BLOCK

Pathology

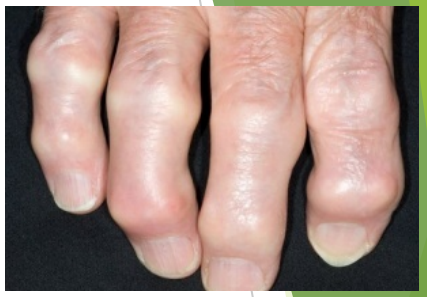
Non-infectious arthritis

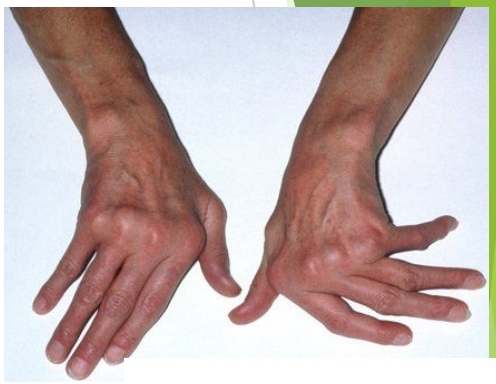
Objectives

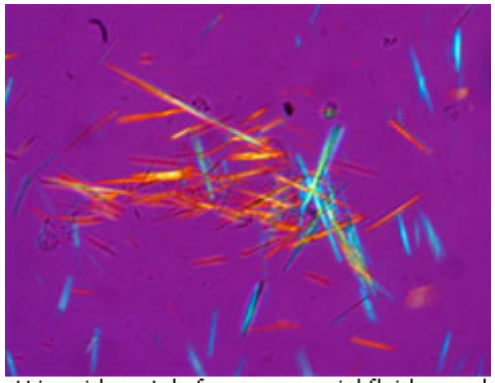
- Know the pathogenesis and clinicopathological features of osteoarthritis (degenerative joint disease),
- Know the pathogenesis and clinicopathological features of rheumatoid arthritis
- Know the pathogenesis and clinicopathological features of gout and calcium pyrophosphate arthropathy [pseudogout]

Inflammatory disease of joints (arthritis and synovitis)

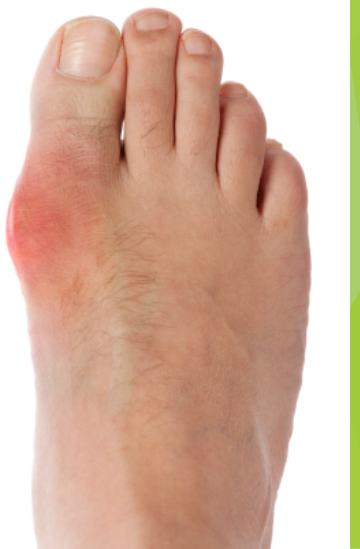
- **has four main causes**
  1. **Degeneration**, e.g. osteoarthritis.
  2. **Autoimmity**, e.g. rheumatoid arthritis, SLE, rheumatic fever
  3. **Crystal deposition**, e.g. gout and other crystalline arthropathies.
  4. **Infection**, e.g. septic arthritis, tuberculous arthritis.







Uric acid crystals from a synovial fluid sampl



Osteoarthritis
Definition and Incidence

- **Osteoarthritis** is the most common type of joint disease and is characterized by the progressive erosion of articular cartilage in weight-bearing joints.
- The incidence increases with age.
- Osteoarthritis can be primary or secondary

Osteoarthritis
Types

- Primary osteoarthritis

- Secondary osteoarthritis

Osteoarthritis
Types

- Primary osteoarthritis:
  - appears insidiously with age and without apparent initiating cause
  - usually affecting only a few jonts.

Osteoarthritis
Types

- Secondary osteoarthritis:
  - some predisposing condition, such as previous traumatic injury, developmental deformity, or underlying systemic disease such as diabetes, ochronosis, hemochromatosis, or marked obesity
  - Secondary osteoarthritis affect young
  - often involves one or several predisposed joints
  - less than 5% of cases

Osteoarthritis
Pathogenesis

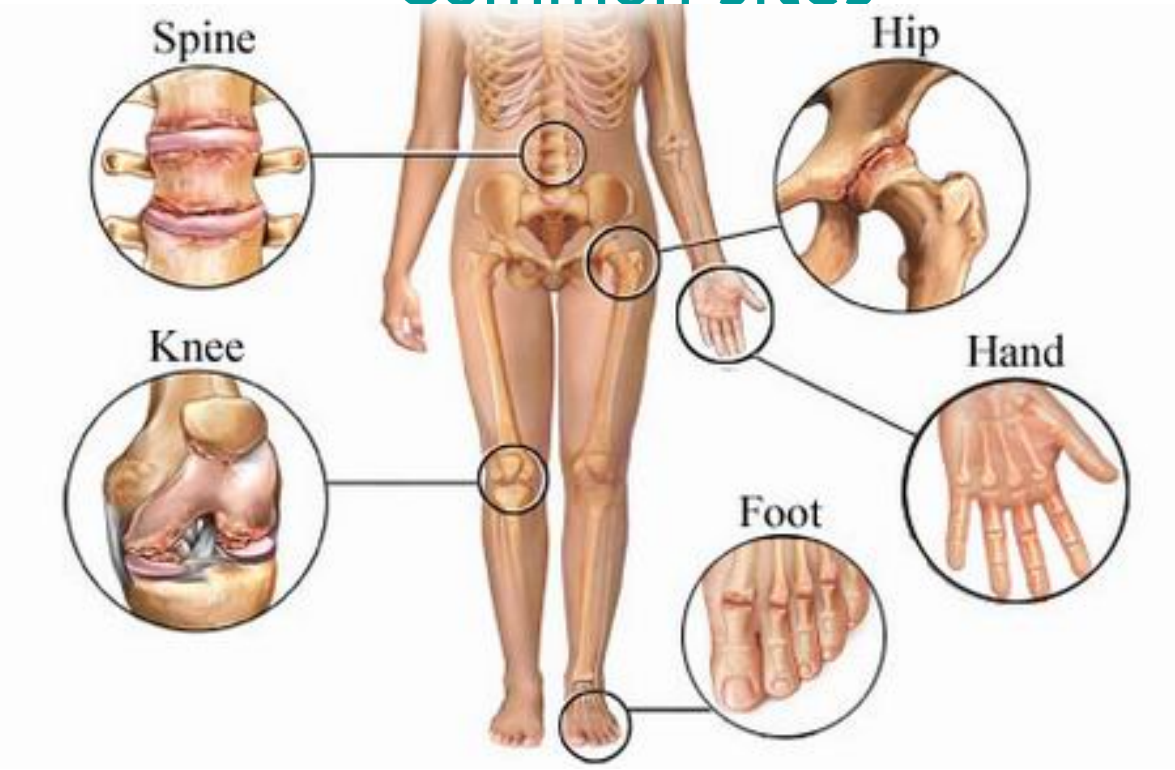
- In general, osteoarthritis affects joints that are constantly exposed to wear and tear.
- **Articular cartilage bears the brunt of the degenerative changes in osteoarthritis.** Normal articular cartilage performs two functions:
- (1) Along with the synovial fluid, it provides virtually friction-free movement within the joint
- (2) in weight-bearing joints, it spreads the load across the joint surface

Pathogenesis

- Early osteoarthritis is marked by degenerating cartilage
- In hyaline cartilage affected by osteoarthritis, the water content is increased and the proteoglycan content is decreased. The elasticity and compliance of the cartilage is, therefore, reduced.
- The very first change seen in osteoarthritis is proliferation of chondroblasts, and it has been proposed that these cells produce enzymes that induce these biochemical changes in the hyaline cartilage.

Osteoarthritis

Common sites

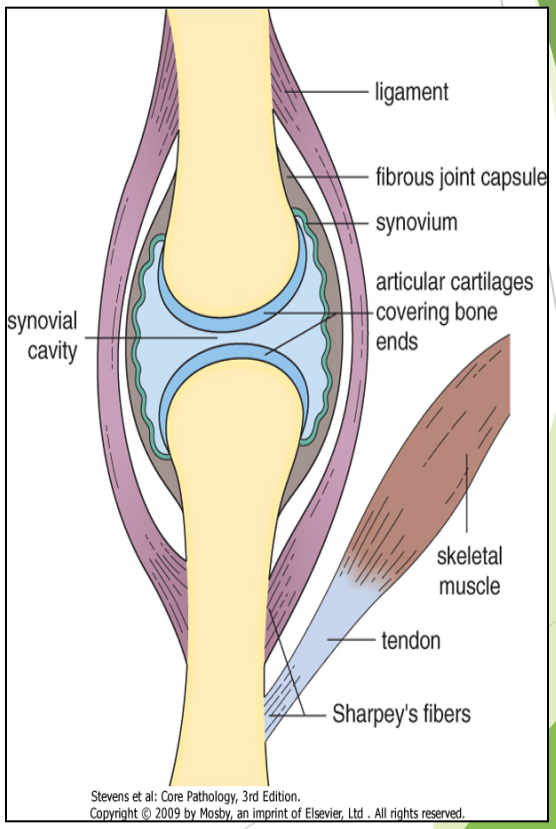


usually one joint or same joint bilaterally

Gender has some influence:
Women : knees and hands
Men : hips

Osteoarthritis

- The pathological changes involve:
  - cartilage
  - bone
  - synovium
  - joint capsule
  - with secondary effects on muscle (atrophy)

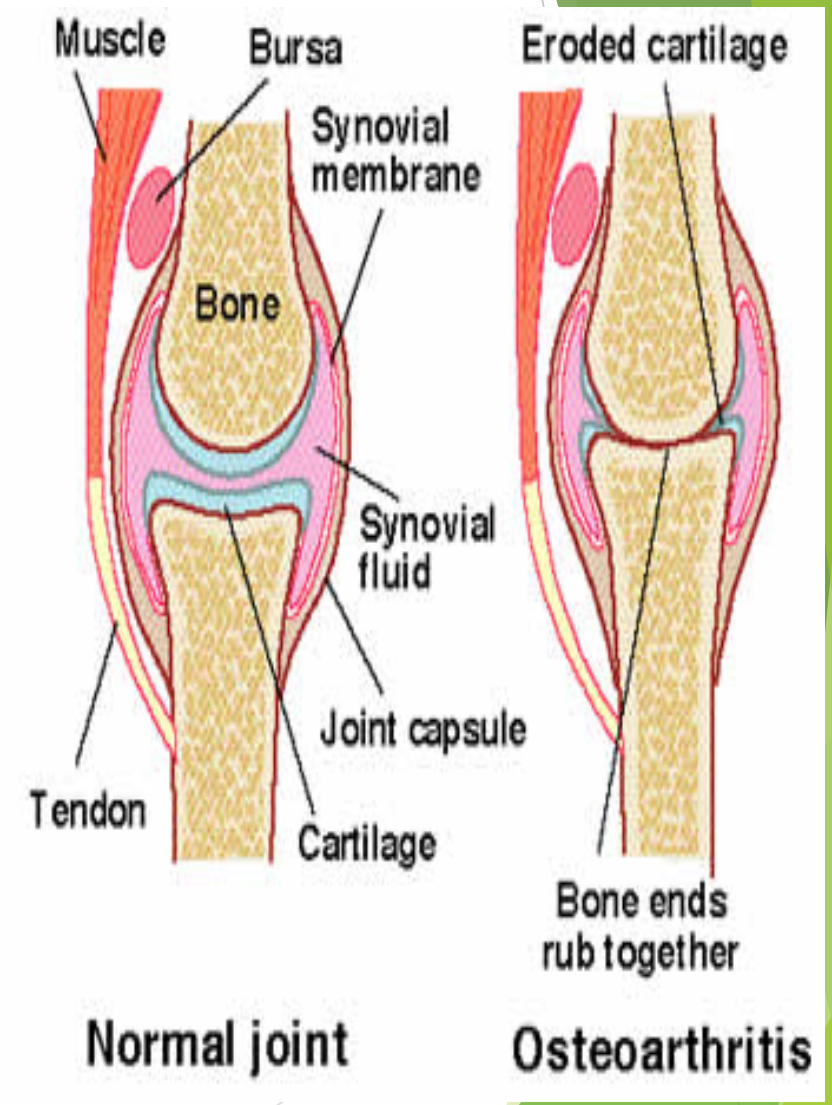


Osteoarthritis Pathogenesis

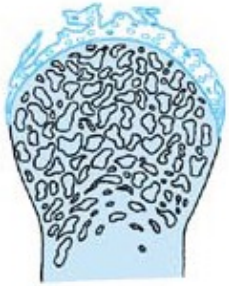
The early change: **destruction of articular cartilage**, which splits (fibrillation), becomes eroded

There is inflammation and thickening of the joint capsule and synovium

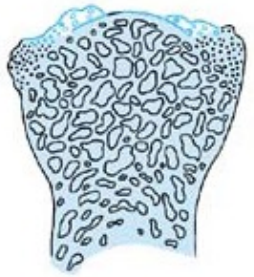
Small fractures can dislodge pieces of cartilage and subchondral bone into the joint, forming loose bodies**(joint mice).**



Normal articular cartilage

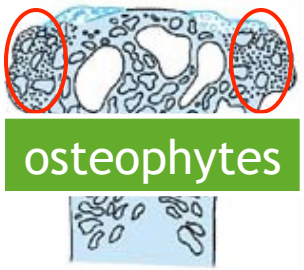


Fragmentation of articular surface and thinning of cartilage



Calcification of cartilage margins. Patchy loss of cartilage revealing bare bone (eburnation).

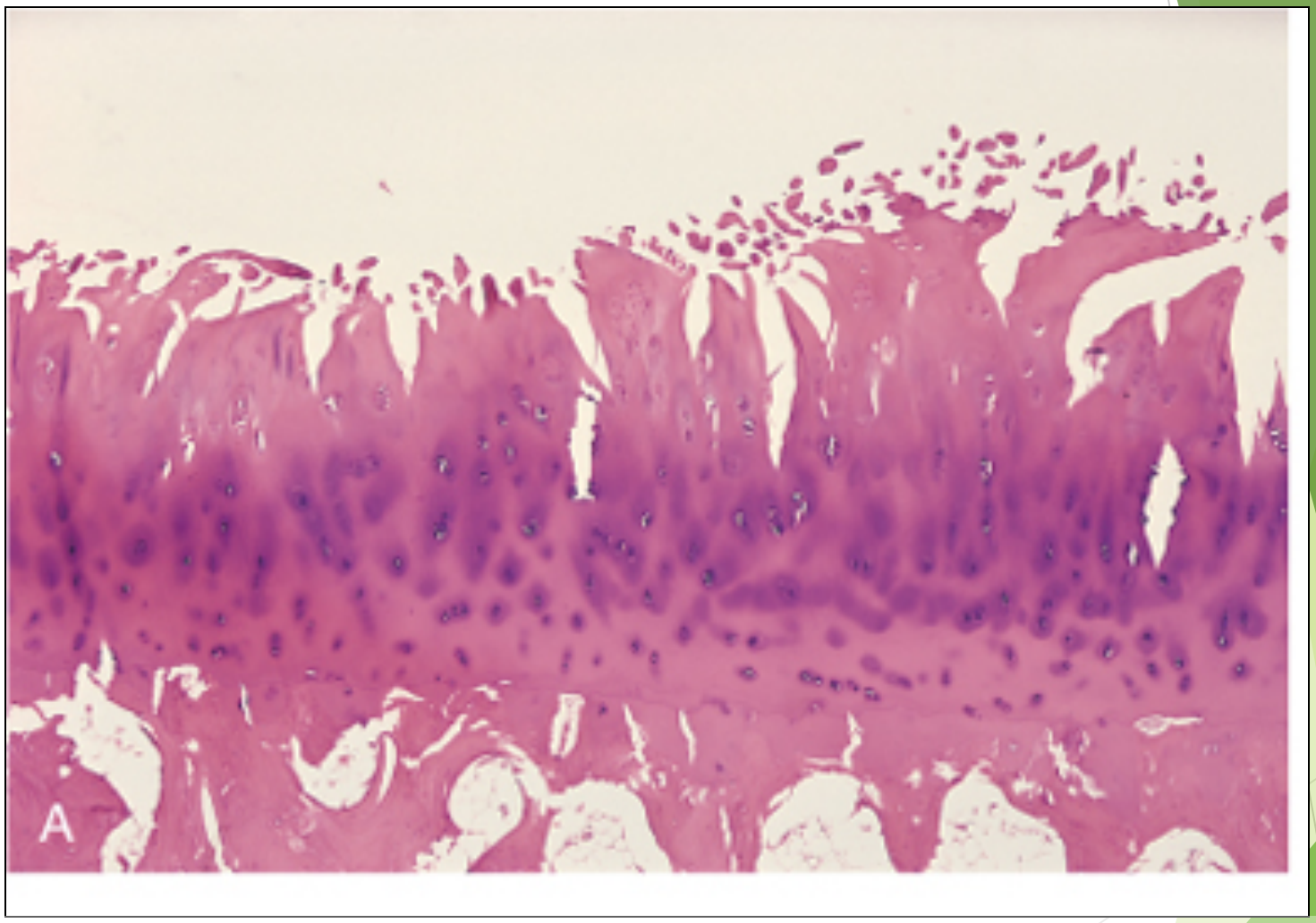
Small cysts develop in the bone



osteophytes

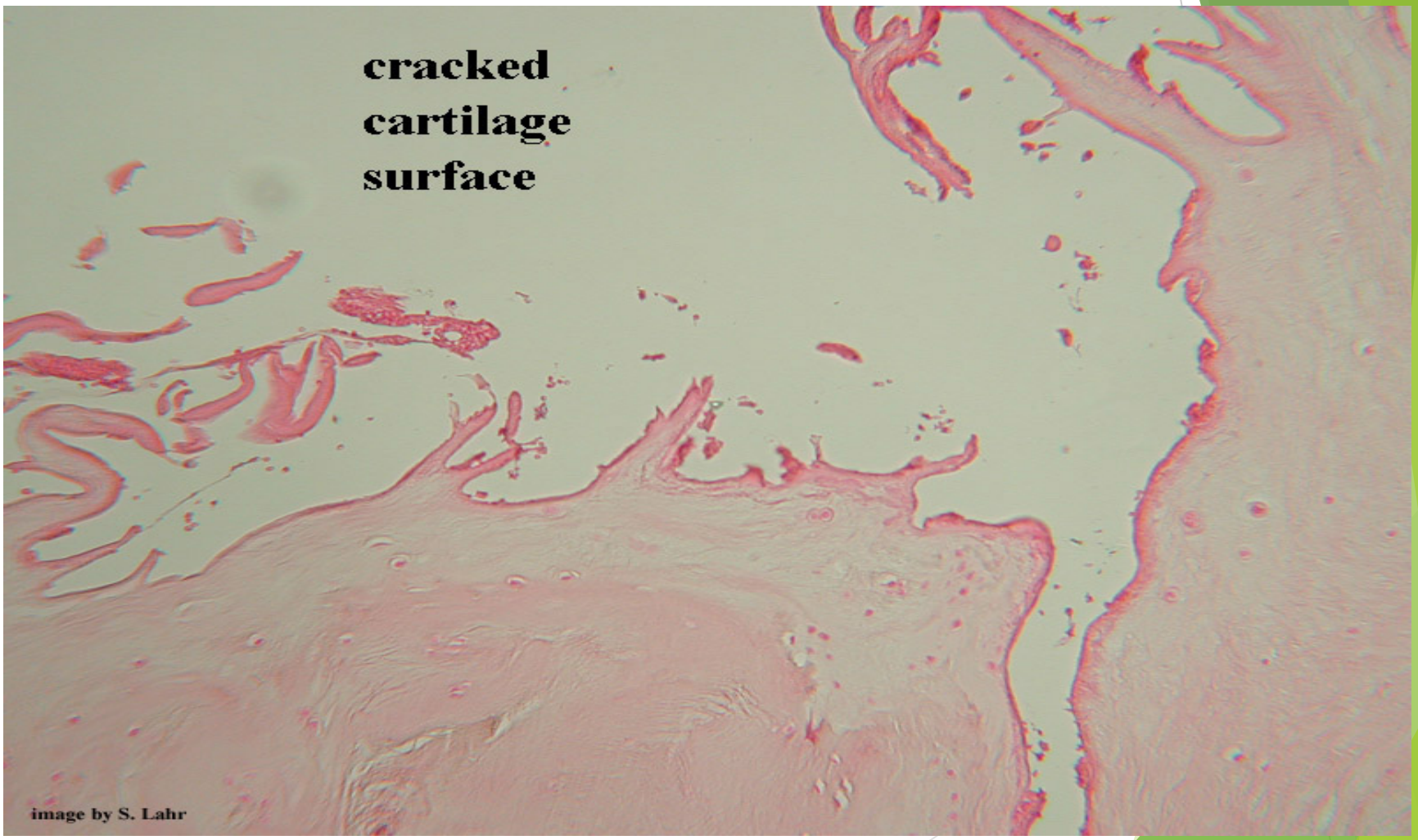
Formation of lips of new bone ("osteophytes")
Extensive loss of cartilage
Cystic degeneration of underlying bone

constant friction of bone surfaces, leading to a polished ivory bony articular surface (eburnation)

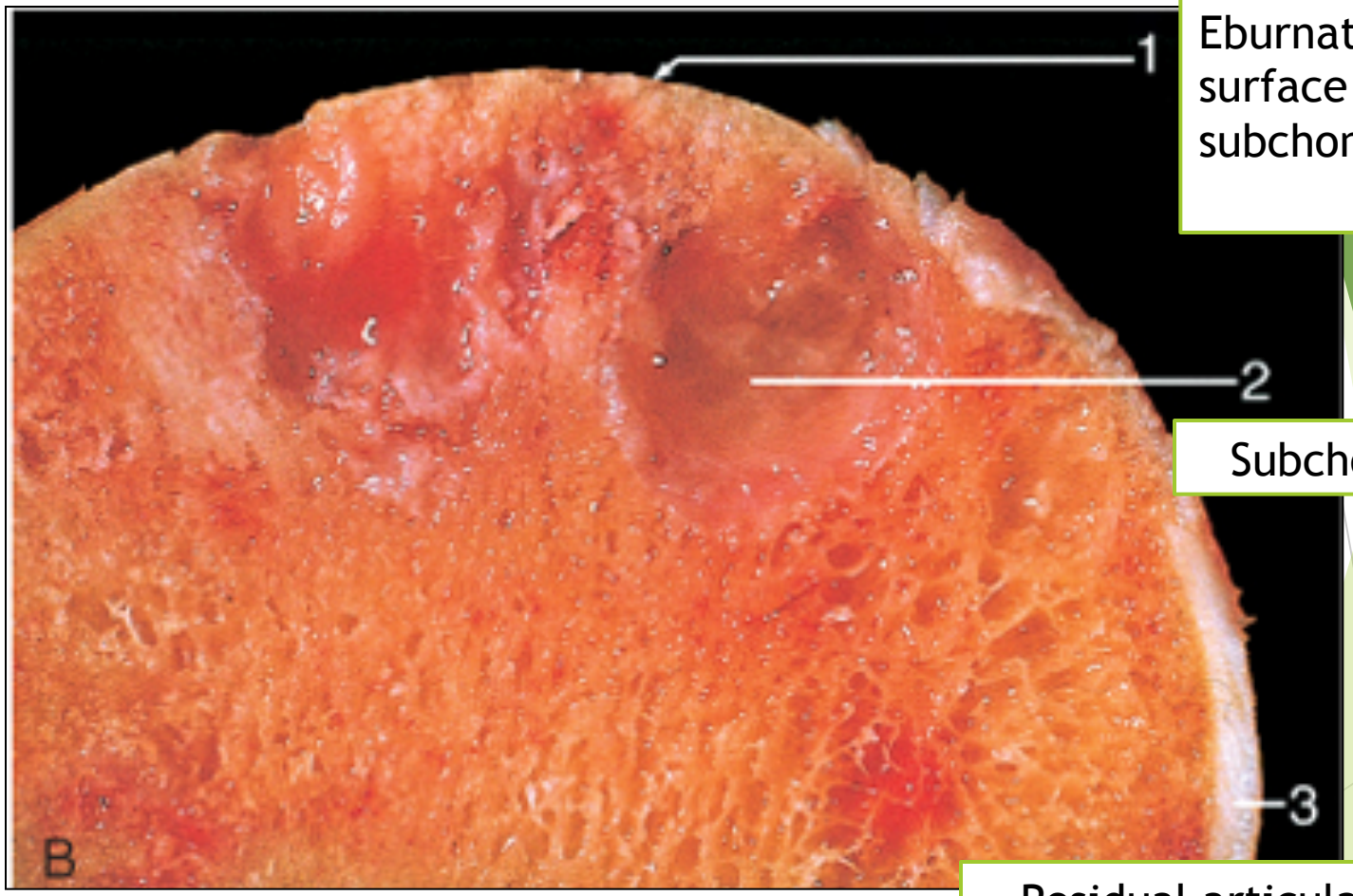


Osteoarthritis. **:** Histologic demonstration of the characteristic fibrillation of the articular cartilage.

Cracking and fibrillation of cartilage



Severe Osteoarthritis

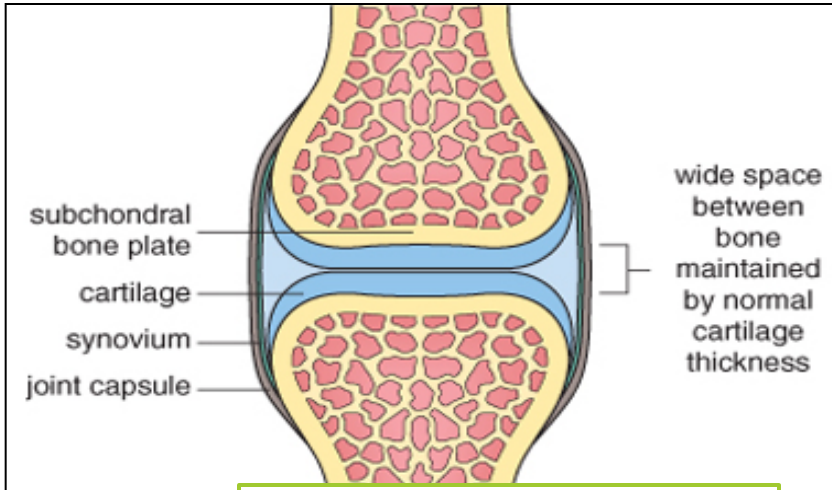


Eburnated articular surface exposing subchondral bone

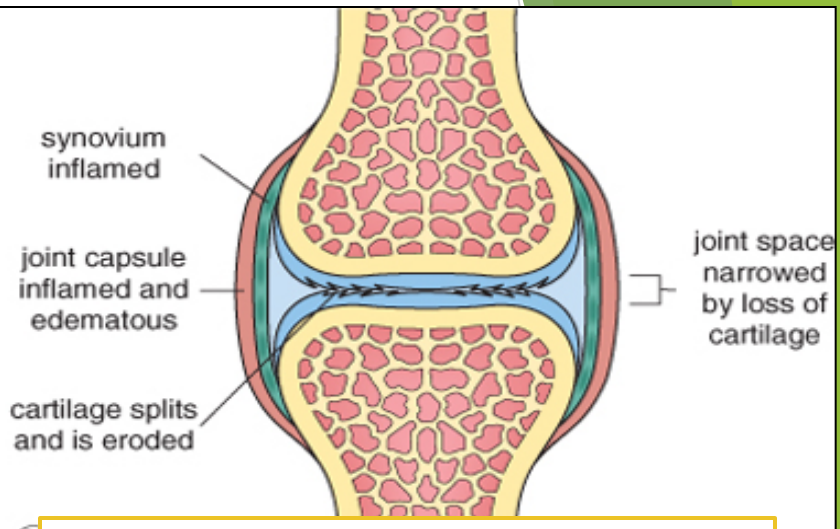
Subchondral cyst

Residual articular cartilage

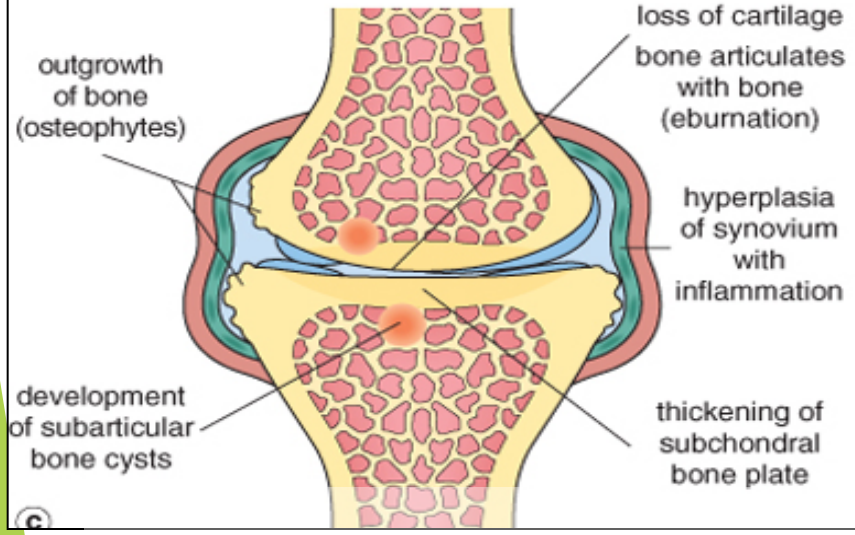
Pathological changes in osteoarthritis

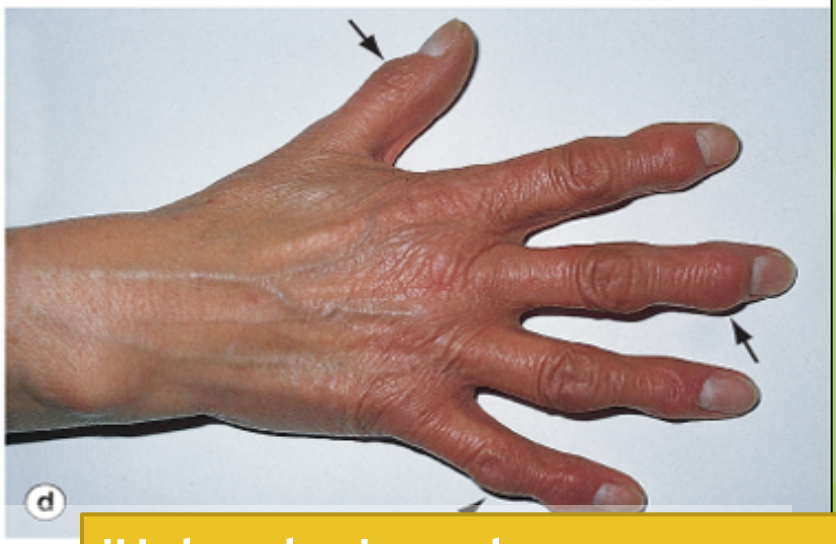


normal synovial joint



early change in osteoarthritis



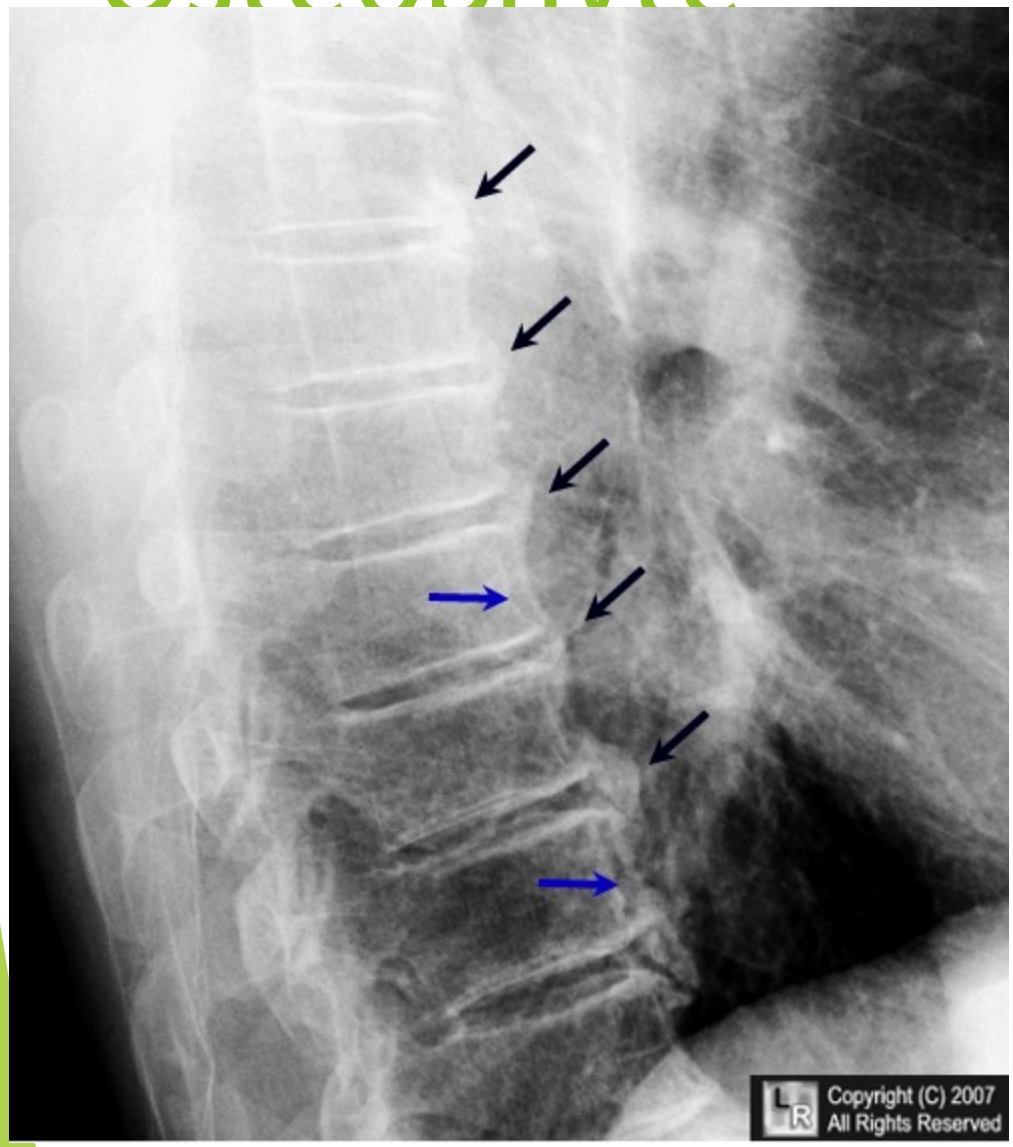


'Heberden's nodes (osteophytes on the interphalangeal joints of the fingers)

Osteoarthritis
Clinical features

- The most frequently affected joints are the hips, the knees, the cervical and lumbar vertebrae, the proximal and distal interphalangeal (PIP and DIP) joint of the hands, the first metacarpophalangeal joint and the first metatarsophalangeal joint.
- Osteophytes at the DIP joints produce nodular swellings called Hebderden's nodes.
- With increasing deformity of the joint the typical symptoms develop, which are pain (which is worse with use), morning stiffness and limitation in joint movement.
- With involvement of the cervical and lumbar spine, osteophytes may impinge on the nerve roots causing symptoms such as pain and pins and needles in the arms or legs.

Osteophyte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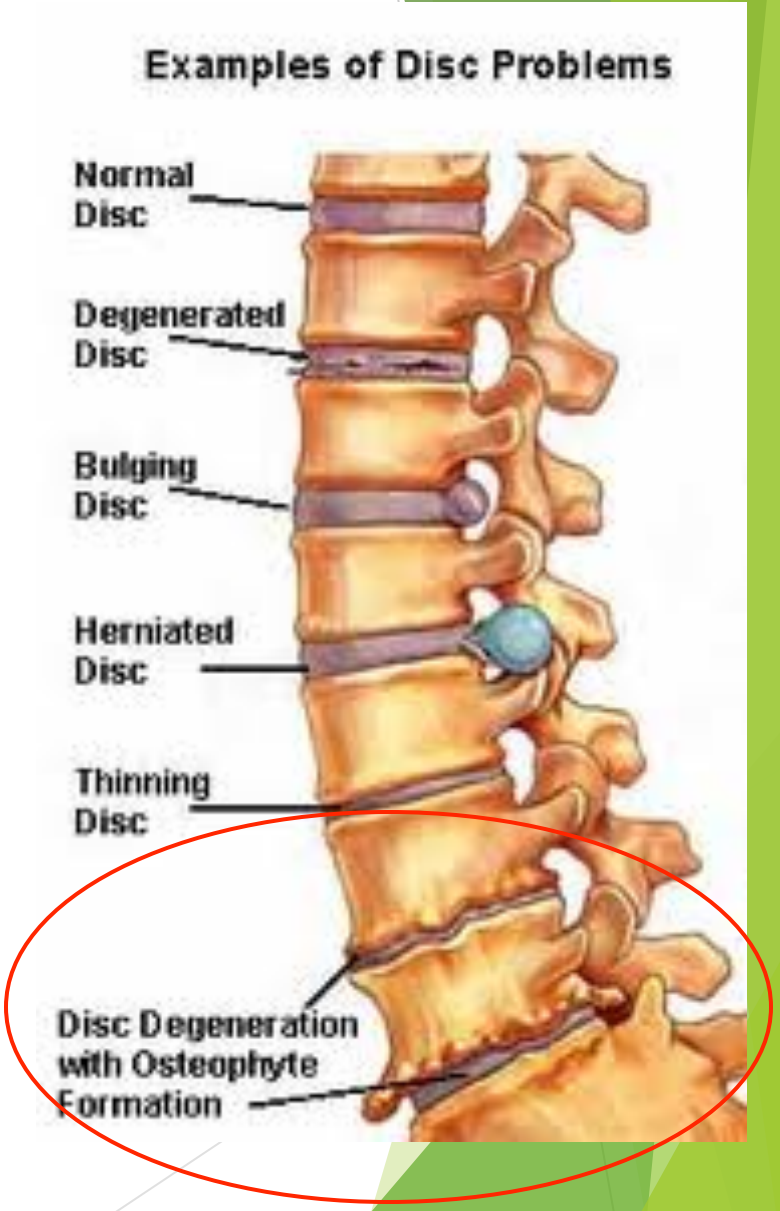

Examples of Disc Problems
Normal Disc
Degenerated Disc
Bulging Disc
Herniated Disc
Thinning Disc
Disc Degeneration with Osteophyte Formation

Course & Prognosis

- Osteoarthrosis is a slowly progressive, chronic joint disability
- Eventually, elderly sufferers may become confined to wheelchairs
- Recent advancements in the technique of joint replacement with prostheses have improved the outlook of these patients

Rheumatoid arthritis

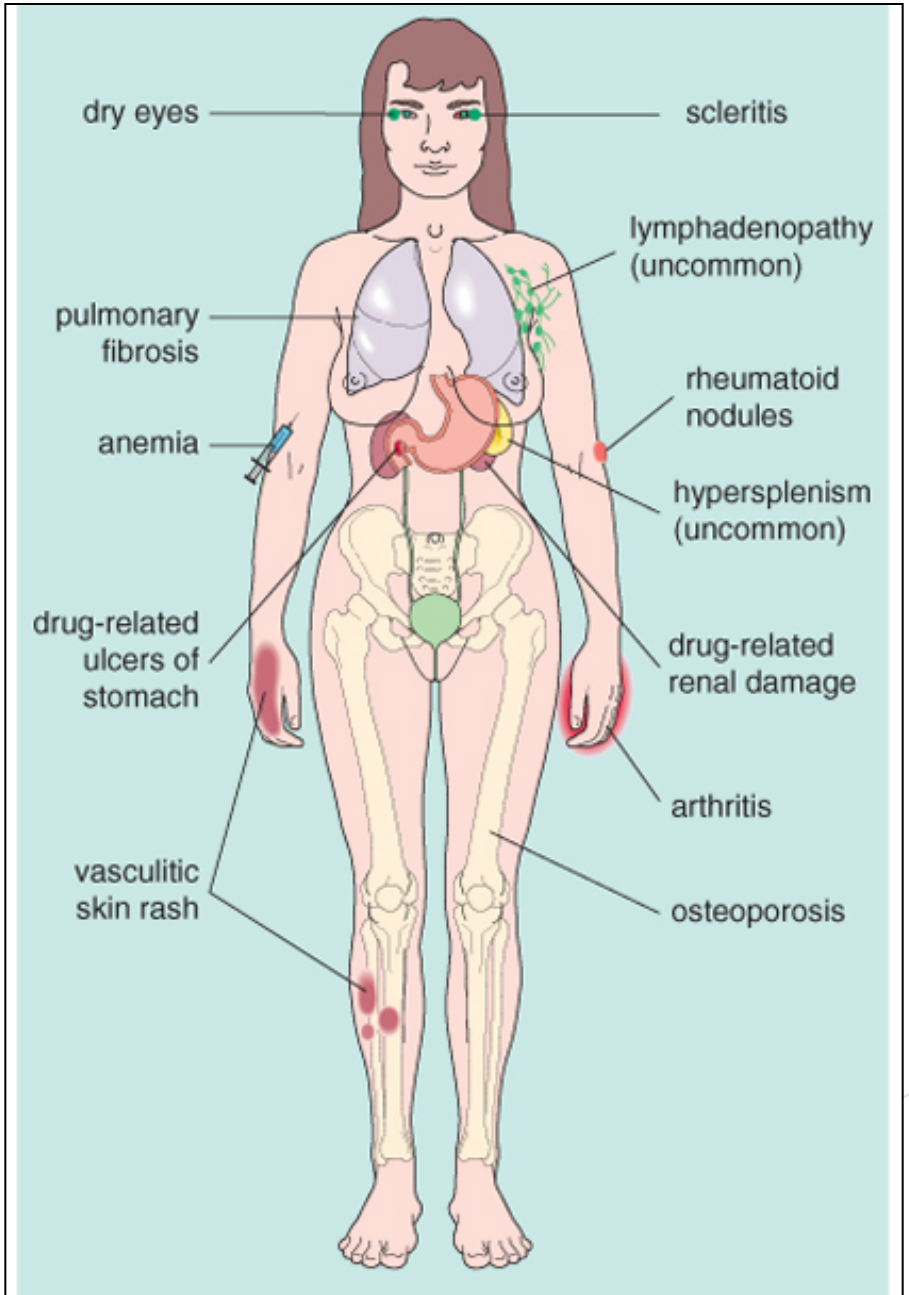
Definition
etiology
pathological features
clinical features
radiological features

Rheumatoid arthritis

Definition

- Rheumatoid arthritis is a chronic inflammatory multisystem disorders but the joints are always involved.
- The condition can affect all age groups. When children are affected, the condition is designated **Still's disease**.
- Females are affected more often than males.
- Produces nonsuppurative proliferative synovitis, may progress to destruction of articular cartilage and joint ankylosis

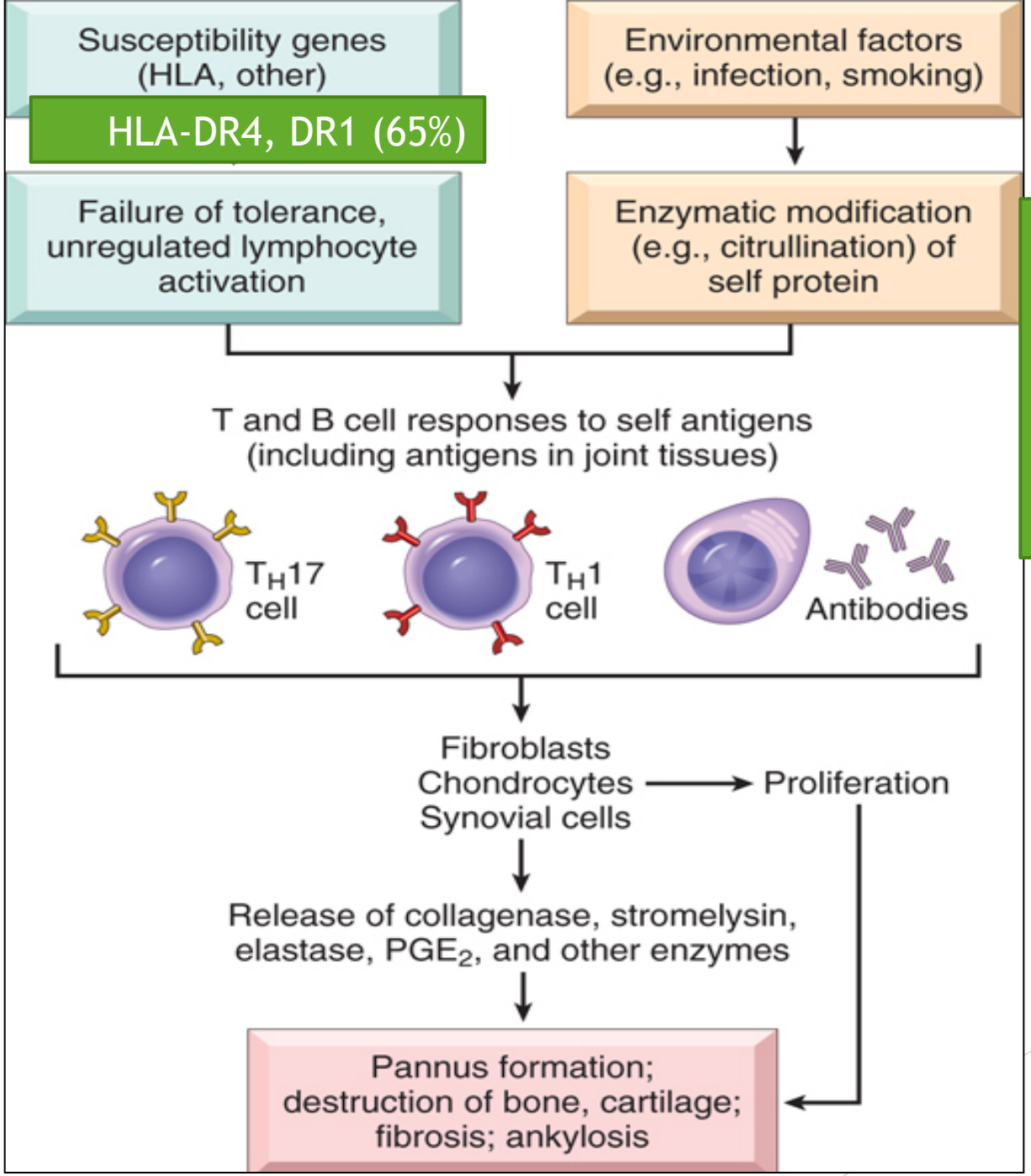
Extra-Articular Manifestations



Rheumatoid arthritis

Aetiology

- The pathogenesis is not well understood, but it is thought that an initiating agent, possibly an organism, triggers immunological dysfunction resulting in persistent chronic inflammation in generatically susceptible individuals.
- In the joints, the ongoing inflammation causes destruction of the articular cartilage.
- Circulating autoantibodies (rheumatoid factors). The exact role of these autoantibodies is uncertain.



Antibodies against cyclic citrullinated peptides (CCP protein antibodies) is the most specific for a diagnosis of rheumatoid arthritis

Rheumatoid arthritis

Laboratory Findings:

- **Rheumatoid factor:** 80% have IgM autoantibodies to Fc portion of IgG
  - not sensitive or specific

- Anti-CCP (cyclic citrullinated peptides)protein antibodies most specific for a diagnosis of rheumatoid arthritis

- ESR and C-reactive proteien

Rheumatoid arthritis

Pathologic Features

1. synovial cell hyperplasia and proliferation
2. dense perivascular inflammatory cell infiltrates

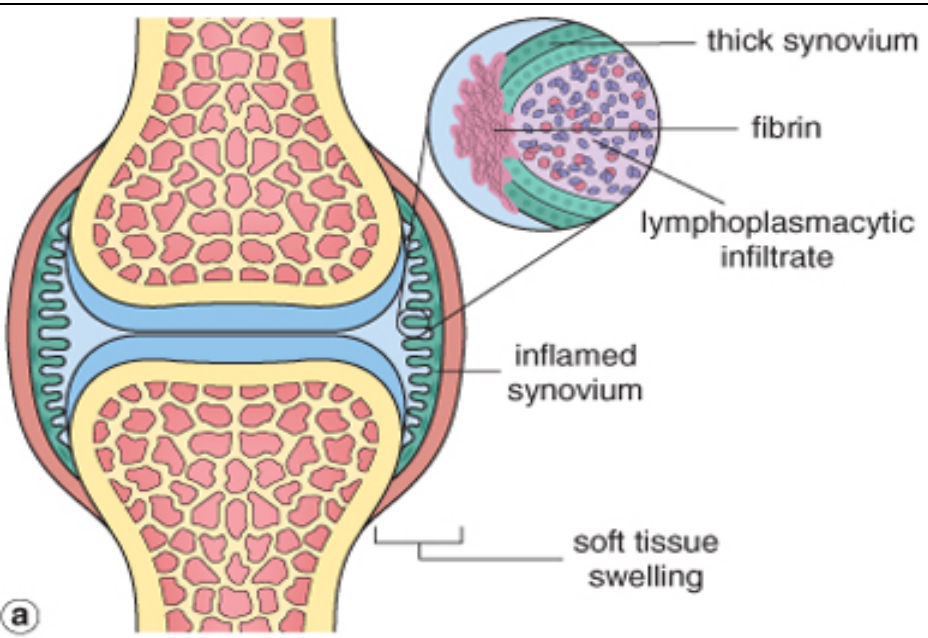
   (frequently forming lymphoid follicles) in the synovium composed of CD4+ T cells, plasma cells, and macrophages
3. increased vascularity due to angiogenesis
4. neutrophils and aggregates of organizing fibrin on the synovial surface
5. increased osteoclast activity in the underlying bone ➔ bone erosion.

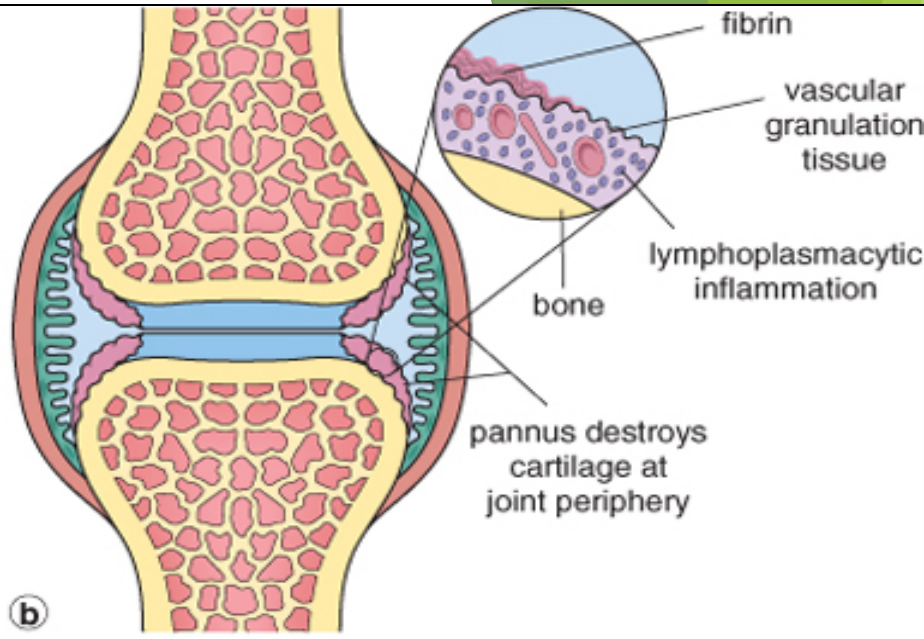
Rheumatoid arthritis

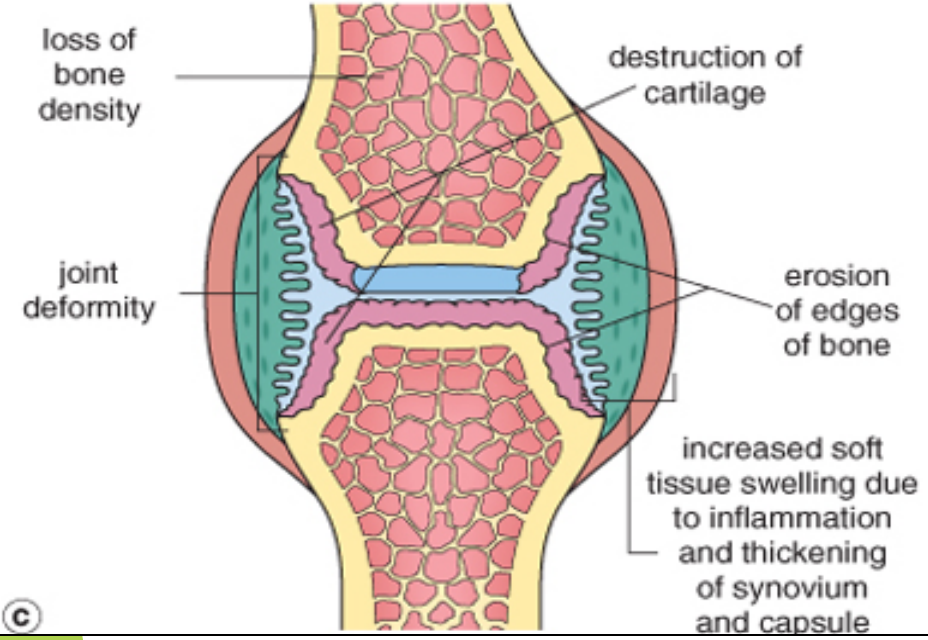
Pathologic Features

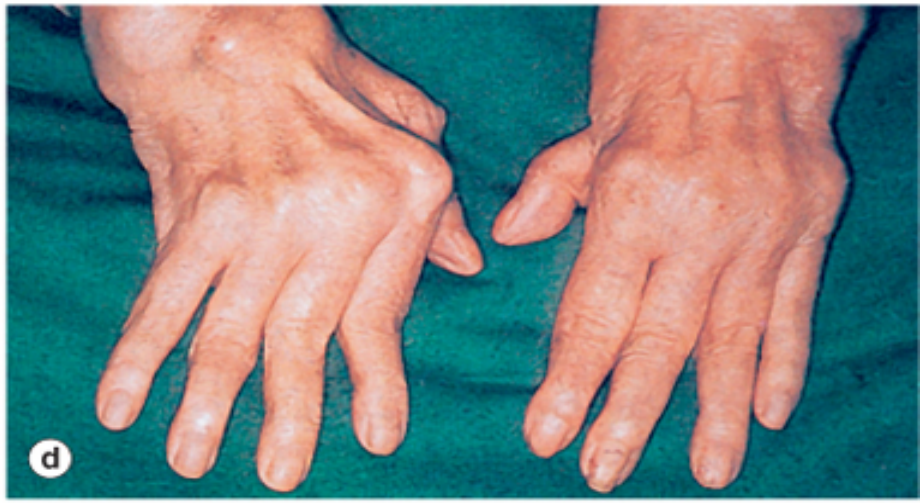
Pannus

- formed by proliferating synovial-lining cells admixed with inflammatory cells, granulation tissue, and fibrous connective tissue
- Eventually the pannus fills the joint space, and subsequent **fibrosis and calcification** may cause permanent **ankylosis.**


thick synovium
fibrin
lymphoplasmacytic infiltrate
inflamed synovium
soft tissue swelling
a


fibrin
vascular granulation tissue
lymphoplasmacytic inflammation
bone
pannus destroys cartilage at joint periphery
b


loss of bone density
destruction of cartilage
joint deformity
erosion of edges of bone
increased soft tissue swelling due to inflammation and thickening of synovium and capsule
c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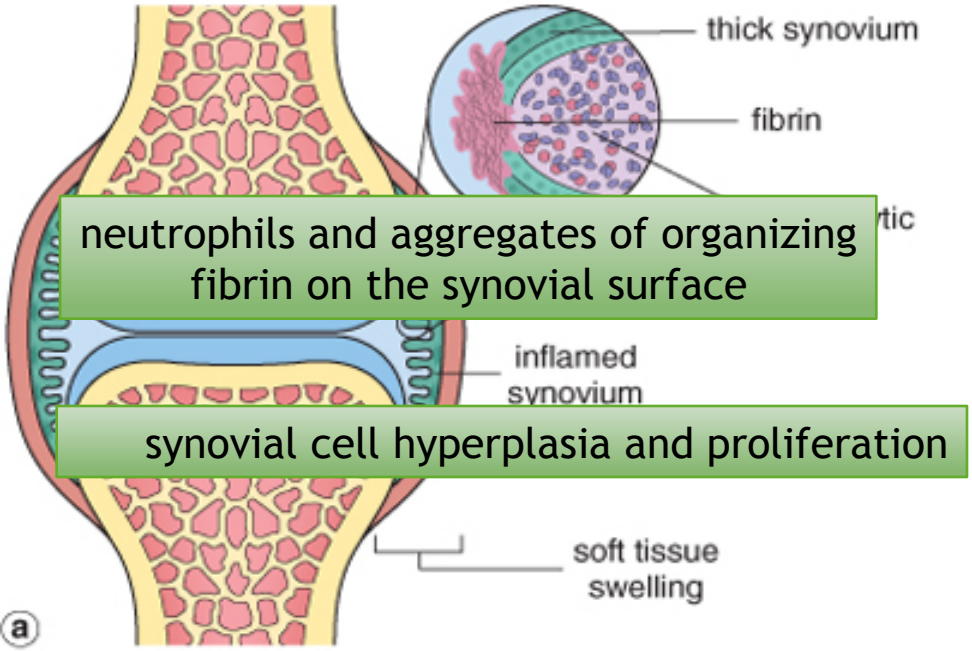
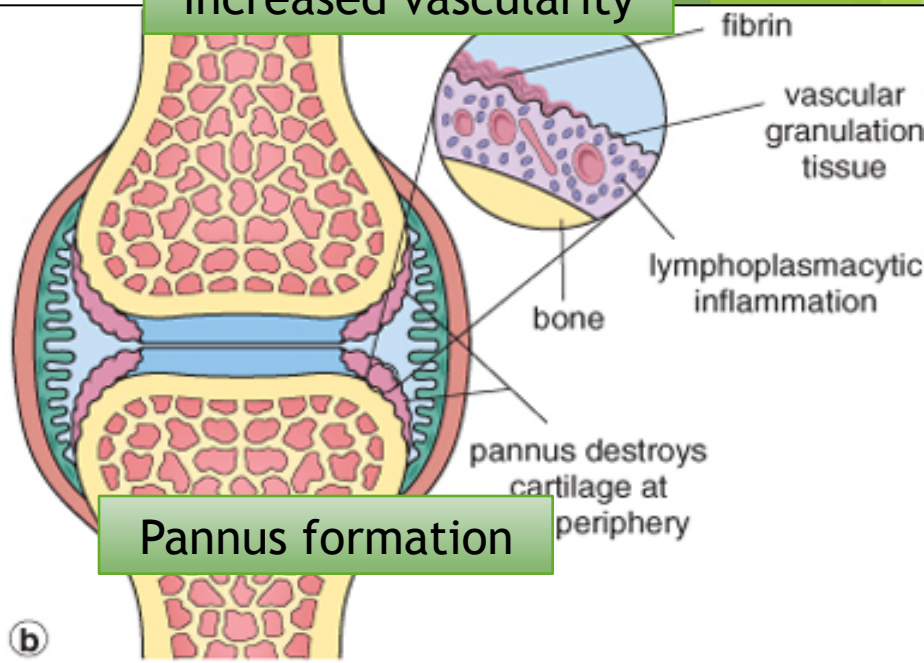
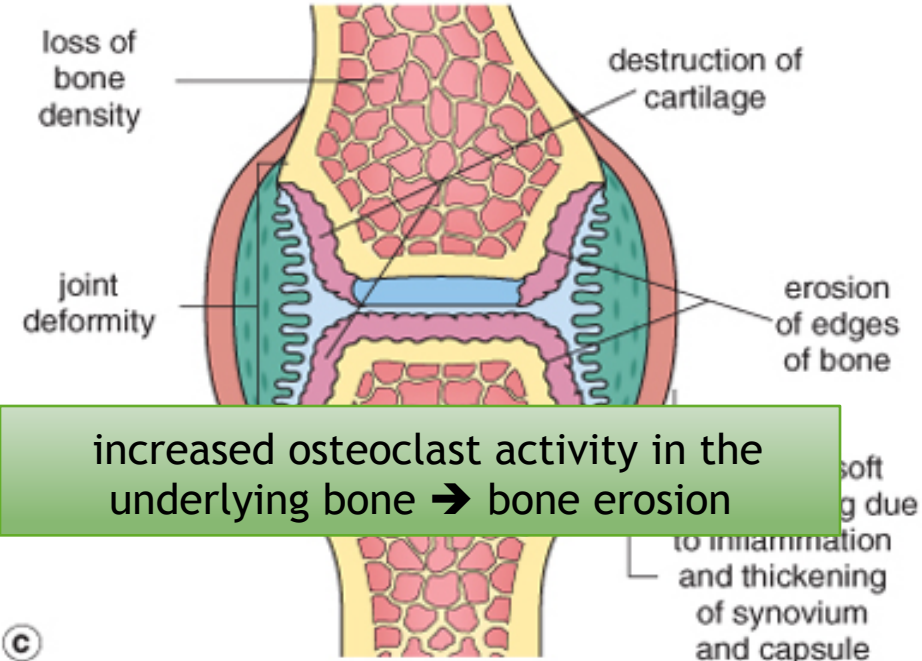
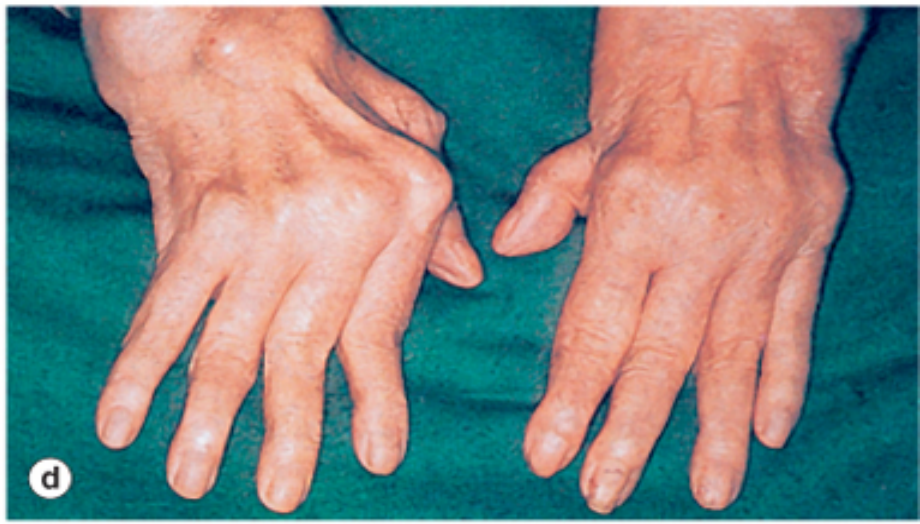
dense perivascular inflammatory cell infiltrates



increased vascularity

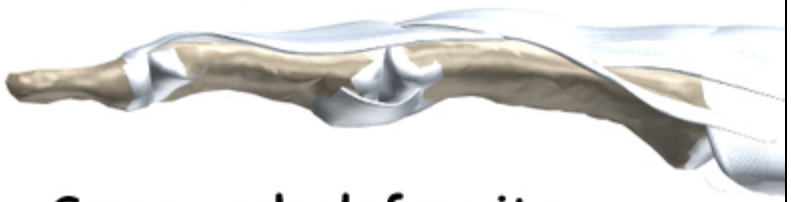




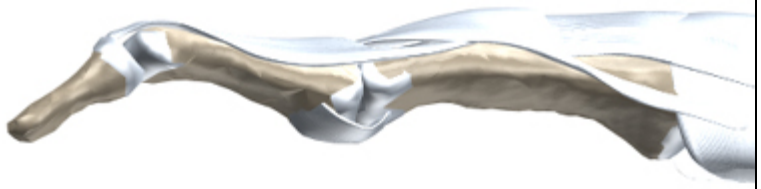


swan neck finger

Normal joint

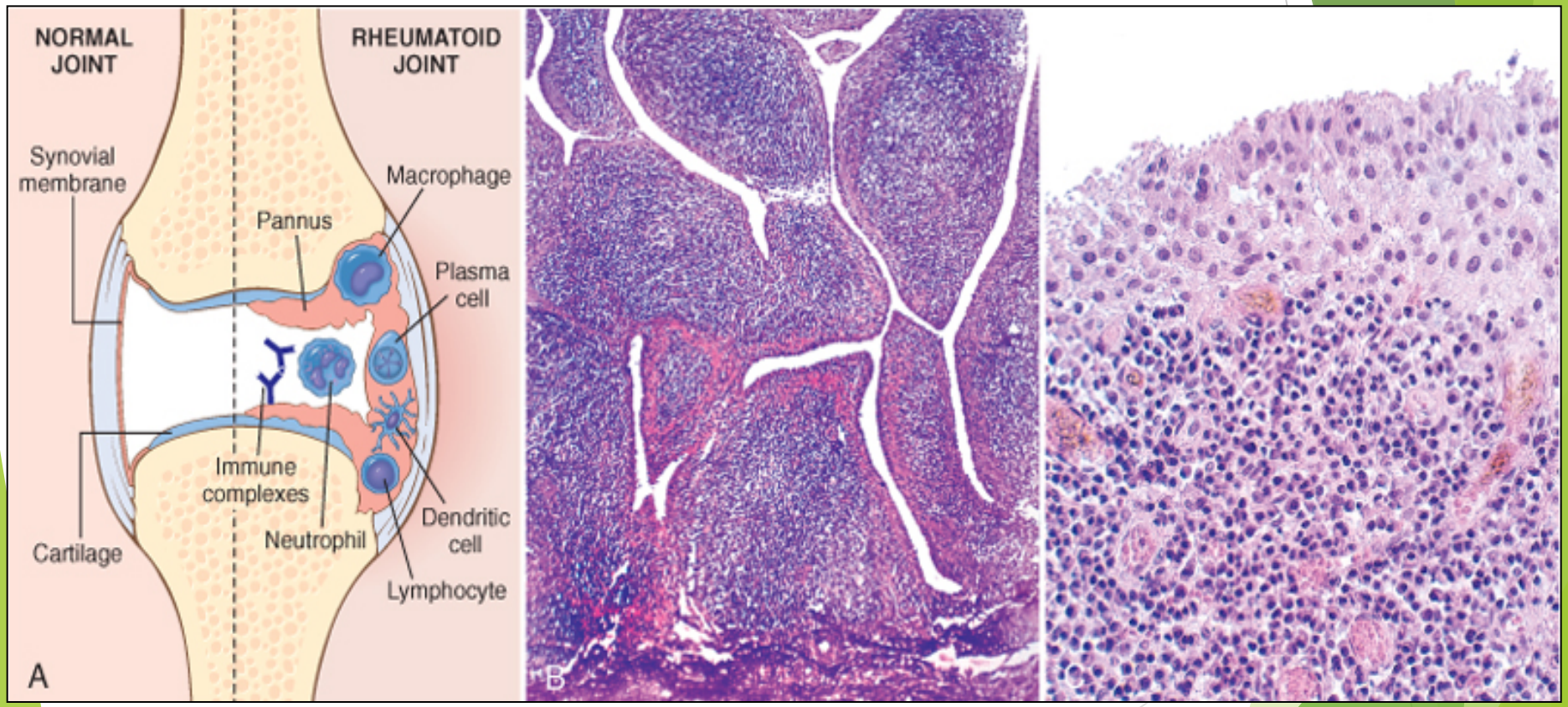


Swan neck deformity

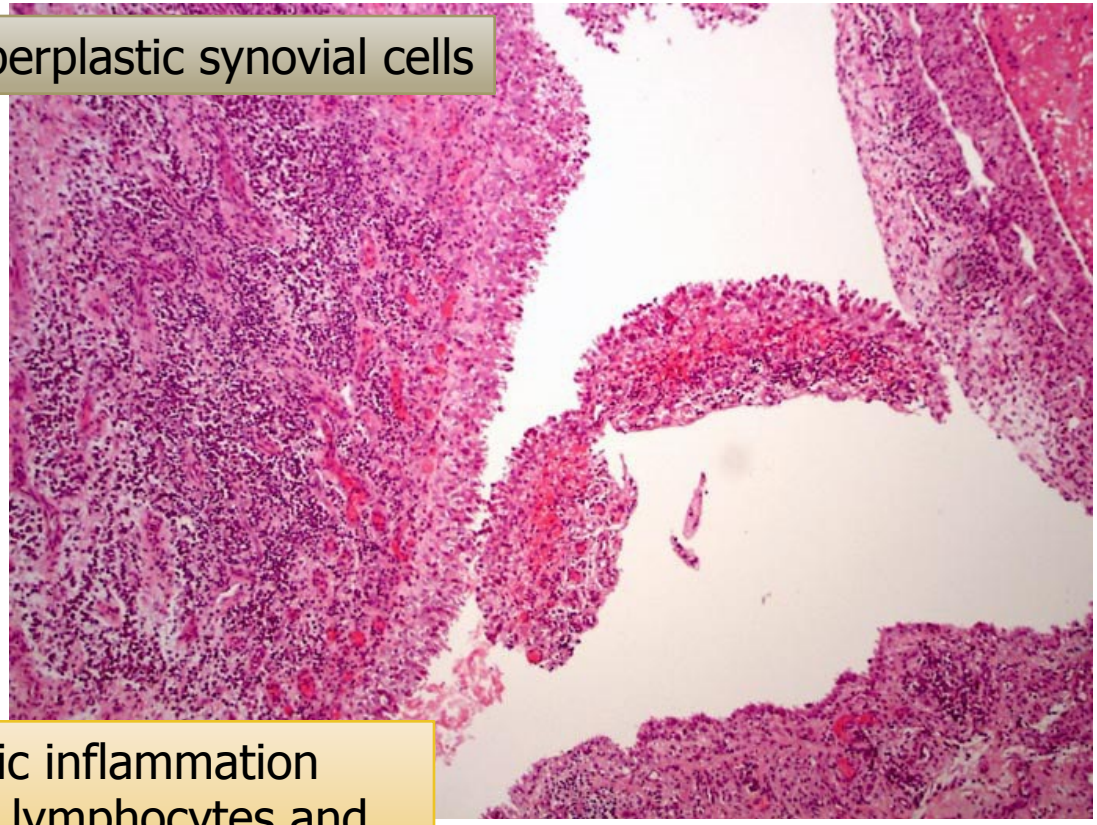


Rheumatoid arthritis

Pathologic Features



Rheumatoid arthritis Microscopic



Dense chronic inflammation consisting of lymphocytes and plasma cells

Rheumatoid arthritis

Clinical Feaures

- joints are warm, swollen, painful with morning stiffness
- symmetric arthritis
- characteristic derformities develop. These include:

Radial deviation at the wrists.

Ulnar deviation at the fingers.

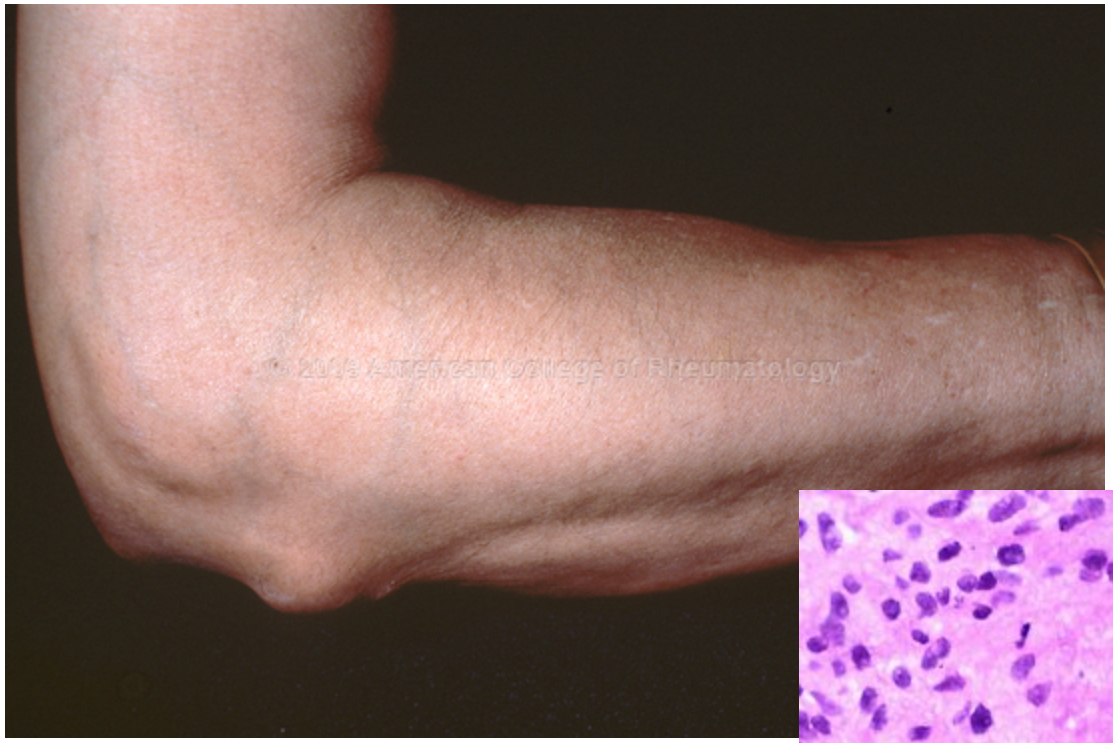
Flexion and hyperextension deformities of the fingers (swan neck and boutonniere deformities).

Rheumatoid arthritis

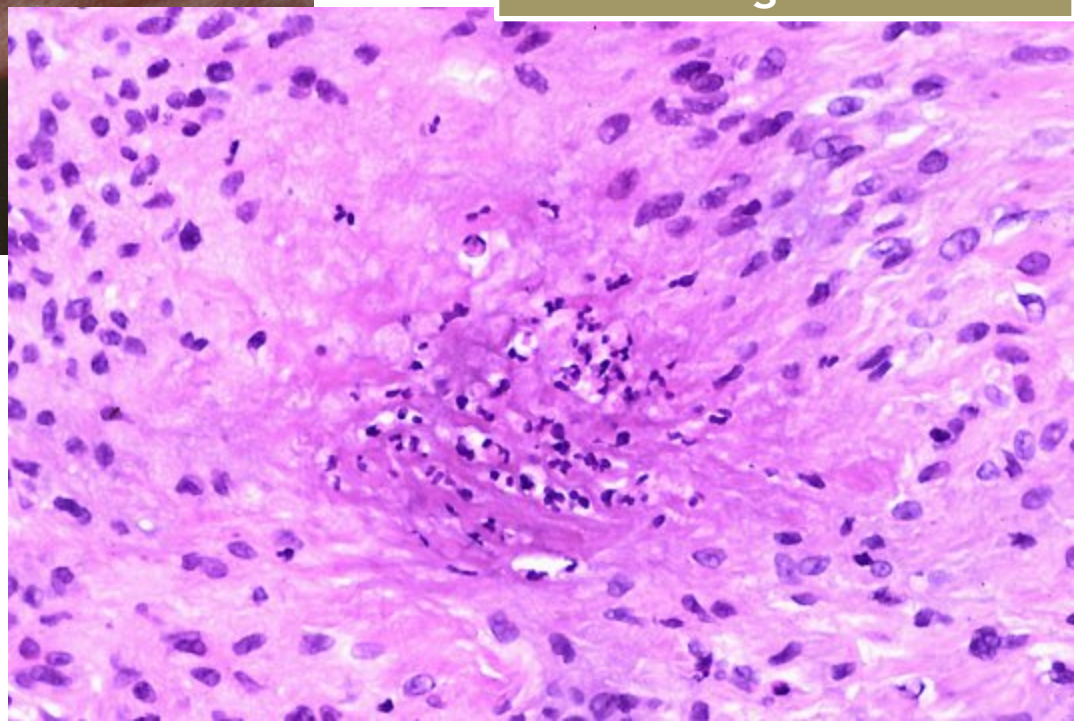
X-ray:

- Loss of articular cartilage leading to narrowing of the joint space.
- Joint effusions.
- Localized osteoporosis.
- Erosions.

Subcutaneous rheumatoid nodule



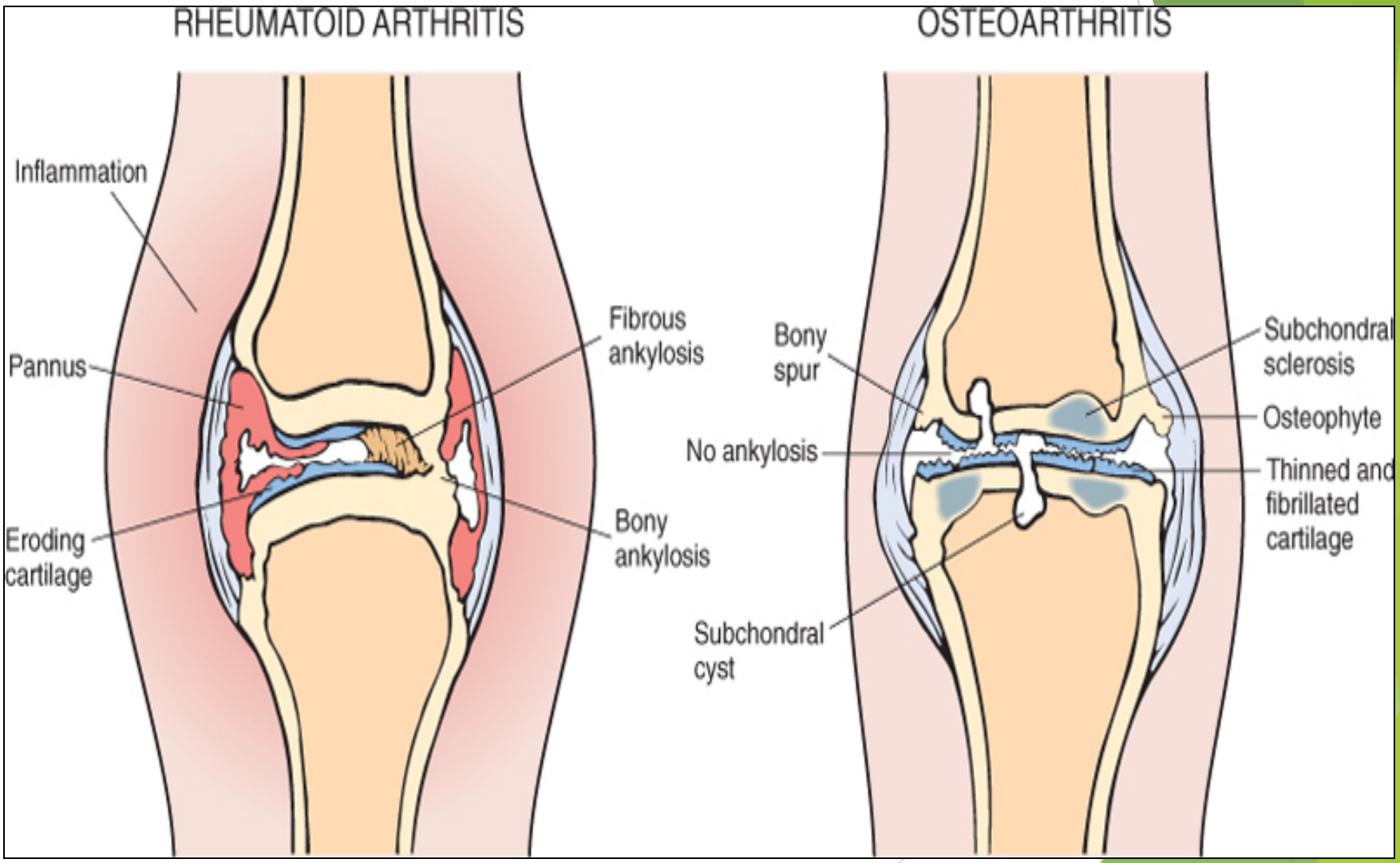
Palisading Granulomas



Rheumatoid arthritis
Prognosis

- Reduces life expectancy by 3-7 years
- Death due to amyloidosis, vasculitis, GI bleeds from NSAIDs, infections from steroids.

Comparison of the morphologic features of RA and osteoarthritis

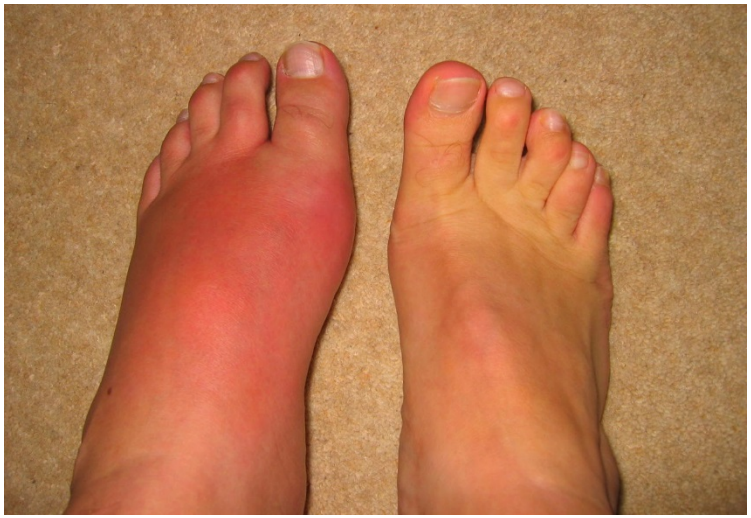


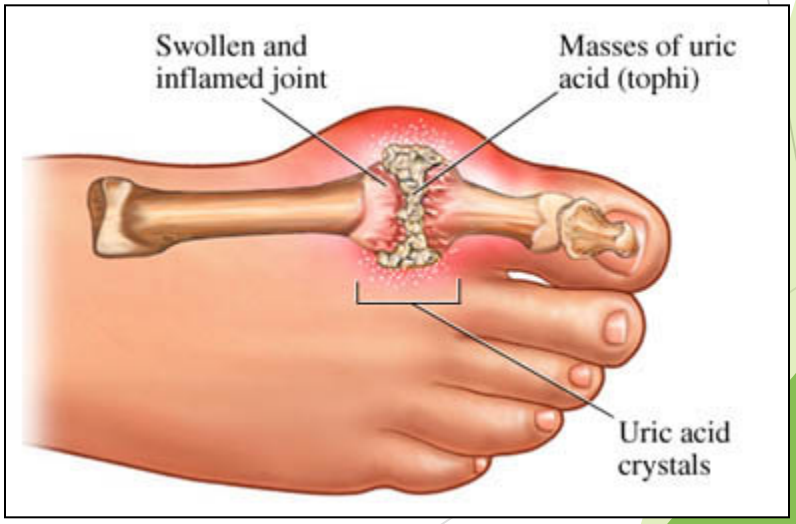
Comparison of Osteoarthrosis & Rheumatoid Arthritis

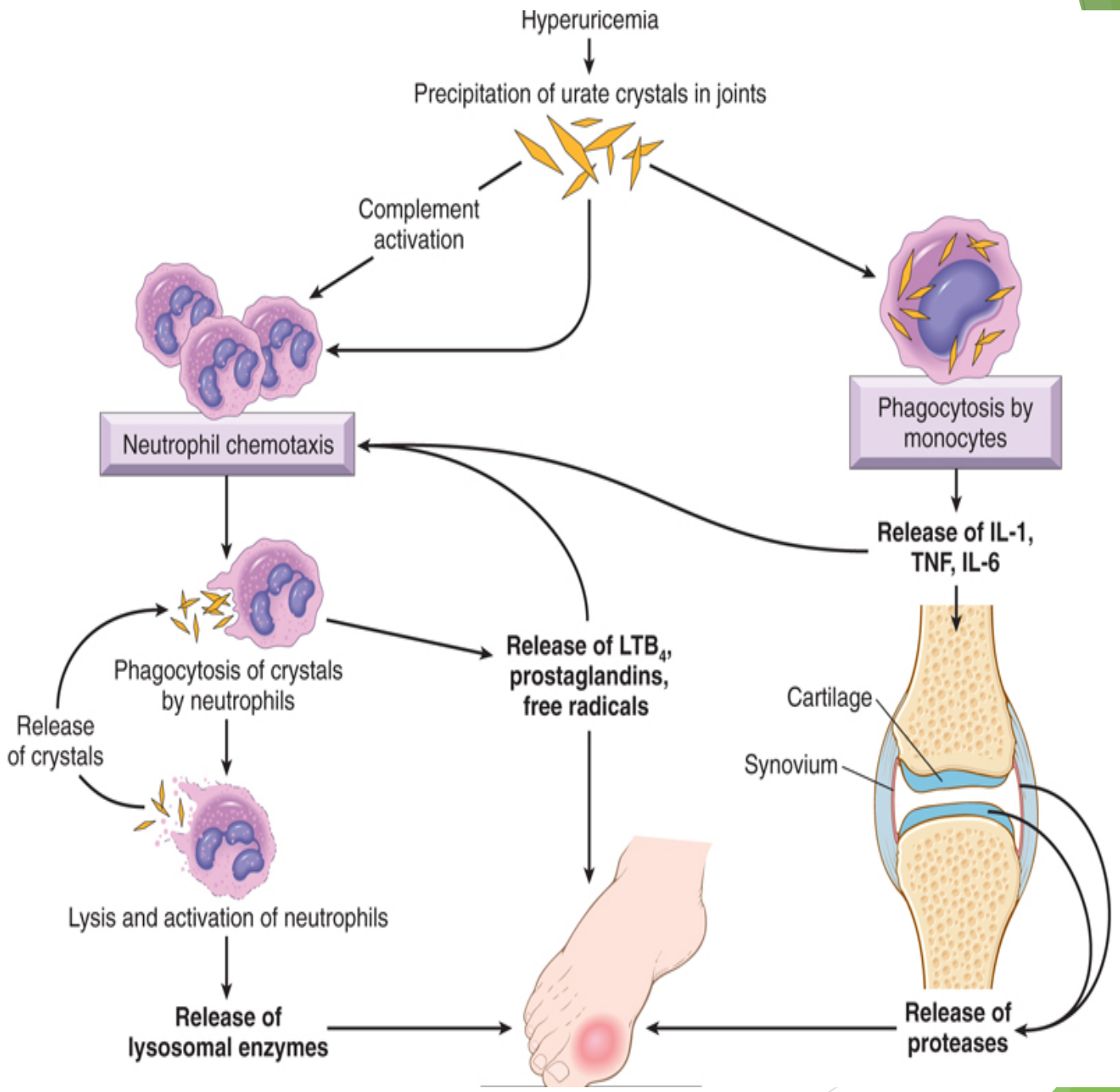
	Osteoarthrosis	**Rheumatoid Arthritis**
Basic process	Degenerative	Immunologic, inflammatory
Site of initial lesion	Articular cartilage	Synovium
Age	50 plus	Any, but peaks at age 20–40 years
Sex	Male or female	Female > male
Joints involved	Especially knees, hips, spine; asymmetric involvement	Hands, later large joints; multiple symmetric involvement
Fingers	Herberden's nodes	Ulnar deviation, spindle swelling
Nodules	No	Rheumatoid nodules
Systemic features	None	Uveitis, pericarditis, etc.
Constitutional symptoms	None	Fever, malaise in some
Laboratory findings	None	Rheumatoid factor; ↑erythrocyte sedimentation rate; anemia, leukocytosis, hyperglobulinemia
Joint fluid	Clear, normally viscous; no inflammatory cells	Clear; low viscosity, high protein; neutrophils, some lymphocytes; immunoglobulins, complement, rheumatoid factor

Gout

- Gout is an **inflammatory** disease.
- The most commonly affected site is: **first metatarsophalangeal joint**.
- It is swollen, red, and very painful.
- Sodium urate crystals have precipitated into the joint, producing an acute inflammatory response.






Hyperuricemia
Precipitation of urate crystals in joints
Complement activation
Neutrophil chemotaxis
Phagocytosis by monocytes
Release of IL-1, TNF, IL-6
Phagocytosis of crystals by neutrophils
Release of crystals
Release of LTB4, prostaglandins, free radicals
Cartilage
Synovium
Lysis and activation of neutrophils
Release of lysosomal enzymes
Release of proteases

Clinical feauters

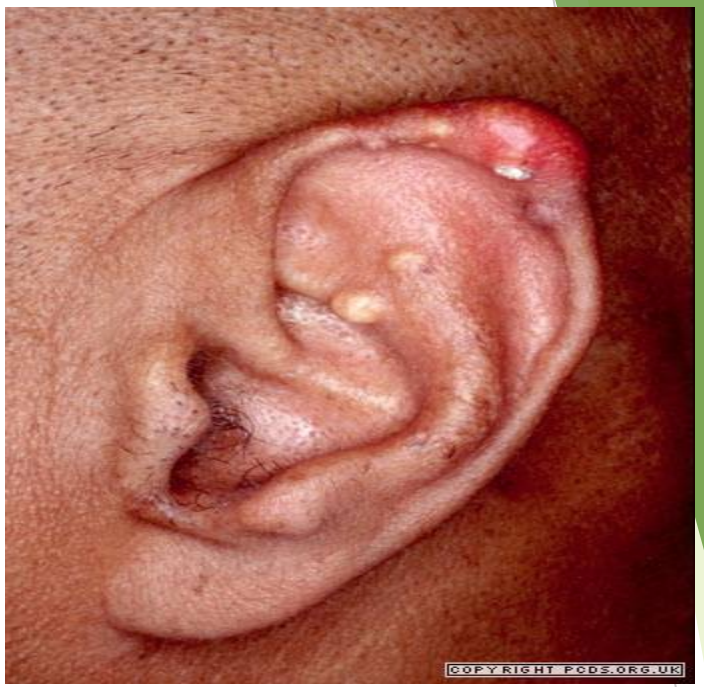
- Gout is more common in men than in women;
- it does not usually cause symptoms before the age of 30.
- Risk factors for the disease include obesity, excess alcohol intake, consumption of purine-rich foods, diabetes, the metabolic syndrome, and renal failure. Polymorphisms in genes involved in the transport and homeostasis of urate

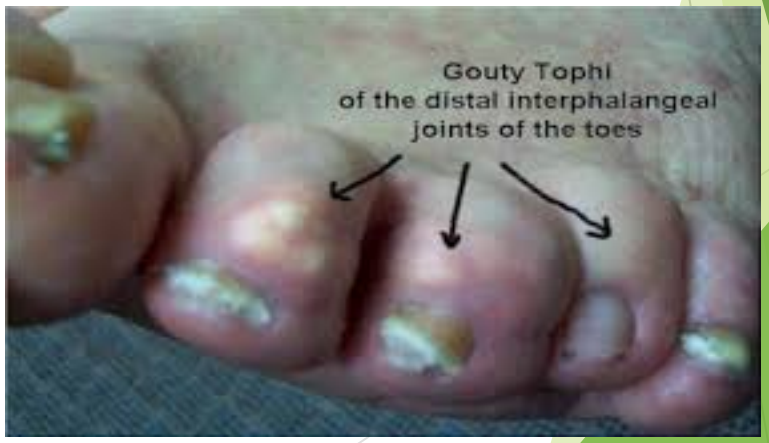
Table 20–3 Classification of Gout

Clinical Category	Metabolic Defect
Primary Gout (90% of cases)	
Enzyme defects—unknown (85% to 90% of cases)	Overproduction of uric acid Normal excretion (majority) Increased excretion (minority) Underexcretion of uric acid with normal production
Known enzyme defects—e.g., partial HGPRT deficiency (rare)	Overproduction of uric acid
Secondary Gout (10% of cases)	
Associated with increased nucleic acid turnover—e.g., leukemias	Overproduction of uric acid with increased urinary excretion
Chronic renal disease	Reduced excretion of uric acid with normal production
Inborn errors of metabolism	Overproduction of uric acid with increased urinary excretion, e.g., complete HGPRT deficiency (Lesch-Nyhan syndrome)

HGPRT, hypoxanthine guanine phosphoribosyl transferase.

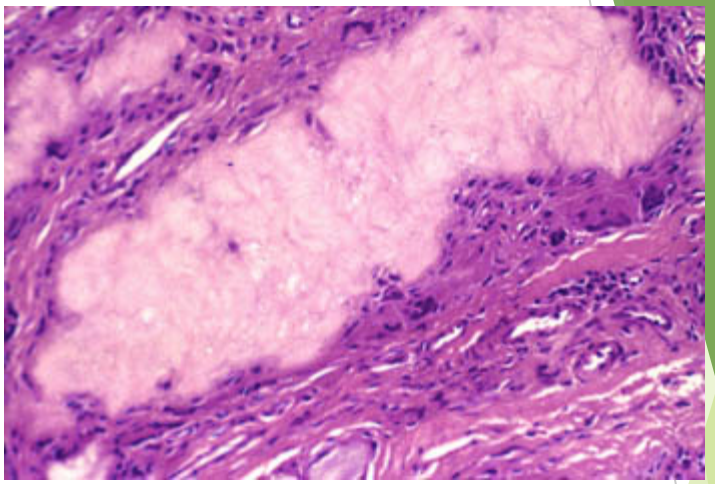
- **Tophi** are large aggregates of urate crystals which are visible with the naked eye. They occur in the joints and soft tissues of people with persistent hyperuricaemia. A common site for tophi is the pinna of the ear.



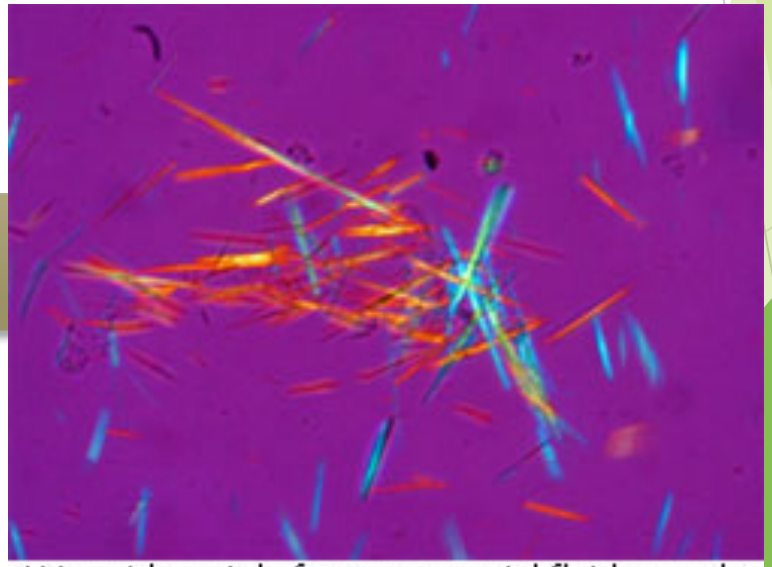


Tophus, gout – Histology

- Tophi consist of crystals that are surrounded by macrophages, lymphocytes, and often foreign body giant cells. In routinely processed sections, the crystals are removed during processing.



Long, slender, needle-shaped **monosodium urate crystals**



Uric acid crystals from a synovial fluid sample

Gout

Besides joints, what other organ is affected in gout?

- approximately 20% of patients die of renal failure.
- Renal lesions are many:
  - precipitation of urates in the medulla forms tophi
  - uric acid stones
  - acute renal failure due to precipitation of urates in the collecting tubes

Pseudogout
Calcium pyrophosphate crystals

- This condition is due to the deposition of calcium pyrophosphate crystals in the synovium (pseudogout) and articular cartilage (chondrocalcinosis). It can occur in three main settings:
- Sporadic (more common in the elderly).
- Hereditary.
- Secondary to other conditions, such as previous joint damage, hyperparathyroidism, hypothyroidism, haemochromatosis and diabetes.
- The crystals first develop in the articular cartilage (chondrocalcinosis), which is usually asymptomatic. From here, the crystals may shed into the joint cavity resulting in an acute arthritis, which mimics gout and is therefore called pseudogout.

- Pseudogout can be differentiated from gout in three ways:
- The knee is most commonly involved.
- X-rays show the characteristic line of calcification of the articular cartilage.
- The crystals look different under polarizing microscopy, they are rhomboid in shape .