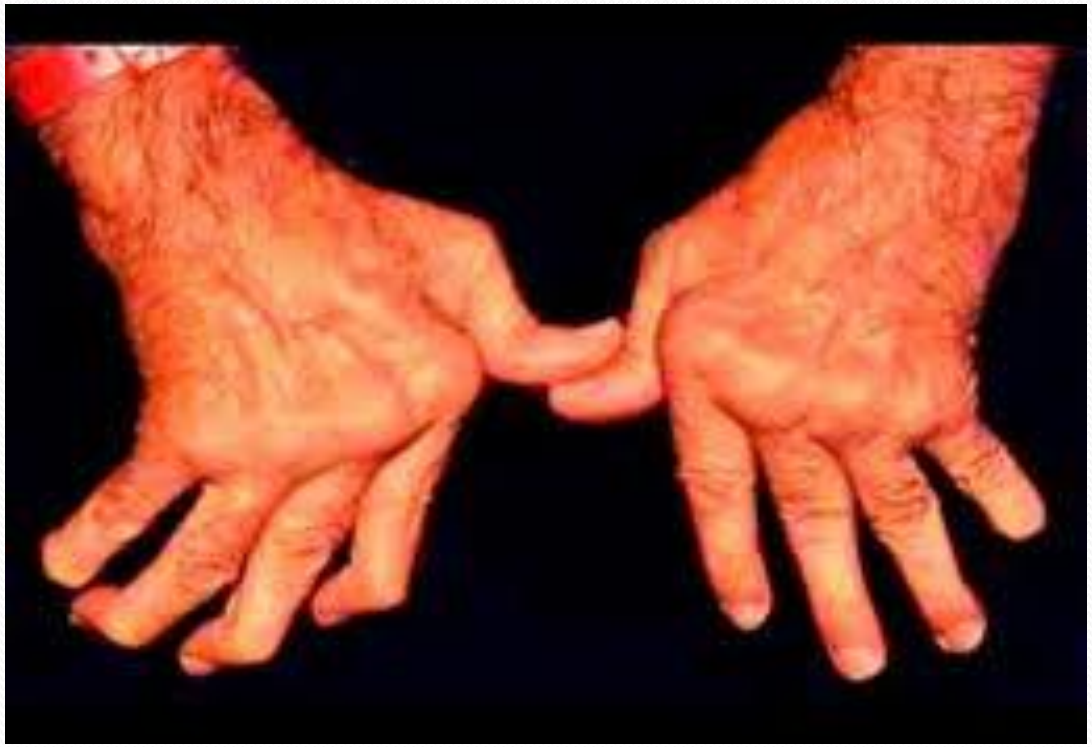


RHEUMATOID ARTHRITIS

Objectives

- Describe aetiology and pathogenesis of Rheumatoid Arthritis
- Discuss clinical and morphological features of Rheumatoid Arthritis
- Enumerate complications of Rheumatoid Arthritis

DEFINITION

- Rheumatoid arthritis (RA) is a chronic and usually progressive inflammatory disorder of unknown etiology characterized by polyarticular symmetrical joint involvement and systemic manifestations.

Overview

- **Rheumatoid arthritis (RA)** is a chronic, systemic autoimmune disease that involves inflammation in the membrane lining of the joints and often affects internal organs.
- Most patients exhibit a chronic fluctuating course of disease that can result in progressive joint destruction, deformity, and disability. Rheumatoid arthritis can affect people of all ages.
- Damage to joints can occur early and does not correlate with the severity of symptoms.
- The "rheumatoid factor" is an antibody that can be found in the blood of 80% of people with rheumatoid arthritis.

- It occurs between 0.5 and 1% of adults in the developed world with 5 and 50 per 100,000 people newly developing the condition each year.

- It occurs three times more often in women, and peaks at age 35 to 50 years.

ETIOLOGY

- **Gender**- Women before the menopause are affected three times more often than men with an equal sex incidence thereafter suggesting an aetiological role for sex hormones.

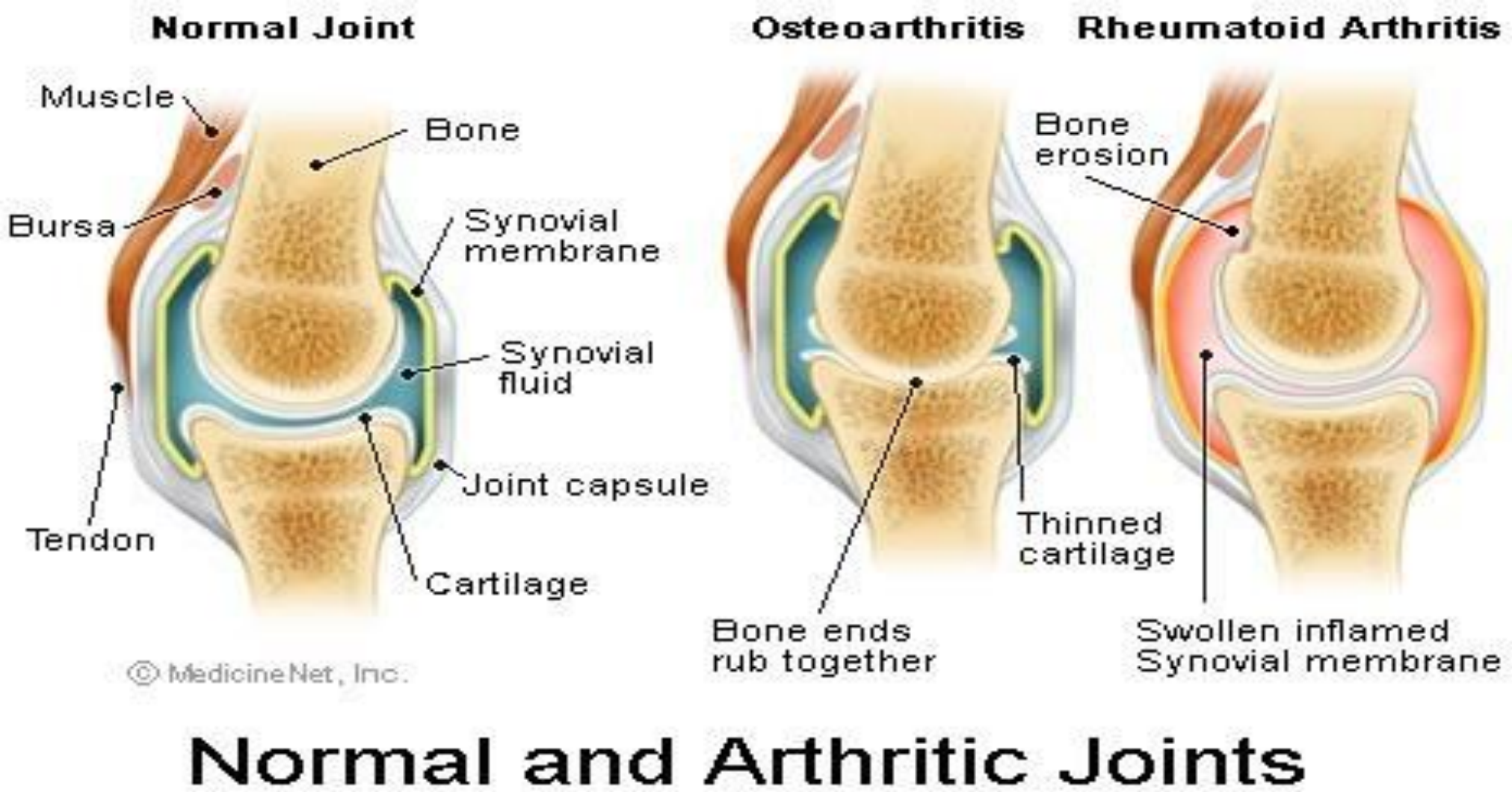
- **Familial** -There is an increased incidence in those with a family history of RA.

- **Genetic Ifactors** - Human leucocyte antigen (HLA)-DR4 and HLA-DRB 1 confer susceptibility to RA and are associated with development of more severe erosive disease
- **Anticitrullinated proteins** and peptides are high specific for RA.

- **Antigen-dependent activation of T lymphocytes** leads to proliferation of the synovial lining, activation of proinflammatory cells from the bone marrow, cytokine and protease secretion, and autoantibody production.
- **Tumor necrosis factor** (TNF-&), **IL-1**, **IL-6**, **IL-8**, and **growth factors** propagate the inflammatory process, and agents found to alter these cytokines show promise in reducing pain and deformity.
- **Inflamed synovium** is a hallmark of the pathophysiology of RA. Synovium proliferates abnormally, growing into the joint space and into the bone, forming a pannus. The pannus migrates to the articular cartilage and into the subchondral bone leading to destruction of cartilage, bone, tendons, and blood vessels.

JOINTS INVOLVEMENT IN RA

- Hands and wrists
- Shoulders
- Elbows
- Feet
- Knees
- Hips
- Cervical spine



Normal and Arthritic Joints

A- Genetics

- HLA class II is strongly linked to RA.
- **HLA DR4** is the major halo-type in ethnic group, **HLA DR1** in Indians and **HLA DW15** in Japanese.
- 50-70 % of caucasian RA patients are HLA DR4, Compared to 20-25 % of the population at large.
- 1st degree relatives of RA patients are 4x .
- 25 % frequency in identical twins
- 5 % Frequency in non-identical twins

B- Auto-Immunity

There is substantial evidence that the initiation of RA is ***T-cell*** mediated.

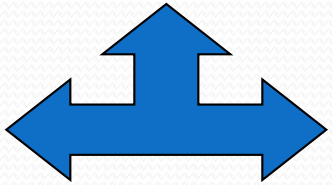
Antigen Specific Process

Once T-Lymphocyte recognize antigens (Arthritogenic antigen)

Therefore:

Auto Immunity Cascade Started

Arthritogenic Antigen



Exogenous

Endogenous

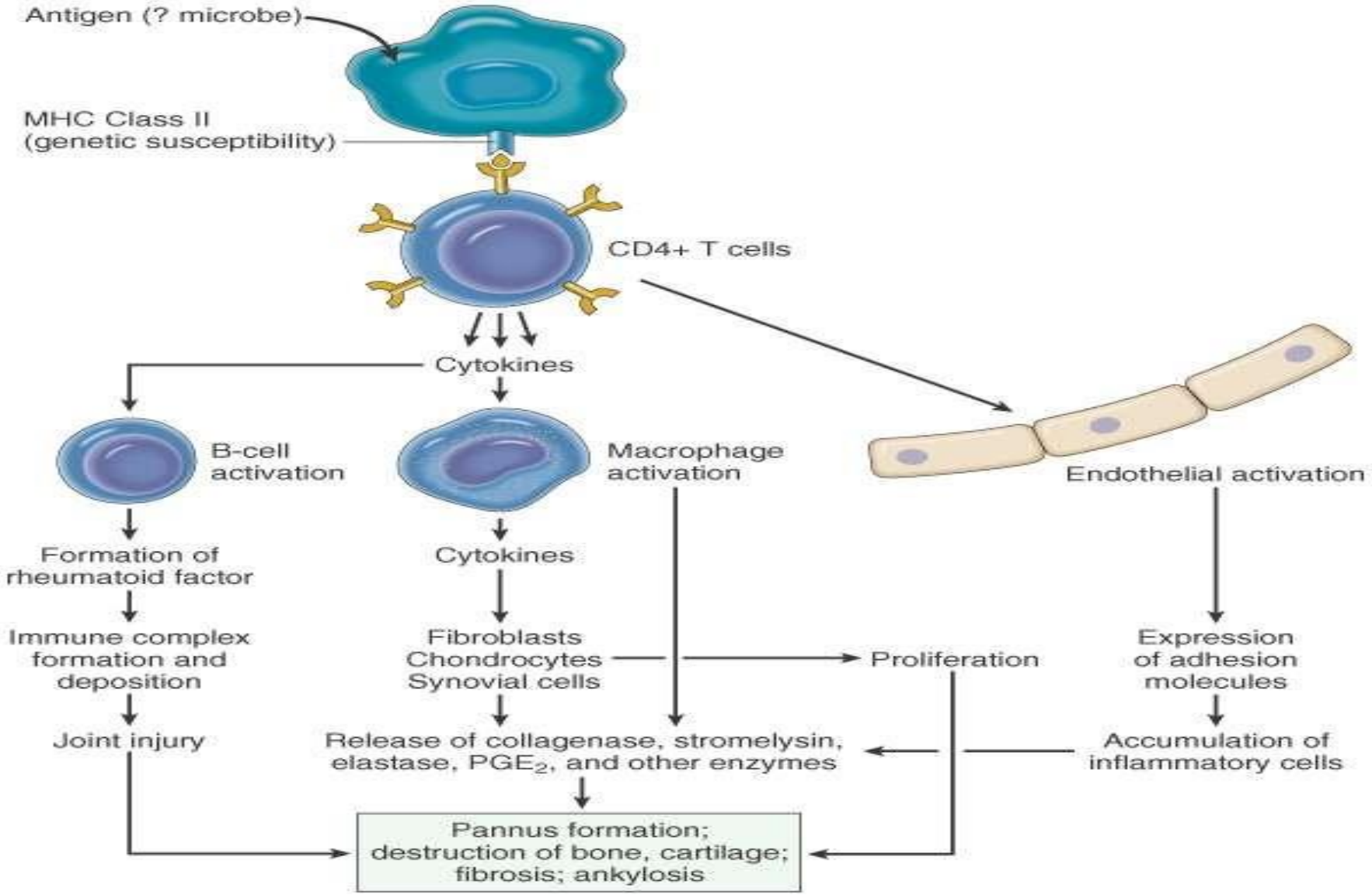
viral

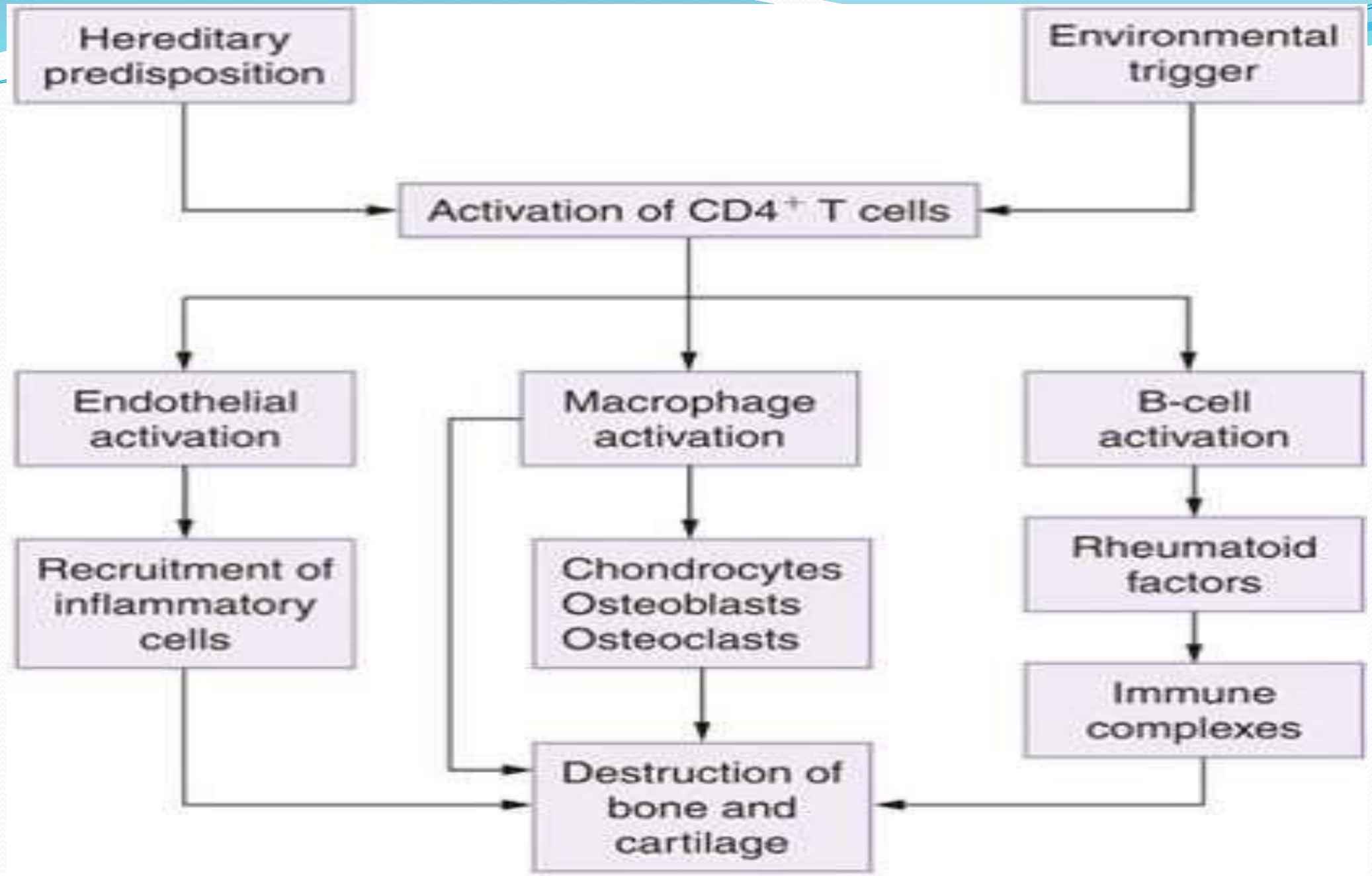
Bacterial

EBV
Hepatitis
Paro Virus B19

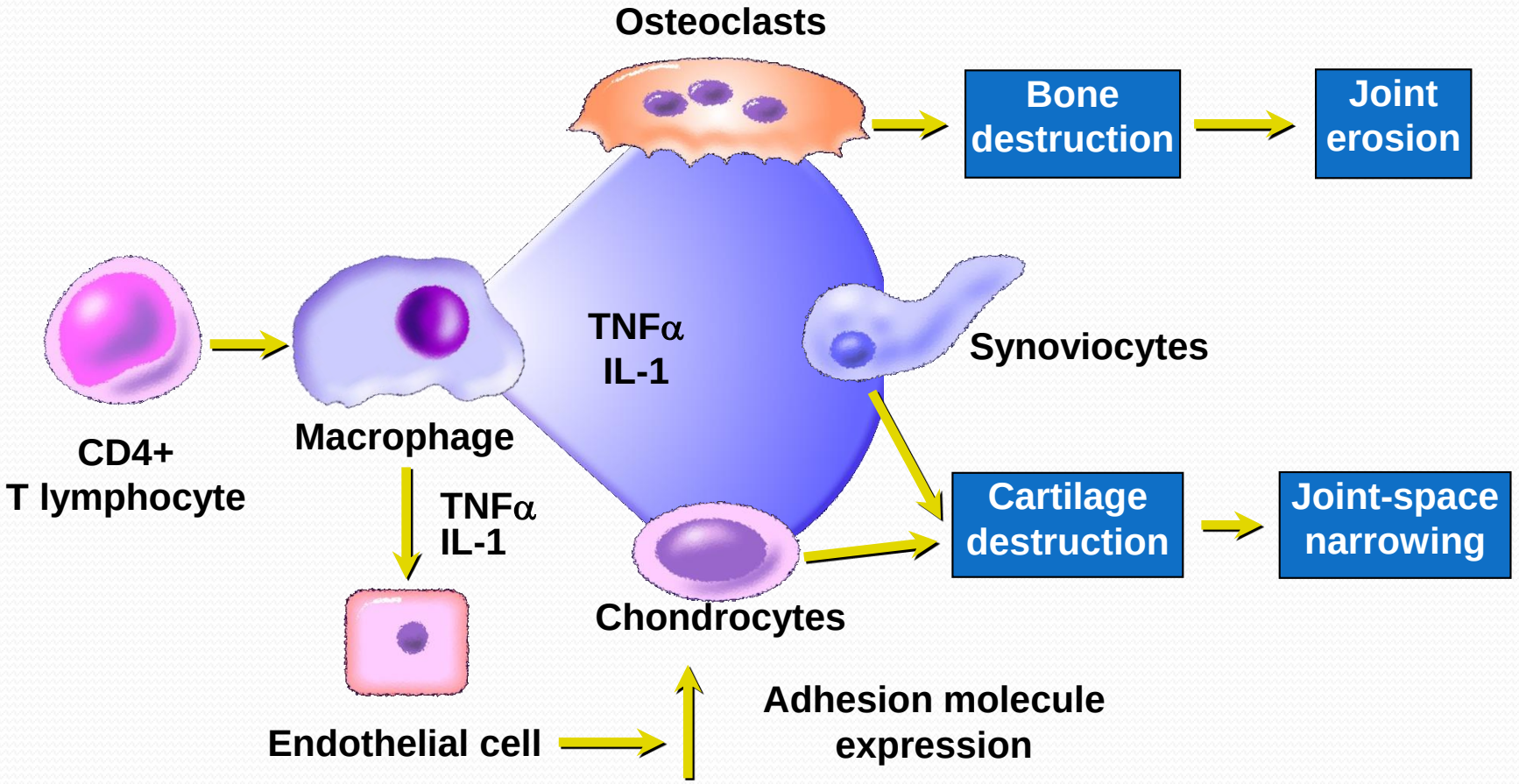
Mycoplasma
MycoBacterium
Yarsenia
Streptococcus

Citrullinated Peptide


Antigen (? microbe)
MHC Class II
(genetic susceptibility)
CD4+ T cells
Cytokines
B-cell
activation
Macrophage
activation
Endothelial activation
Formation of
rheumatoid factor
Cytokines
Immune complex
formation and
deposition
Fibroblasts
Chondrocytes
Synovial cells
Proliferation
Expression
of adhesion
molecules
Joint injury
Release of collagenase, stromelysin,
elastase, PGE_2, and other enzymes
Accumulation of
inflammatory cells
Pannus formation;
destruction of bone, cartilage;
fibrosis; ankylosis


Hereditary predisposition
Environmental trigger
Activation of CD4+ T cells
Endothelial activation
Macrophage activation
B-cell activation
Recruitment of inflammatory cells
Chondrocytes
Osteoblasts
Osteoclasts
Rheumatoid factors
Immune complexes
Destruction of bone and cartilage

Mechanisms of Structural Damage in Rheumatoid Arthritis



Adapted from Arend WP. *J Rheumatol* Suppl. 2002;65:16-21. Permission to reproduce granted by *Journal of Rheumatology* and Dr WP Arend.

PATHOGENESIS

- In susceptible individuals with either genetic predisposition or environmental triggers the enzymatic change in the self proteins like collagen ,vimentin etc takes place post translationally ,one of the amino acid arginine is changed to citrulline
- Activation of T cells starts a series of intercellular reactions
- Lymphocytes, monocytes/ macrophages, and synovial fibroblasts are stimulated to release pro inflammatory cytokines.
- Cytokines induce synovial proliferation and release of destructive enzymes and proteases.
- Chronic inflammation of the synovial tissue lining the joint capsule results in the proliferation of this tissue. The inflamed, proliferating synovium contains germial centers, plasma cells, and autoantibodies against self antigens .This is acharacteristic of rheumatoid arthritis and is called *pannus*. This pannus invades the cartilage and eventually the bone surface, producing erosions of bone and cartilage and leading to destruction of the joint. The factors that initiate the inflammatory process are unknown.

The immune system is a complex network of checks and balances designed to discriminate self from non- self (foreign) tissues. It helps rid the body of infectious agents, tumor cells, and products associated with the breakdown of cells. In rheumatoid arthritis, this system no longer can differentiate self from non-self tissues and attacks the synovial tissue and other connective tissues.

CONCLUSION OF PATHOGENESIS

- Whatever the initiating stimulus…..

RA is characterized by :

1. Persistent cellular activation
2. Genetically susceptible host
3. Auto-immunity

At the site of articular and extra-articular tissue

chronic inflammation
(PANUS)
and
(JOINT DESTRUCTION)

MORPHOLOGY

- Synovial hyperplasia.
- Infiltration of synovium by dense perivascular inflammatory cells(B cells,CD4+T cells, at places forming lymphoid aggregates,plasma cells and macrophages).
- Increased vascularity .
- Deposition of fibrin in synovium and accumulation of neutrophils in synovial fluid.
- Osteoclastic activity in underlying bone.
- **PANNUS:** Neovascularization, inflammation, and fibrinoid deposits, which progressively destroys the underlying cartilage and subchondral bone.

PRESENTATION

- 70% insidious onset (weeks to months)
- 10% acute (fulminant onset)
- 20% sub acute onset

PATTERNS OF JOINTS INVOLVEMENT

- Oligoarticular 45%

- Polyarticular 35% ➔ 60% small joints
  30 % large joints
  10 % Both

- Monoarticular 20% ➔ 50% knee only

  50% ➔ wrist, elbow, shoulder, ankle, hips

SIGNS AND SYMPTOMS

- Fatigue.
- Stiffness, especially in early morning and after sitting a long period of time.
- Low Grade Fever, Weakness.
- Muscle pain and pain with prolonged sitting.
- Symmetrical, affects joints on both sides of the body.
- Rheumatoid nodules.
- Deformity of your joints over time.
- Reynaud's phenomenon.
- Pain
- As the disease progresses there is weakening of joint capsules
  - joint instability
  - Subluxation
  - deformity

NON-ARTICULAR MANIFESTATIONS OF RA

- **Systemic** – Fever, Fatigue, Weight loss
- **Eyes**- Scleritis, Scleromalacia perforans (perforation of the eye)
- **Neurological**- Carpal tunnel syndrome, Cord compression
- **Haematological**- Lymphadenopathy, Felty's syndrome (rheumatoid arthritis, splenomegaly, neutropenia), Anaemia (chronic disease, NSAID- induced, gastrointestinal blood loss, haemolysis, hypersplenism), Thrombocytosis

- **Pulmonary** - Pleural effusion, Lung fibrosis, Rheumatoid nodules, Rheumatoid pneumoconiosis
- **Heart and peripheral vessels** – Pericarditis, Pericardial effusion, Raynaud's syndrome
- **Vasculitis** – Leg ulcers, Nail fold infarcts, Gangrene of fingers and toes
- **Kidneys** - Amyloidosis causes the nephrotic syndrome and renal failure

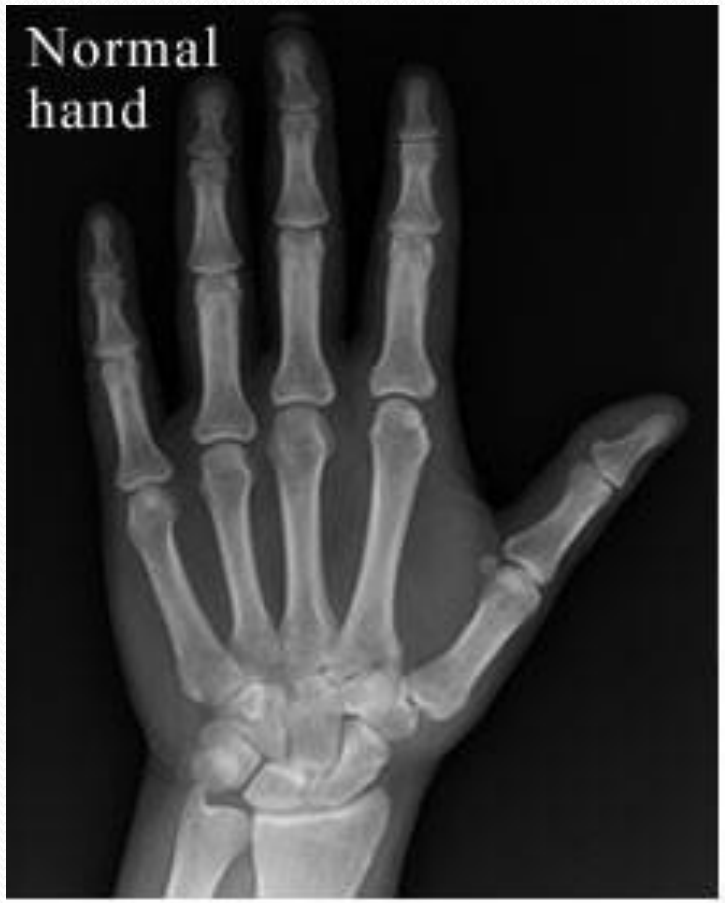


Figure 1

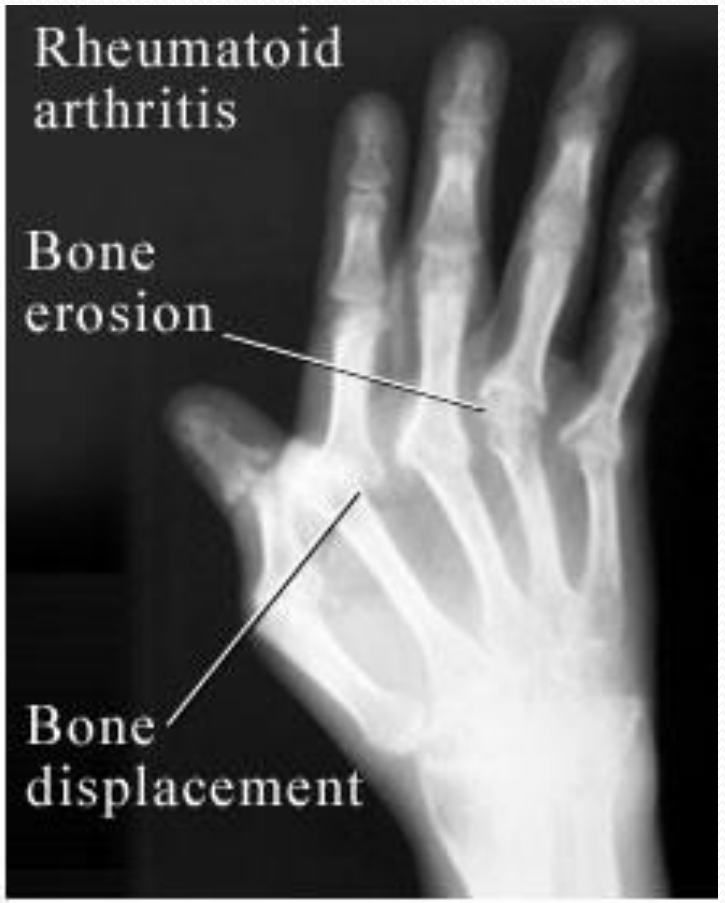


Figure 2

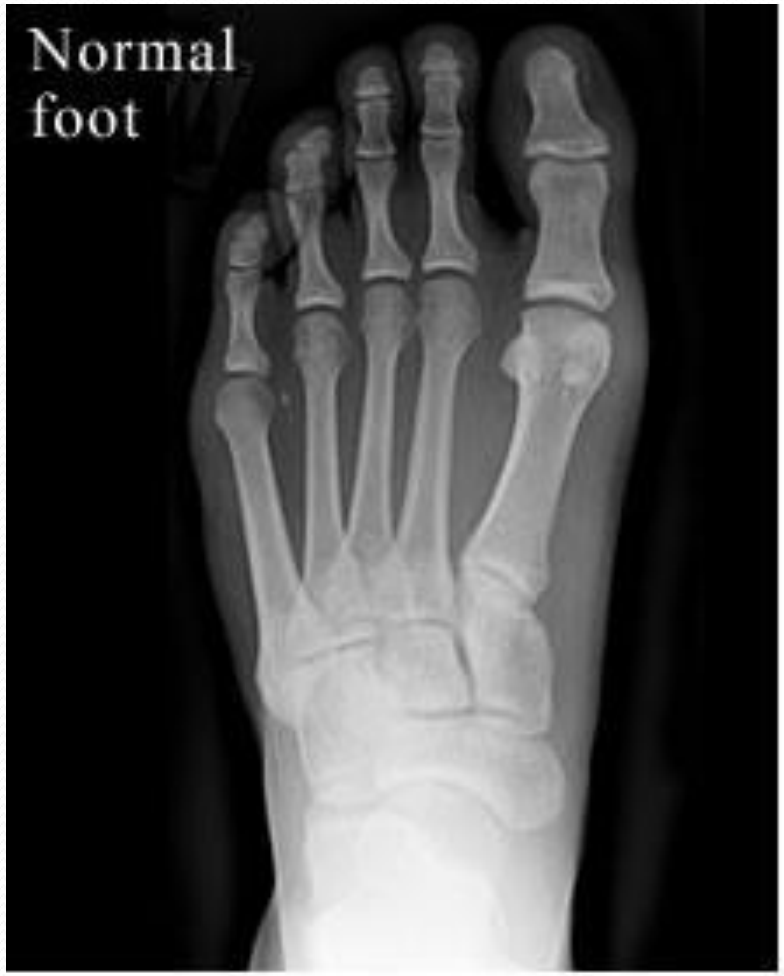


Figure 1

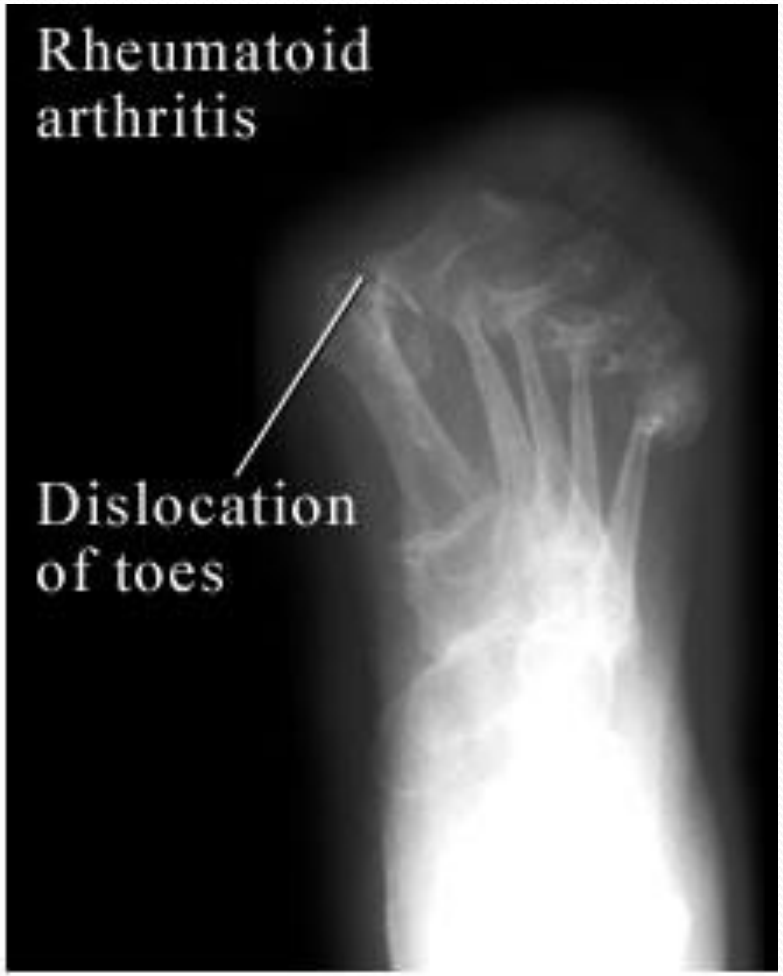


Figure 2

COMPLICATIONS OF RH

Firm, nontender, and round to oval, (Rhematiod nodules)

Vasculitis (can involve the pleura, pericardium or lung evolving into chronic fibrosing processes.

digital arteries are obstructed by an obliterating endarteritis resulting in peripheral neuropathy,

Ruptured tendons

Ruptured joints (Baker'scysts)

Joint infection

Spinal cord compression (upper cervical spine)

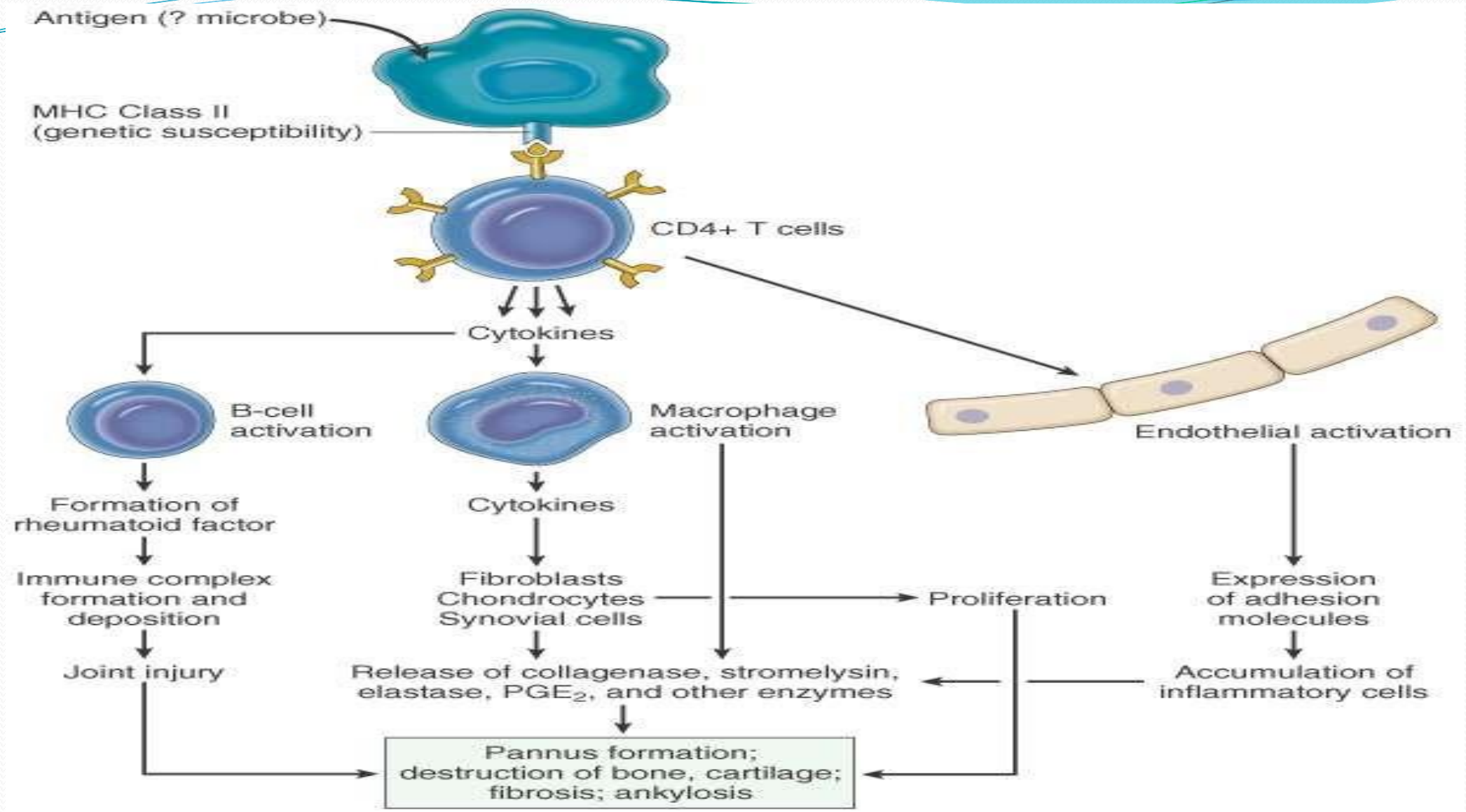
Amyloidosis (rare)

Ankylosis

Side-effects of therapy

MAIN DIFFERENCES B/W OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

	RA	OA
1.PATHOGENESIS	Inflammatory	Degenerative(wear/tear)
2.Age/Peak	30-40	60-80
3.Sex	female:male3:1	male=female
4.Joint involved	symmetric	asymmetric
5.Preferential site	small joints of hand	weight-bearing joints.
6. Pathology		
Joint	Ankylosis	Osteoporosis
Bone	Osteosclerosis	Osteophytes
Extraarticular	Rheumatoid nodules	No
Internal organs	Yes	No
Systemic findings	YES	No


Antigen (? microbe)
MHC Class II
(genetic susceptibility)
CD4+ T cells
Cytokines
B-cell activation
Macrophage activation
Endothelial activation
Formation of rheumatoid factor
Cytokines
Immune complex formation and deposition
Fibroblasts
Chondrocytes
Synovial cells
Proliferation
Expression of adhesion molecules
Joint injury
Release of collagenase, stromelysin, elastase, PGE_2, and other enzymes
Accumulation of inflammatory cells
Pannus formation; destruction of bone, cartilage; fibrosis; ankylosis

THANKYOU