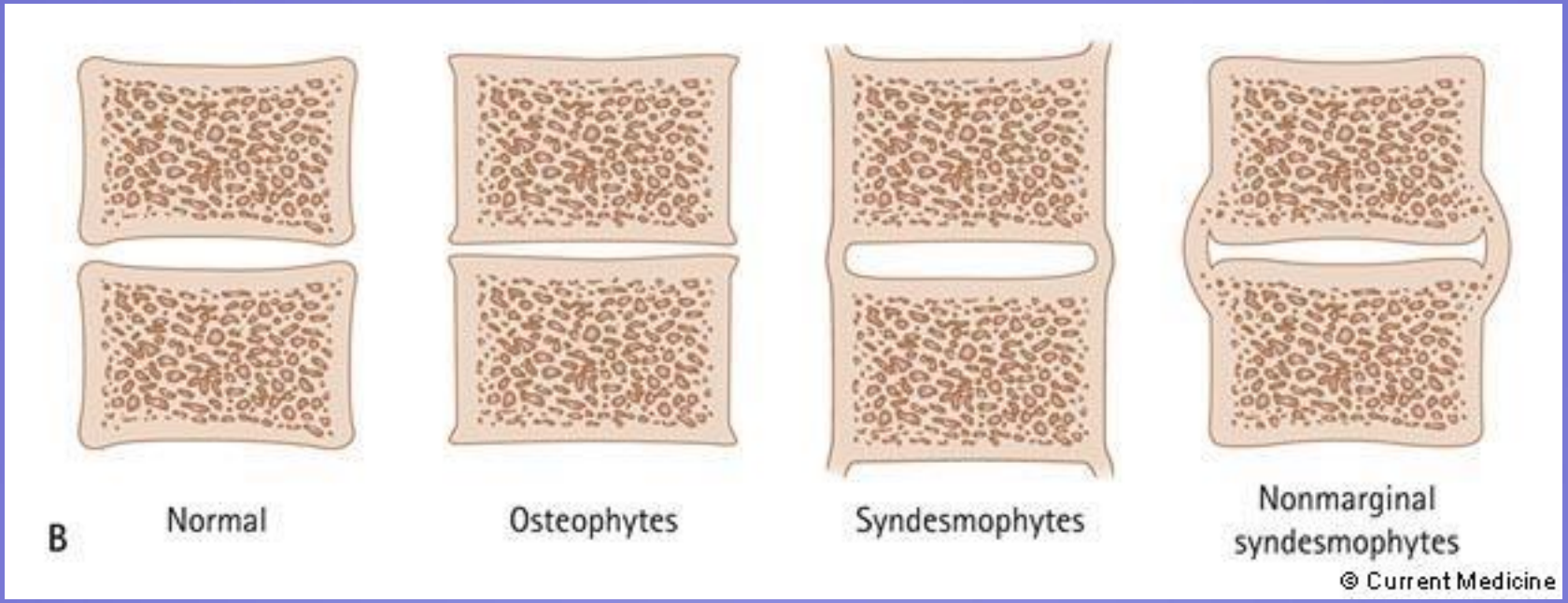
Spectrum of SpA



Ankylosing spondylitis: characteristics of back pain

- **Onset of back discomfort before age 40**
- **Insidious onset**
- **Duration longer than 3 months**
- **Associated with morning stiffness/worse with inactivity/nocturnal**
- **Improvement with exercise**
- **Buttock pain radiates post aspect of hip**

Inflammation in ankylosing spondylitis (B)

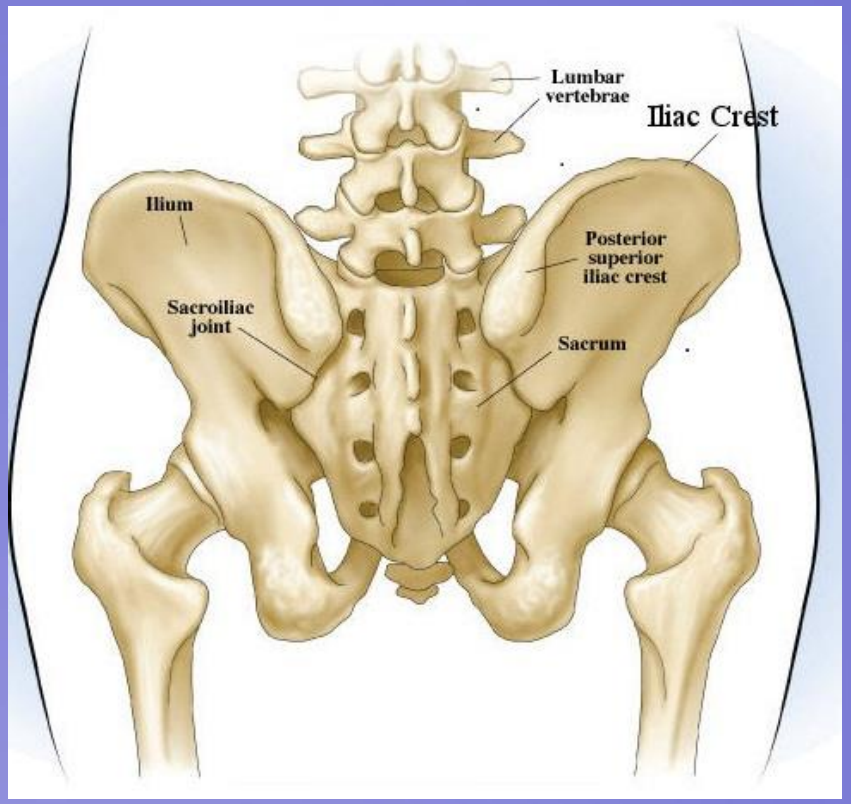


Spondylarthropathies: nonvertebral manifestations

- Asymmetric peripheral arthritis
- Sausage digits
- Enthesopathy
  - Iliac crest
  - Post iliac spine insertion
  - Achilles tendon insertion
  - Plantar fasciitis
  - Costochondritis
- Acute anterior

  uveitis/iridocyclitis

  Mucocutaneous lesions
- nail involvement

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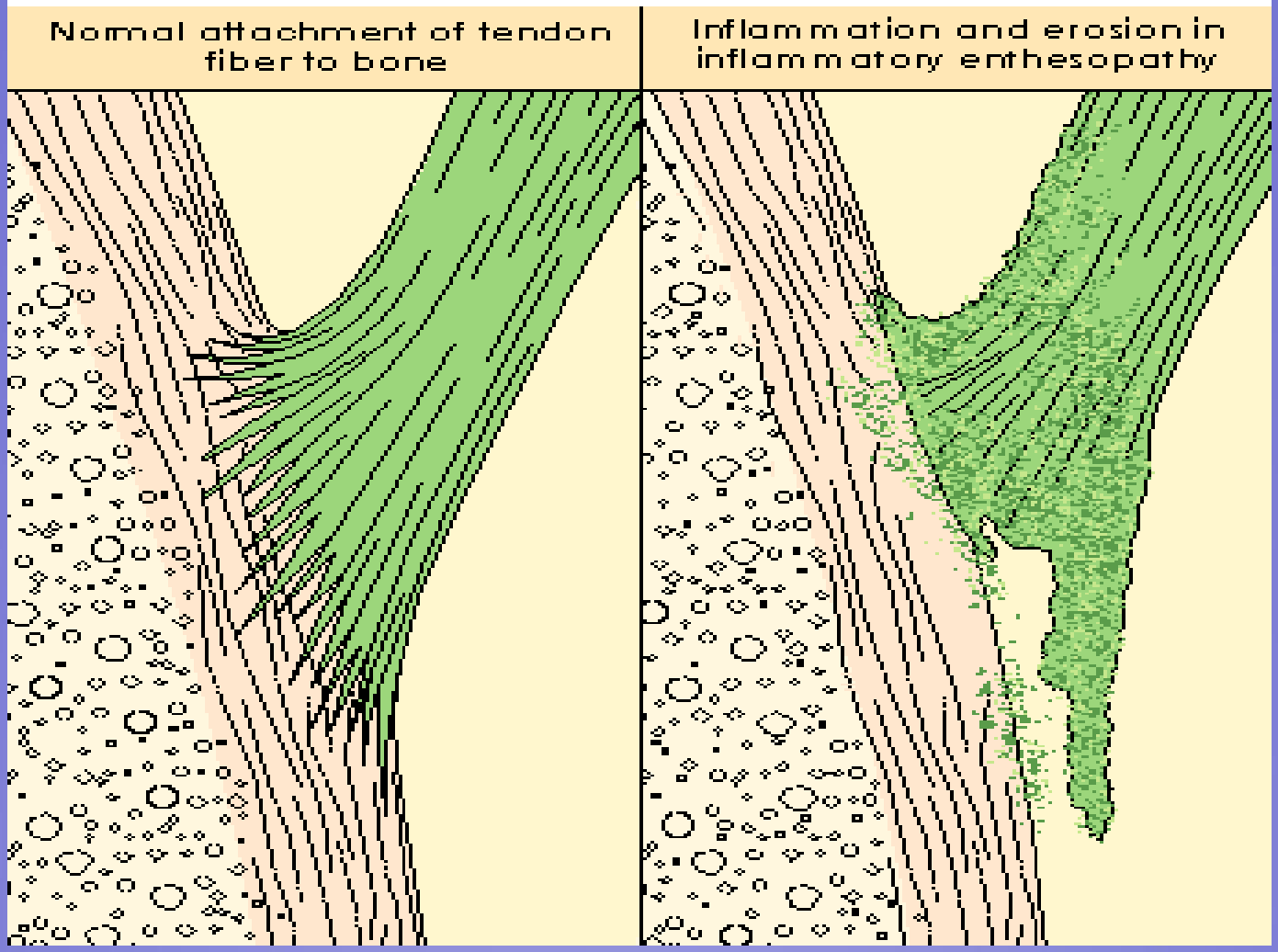
INFLAMMATORY ENTHESOPATHY OF A TENDON ATTACHMENT



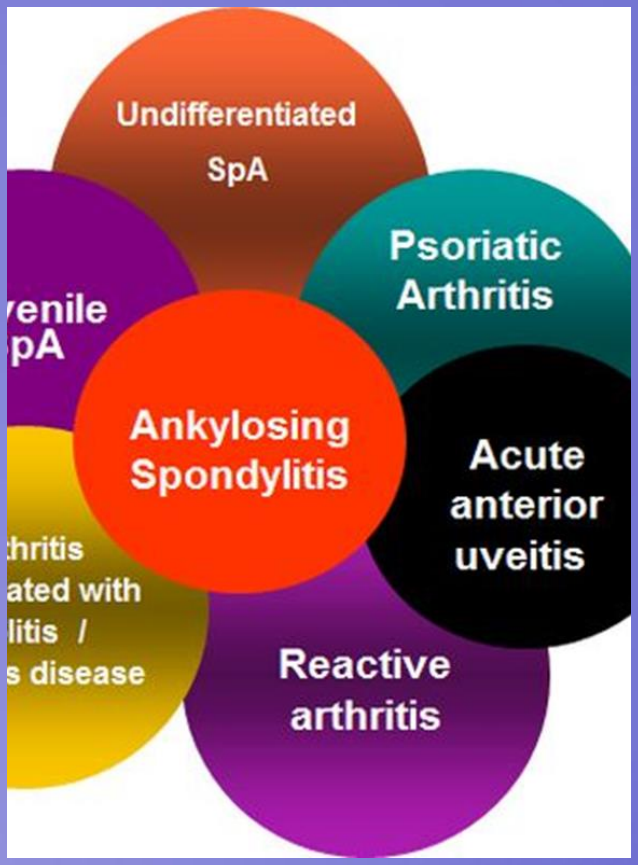
Joint Manifestations in HIV Infection

- **Musculoskeletal manifestations can occur at any phase of the infection but they are commonly seen in late phase:**

- **Musculoskeletal conditions affect 72% of HIV-infected individuals**

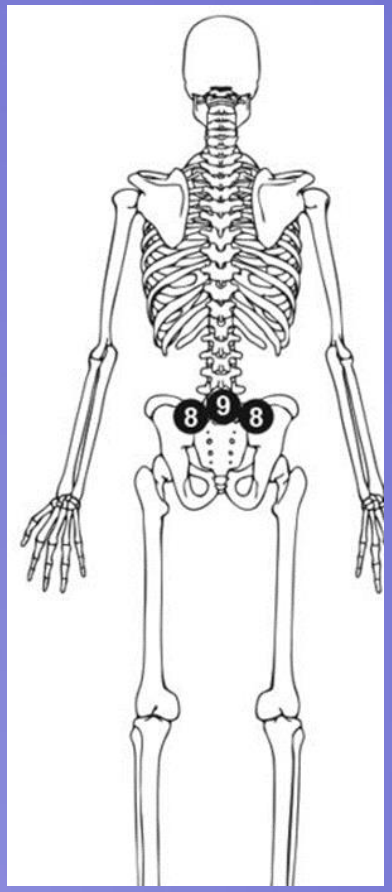
Joint manifestations in HIV include –

- **HIV associated arthralgia**
- **Painful articular syndrome**
- **HIV associated arthritis**
- **Reactive arthritis**
- **Psoriatic arthritis**
- **Undifferentiated spondyloarthritis**
  - Enthesopathy



Principles of therapy Ankylosing Spondylitis

- **Physiotherapy**
- **Posture**
- **NSAIDs**
- **Intralesional steroids - enthesitis**
- **Refractory- TNF blockade**



RHEMATOID ARTHRITIS

© www.rheumtext.com - Hochberg et al (eds)

ACR/EULAR Criteria- RA

Four Domains

- **Joint involvement**
- **Serology**
- **Duration of synovitis**
- **Acute phase reactants**

Domain: Joint involvement

- 1 medium-large joint (0 points)
- 2-10 medium-large joints (1 point)
- 1-3 small joints (2 points)
- 4-10 small joints (3 points)
- More than 10 small joints (5 points)

- swollen or tender joints excluding DIP hands and feet,1st MCP and 1st MTP.

Domain: Serology

- **rheumatoid factor or anti–citrullinated peptide antibody negative (0 points)**
- **At least one of these two tests are positive at low titer (2 points)**
- **At least one test is positive at high titer->three times the upper limit of normal (3 points)**

Domain: Duration of synovitis

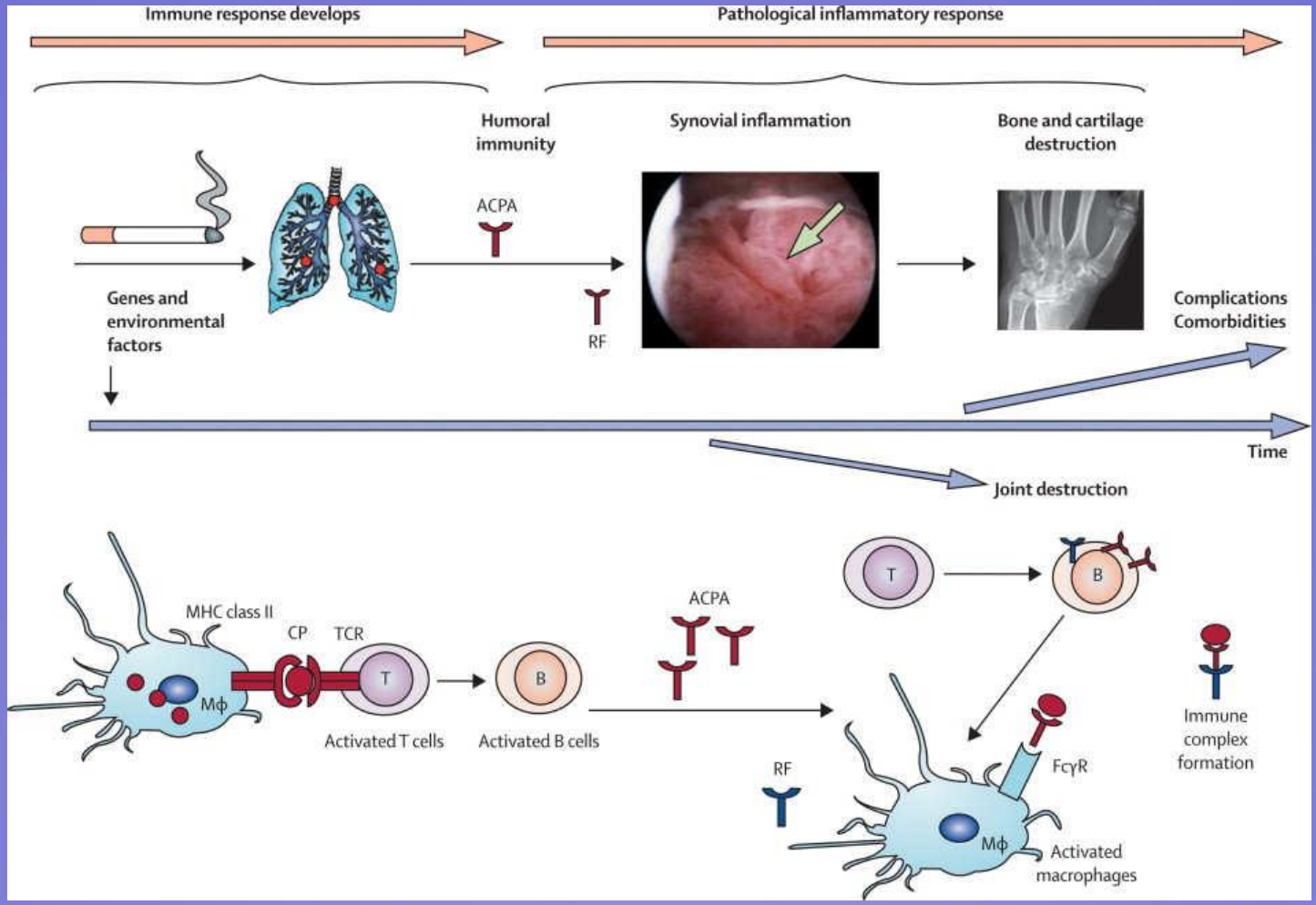
- **Less than 6 weeks (0 points)**
- **6 weeks or longer (1 point)**

Domain: Acute phase reactants

- **C-reactive protein - erythrocyte sedimentation rate is abnormal (0 points)**
- **Abnormal CRP or abnormal ESR (1 point)**

Patients are definitively diagnosed with RA if they score 6 or more points

RA - PATHOGENIC MECH.



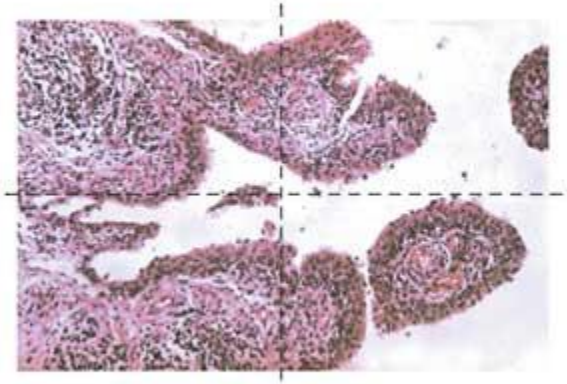
Klareskog L, Catrina A, Paget S: Lancet (Seminar) Feb 21, 2009

Pathology RA-early/late

Cellular recruitment
Adhesion-molecule expression
Neovascularization
Synovial addressins

Immunologic activation and organization
T-cell activation
Co-stimulation
Lymphoid structure

TNF, IL-1
IL-6, IL-18
VEGF
Chemokines



IL-23, IL-27
IL-12, IL-15, IL-18
Chemokines, LTα

IFNα/β, IL-15
TNF

IL-17, BMPs
RANKL, TGFβ

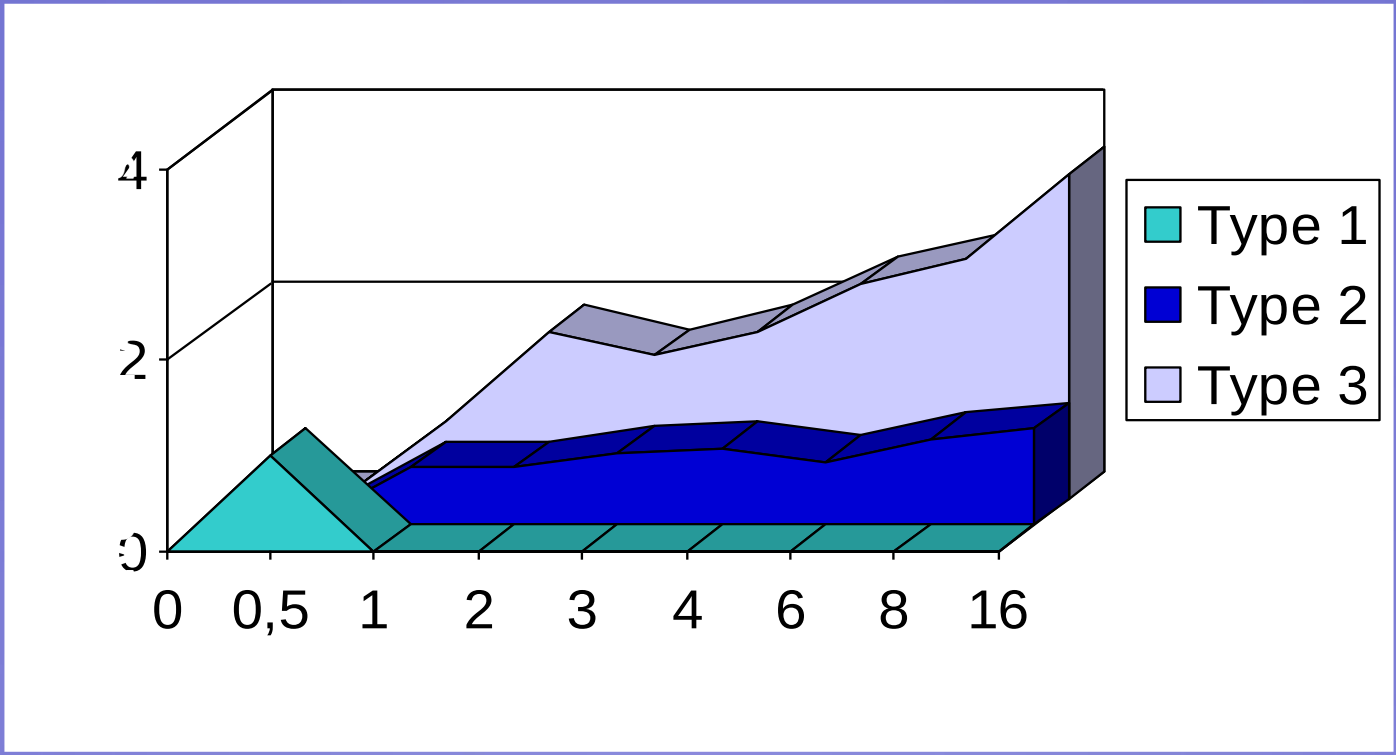
Cellular retention and survival
Apoptosis
Lymphatic endothelium
Lining layer structure (cadherin)

Tissue response
Fibrosis
Matrix destruction
Biomechanics

EARLY RA

- Symptoms >12 weeks.
- MCP/MTP tenderness.
- Morning stiffness >30 min.
- 3 or more swollen joints.

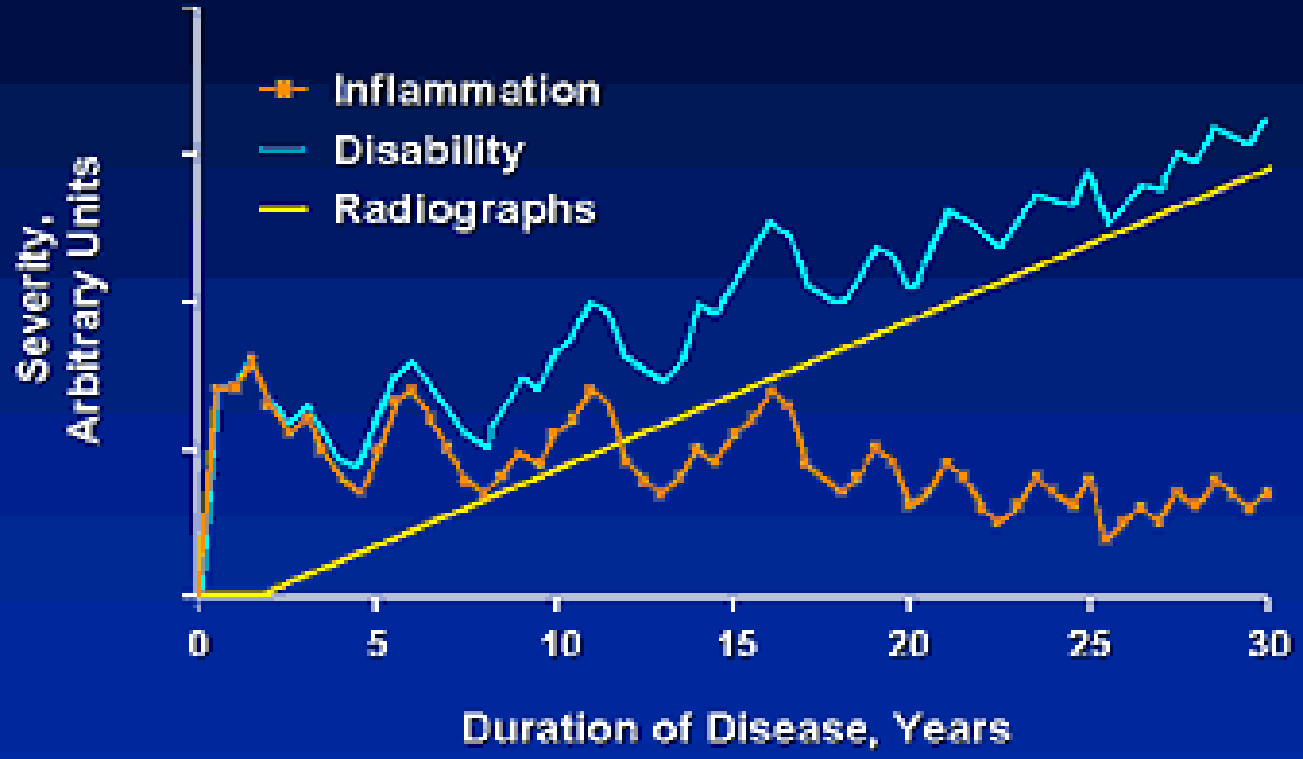
What is the natural history of RA?



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.

Course of RA: Schematic Representation



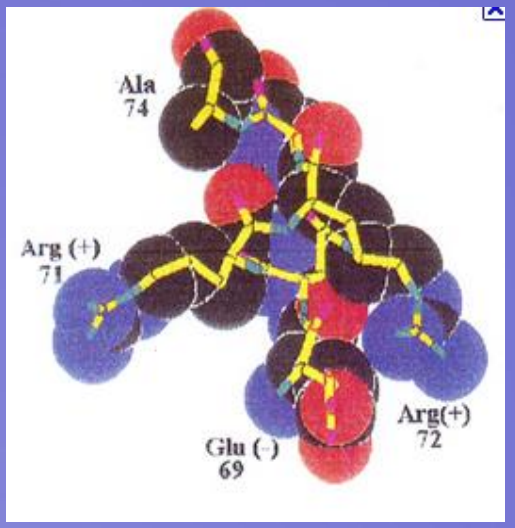
Kirwan. *J Rheumatol*. 1999;26:720-725.

Poor prognostic markers:

- RF ⊕; Anti CCP ⊕.
- Poor functional class.
- > 20 joints involved.
- Extra-artricular manifestations.
- ↑ ESR/ CRP.
- Radiographic erosions within 2 years of disease onset.
- HLR DR_4/Sub classes.
- Education level.

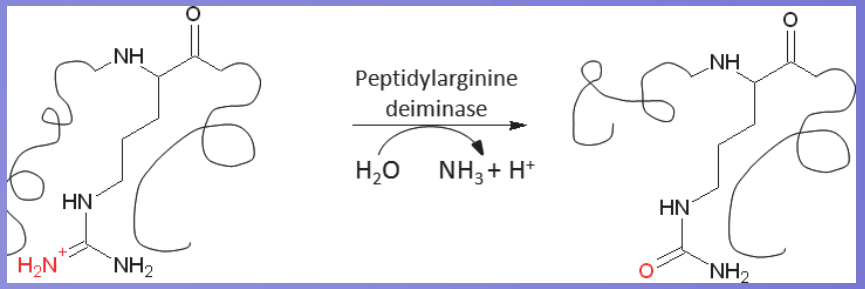
Poor prognostic factors

- HLA DR –SE
- Increased risk
- Severity



Citrulination of arginine

citrullinated peptides



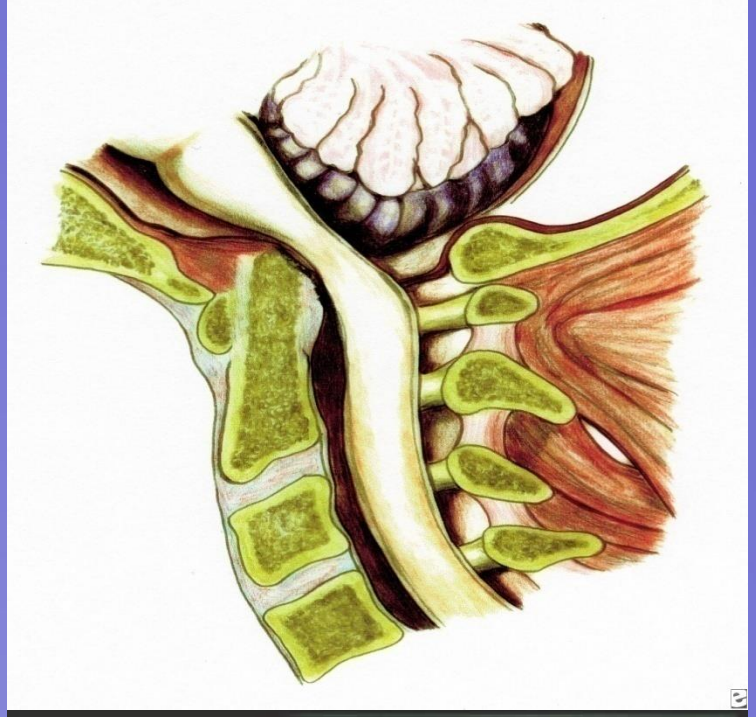
Poor prognostic factors

Extra-articular Manifestations of RA

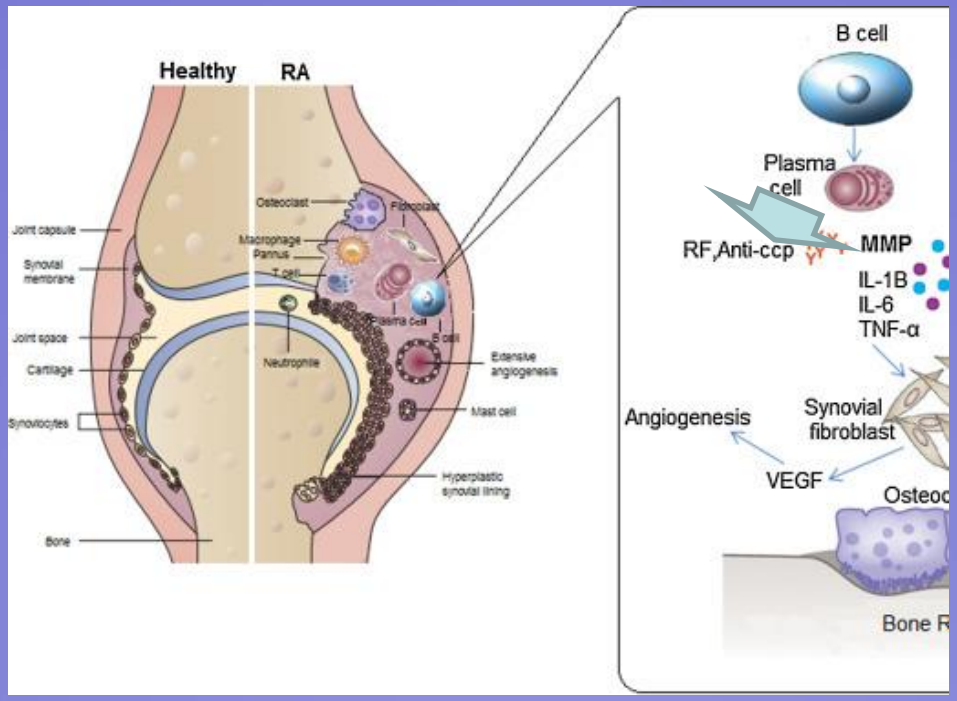
Cutaneous	Ocular	Pulmonary	Cardiac	Neurologic	Hematologic
•Nodules •Vasculitis	•Sicca •Episcleritis •Scleritis	•Pleuritis •Nodules •Interstitial lung disease •Fibrosis	•Pericarditis •Atherosclerosis •Myocardial infarction	•Peripheral-neuropathy •Cervical myelopathy	•Leukopenia •Anemia of chronic disease •Lymph-adenopahty

RA - Cervical Spine

- Atlantoaxial Instability
  - C1-C2
  - Erosion of odontoid process of C2
    - Cranial settling
  - Neck/Occiput pain, Paresthesias, Pathologic reflexes

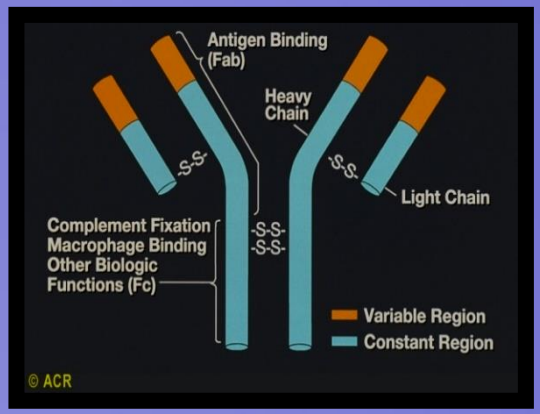


Auto antibodies-inflammatory arthritis



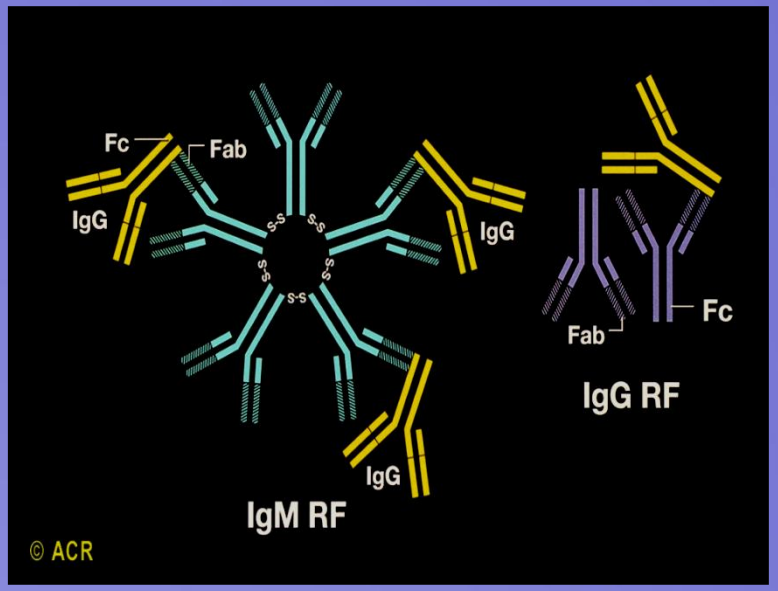
What are rheumatoid factors, and how are they measured?

- Autoantibody directed against antigenic determinants on the Fc fragment of immunoglobulin G.
- RF may be of any isotype:
  - IgM, IgG, IgA, or IgE.
- IgM RF is the only one routinely measured by clinical laboratories.



RF Positive

- may antedate clinical manifestations.
- RF positive in only 50-60% and early disease
- RF-positive tend to have more aggressive disease
- Increased risk extra-articular manifestations.



Causes of a Positive Rheumatoid Factor.

- Chronic disease, especially hepatic and pulmonary diseases
- Rheumatoid arthritis, 80-85% of patients
- Other rheumatic diseases - SS (75-95%).
- Neoplasms, especially after radiation or chemotherapy
- Infection, e.g., AIDS, tuberculosis, subacute bacterial endocarditis, hepatitis C.

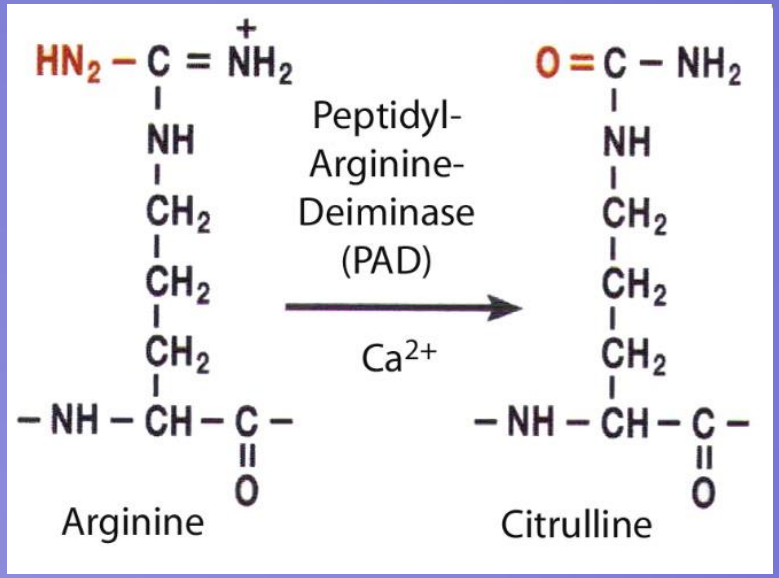
Rheumatoid factors are present in some normal people, especially the elderly.

Frequency of Positive RF in Normal Individuals of Different Ages

AGE	FREQUENCY OF RF
20-60 yrs	2-4%
60-70 yrs	5%
>70 yrs	10-25%

Anti-cyclic citrullinated peptide antibodies(ACPA)

- **Citrullination**
- **'normal' chemical change in inflammation.**
- **Genetic factors - generate Ab**
- **Environmental Triggers**
  - **smoking**
  - **Infections**

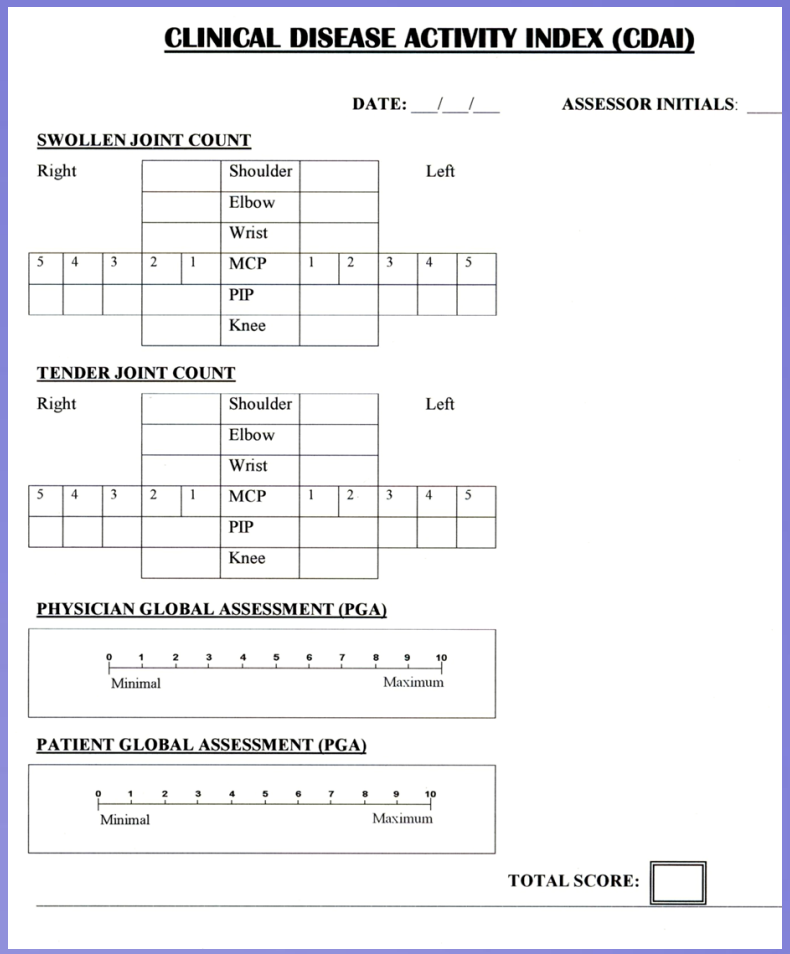


Anti-cyclic citrullinated peptide antibodies

- **Highly specific (98%) and moderately sensitive (68%) for RA.**
- **May predate onset of RA**
- **Predict progression to RA - patients with UIA**
- **Markers of poor prognosis or of disease severity**

Serial testing for change in titre not useful for measuring disease activity :

- **RF**
- **CCP Ab**



CLINICAL DISEASE ACTIVITY INDEX (CDAI)

DATE: ___/___/___ ASSESSOR INITIALS: ____

SWOLLEN JOINT COUNT

Right											Left
					Shoulder						
					Elbow						
					Wrist						
5	4	3	2	1	MCP	1	2	3	4	5	
					PIP						
					Knee						

TENDER JOINT COUNT

Right											Left
					Shoulder						
					Elbow						
					Wrist						
5	4	3	2	1	MCP	1	2	3	4	5	
					PIP						
					Knee						

PHYSICIAN GLOBAL ASSESSMENT (PGA)

0 1 2 3 4 5 6 7 8 9 10

Minimal Maximum

PATIENT GLOBAL ASSESSMENT (PGA)

0 1 2 3 4 5 6 7 8 9 10

Minimal Maximum

TOTAL SCORE:

How should Rheumatoid Arthritis disease activity be meesured in Clinical Care

- "Clinicians may all too easily spend years writing 'doing well' in the notes of a patient who has become progressively crippled before their eyes".
- Clin Exp Rheumatol 2005; 23 (Suppl 39)
-

Measures of RA disease activity

- Measures used in assessment of RA disease activity include:
  - formal joint counts by the physician
  - laboratory tests
  - patient self-report questionnaire measures of physical function
  - pain
  - global status
  - Fatigue
  - Duration morning stiffness

Challenges to measures of RA disease activity

- The number of swollen and tender joints -the best measure of status in usual clinical care.
- Joint counts are not as sensitive for detecting inflammatory activity as ultrasound or magnetic resonance imaging.
- ESR and CRP are normal in about 40% of patients with RA.

Cut off values for different disease activity states

Index	Disease activity state	Original definition	Newly proposed definition
CDAI	Remission	-	≤ 2.8
	Low disease activity	-	≤ 10
	Moderate disease	-	≤ 22
	activity	-	> 22
	High disease activity		

Inflammation and co morbidity

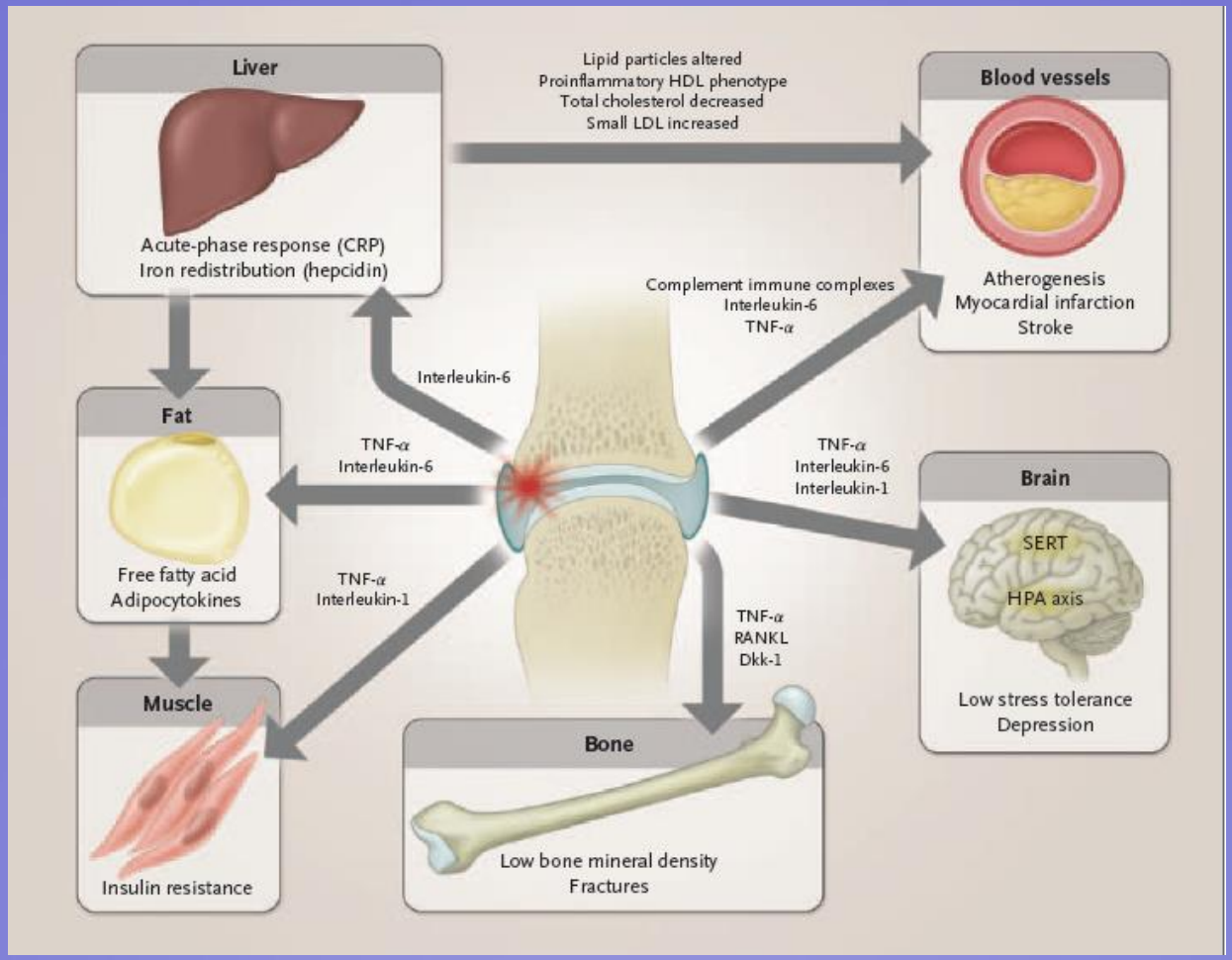


Fig :NEJM Dec 2011 365;23 p 2210

CARDIOVASCULAR DISEASE

- **Multifactorial:**
  - Traditional risk factor.
  - Systemic inflammation.
    - BMI < 20.

- **Medication:**
  - Steroids.
  - Nsaids.

Pharmacological treatment

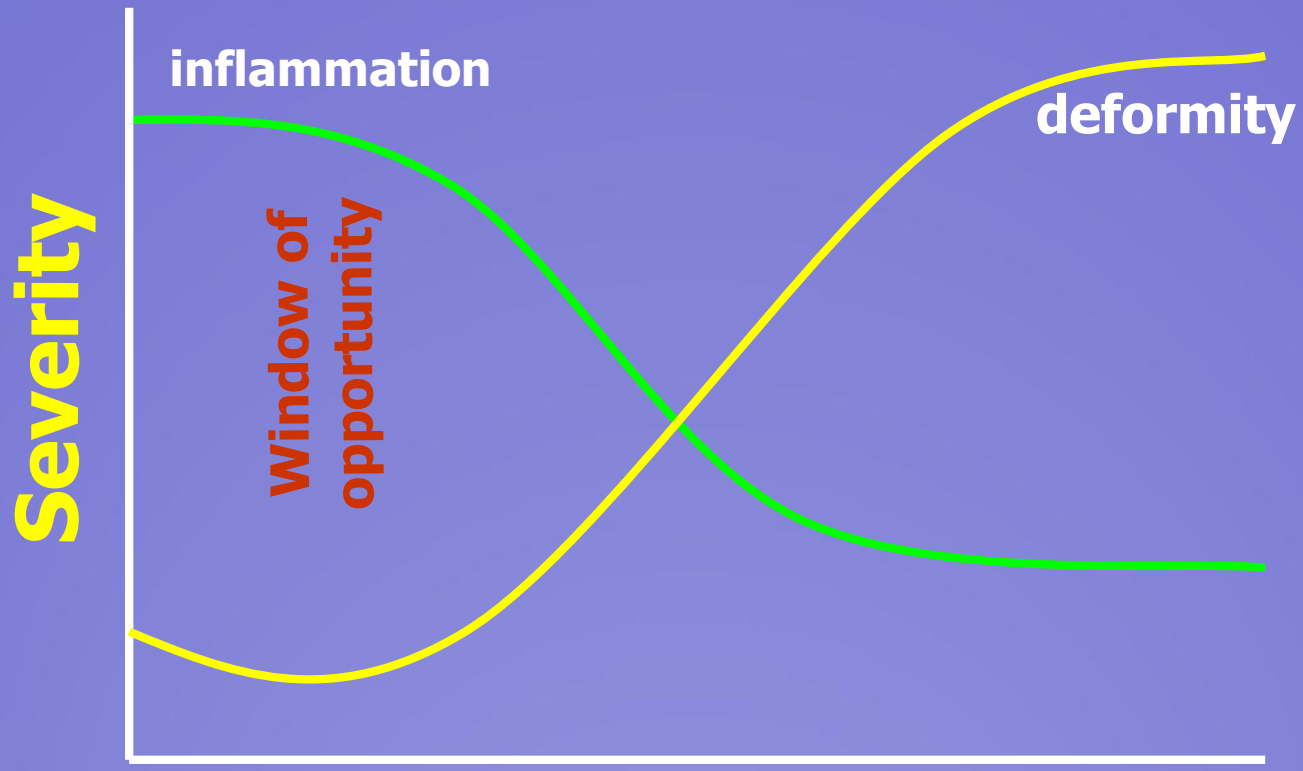
- Disease modifying anti-rheumatic drugs cornersone of therapy
- Conventional and biologic
- Measuring disease activity essential component

Pain management

- **Does not modify disease progression in inflammatory arthritis**

Principles of management

- **Paradigm shift:**
  - **Early aggressive treatment with DMARDs.**
  - **Window of opportunity first 2 years.**



Importance of early intervention

DMARDs

- Pain management ≠ Disease management

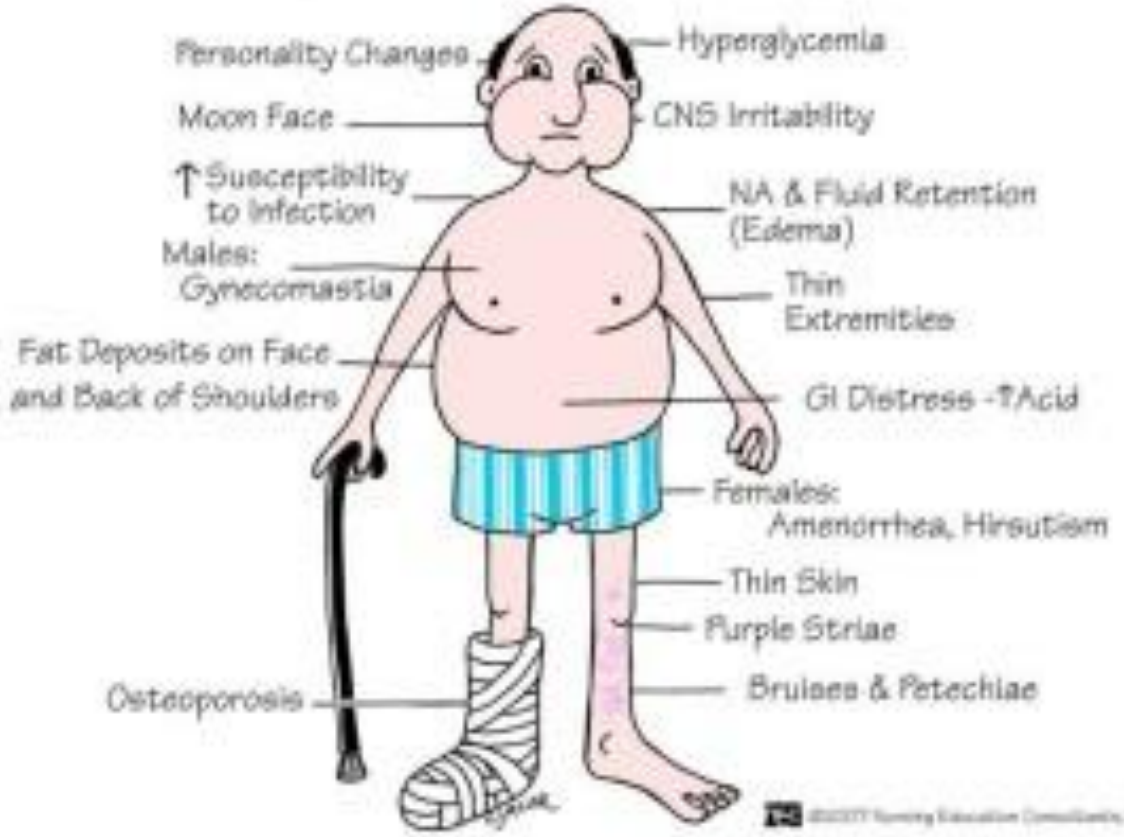
- All patients must be on a DMARD
  (MTX/SZP/Chloroquine/leflunomide)

- Steroids not effective as monotherapy.

What is the role corticosteroids

- Effective as 'bridging' therapy.
- Intra-articular injections are safe and effective.
- Prednisone ≤ 10mg/d for joint disease.
- Wean off by 6 months

CUSHING'S SYNDROME



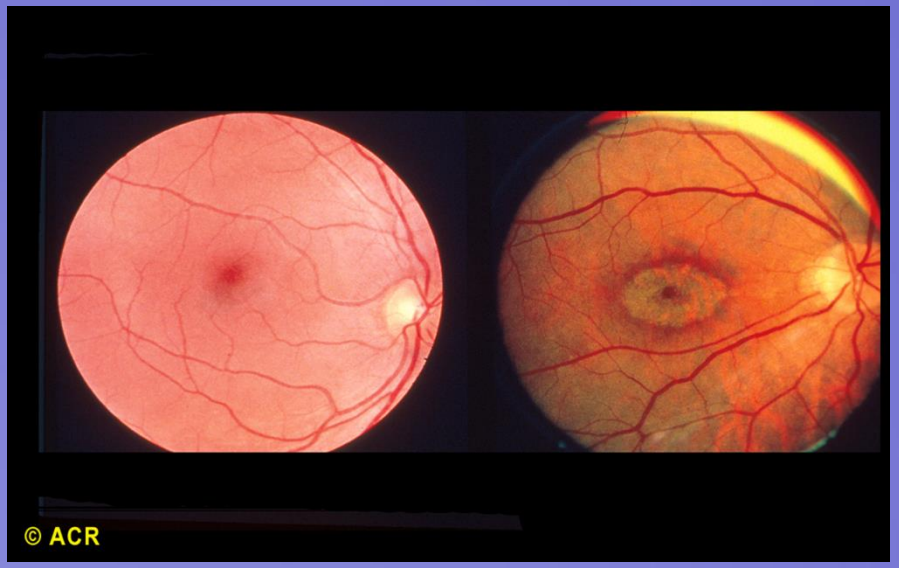

1
3

DMARDS

- **Sulphasalazine:**
  - Modulates B-cell response and angiogenesis[4].
  - Can cause a flare up of lupus
- **Chloroquine:**
  - Modulates cytokine secretion, lysosomal enzymes, and macrophage function[4].

ANTIMALARIAL

Toxicities



Retinal

Gastrointestinal intolerance

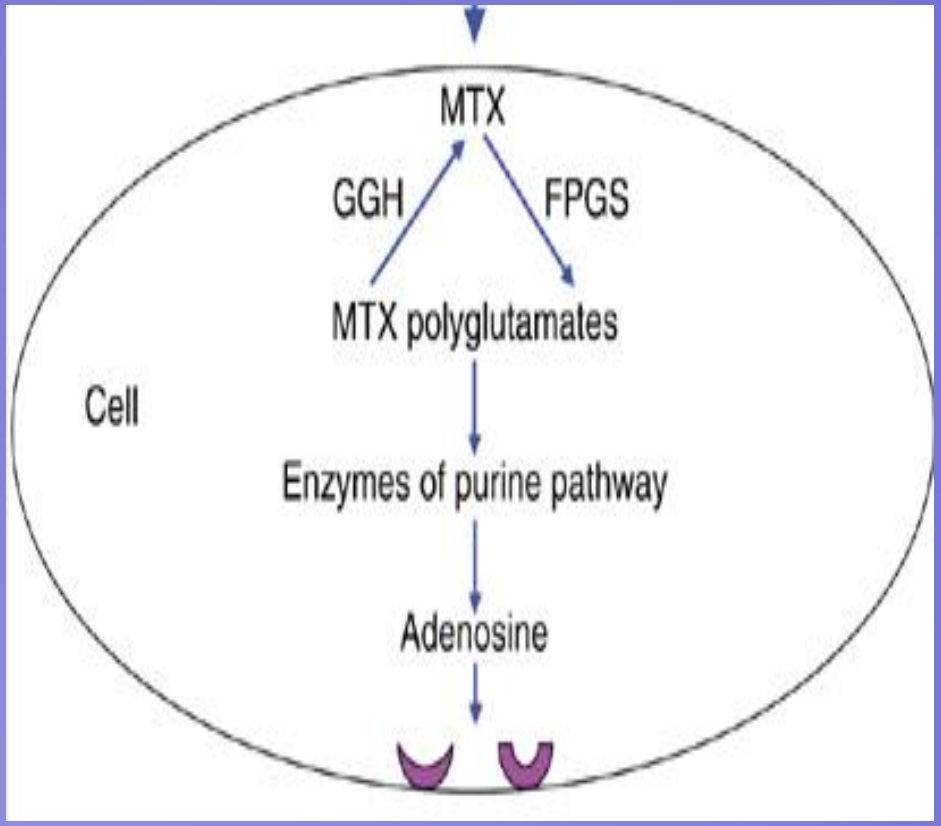
Cutaneous eruptions

Central nervous system toxicities

- headaches, emotional changes, psychosis, ataxia, and seizures discontinued in patients with suspected neuropsychiatric manifestations of lupus

methotrexate

- **Inhibits dihydrofolate reductase (purine synthesis)**
- **induces adenosine release → anti-inflammatory effects.**



MTX

- Dosage escalation over 2-3 months up to 25 mg weekly(start 10-15mg)
- Approximately 4-6 weeks for response to start
- Doses should be administered in the evening to avoid nausea

MTX

- toxicity rather then lack of efficacy account for discontinuation
- administration of folic acid 5mg daily reduces side effects but does not diminish efficacy.
- doses $\geq$ 20mg may benefit form switching to subcutaneous route
- increased toxicity – renal dysfunction and in the elderly

Toxicity

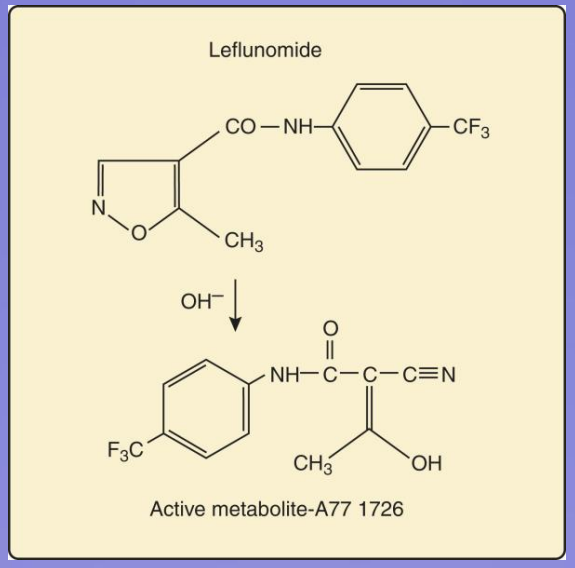
- Nausea, diarrhoea, rashes, alopecia, mouth ulcers and stomatitis
- Marrow suppression
- Liver toxicity
- Pulmonary toxicity

MTX

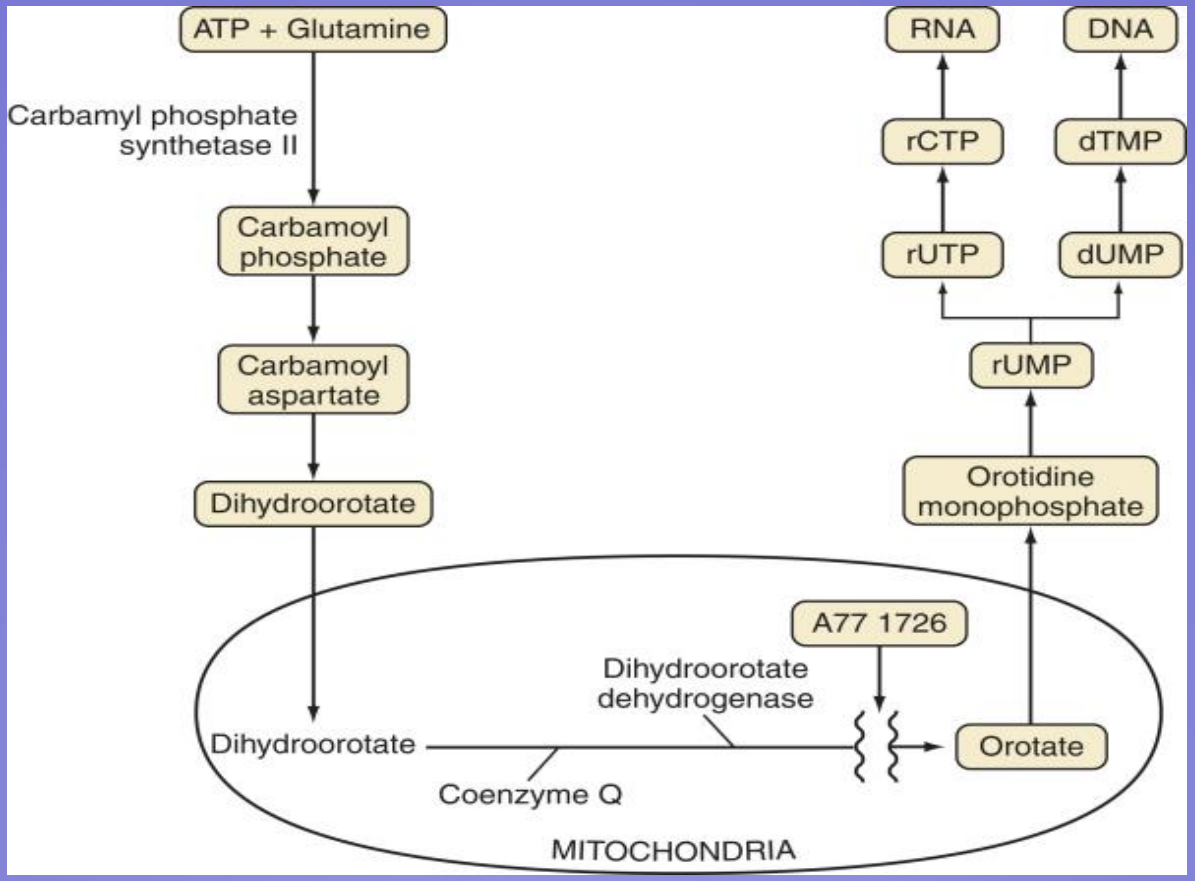
- Chest X-ray before start of therapy
- Routine monitoring - FBC and liver function assessments – AST, ALT.
- Blood tests must be done at baseline, then monthly for 3 months, and thereafter 4-12 weekly.

Leflunomide

- prodrug and is rapidly and completely converted to its active metabolite, malononitriloamide A77 1726



- **Inhibits pyrimidine synthesis, thereby inhibiting DNA synthesis and cellular proliferation**

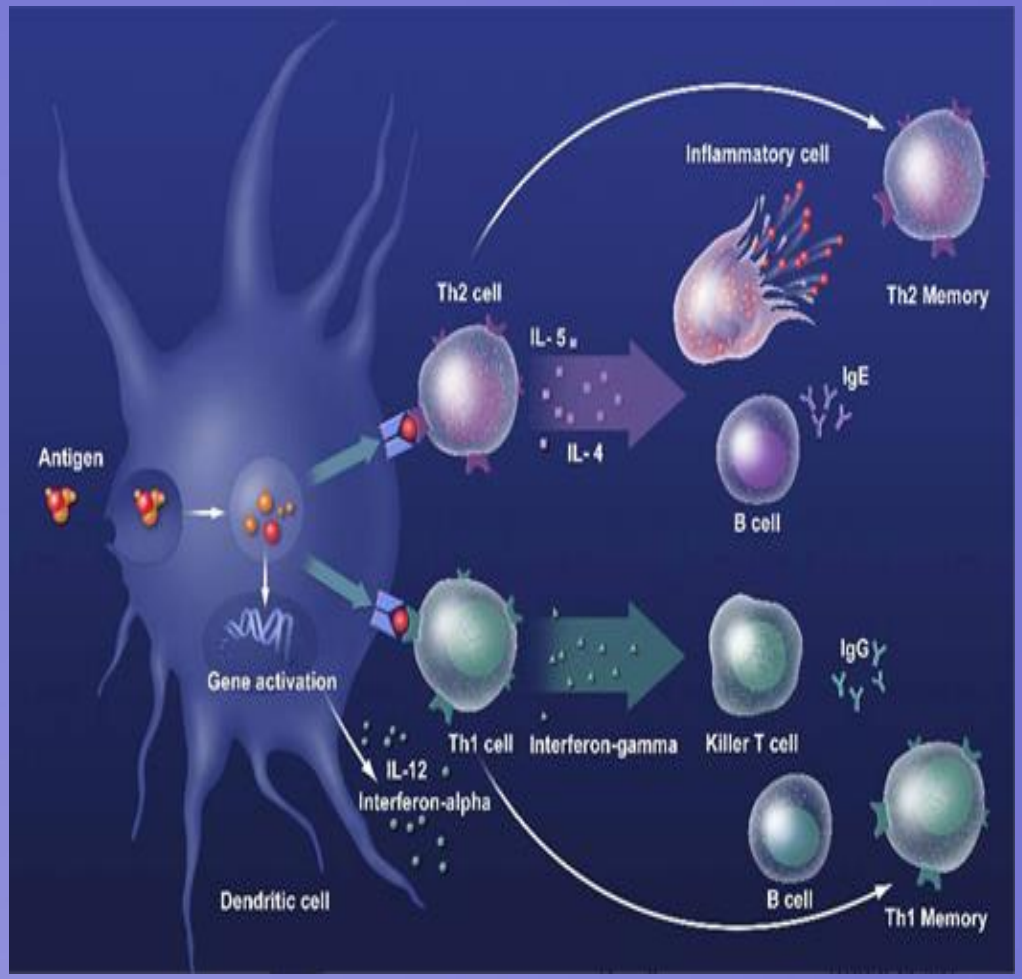


Leflunomide

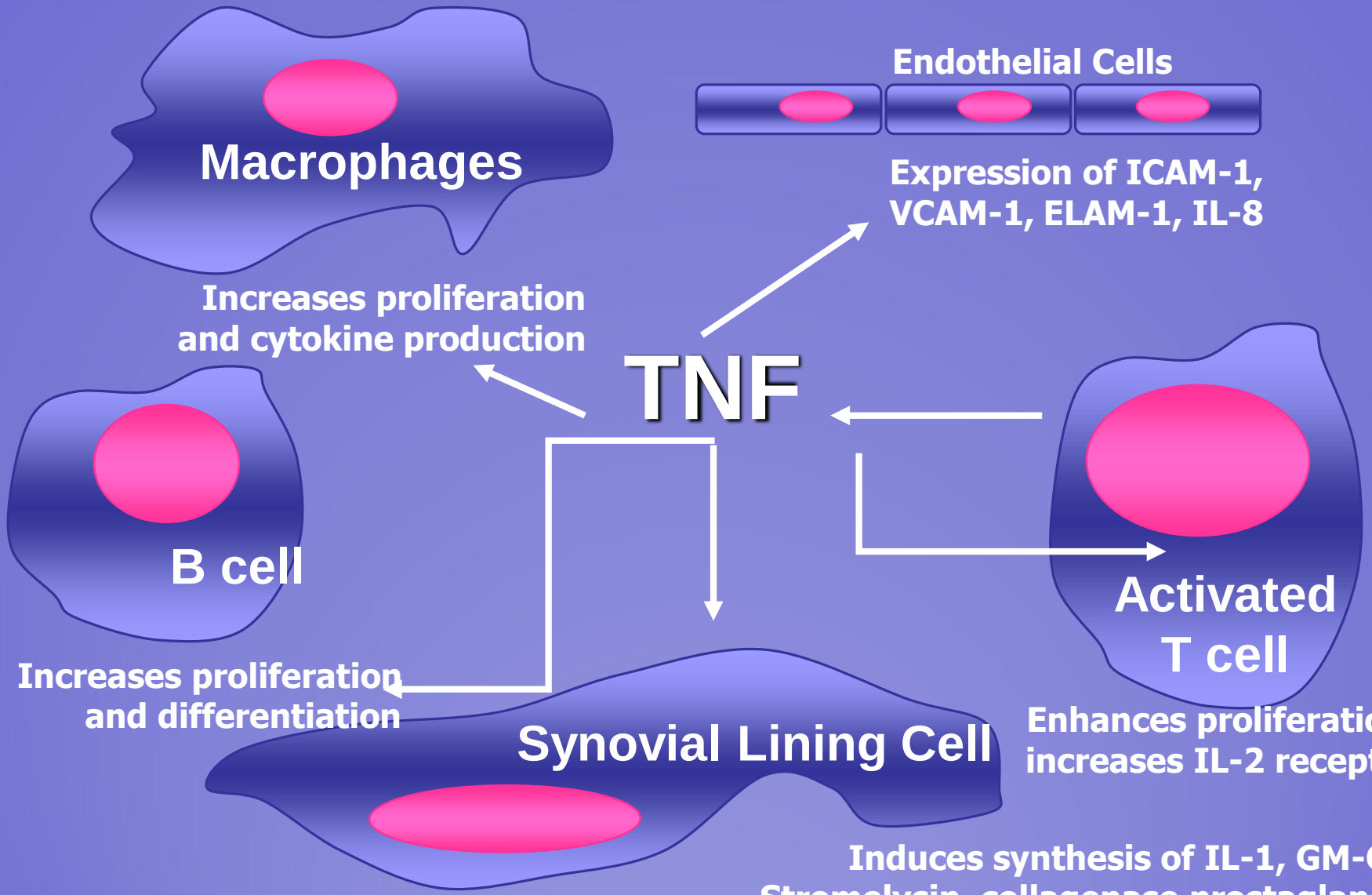
- a half-life of approximately 2 weeks
- enterohepatic recirculation
- may be present in the body months or years later
- cholestyramine
- 8 g three times daily, can reduce the apparent half-life of A77 1726 to 1 to 2 days

Therapeutic targets

- Cytokines
- T Cell
- B – Cell depletion
- Intracellular signalling



TNF: A Pivotal Cytokine in RA



From Harris Jr. ED: Rheumatoid Arthritis

TNF alpha inhibitors

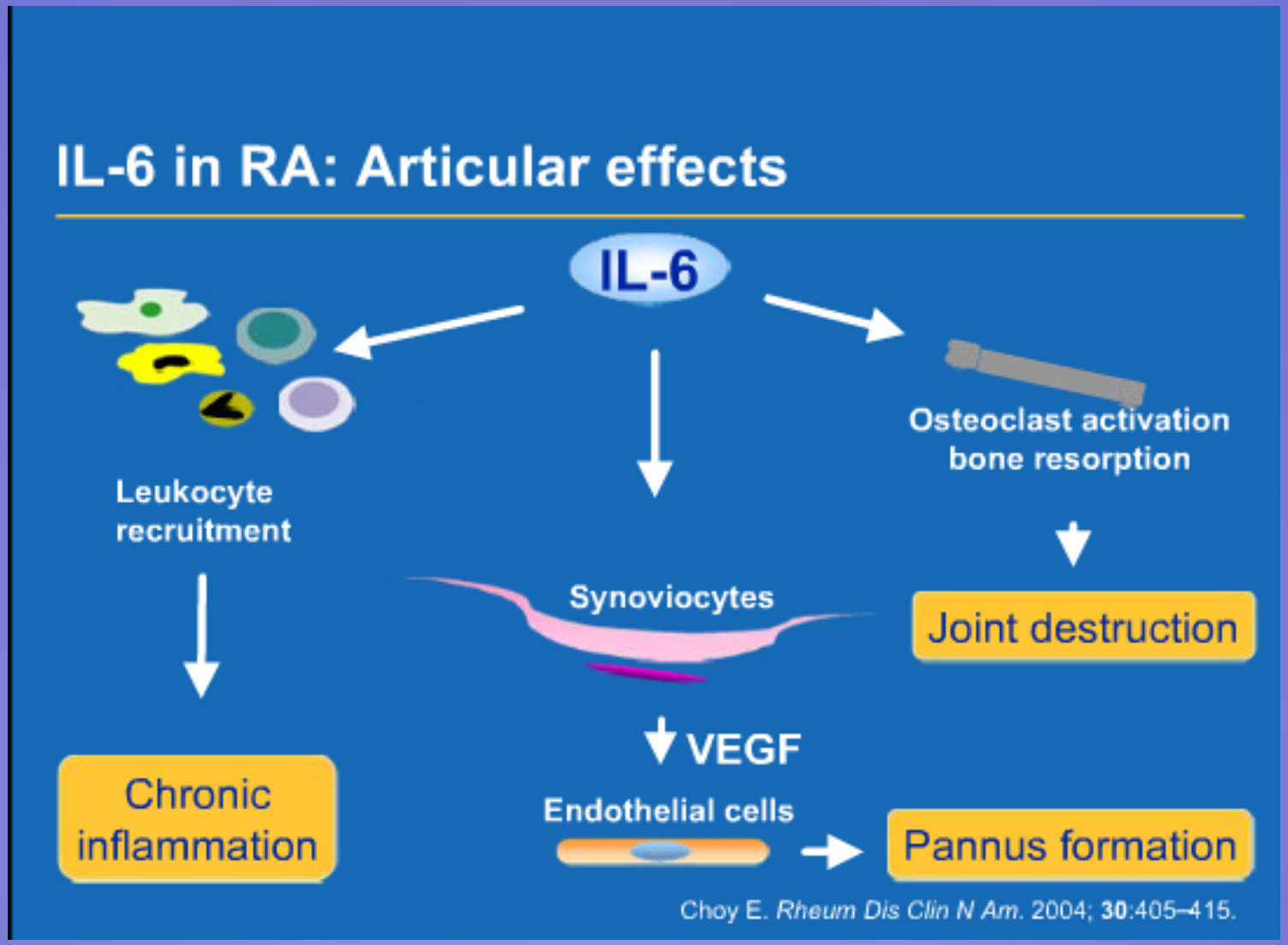
- Four agents:
  - infliximab
  - etenercept
  - Adalimumab
  - Golimumab.
- Rapid clinical response.
- Radiographic damage significantly less over 2 years.
- Cost.

TNF Antagonists

- Safety Issues-

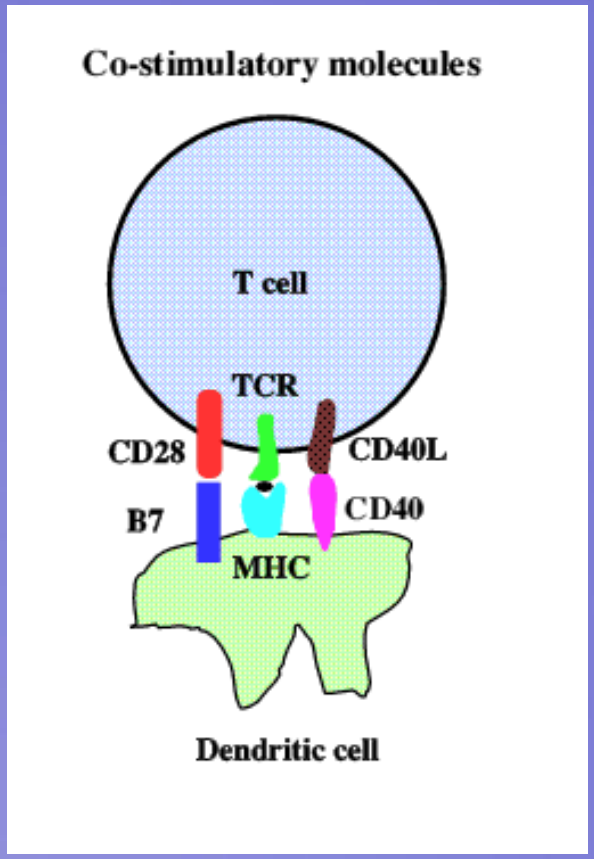
- Infection - common/opportunistic.
- Pancytopenia/aplastic anemia.
- Demyelinating disorders.
- SLE-like symptoms.
- Congestive heart failure.
- Lymphoproliferative disorders.

IL 6


IL-6 in RA: Articular effects
IL-6
Leukocyte recruitment
Osteoclast activation bone resorption
Synoviocytes
Joint destruction
VEGF
Chronic inflammation
Endothelial cells
Pannus formation
Choy E. Rheum Dis Clin N Am. 2004; 30:405–415.

Abatacept

- **T Cell co-stimulation blocker.**



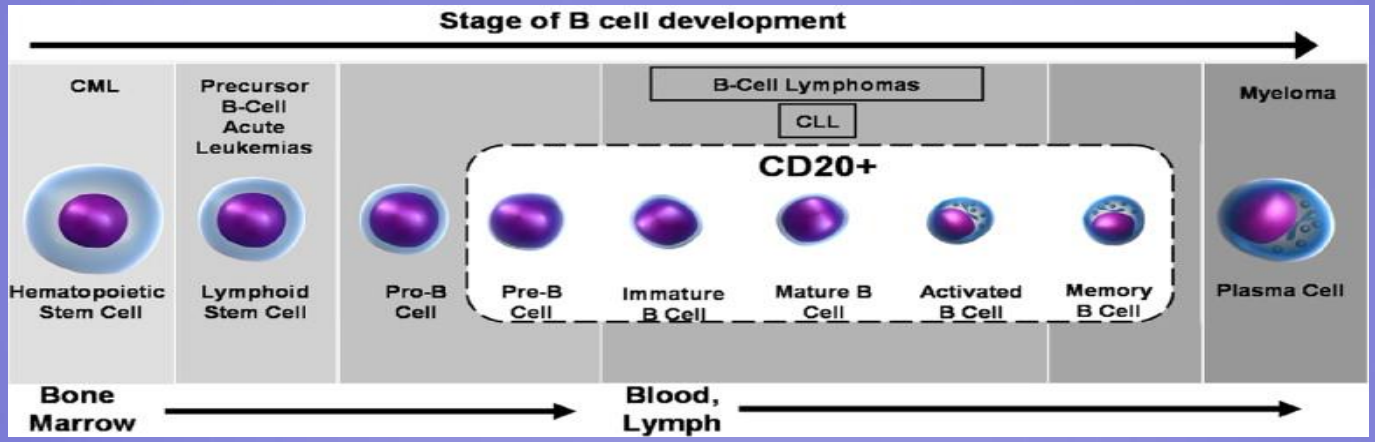
Rituximab

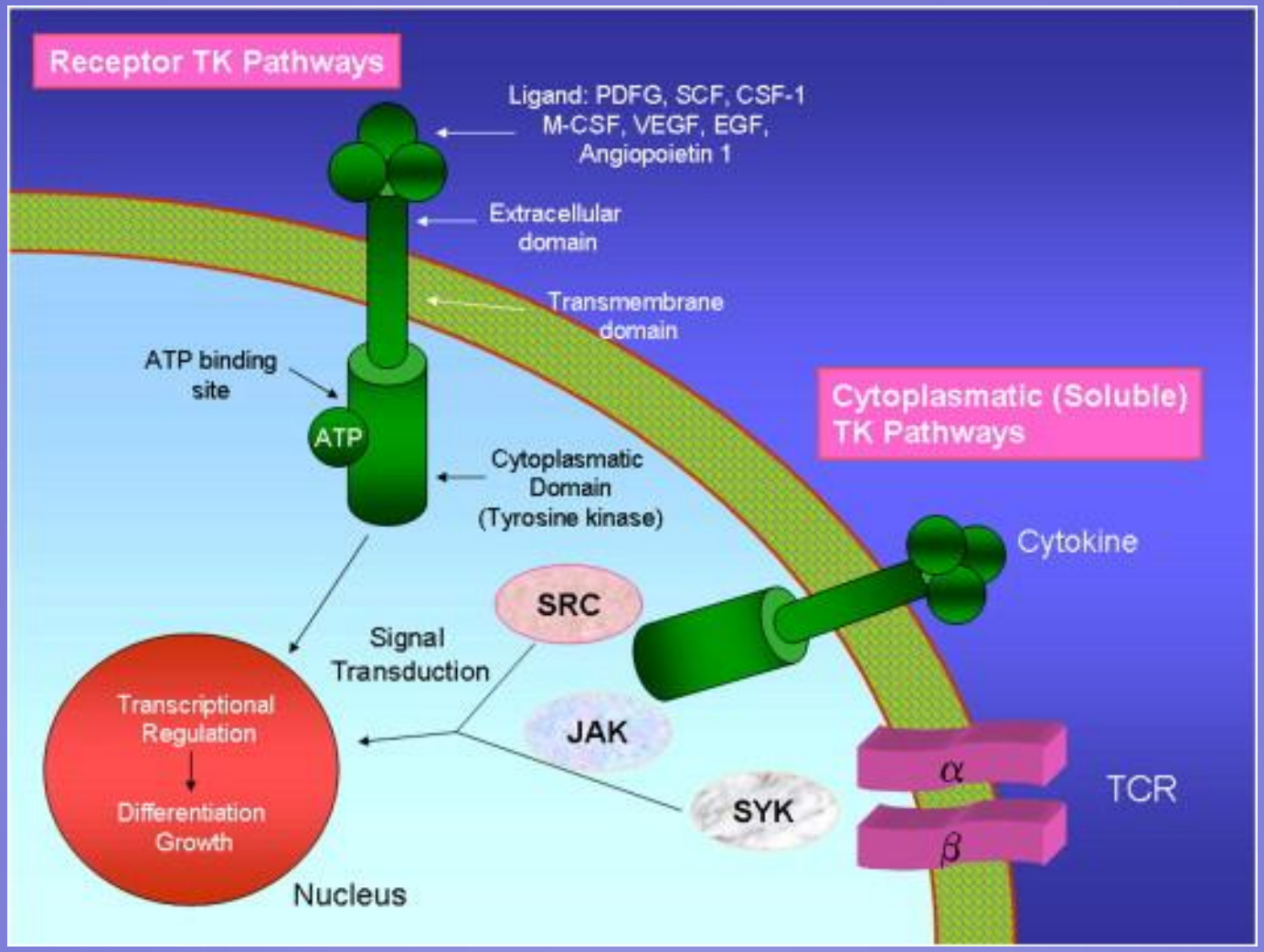
- Eliminate memory B cells making autoantibody (RF) decreasing amount of immune complexes.
- Eliminate the B cell presenting the antigen to T cells.

- Inflammatory arthritis
- SLE
- Juvenile dermatomyositis
- vasculitis

Adverse events

- Infections PML
- Immunization
- ? Safer TB





International Immunopharmacology
Volume 9, Issue 1, January 2009,
Pages 1–9

Early Management

Connective tissue diseases

When to consider a connective tissue disease

Non specific

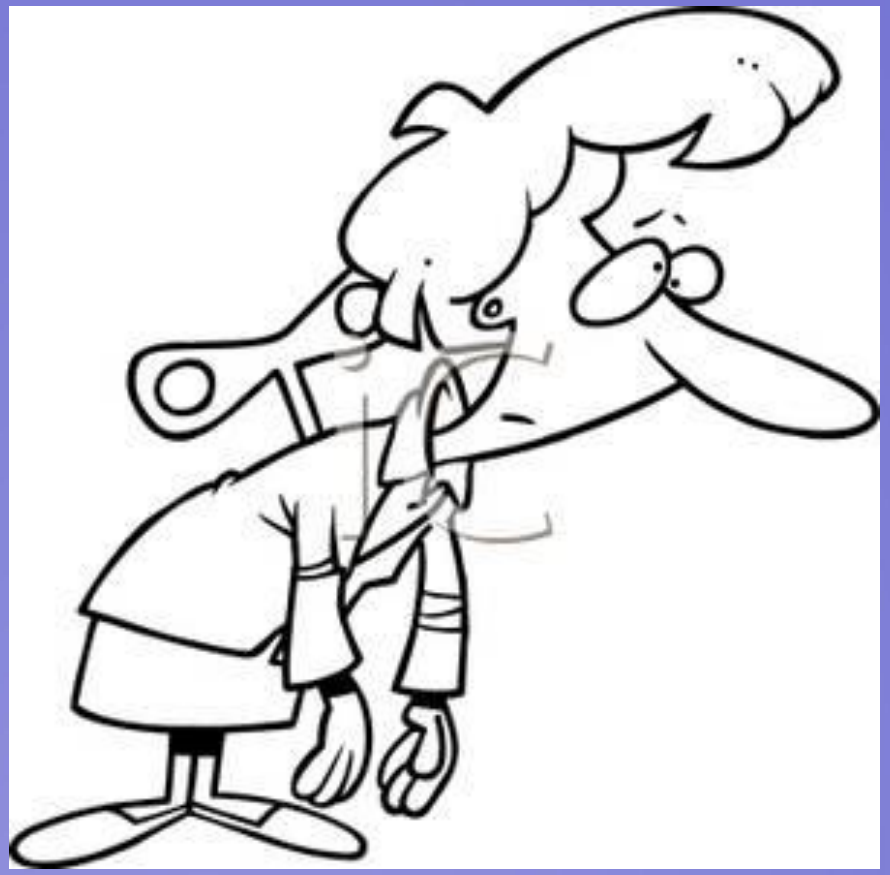
Specific

Multisystem disease

Major organ involvement

SYSTEMIC SYMPTOMS

Fatigue
malaise
fever
anorexia
weight loss
arthralgia



SYSTEMIC LUPUS ERYTHEMATOSUS

SLICC Diagnostic Criteria :

CLINICAL CRITERIA	IMMUNOLOGIC
1. Acute cutaneous lupus **2. Chronic cutaneous lupus** **3. Oral or nasal ulcers** 4. Non-scarring alopecia 5. Arthritis 6. Serositis **7. Renal dysfunction** 8. Neurologic dysfunction 9. Hemolytic anaemia 10. Leukopenia 11. Thrombocytopenia (<100,000/mm^3)	**1. ANA** 2. Anti-DNA 3. Anti-Sm 4. Antiphospholipid Ab 5. Low Complement (C3, C4, CH50) 6. Direct Coombs' test

- Occurs after sun exposure; followed by systemic manifestatons within few weeks
- Localised form: malar rash
- Generalised form: can involve whole body; systemic manifestations are present

ACUTE CLE

- Subtypes include:
  1.DLE(localised or generalised)
  2.Hypertrophic DLE
  3.Lupus profundus
  4.Mucosal LE
  5.Chilblain lupus

CHRONIC CLE

mucocutaneous

- **Photosensitivity**
- **Oral or nasopharyngeal ulcers usually painless**

Muco-cutaneous Manifestations

- Malar (butterfly) rash
- Discoid skin rash
- Alopecia
- Vasculitis
- Raynaud's syndrome

Raynaud's phenomenon

Episodic, reversible digital skin color change
- **white to blue to red**
- **well-demarcated**

Due to vasospasm

Usually cold-induced

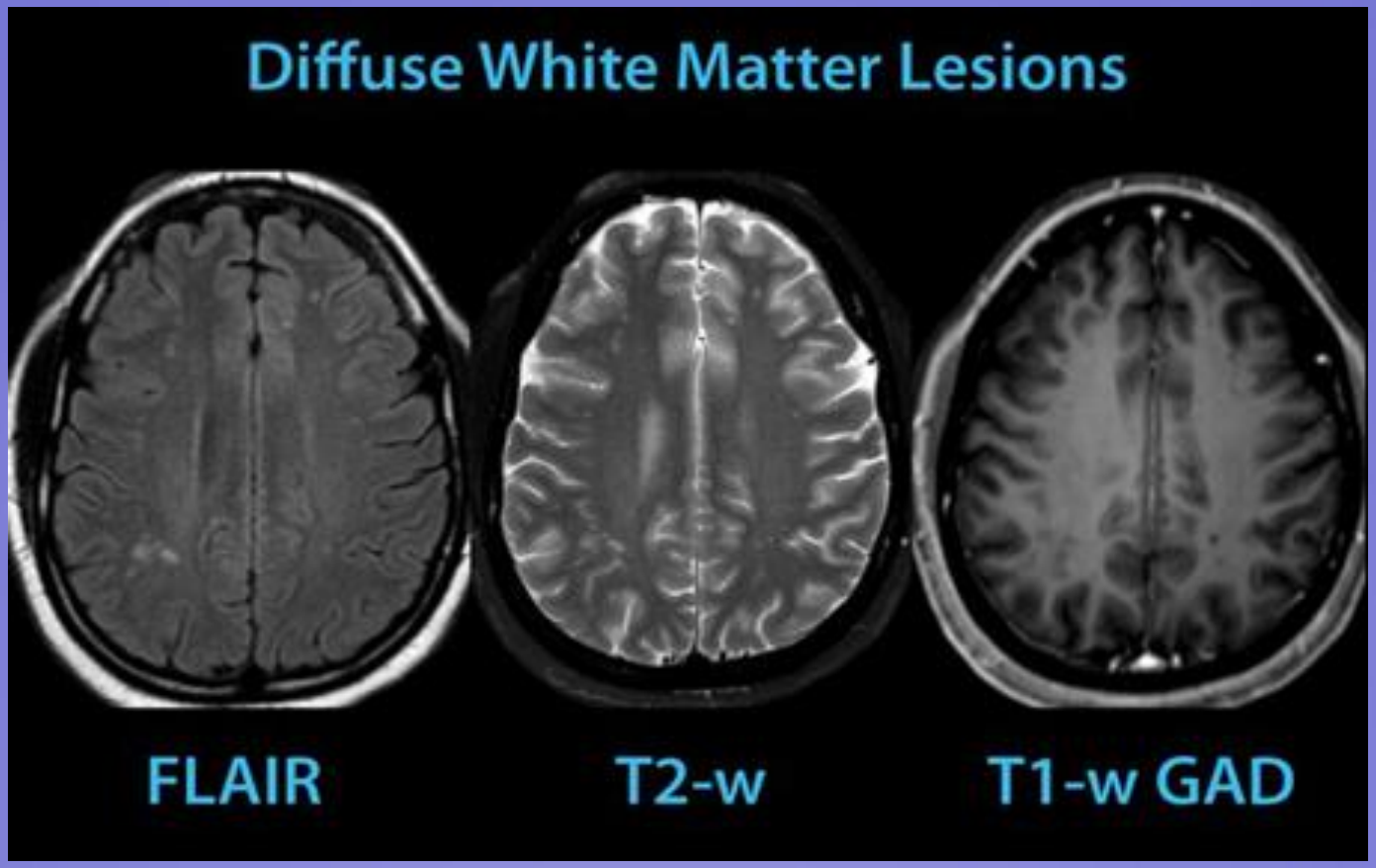
Primary (Raynaud's disease)

and secondary forms

Arthritis
Nonerosive-inflammatory

Renal disorder Persistent proteinuria or cellular casts

Neurologic disorder Seizures or psychosis



Heamatologic

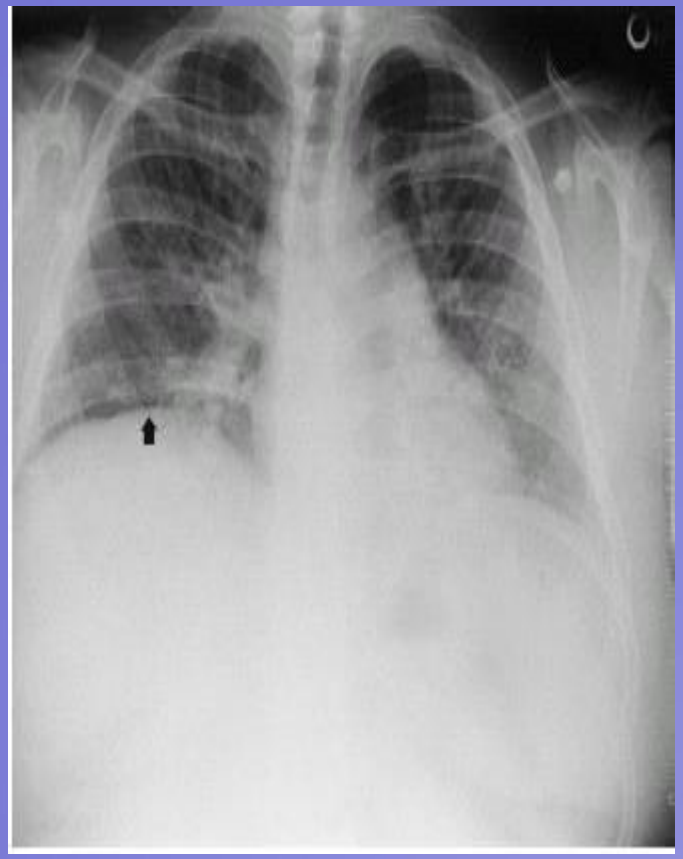
Hemolytic anemia

leukopenia (<4,000/mm^3)

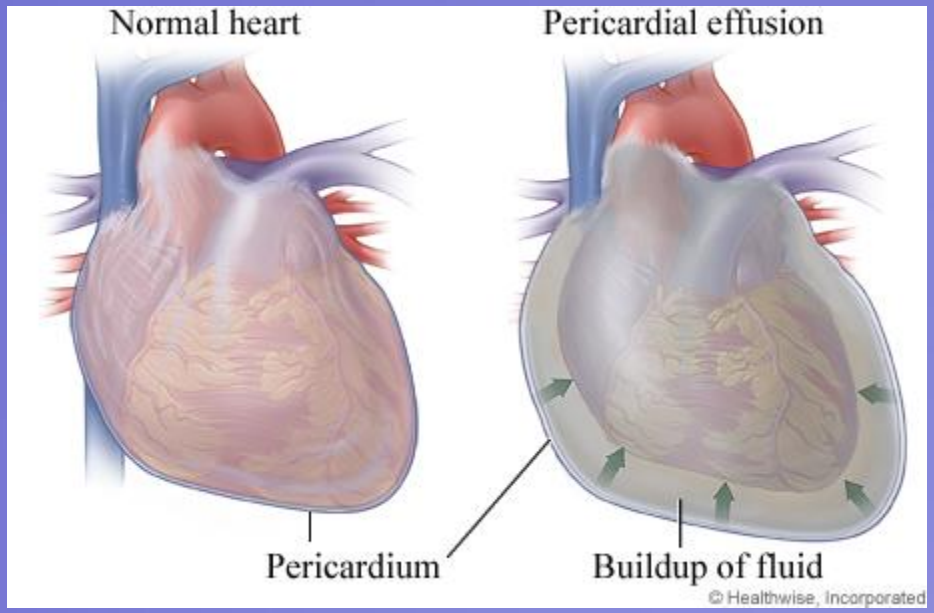
lymphopenia(<1,500/mm^3)

thrombocytopenia (<100,00/mm^3)

Serositis
Pleuritis or pericarditis



Serositis



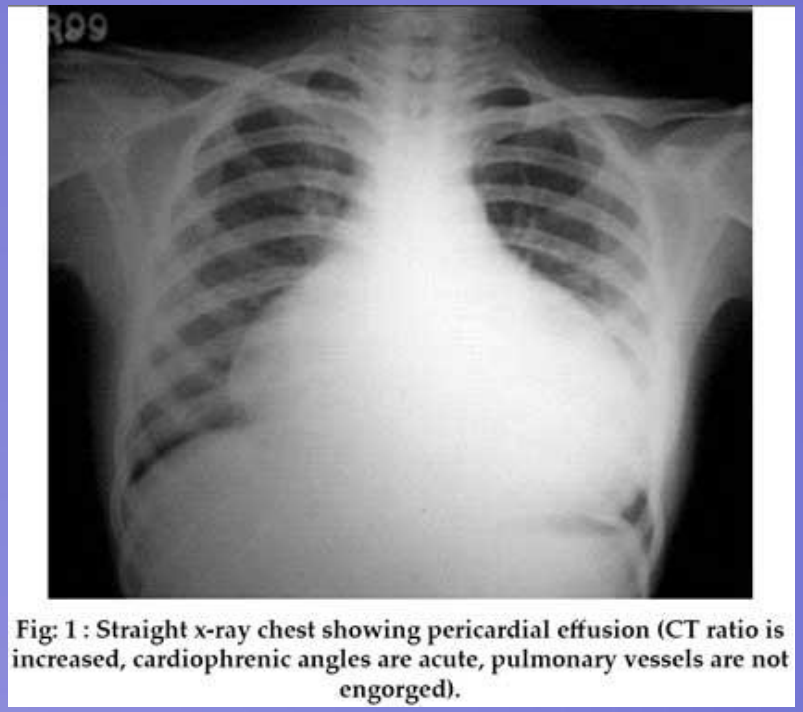
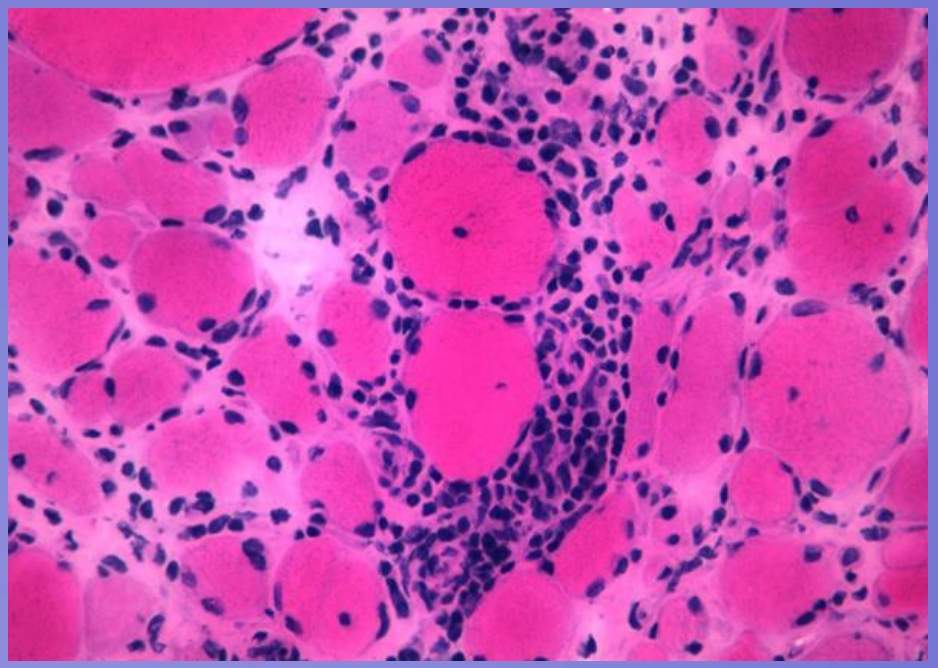
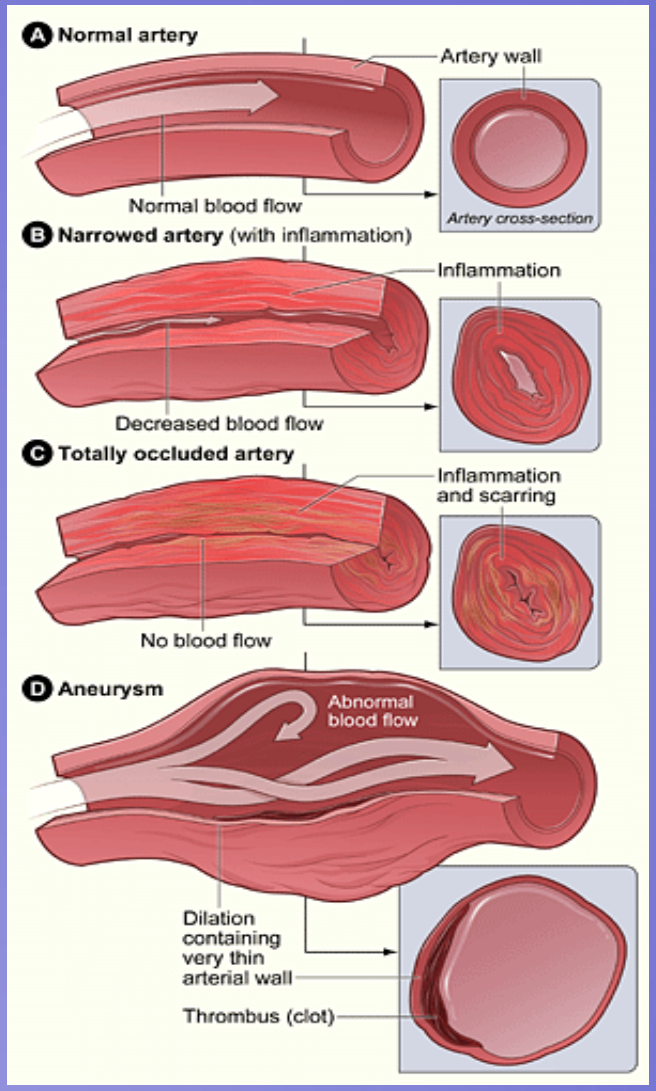


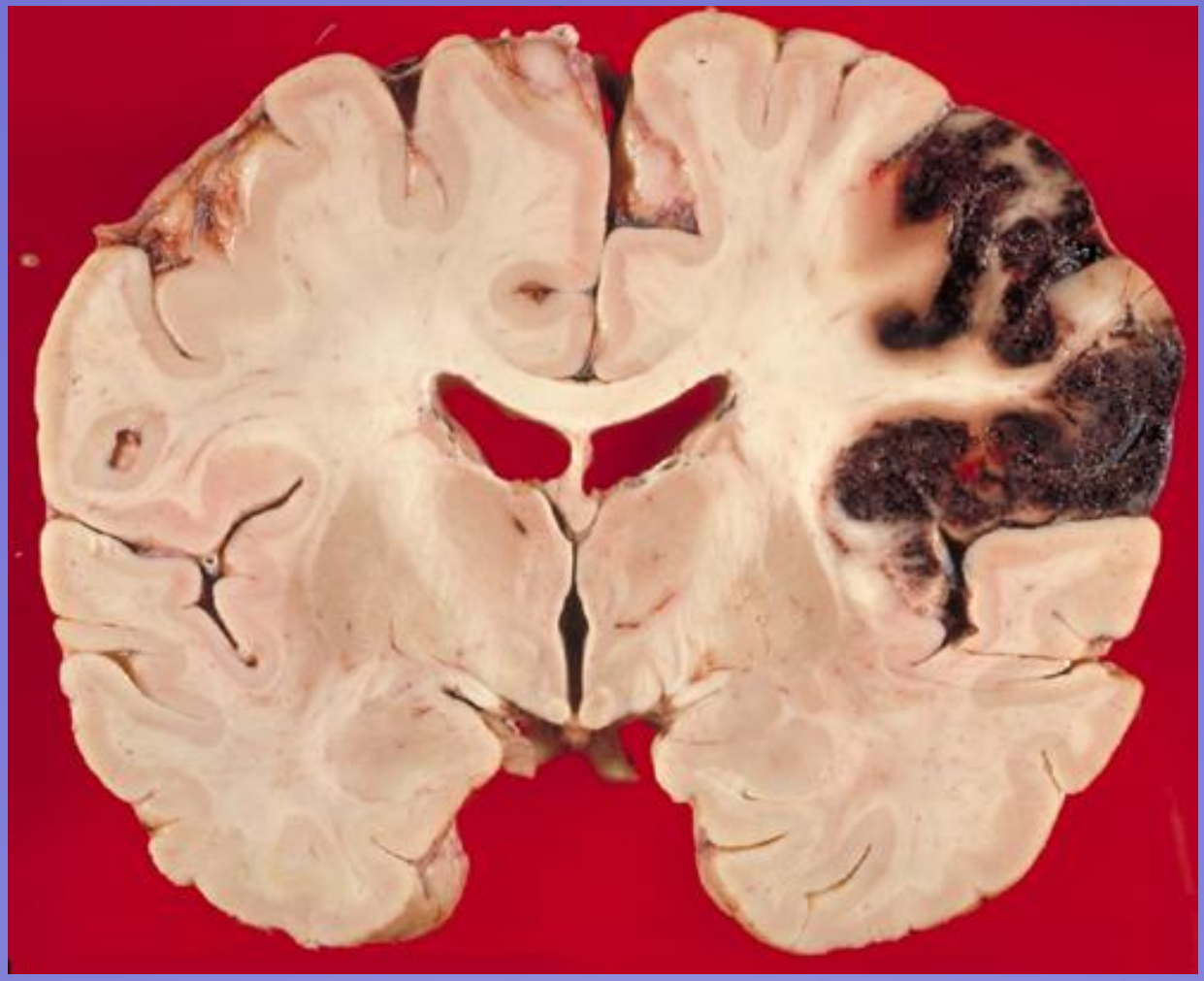
Fig: 1 : Straight x-ray chest showing pericardial effusion (CT ratio is increased, cardiophrenic angles are acute, pulmonary vessels are not engorged).

Proximal myopathy-myositis associated with CTD



VASCULITIS


A Normal artery
Artery wall
Normal blood flow
Artery cross-section
B Narrowed artery (with inflammation)
Inflammation
Decreased blood flow
C Totally occluded artery
Inflammation and scarring
No blood flow
D Aneurysm
Abnormal blood flow
Dilation containing very thin arterial wall
Thrombus (clot)



Systemic lupus erythematosus: digital gangrene, hands

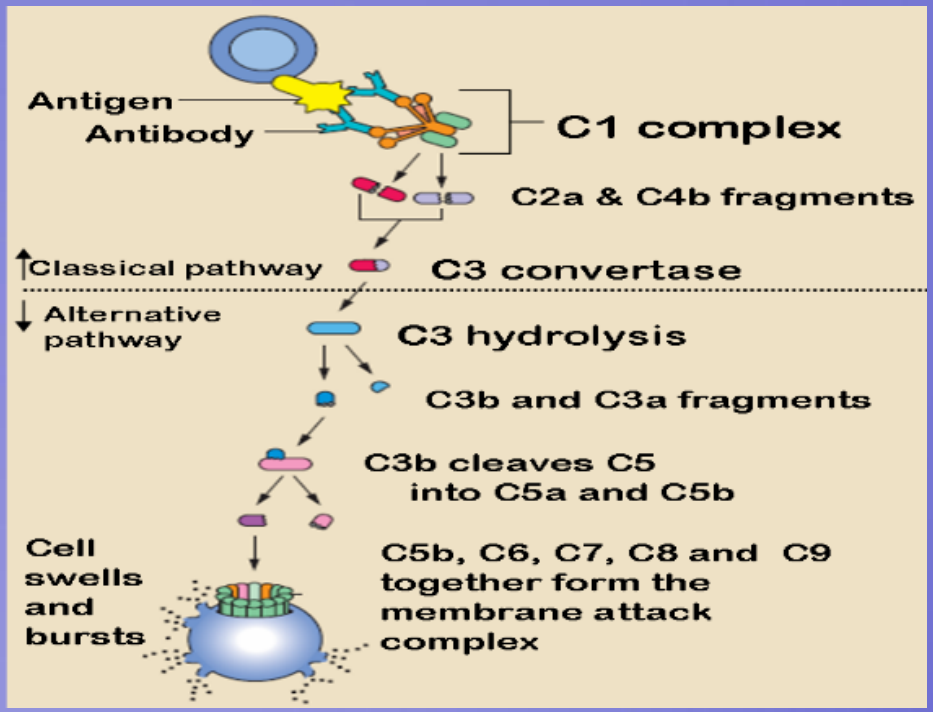
Vasculitis: purpuric eruption, feet

Disease activity SLE

- DsDNA ↑
- C3 ↓
- C4 ↓

- ANF titre does **NOT** correlate with disease activity

- Compliment
- Innate response
- Cascade of interacting proteins > cell lysis



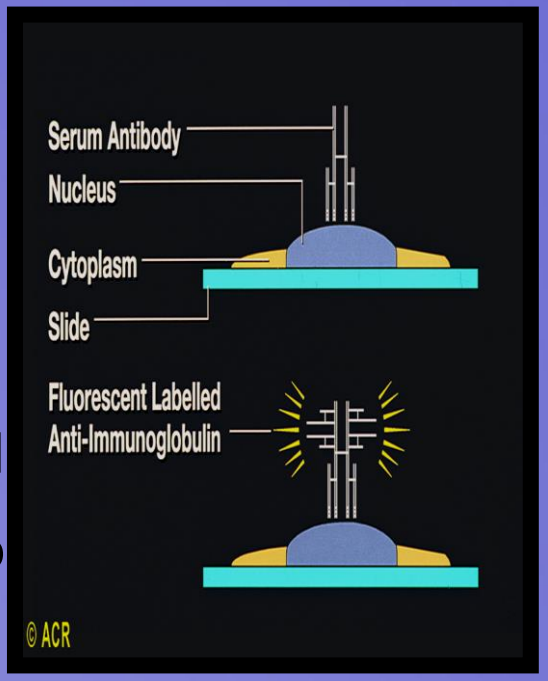
Investigation in the connective tissue diseases

AUTO - ANTIBODIES

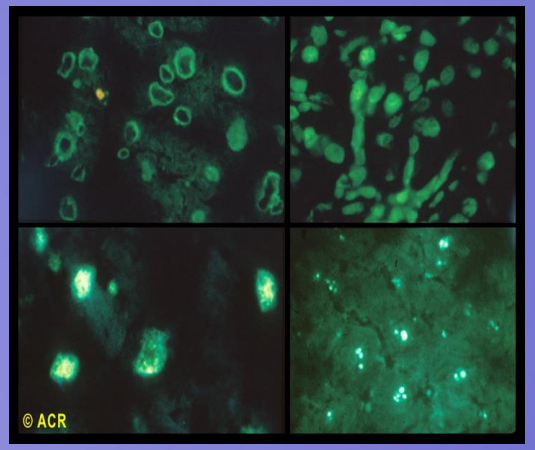
Anti-Nuclear Antibodies Nomenclature

- Chemical structure (e.g. double-stranded ds DNA,RNP).
- Disease association (e.g. SS-A and SS-B in Sjögren's syndrome).
- The individual in whom they were first described (e.g. Ro, La, Sm).
- Their cytological location (e.g. nucleolar, centromere).

How are antinuclear antibodies measured?

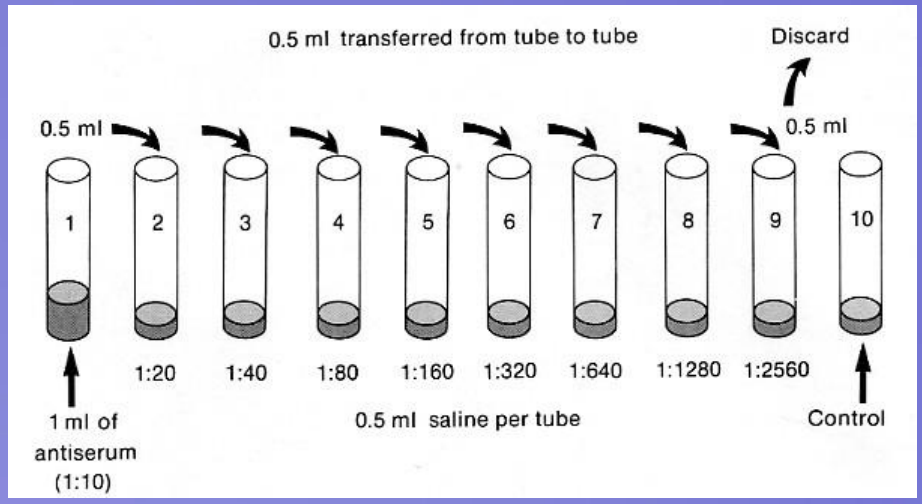


- **Fluorescence microscopy.**
- **Cells fixed microscope slide and incubated with the patient's serum, allowing ANAs to bind to the cell nuclei.**
- **Fluoresceinated second antibody is added.**
- **Cells are visualized through a fluorescence microscope to detect nuclear fluorescence.**



- **The greater the dilution (titer) at which nuclear fluorescence is detected the greater the amount to ANAs**
- **Titre >1:160**
- **HEp-2 cells - proliferating cell line derived from a human epithelial tumor cell line.**

  (100-150 nucleur antigens)



Can a positive ANA occur in a normal individual?

- **5% of normals can be ANA-positive.**
- **Titers are usually ≤ 1 : 160**
- **Nuclear staining pattern is most often speckled.**

ANA

- **High sensitivity in SLE, but poor specificity**
- **ANA found in 5-10% of pts without CTD**
  - **Healthy pts, chronic infections (e.g., Hep C), multiple meds, etc.**

ANA

Condition	% ANA-positive
SLE	99%
Drug induced lupus	95-100%
MCTD	95-100%
Autoimmune liver dz	60-100%
Sjogren's syndrome	75-90%
Polymyositis	30-80%
RA	30-50%

Adapted from Hobbs, K in West, S *Rheumatology Secrets*, 2002.

ANA

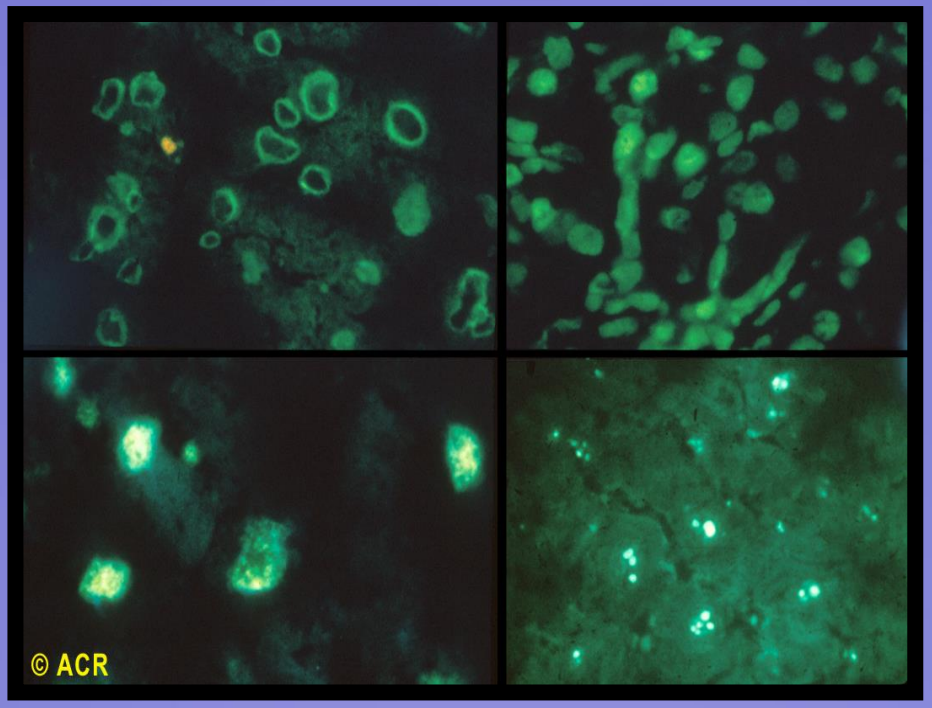
Condition	% ANA-positive
Multiple sclerosis	25%
Pts with silicone breast implants	
Healthy relatives of pts with SLE	15-25%
Neoplasms	
Normal elderly (>70 yrs)	20%

Adapted from Hobbs, K in West, S. Rheumatology Secrets, 2002

Drug-induced ANAs

- **Common drugs that cause positive ANAs**
  - **Procainamide**
  - **Hydralazine**
  - **Phenothiazines**
  - **Diphenylhydantoin**
  - **Isoniazid**
  - **Quinidine**

Antinuclear antibodies-patterns



Specific ANAs

Antigen	Condition
Anti-dsDNA Ab	SLE
Anti-Sm Ab	SLE
Anti-Ro/SSA Ab	Sjogren's, SCLE
Anti-La/SSB Ab	Sjogren's, SCLE
Scl-70	Scleroderma
Anticentrome	CREST
Anti-U-3 RNP	Scleroderma

Colglazier, CL et al. Southern Medical Journal.2005

Antigen	Condition
Anti-dsDNA Ab	SLE
Anti-Sm Ab	SLE

Chronic cutaneous lupus

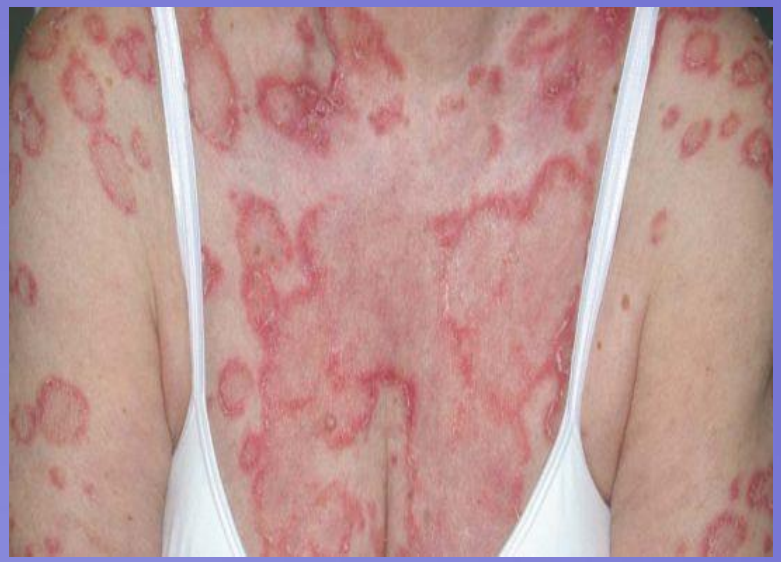
Mucosal lupus

Chronic cutaneous lupus

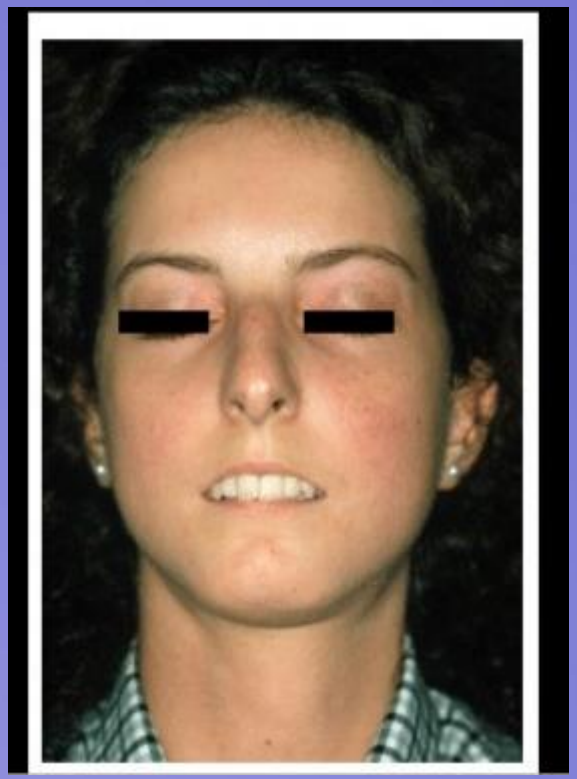
5. Lupus erythematosus tumidus

Erythematous, succulent, edematous, nonscarring plaques in sun-exposed areas

Antigen	Condition
Anti-Ro/SSA Ab	Sjogren's, SCLE
Anti-La/SSB Ab	Sjogren's, SCLE



Antigen	Condition
Scl-70	Scleroderma
Anticentrome	CREST



Scleroderma

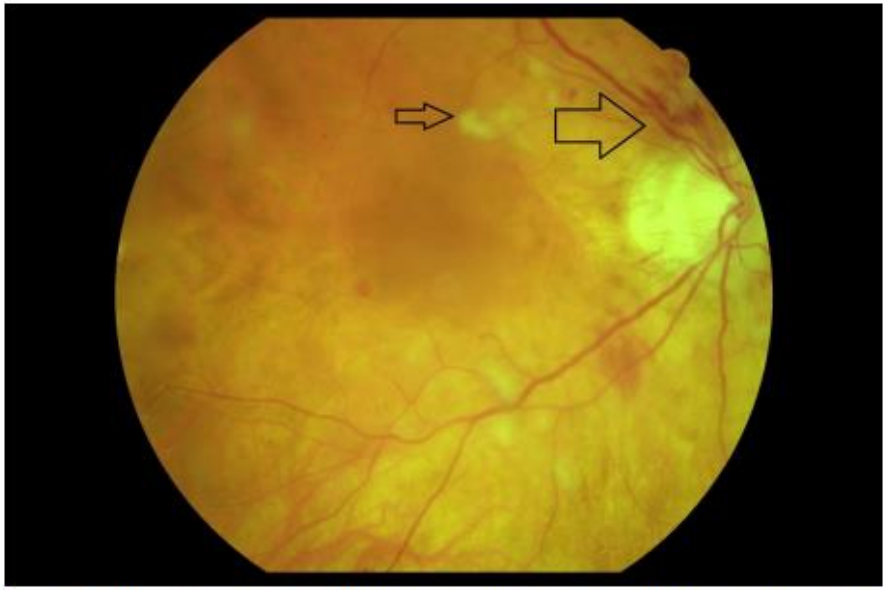
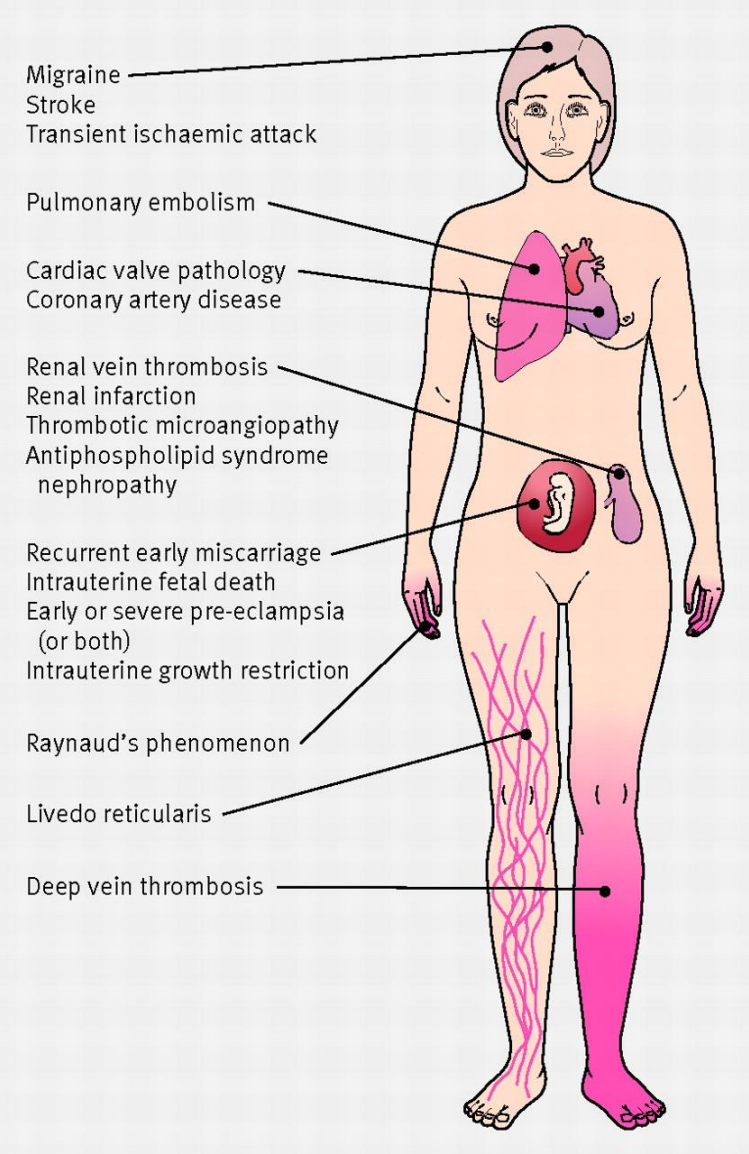


Fig 3 Fundoscopy, showing cotton wool spots (small arrow) and flame haemorrhages (large arrow)

Antiphospholipid antibodies

- **Heterogeneous group of Ab bind to plasma proteins affinity for phospholipid**
  - **Anti-cardiolipin Ab (ACL)**
  - **Lupus anticoagulant (LAC)**
  - **Beta 2-glycoprotein I**



Antiphospholipid antibodies

Principles of management CTD

- **SLE – immune modulation related to severity of manifestations**
- **Scleroderma – avoid corticosteroids**

MANAGEMENT SLE

- **Relapses and remissions**
- **Rx for acute flares**
- **Mx long-term-monitoring**

DRUGS USED IN LUPUS MANAGEMENT

Approved	Manifestation of SLE				
	Constitutional	Musculosceletal	Serositis	Cutanous	Major organ
NSAID's	+	+	+		
Corticosteroid					
Topical				+	
Low Dose	+	+	+	+	
High Dose					+
Antimalarials	+	+	+	+	

DRUGS USED IN LUPUS MANAGEMENT

Investigational	Manifestation of SLE				
	Constitutional	Musculosceletal	Serositis	Cutanous	Major organ
Azathioprine		+	+	+	+
Cyclophosphamide					+
Methotrexate		?+	?+		
Dapsone	?+			+	
Immuneglobuline					+ thrombocytopenia
Danazol					+ thrombocytopenia
Cyclosporin A					??

Rheumatic Diseases

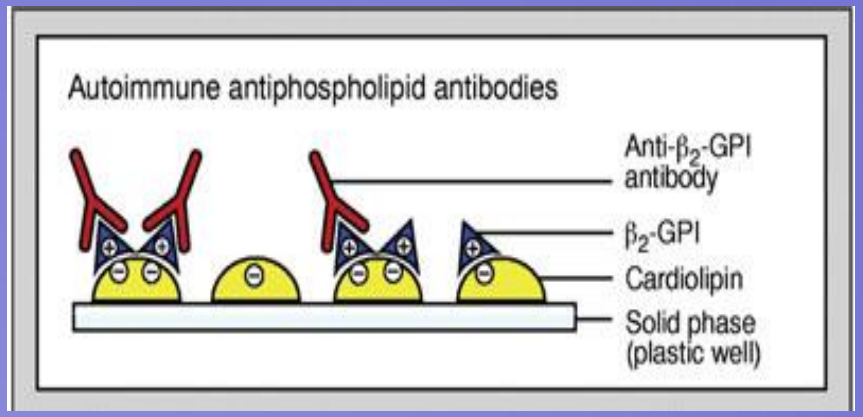
- **Wide array of clinical presentations**
- **Differing pathogenic mechanisms**
- **Significant functional impairment**
- **Premature mortality**
- **Recent advance allow for markedly improved outcomes.**

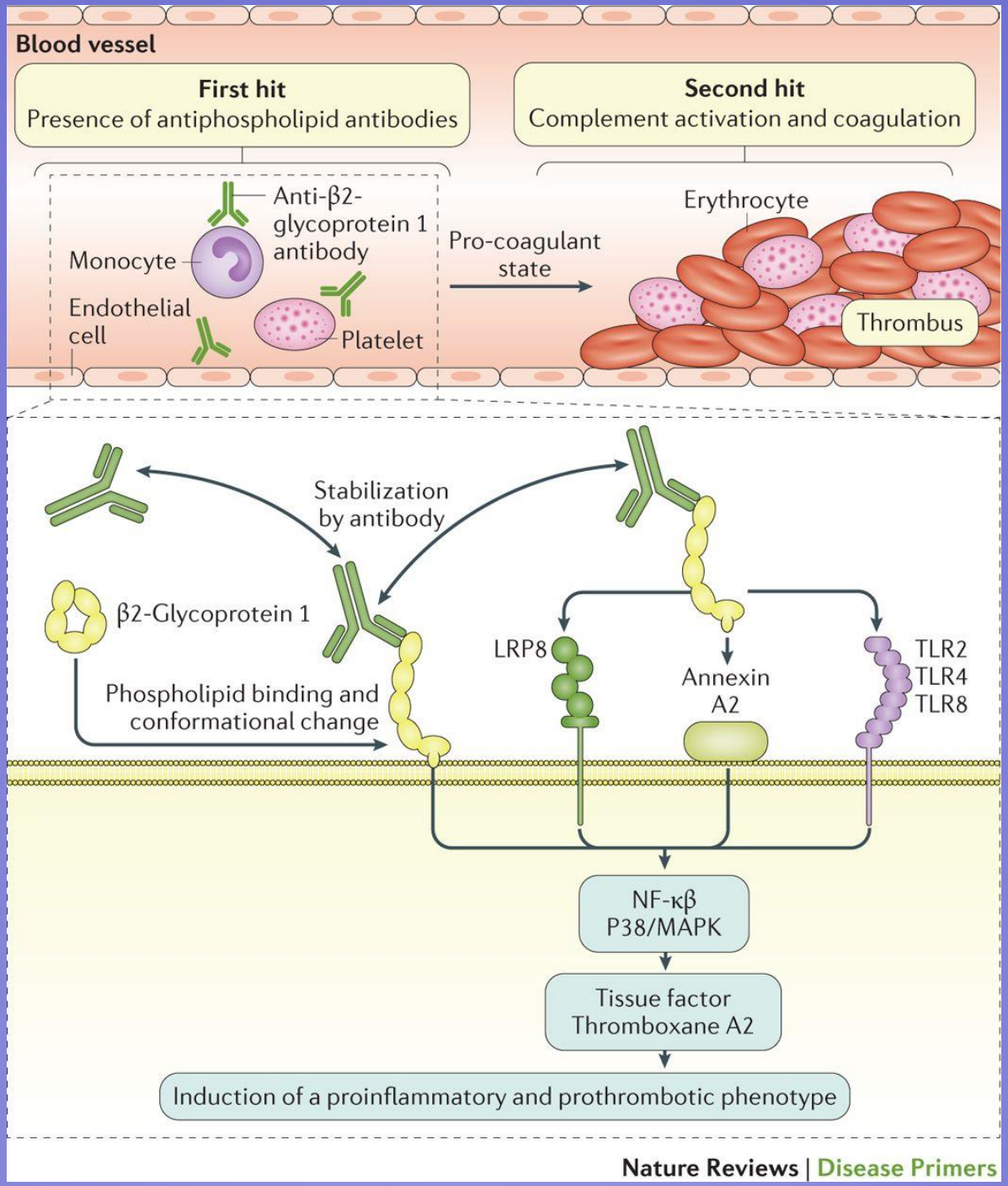
Anti-Cardiolipin Antibodies and Antibodies to β2 Glycoprotein-I

- **Beta-2 glycoprotein-I (β2GPI) is the major phospholipid-binding protein (IgG, M, A)**

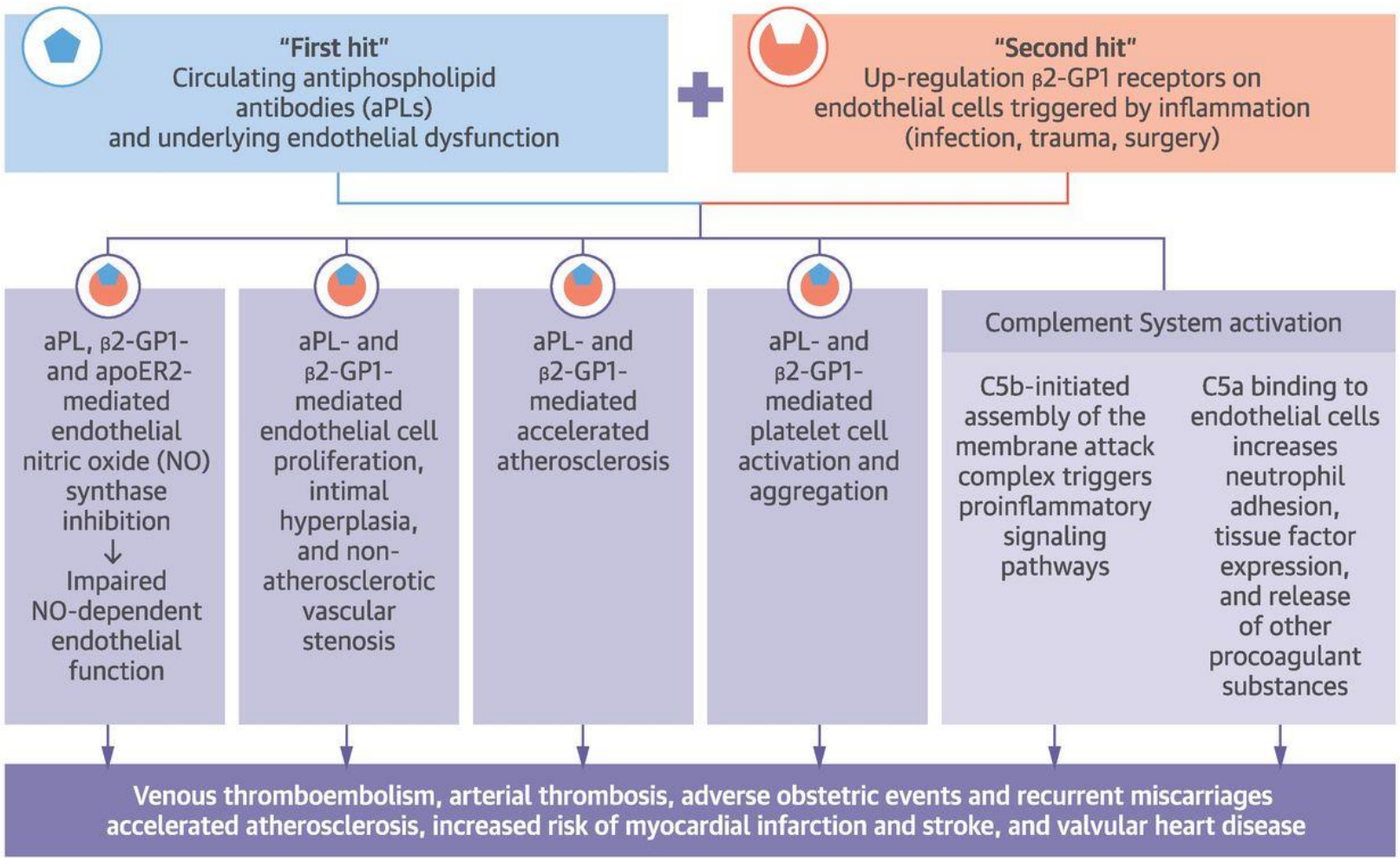
- **ACL Ab**
- **False-positive**
  - **hepatitis C**
  - **mycoplasma**
  - **Tuberculosis**
  - **HIV.**

- **Confirmatory test 12 weeks apart**



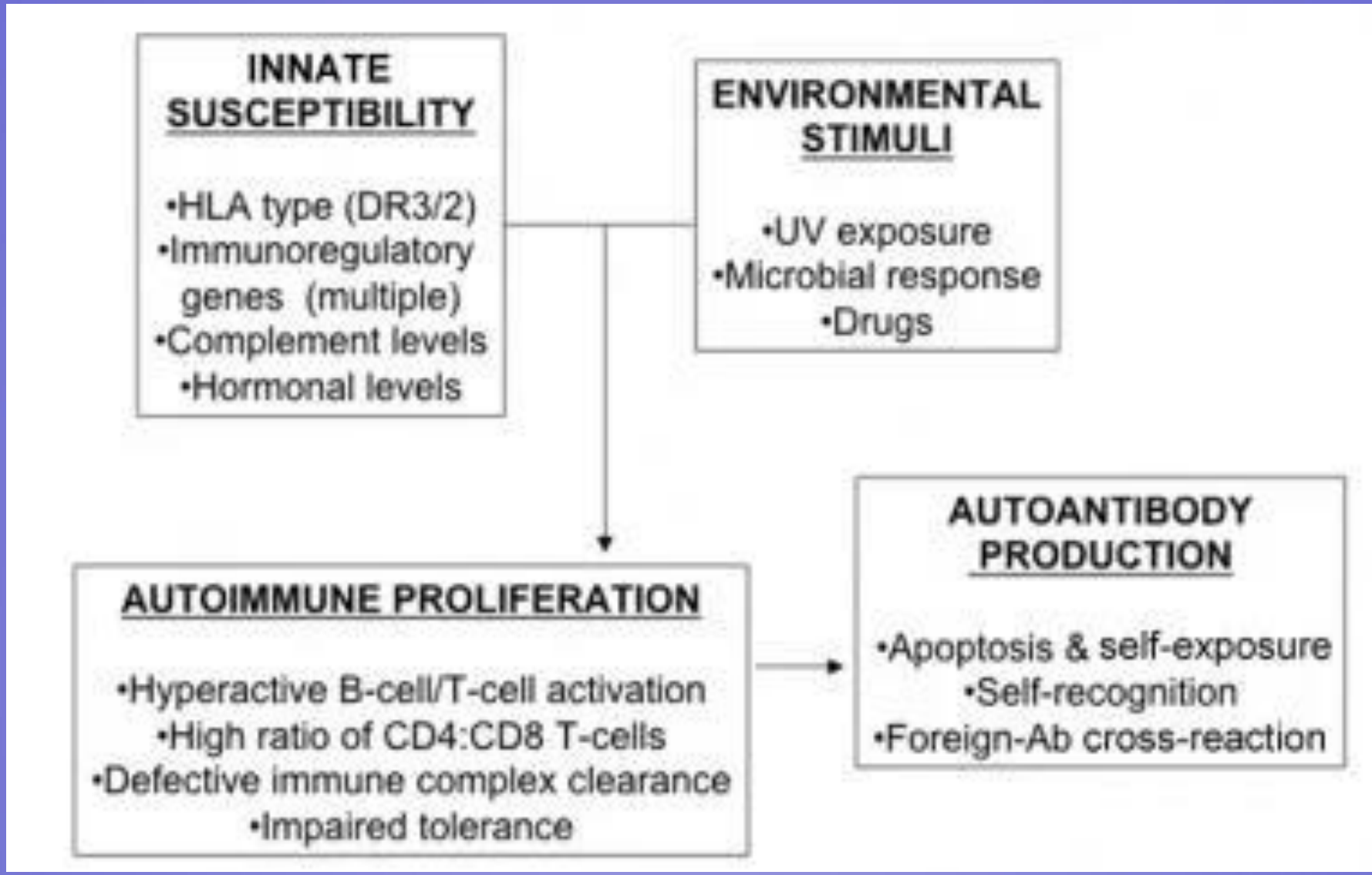

Blood vessel
First hit
Presence of antiphospholipid antibodies
Second hit
Complement activation and coagulation
Anti-β2-glycoprotein 1 antibody
Monocyte
Endothelial cell
Platelet
Pro-coagulant state
Erythrocyte
Thrombus
Stabilization by antibody
β2-Glycoprotein 1
Phospholipid binding and conformational change
LRP8
Annexin A2
TLR2
TLR4
TLR8
NF-κβ
P38/MAPK
Tissue factor
Thromboxane A2
Induction of a proinflammatory and prothrombotic phenotype
Nature Reviews | Disease Primers

CENTRAL ILLUSTRATION: Antiphospholipid Syndrome Pathogenesis



Recommended areas for research:
aPL and β2-GP1 interaction, β2-GP1 and apoER2 interaction, and Complement System activation

Corban, M.T. et al. J Am Coll Cardiol. 2017;69(18):2317–30.


INNATE SUSCEPTIBILITY
•HLA type (DR3/2)
•Immunoregulatory genes (multiple)
•Complement levels
•Hormonal levels
ENVIRONMENTAL STIMULI
•UV exposure
•Microbial response
•Drugs
AUTOIMMUNE PROLIFERATION
•Hyperactive B-cell/T-cell activation
•High ratio of CD4:CD8 T-cells
•Defective immune complex clearance
•Impaired tolerance
AUTOANTIBODY PRODUCTION
•Apoptosis & self-exposure
•Self-recognition
•Foreign-Ab cross-reaction