MUSCULOSKELETAL BLOCK

Pathology

Disease of Joints

2014

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Objectives

- Osteoarthritis (degenerative joint disease)

1. The primary articular defect in osteoarthritis.
2. Pathogenesis
3. Morphology
4. Major joints affected
5. Clinical course

- Rheumatoid arthritis

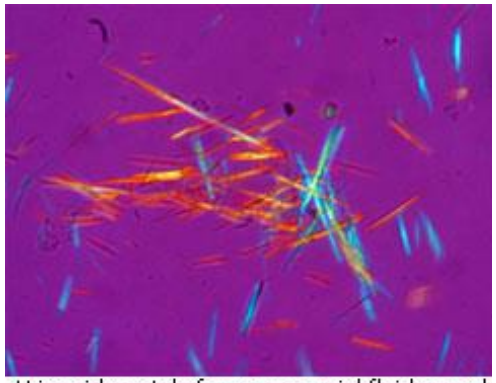
1. Pathogenesis
2. Morphology
3. Major joints affected
4. Clinical course

- Gout and gouty arthritis

1. Pathogenesis
2. Morphology of acute and chronic articular lesions
3. Clinical course

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

Clinical Manifestations of Joint Disease

- Joint Pain (Arthralgia)
- Joint Swelling
- Joint Crepitus
- Abnormal Joint Mobility

A clinical sign characterized by a peculiar crackling, crinkly, or grating feeling or sound in the joints. It indicates cartilage wear in the joint space

Osteoarthritis
Definition and Incidence

- **Osteoarthritis is a** nonneoplastic disorder of progressive erosion of articular cartilage.
- Common and important degenerative disease, with both destructive and reparative components
- Usually age 50+ years (present in 80% at age 65 years)

Osteoarthritis
Aetiology

- The main factors in the development of osteoarthritis are:
  1. aging
  2. abnormal load on joints
  3. inflammation of joints

Osteoarthritis
Pathogenesis

- In general, osteoarthritis affects joints that are constantly exposed to wear and tear.
- It is an important component of occupational joint disease

e.g. osteoarthritis of

the fingers in typists

the knee in professional footballers

Pathogenesis

- **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
- These functions require the cartilage to be elastic and to have high tensile strength. These attributes are provided by proteoglycans and type II collagen, both produced by chondrocytes.

Pathogenesis

- Early osteoarthritis is marked by degenerating cartilage containing more water and less proteoglycan. The type II collagen network also is diminished, presumably as a result of decreased local synthesis and increased breakdown; chondrocyte apoptosis is increased.

Osteoarthritis
Types

- Primary osteoarthritis

- Secondary osteoarthritis

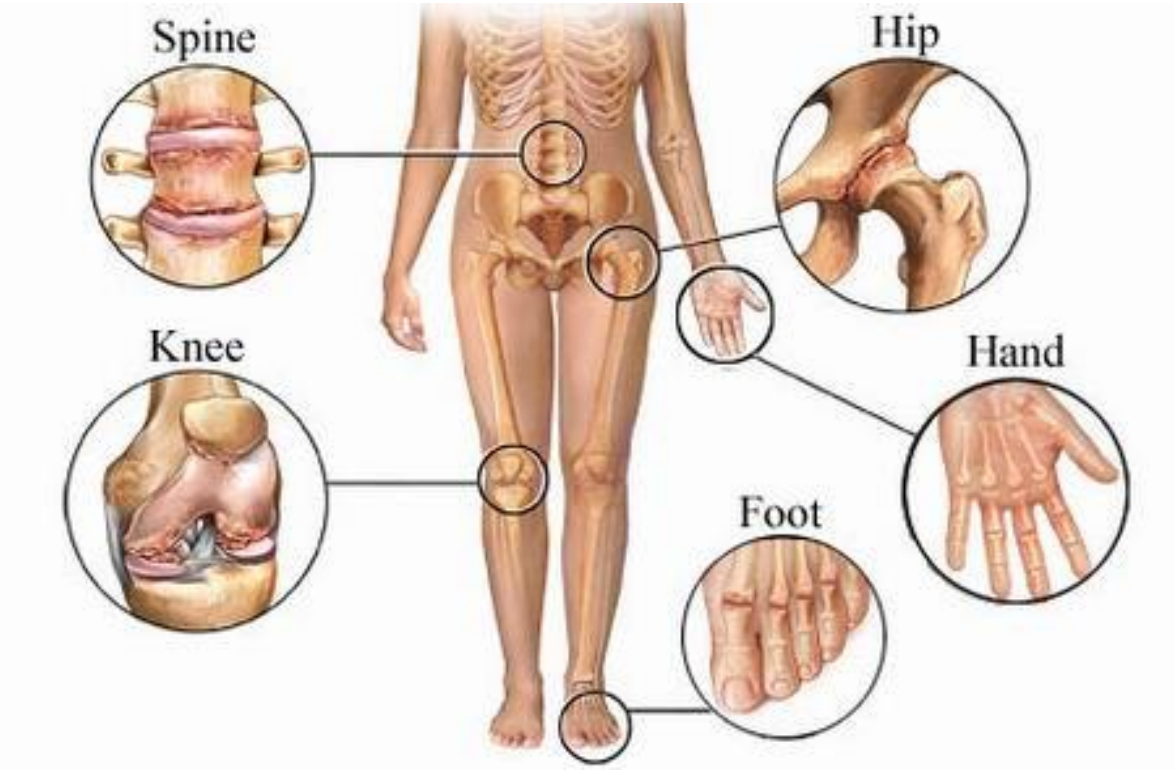
Osteoarthritis
Types

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

Osteoarthritis
Types

- Primary osteoarthritis
- 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
Common sites

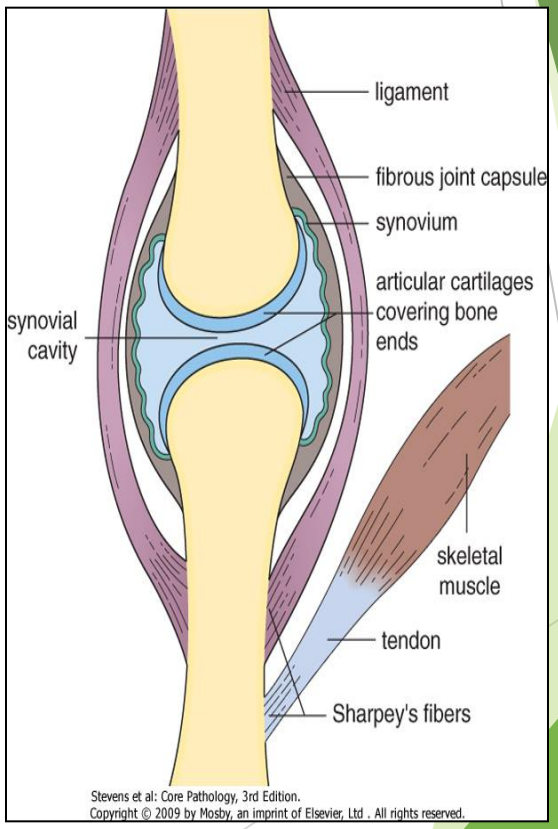


usually one joint or same joint bilaterally

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)

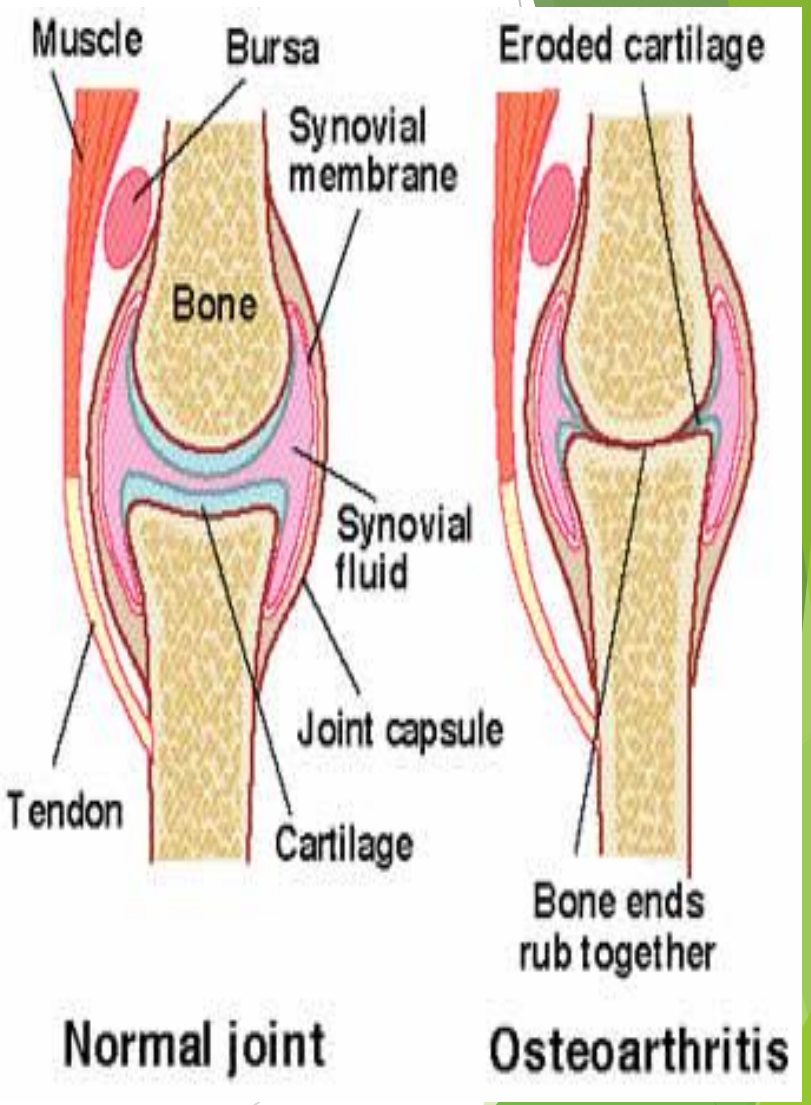


Osteoarthritis Pathogenesis

The early change: **destruction of articular cartilage**, which splits (fibrillation), becomes eroded, and leads to narrowing of the joint space on X ray

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).**



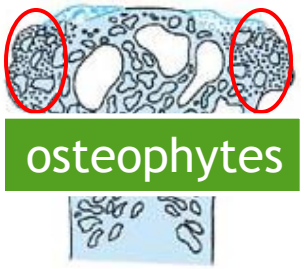
Normal articular cartilage

Fragmentation of articular surface and thinning of cartilage

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

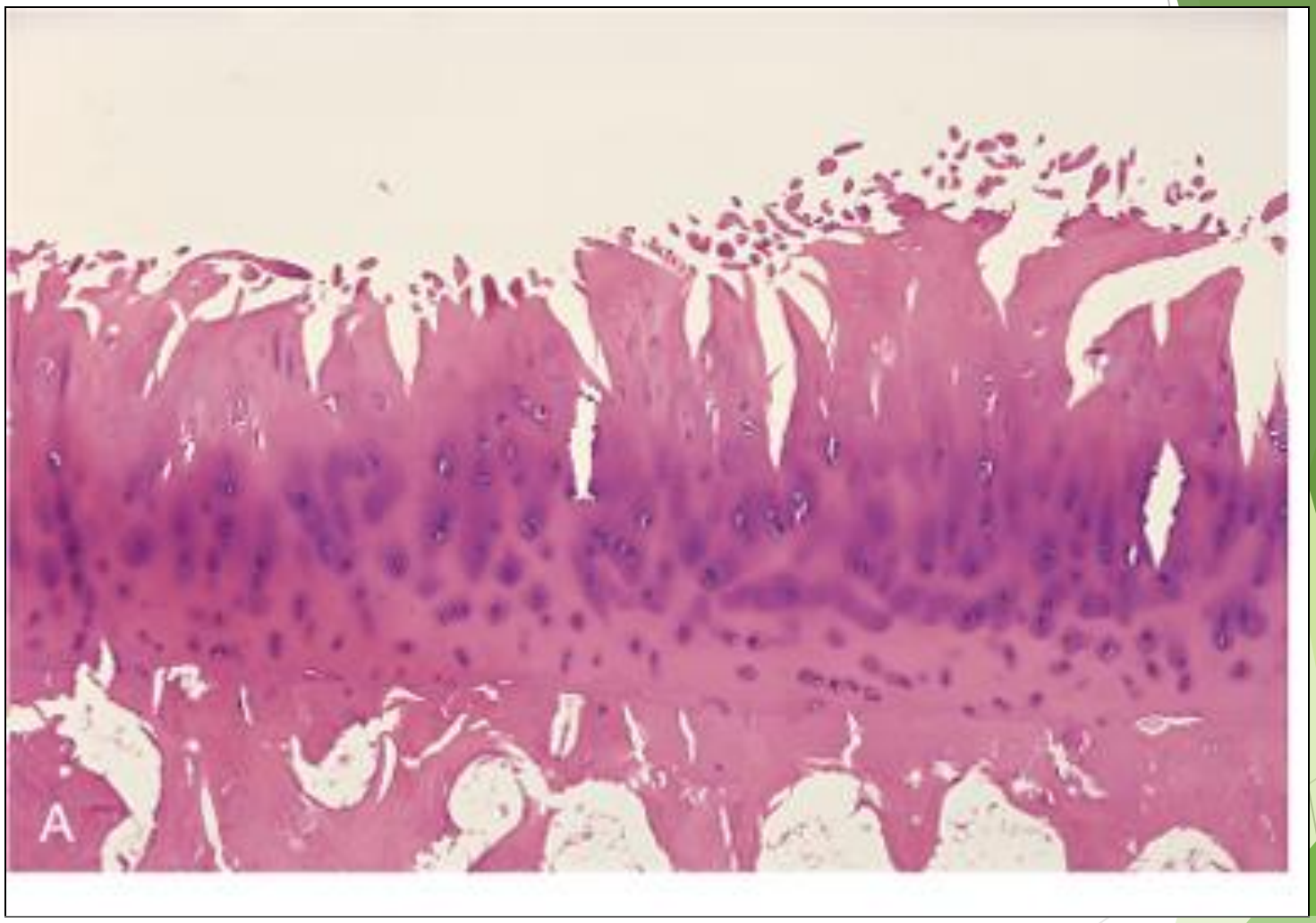
constant friction of bone surfaces, leading to a highly polished bony articular surface (eburnation)

Small cysts develop in the bone



osteophytes

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



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

Cracking and fibrillation of cartilage

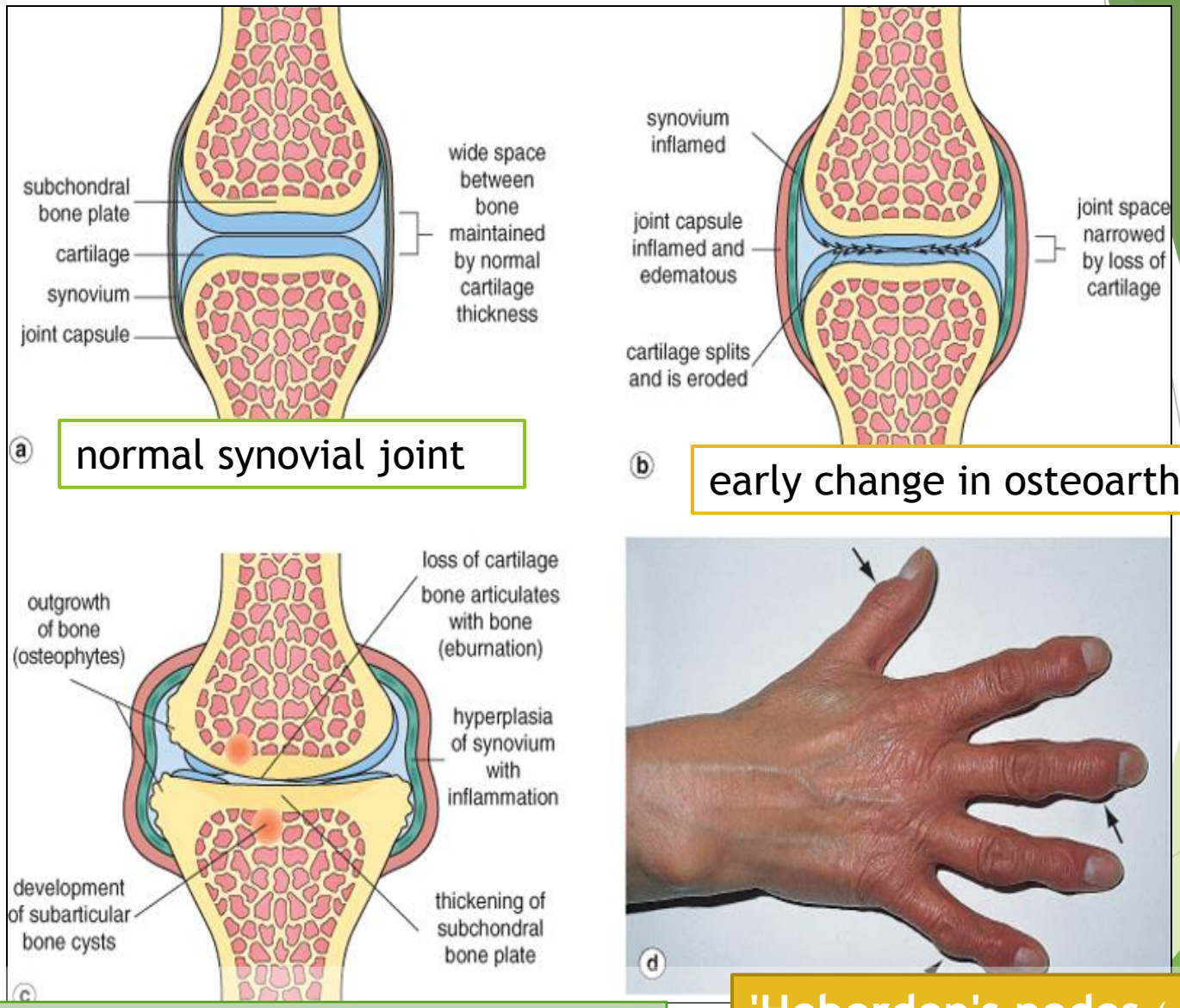
Severe Osteoarthritis

Eburnated articular surface exposing subchondral bone

Subchondral cyst

Residual articular cartilage

Pathological changes in osteoarthritis



normal synovial joint

early change in osteoarthritis

Eburnation & osteophytes formation

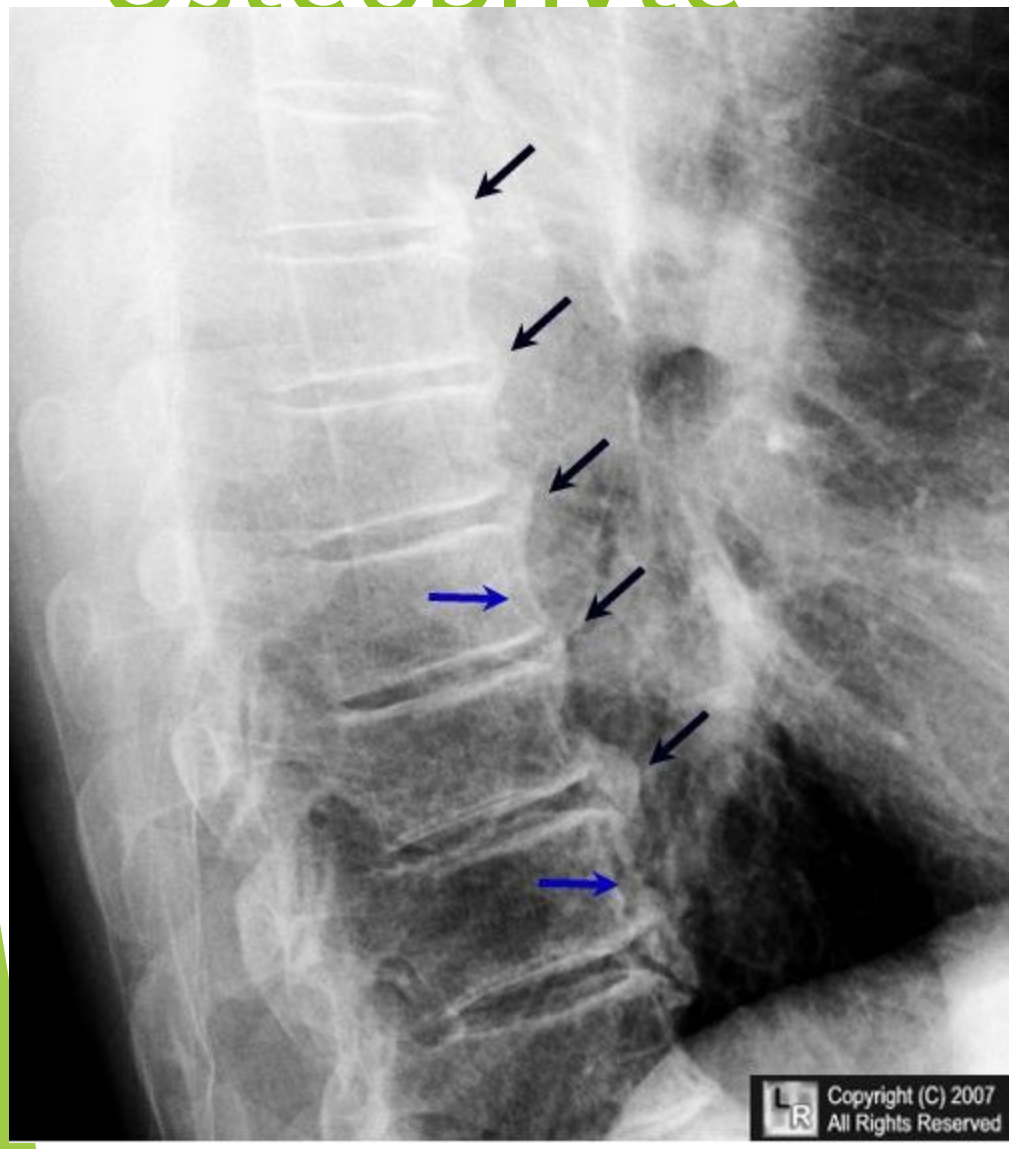
'Heberden's nodes (osteophytes on the interphalangeal joints of the fingers)

Osteoarthritis
Clinical features

An insidious disease predominantly affecting patients beginning in their 50s and 60s.

- Characteristic symptoms include deep, aching pain exacerbated by use, morning stiffness and limited range of movement
- swelling of affected joints
- Osteophyte impingement on spinal foramina can cause nerve root compression with radicular pain, muscle spasms, muscle atrophy, and neurologic deficits.
- Heberden nodes in fingers of women (osteophytes at DIP joints)
- Loose bodies: may form if portion of articular cartilage breaks off

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

Osteoarthritis
Summary

- Incidence: common after 50 year
- Primary and secondary types: underlying conditions
- Pathogenesis: erosion of articular cartilage
- Clinical features: pain and limitation of function

Rheumatoid arthritis

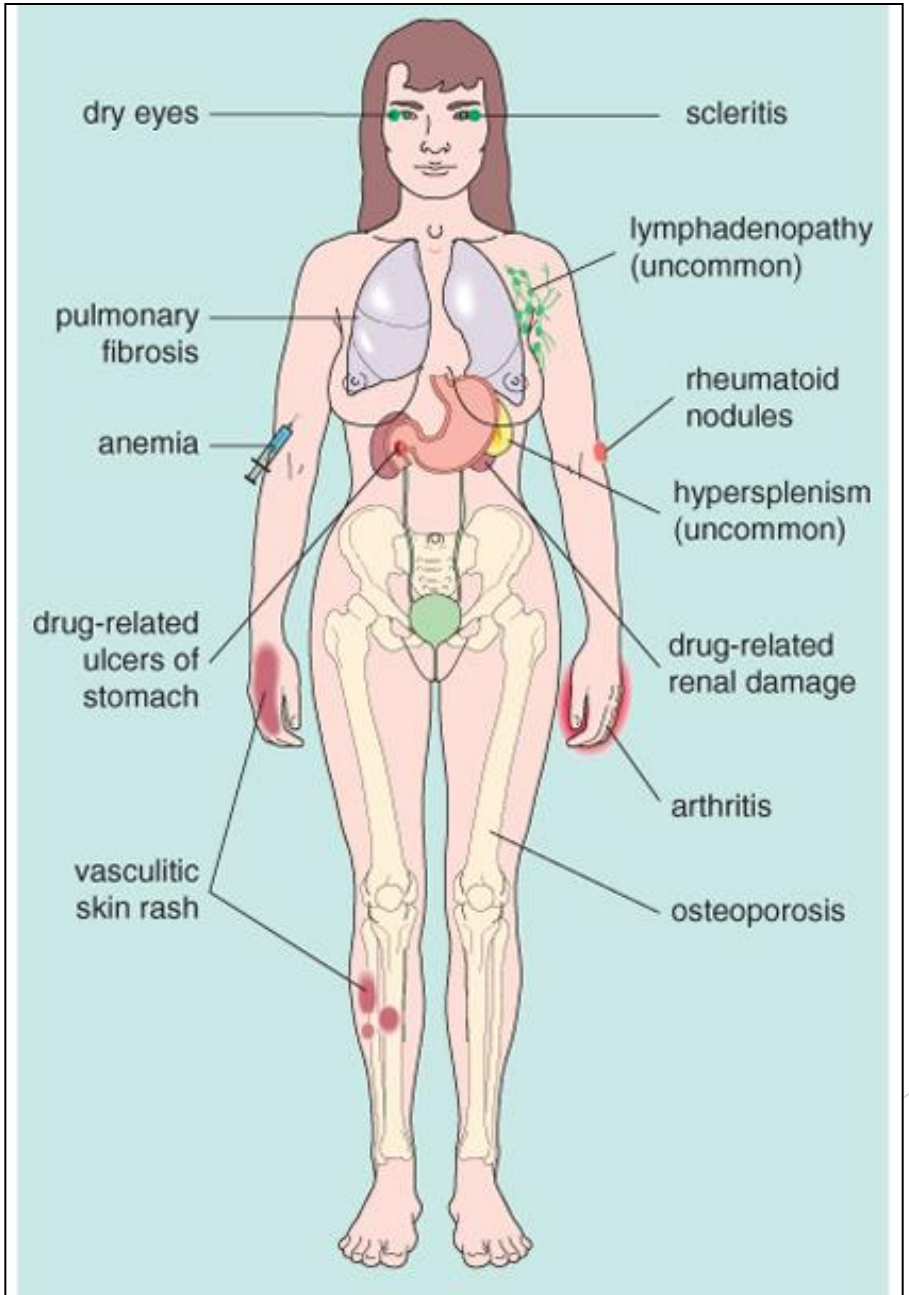
Definition
aetiology
pathological features
clinical features
radiological features

Rheumatoid arthritis

Definition

- Chronic systemic inflammatory disorder affecting synovial lining of joints, bursae and tendon sheaths; also skin, blood vessels, heart, lungs, muscles
- Produces nonsuppurative proliferative synovitis, may progress to destruction of articular cartilage and joint ankylosis
- 1% of adults, 75% are women, peaks at ages 10-29 years; also menopausal women

Extra-Articular Manifestations



Rheumatoid arthritis

Aetiology

- The joint inflammation in RA is immunologically mediated
- Genetic and environmental variables

Rheumatoid arthritis

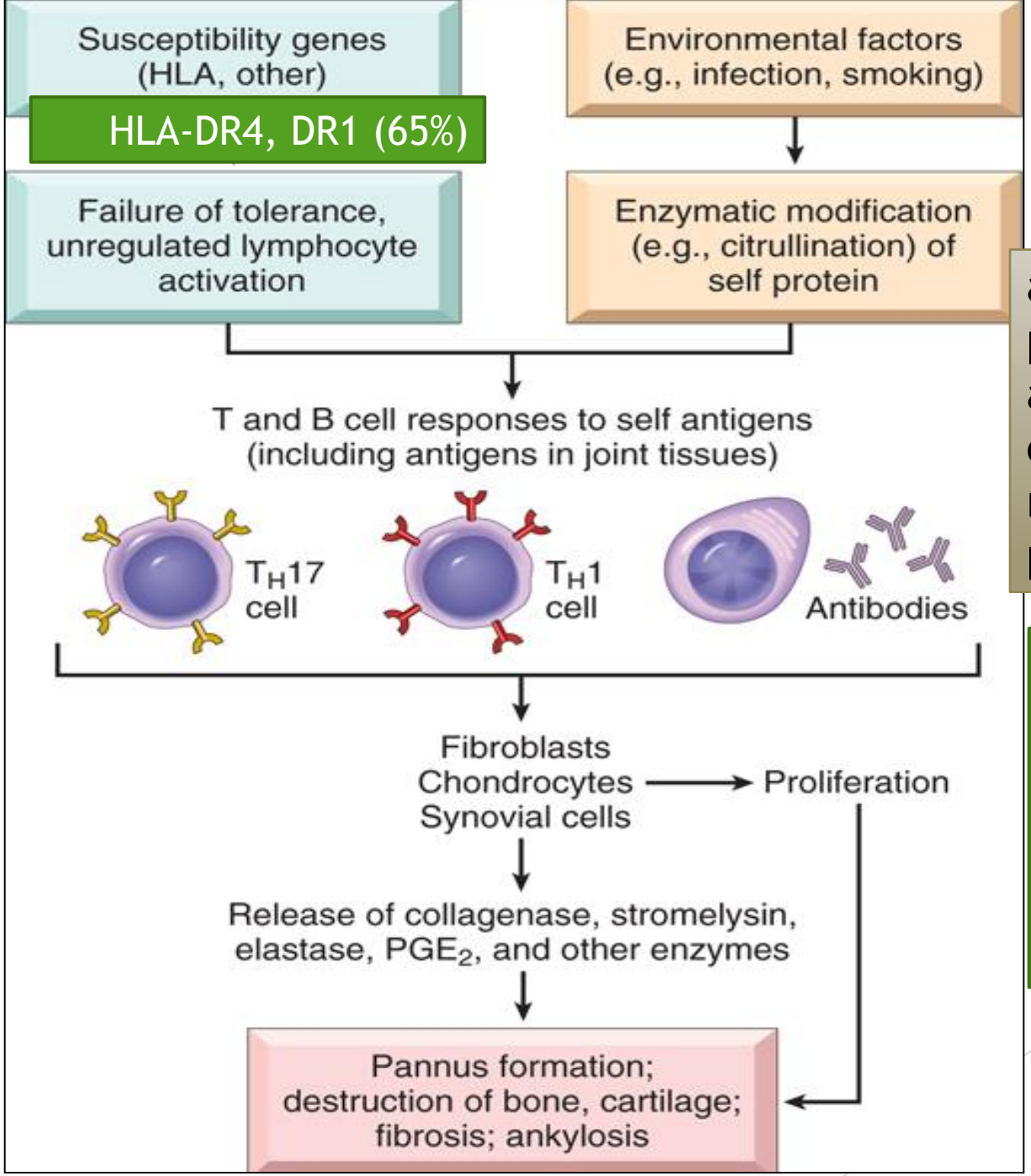
Aetiology

- triggered by exposure of immunogenetically susceptible host to a microbial antigen

➔ autoimmune reaction then occurs with T helper activation and release of inflammatory mediators, TNF and cytokines, that destroys joints

➔ circulating immune complexes deposit in cartilage, activate complement, cause cartilage damage

- Parvovirus B19 may be important in pathogenesis



are derived from proteins in which arginine residues are converted to citrulline residues posttranslationally

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
- Other antibodies include antikeratin antibody (specific, not sensitive), antiperinuclear factor, anti-rheumatoid arthritis associated nuclear antigen (RANA), ESR and C-reactive protein
- **Synovial fluid** has increased neutrophils (particularly in acute stage) & protein
- **Genetics:** HLA-DR4, DR1 (65%)

Rheumatoid arthritis

Pathologic Features

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

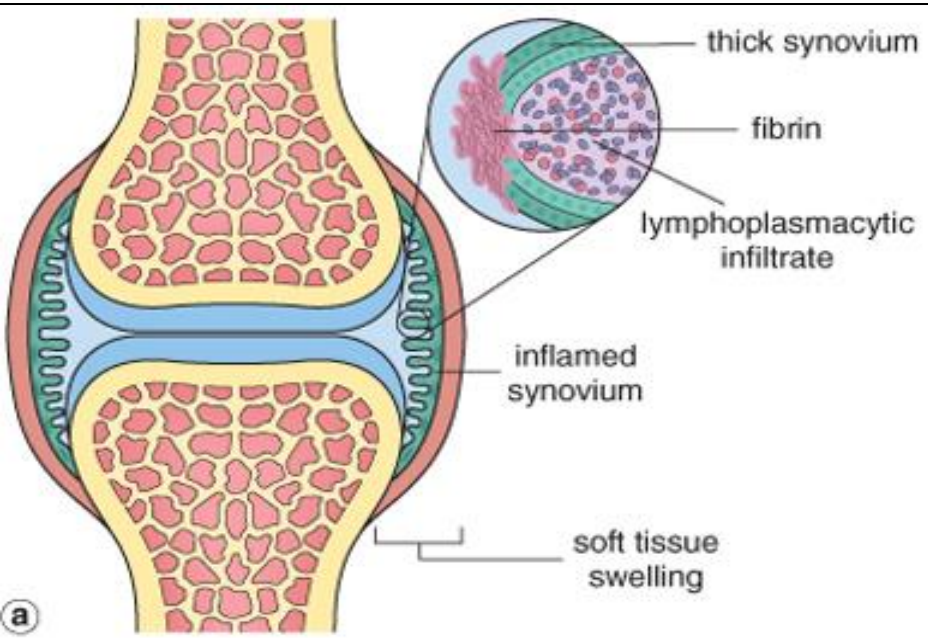
   (frequently forming lymphoid follicles) in the synovium composed of CD4+ T cells, plasma cells, and macrophages
3. increased vascularity due to angiogenesis
4. neutrophils and aggregates of organizing fibrin on the synovial surface
5. increased osteoclast activity in the underlying bone ➔ bone erosion.

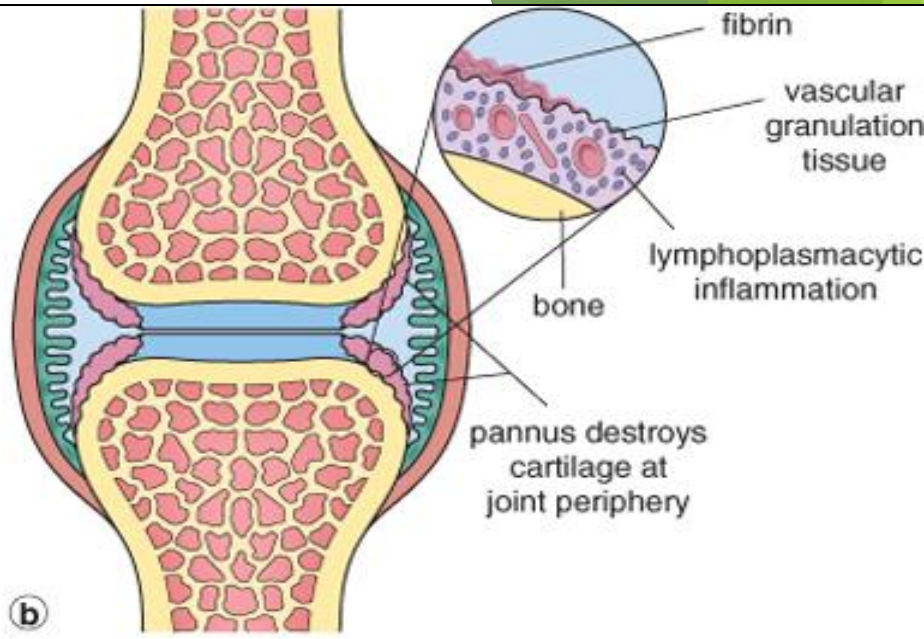
Rheumatoid arthritis

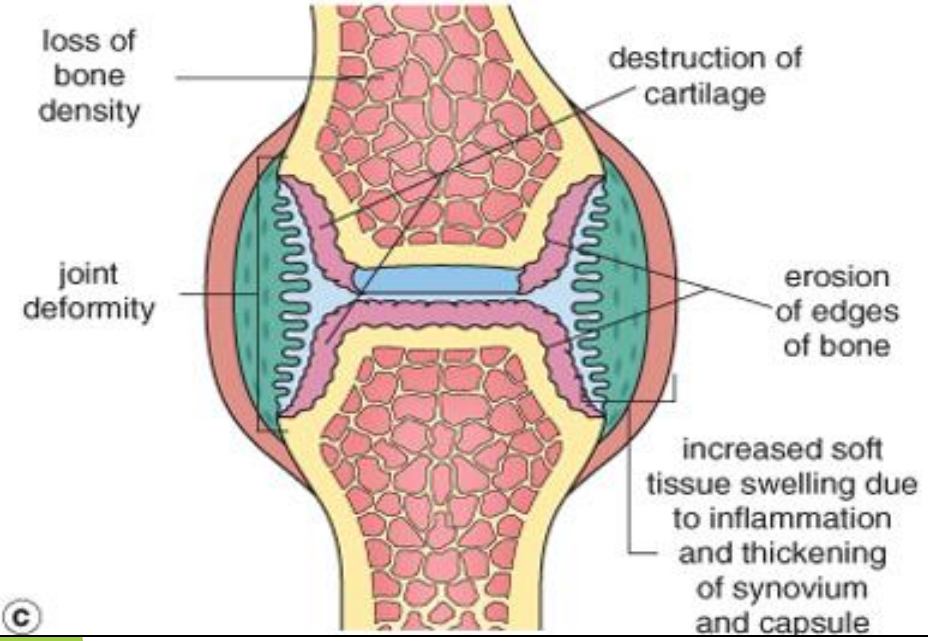
Pathologic Features

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.**

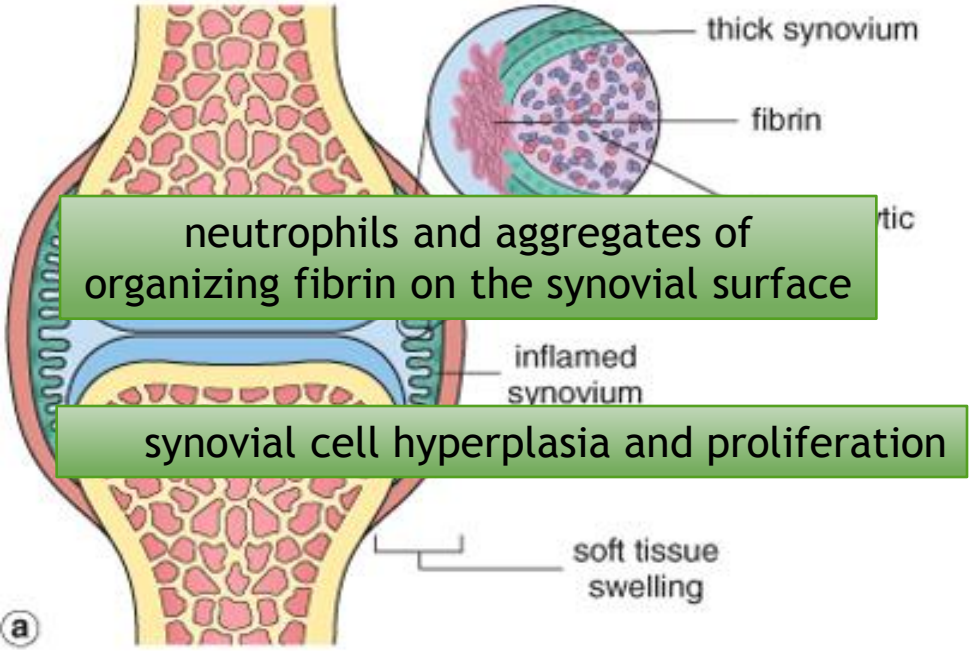

thick synovium
fibrin
lymphoplasmacytic infiltrate
inflamed synovium
soft tissue swelling
a


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

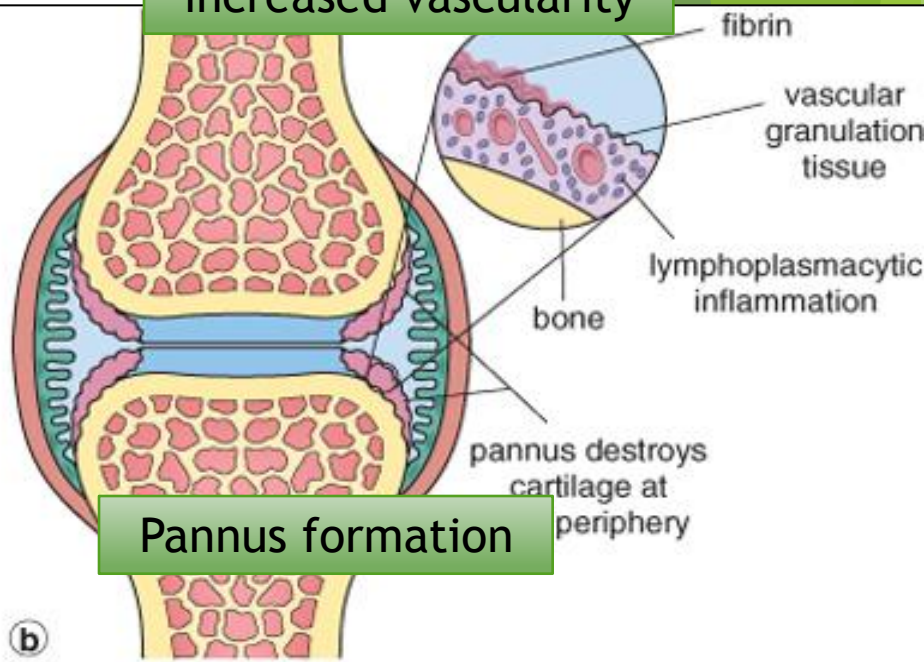

loss of bone density
destruction of cartilage
joint deformity
erosion of edges of bone
increased soft tissue swelling due to inflammation and thickening of synovium and capsule
c

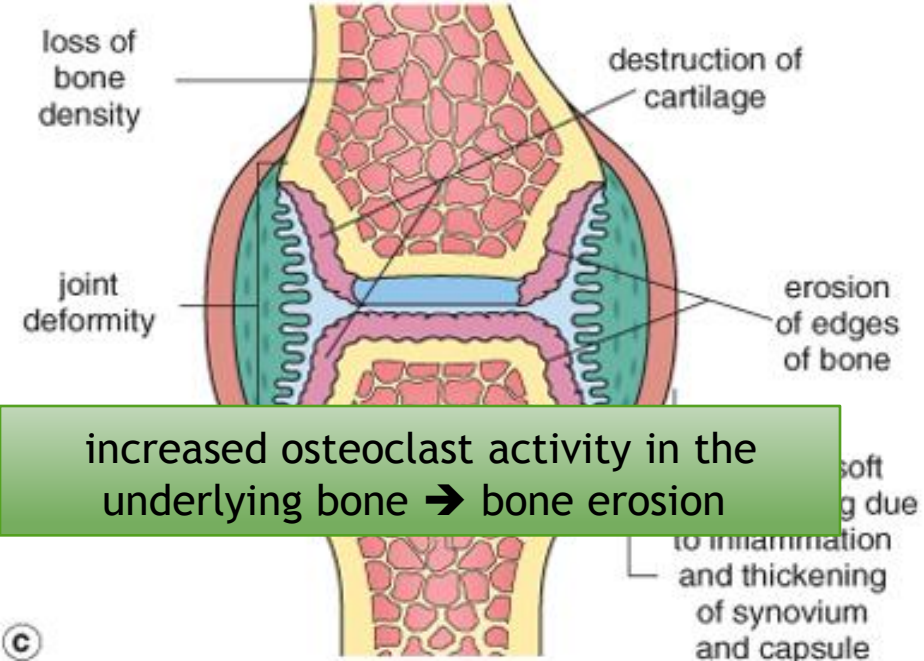

d

dense perivascular inflammatory cell infiltrates



increased vascularity





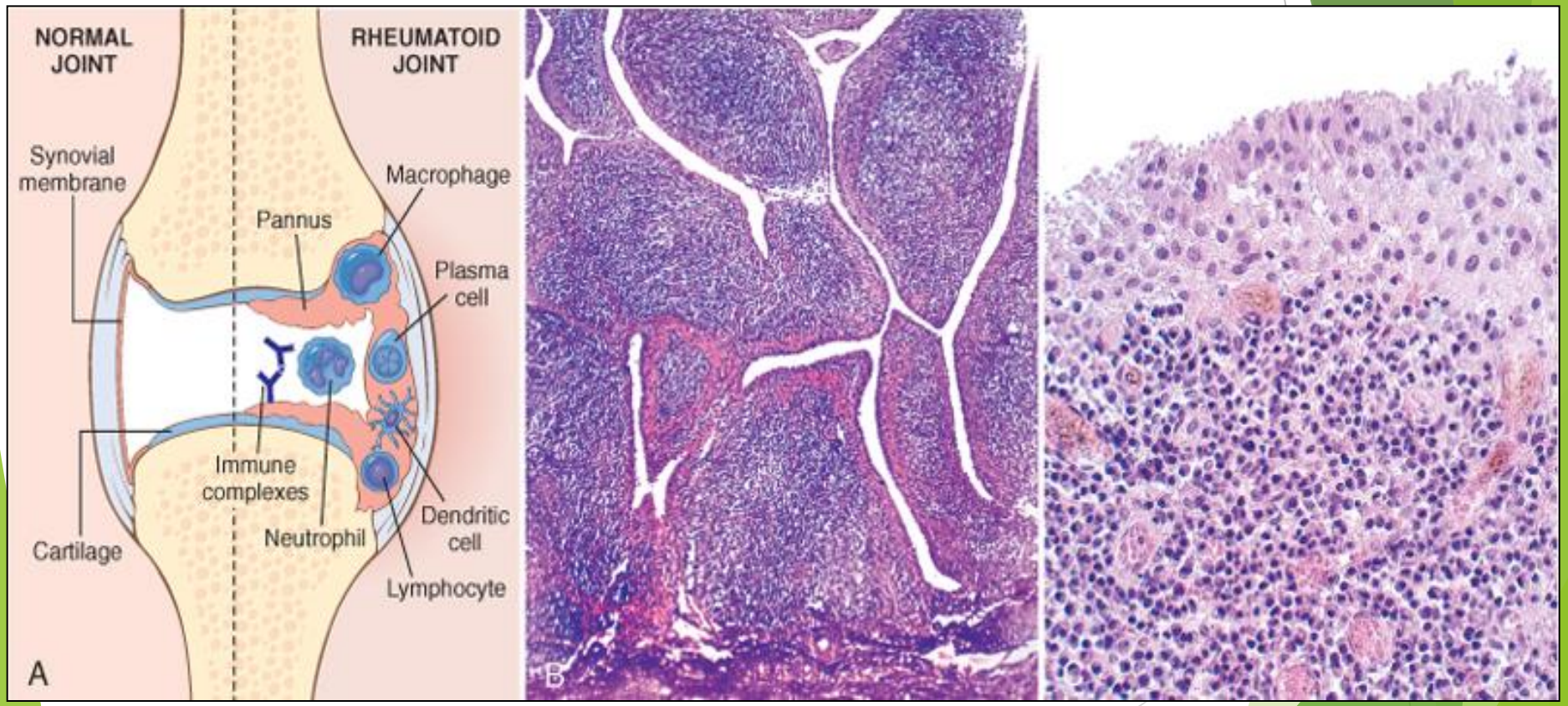
swan neck finger

Normal joint

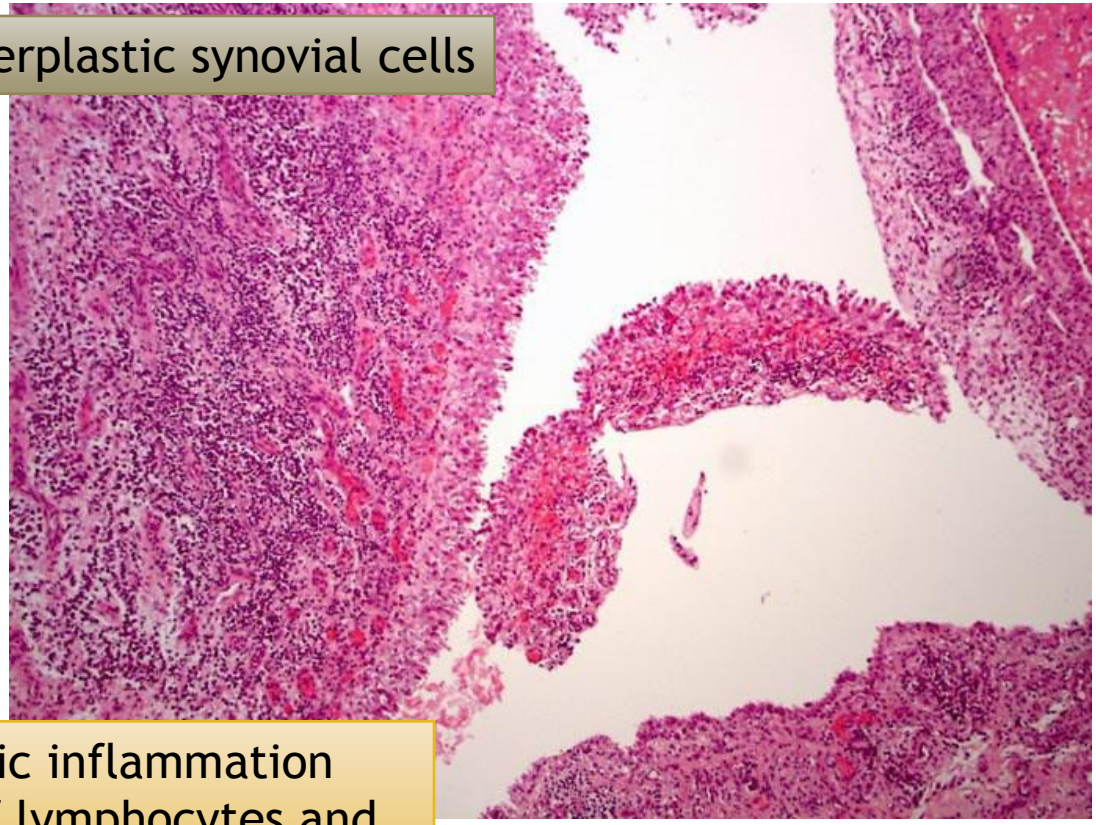
Swan neck deformity

Rheumatoid arthritis

Pathologic Features



Rheumatoid arthritis Microscopic



Dense chronic inflammation consisting of lymphocytes and plasma cells

Rheumatoid arthritis

Clinical Feaures

- morning stiffness, arthritis in 3+ joint areas
- arthritis in hand joints,
- symmetric arthritis,

Rheumatoid arthritis

X-ray:

- joint effusions, juxta-articular osteopenia, erosions

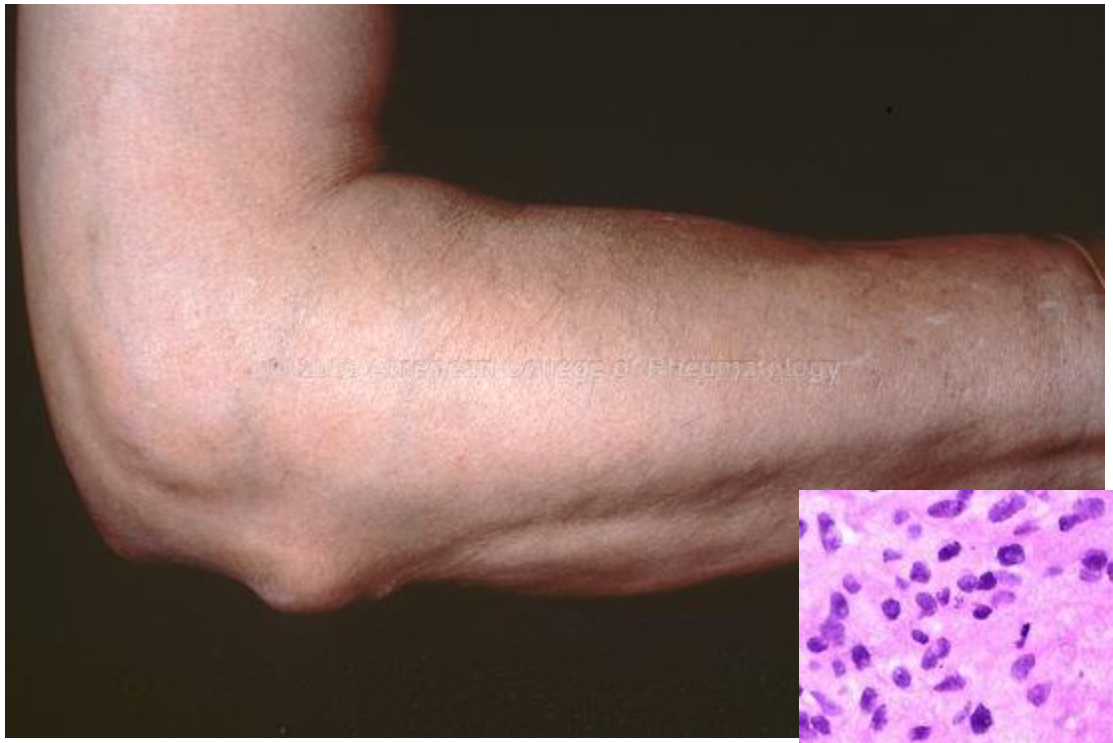
- narrowing of joint space; destruction of tendons, ligaments and joint capsules produce radial deviation of wrist, ulnar deviation of digits, swan neck finger abnormalities

Rheumatoid arthritis

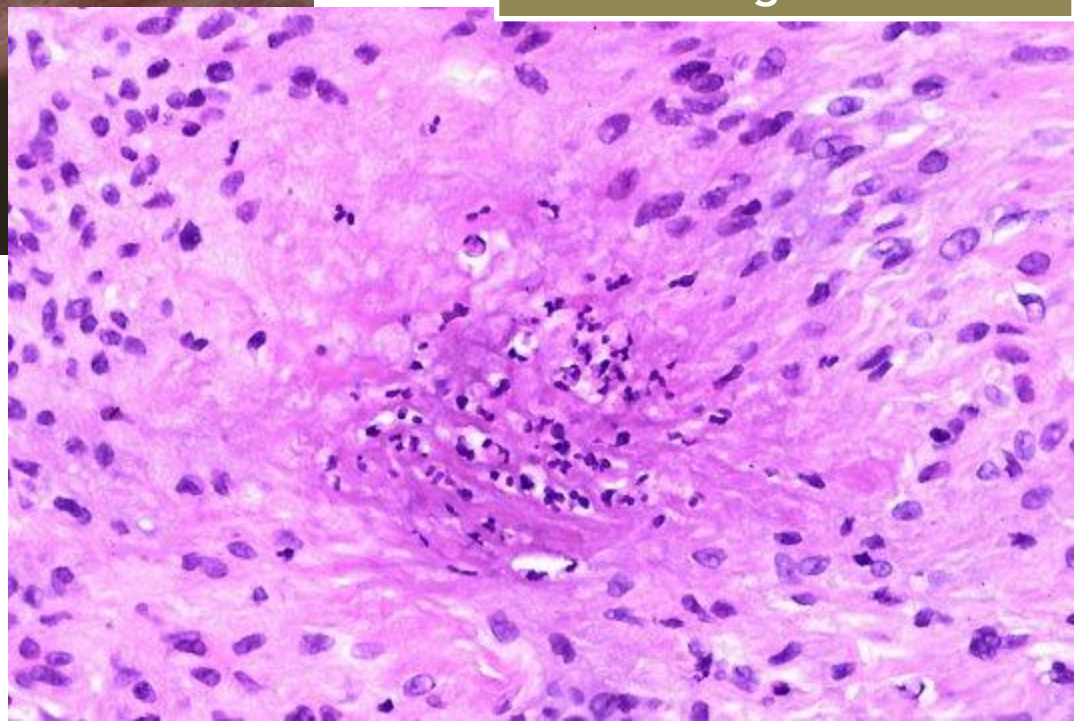
Clinical course:

- variable; malaise, fatigue, musculoskeletal pain and joint involvement
- joints are warm, swollen, painful, stiff in morning
- 10% have acute onset of severe symptoms, but usually joint involvement occurs over months to years
- 50% have spinal involvement
- rheumatoid nodules, rheumatoid factor, typical radiographic changes

Subcutaneous rheumatoid nodule



Palisading Granulomas



Rheumatoid arthritis
Prognosis

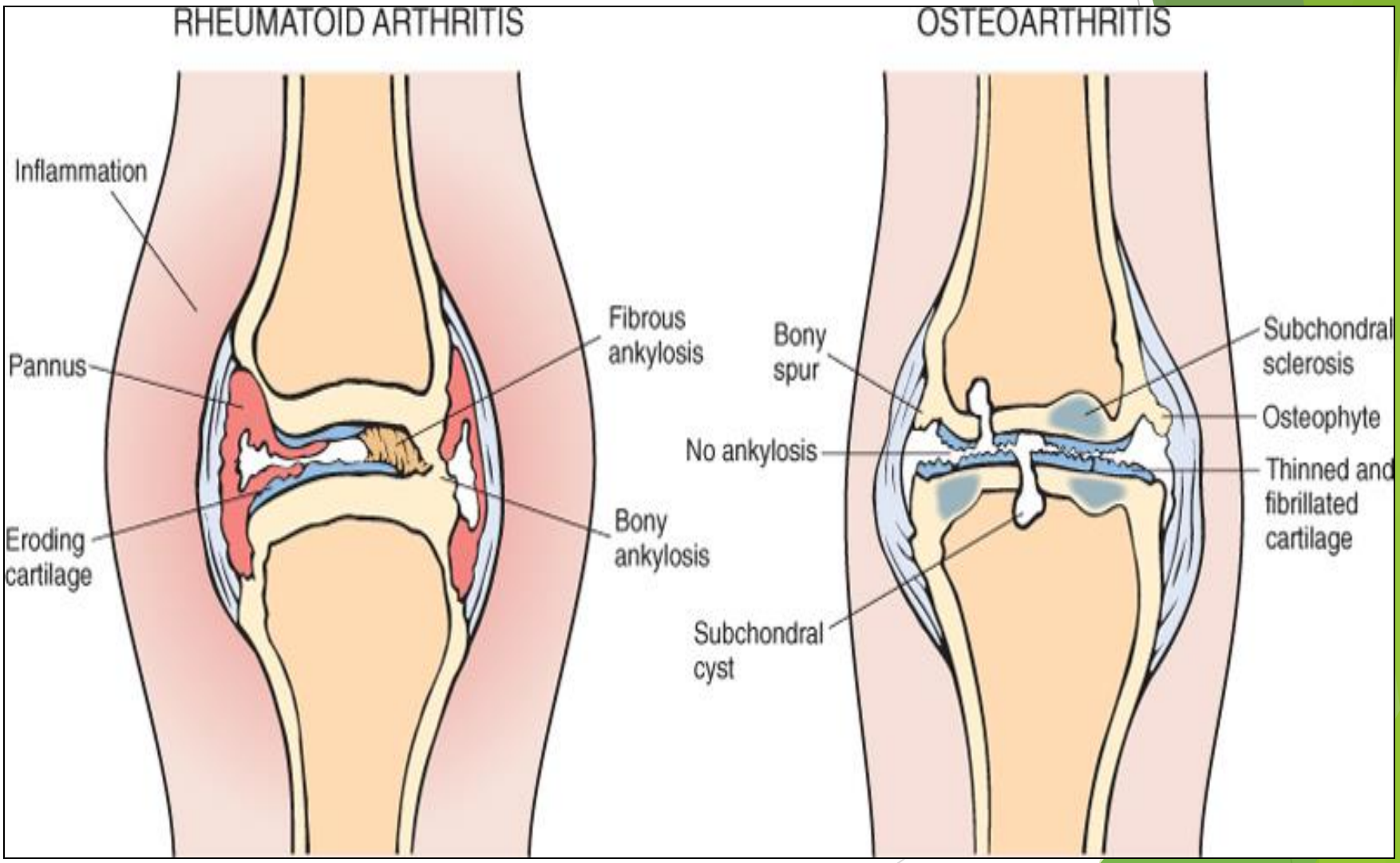
- Reduces life expectancy by 3-7 years
- Death due to amyloidosis, vasculitis, GI bleeds from NSAIDs, infections from steroids.

Rheumatoid arthritis

Summary

- RA is a chronic inflammatory disease that affects mainly the joints, especially small joints, but can affect multiple tissues
- The disease is caused by an autoimmune response against an unknown self antigen(s)
- This leads to T-cell reactions in the joint with production of cytokines that activate phagocytes that damage tissues and stimulate proliferation of synovial cells (synovitis)
- The cytokine TNF plays a central role, and antagonists against TNF are of great benefit

Comparison of the morphologic features of RA and osteoarthritis

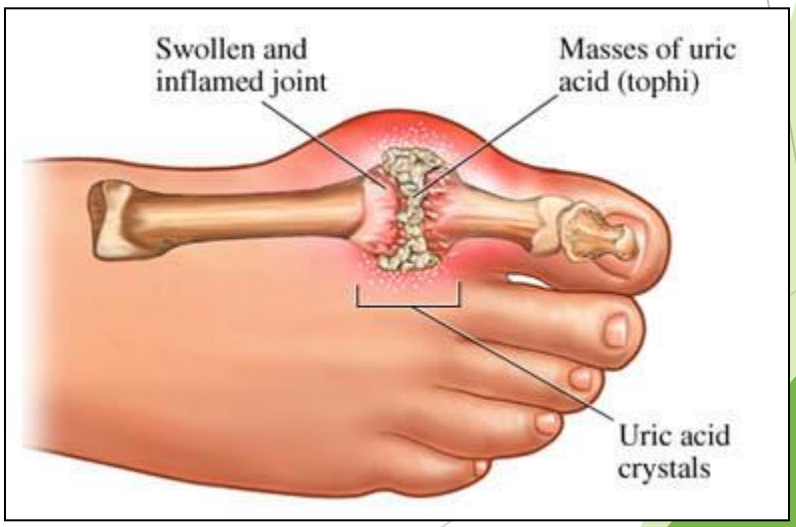


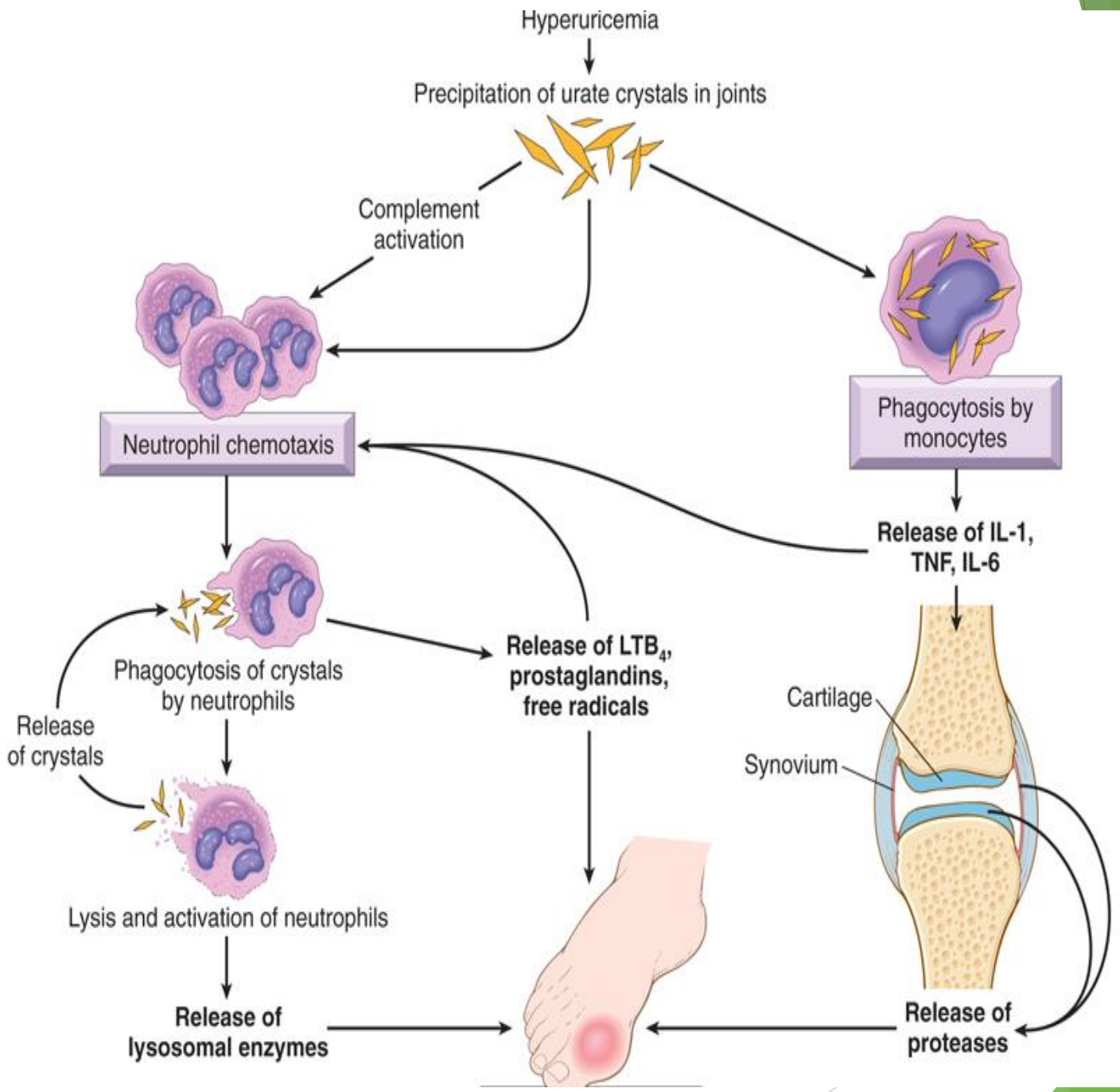
Comparison of Osteoarthrosis & Rheumatoid Arthritis

	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)

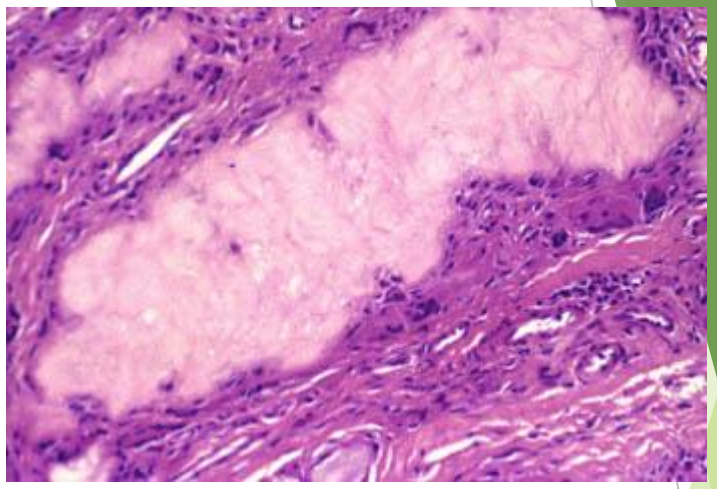
HGPRT, hypoxanthine guanine phosphoribosyl transferase.

Hands, chronic gout - Clinical presentation

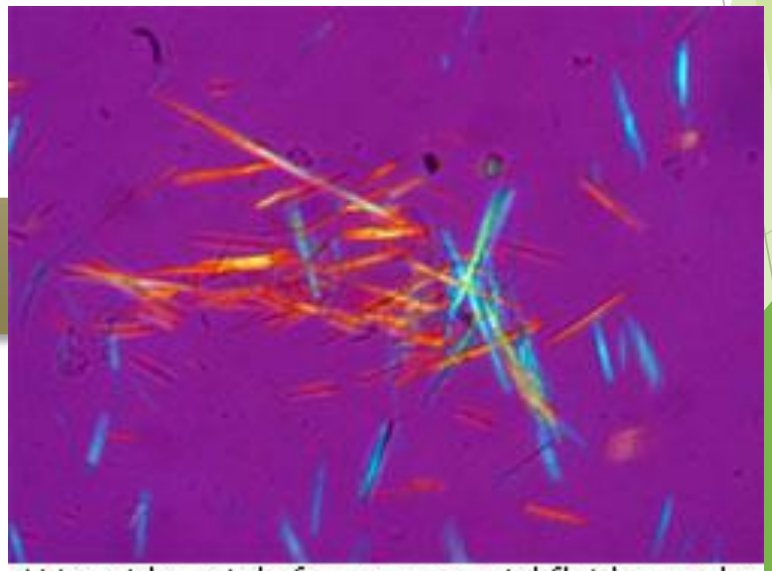
- This is an example of chronic gout with gouty tophi. Note that there are numerous asymmetrical, periarticular swellings.
- These represent inflammatory reaction to sodium urate crystals.
- Tophi appear only after repeated attacks of gout in patients whose hyperuricemia has not been treated.

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

- *Chondrocalcinosis*
- The crystal deposits first appear in structures composed of cartilage such as menisci, intervertebral discs, and articular surfaces. When the deposits enlarge enough, they may rupture, inducing an inflammatory reaction.
- Much of the subsequent joint pathology in pseudogout involves the recruitment and activation of inflammatory cells.
- Duration of clinical signs can be from several days to weeks, and joint involvement may be monoarticular or polyarticular; the knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected