

MUSCULOSKELETAL BLOCK

Pathology

Non-infectious arthritis

Dr.Amany Fathaddin

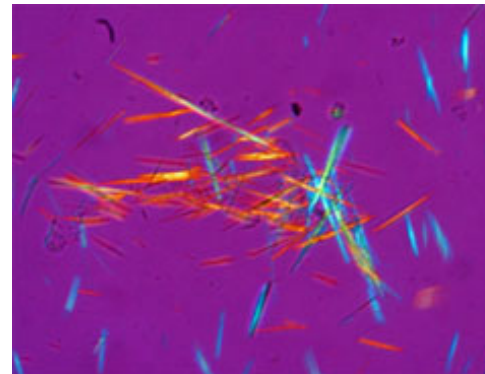
Objectives

- ▶ 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. Autoimmunity, e.g. rheumatoid arthritis, SLE
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 sample



Osteoarthritis

Definition and Incidence

- ▶ **Osteoarthritis** (degenerative joint disease) is the most common joint disease and is characterized by the progressive degeneration of articular cartilage in weight-bearing joints.
- ▶ Osteoarthritis can be: primary or secondary

Osteoarthritis

Types

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

Osteoarthritis

Types

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

Osteoarthritis

Pathogenesis

- ▶ Articular cartilage bears the brunt of the degenerative changes in osteoarthritis.

Normal articular cartilage performs two functions:

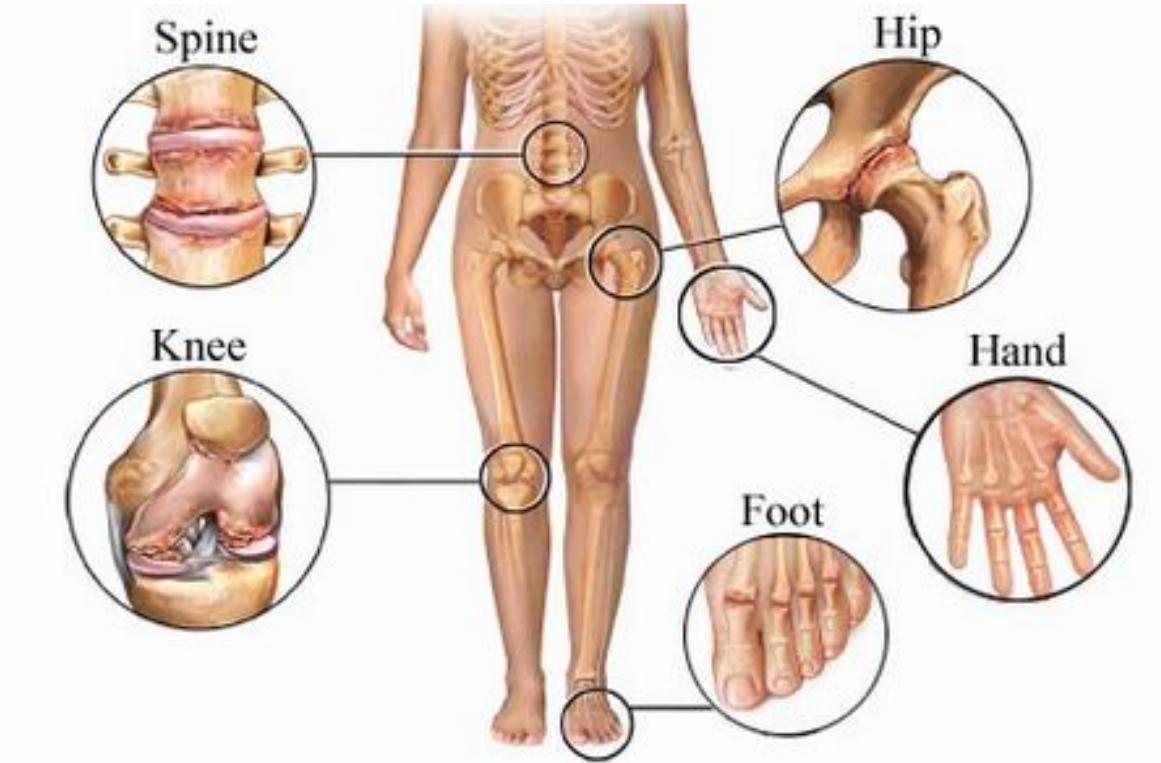
- ▶ (1) Along with the synovial fluid, it provides virtually friction-free movement within the joint
- ▶ (2) In weight-bearing joints, it spreads the load across the joint surface
- ▶ These functions require the cartilage to be elastic (i.e., to regain normal architecture after compression) and to have high tensile strength. These attributes are provided by proteoglycans and type II collagen, both produced by chondrocytes

Pathogenesis

- ▶ Chondrocyte function is affected by a variety of influences: mechanical stresses , aging and Genetic factors.
- ▶ Regardless of the inciting stimulus, there is an imbalance in the expression, activity, and signaling of cytokines and growth factors that results in degradation and loss of matrix.
- ▶ 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

Osteoarthritis

Common sites



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



Normal articular cartilage



Fragmentation of articular surface and thinning of cartilage

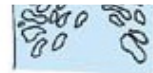


Calcification of cartilage margins. Patchy loss of cartilage revealing bare bone (eburnation).

Small cysts develop in the bone



osteophytes

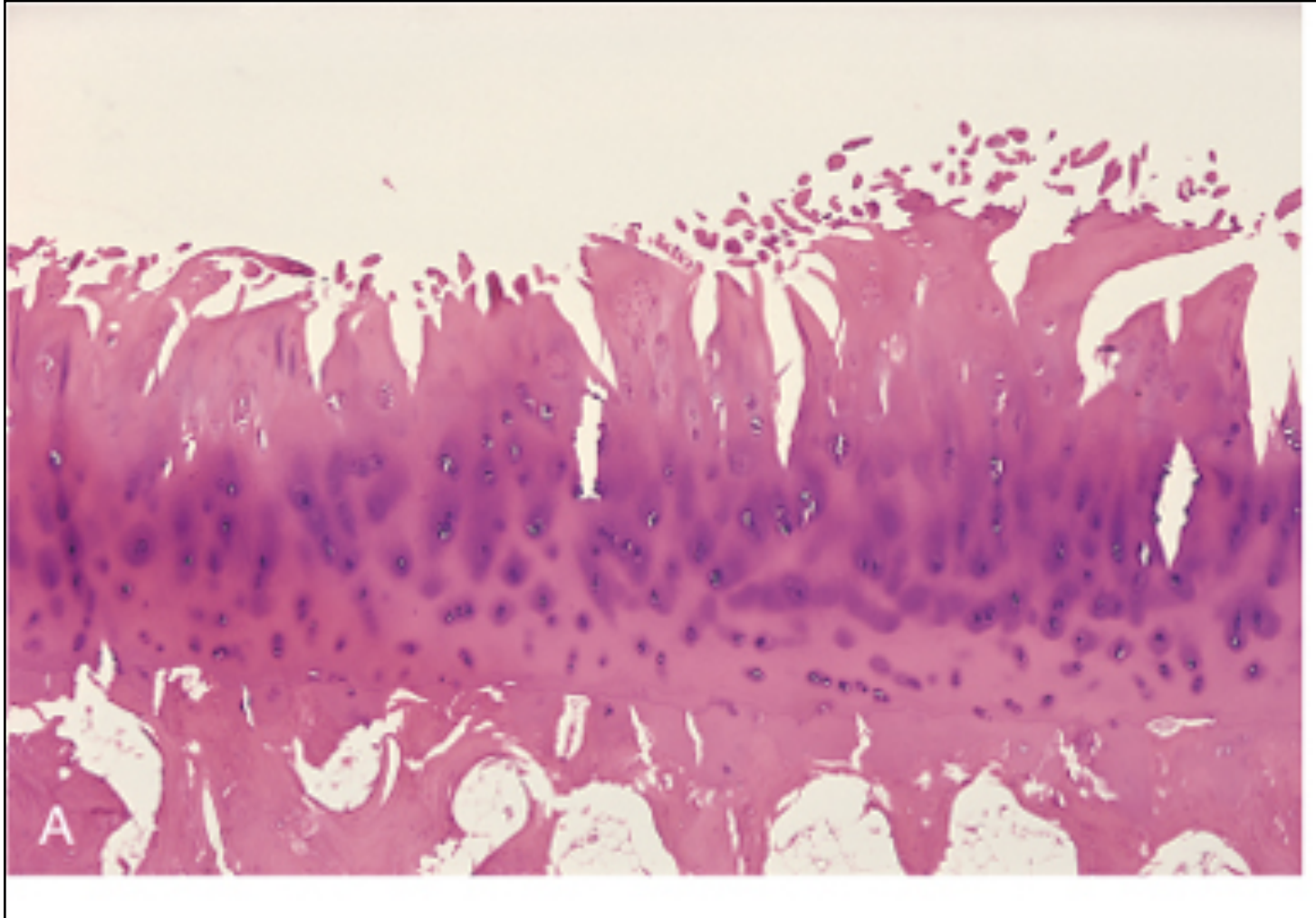


constant friction of bone surfaces, leading to a polished ivory bony articular surface (eburnation)

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

Morphology

- ▶ **fibrillation and cracking of the matrix** occur as the superficial layers of the cartilage are degraded
- ▶ Eventually, full-thickness portions of the cartilage are lost, and the subchondral bone plate is exposed and is smoothed by friction, giving it the appearance of polished ivory (**bone eburnation**)
- ▶ Small fractures can dislodge pieces of cartilage and subchondral bone into the joint, forming loose bodies (**joint mice**).
- ▶ The fracture gaps allow synovial fluid to be forced into the subchondral regions to form fibrous walled **cysts**.
- ▶ Mushroom-shaped **osteophytes** (bony outgrowths) develop at the margins of the articular surface

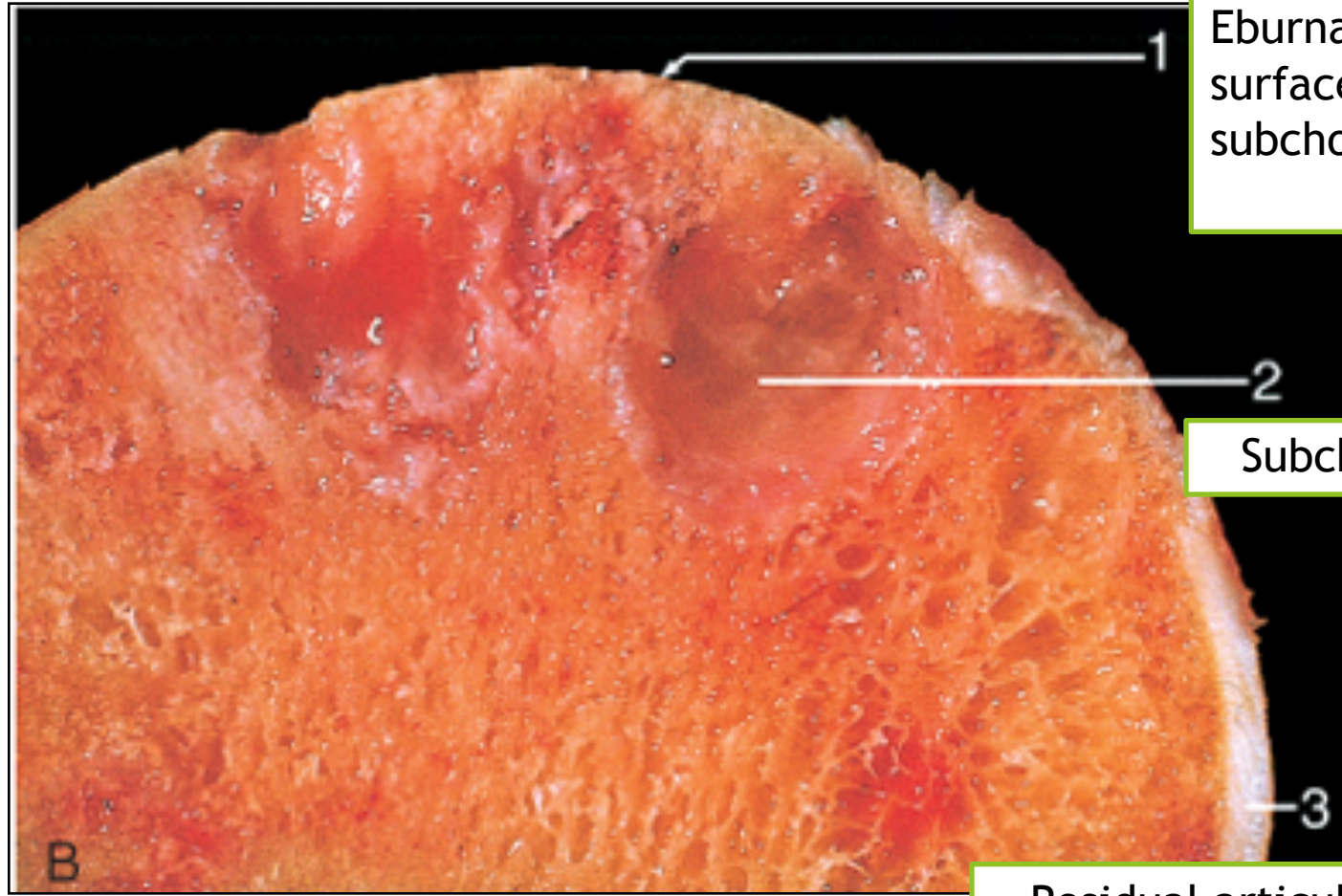


Osteoarthritis. : Histologic demonstration of the characteristic fibrillation of the articular cartilage.

Cracking and fibrillation of cartilage



Severe Osteoarthritis

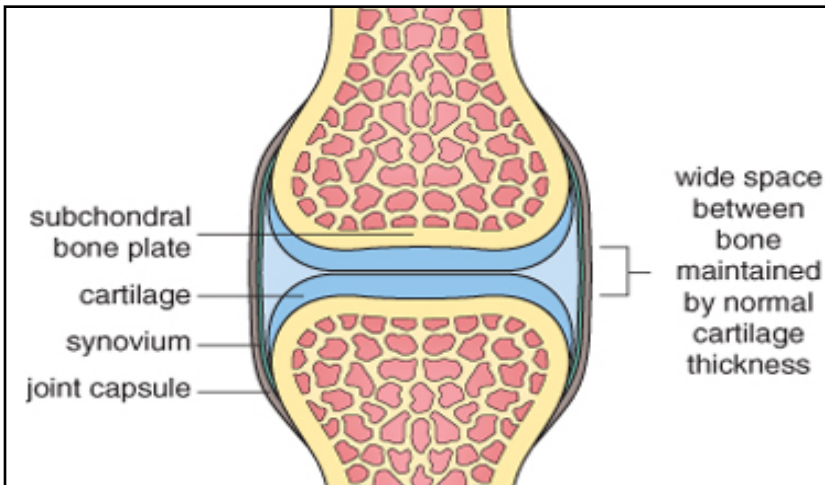


1
Eburnated articular surface exposing subchondral bone

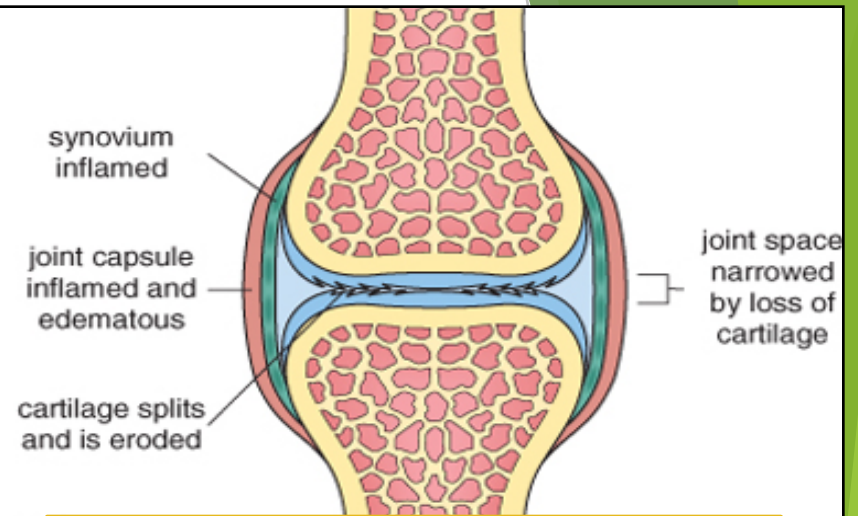
2
Subchondral cyst

3
Residual articular cartilage

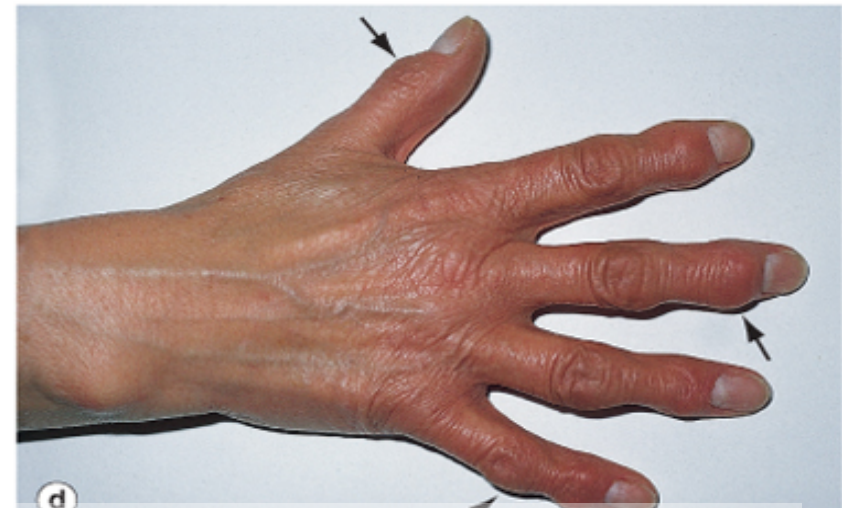
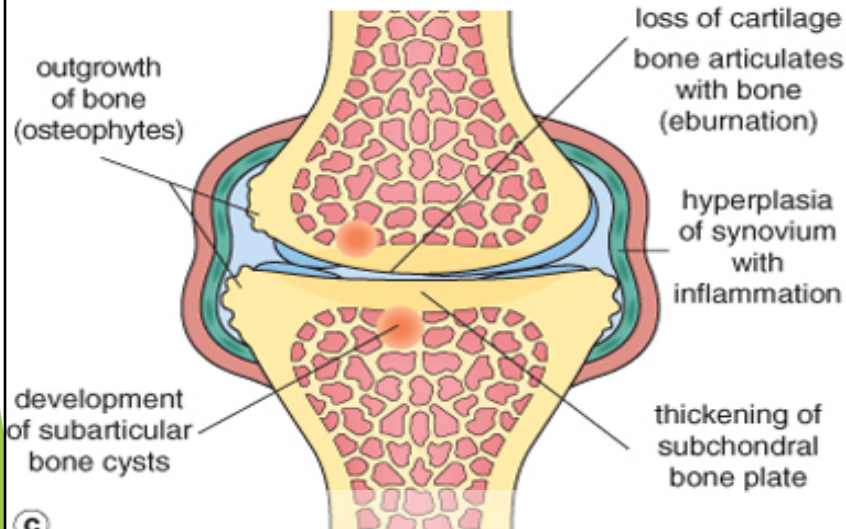
Pathological changes in osteoarthritis



a normal synovial joint



b early change in osteoarthritis

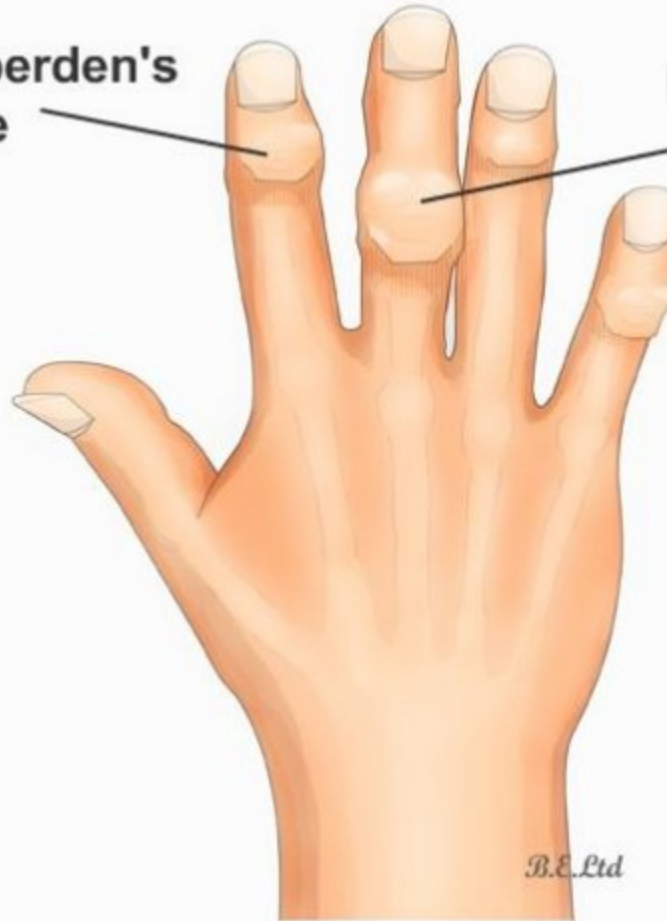


'Heberden's nodes' (osteophytes on the interphalangeal joints of the fingers)

Osteoarthritis

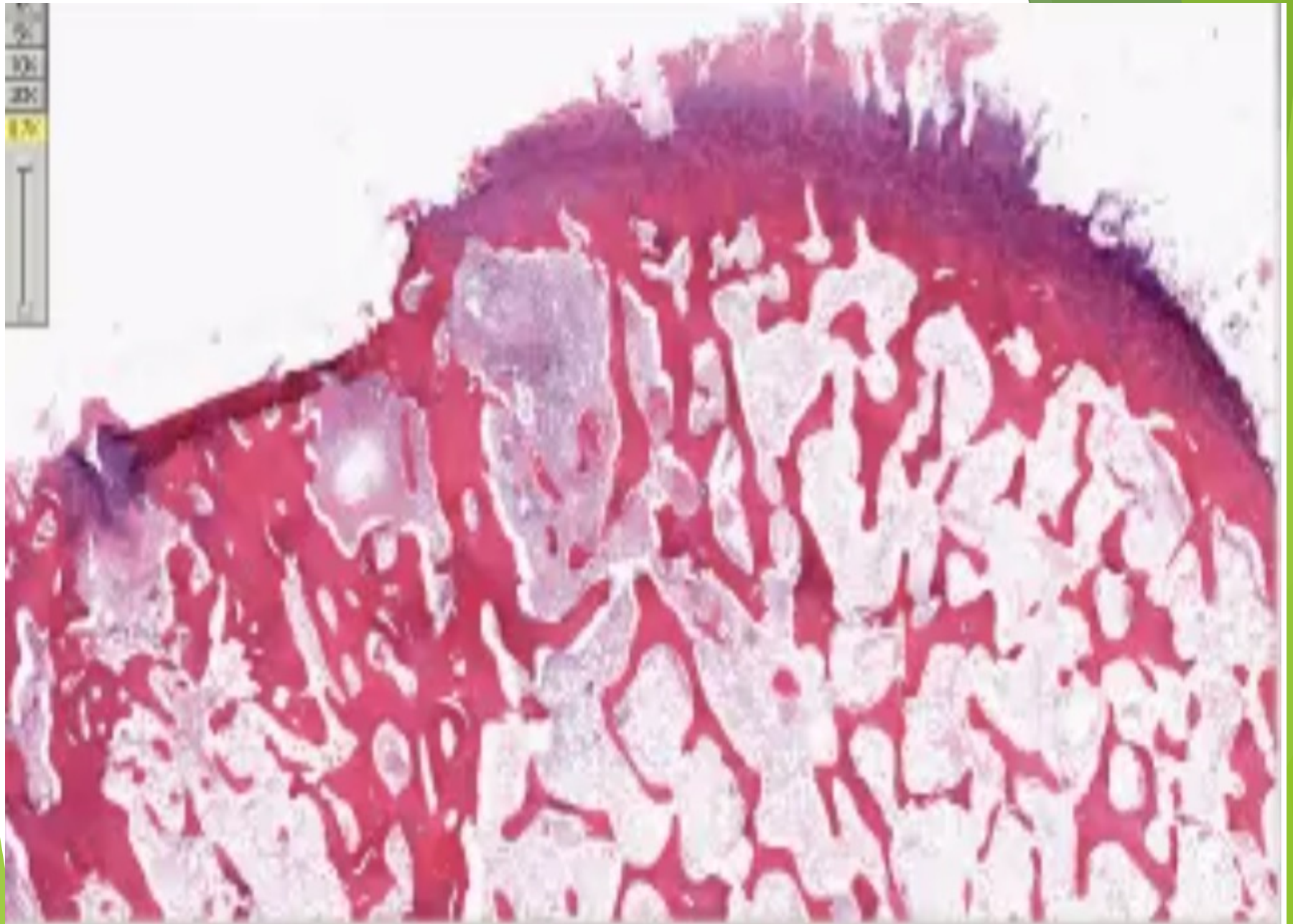
Herberden's
node

Bouchard's
node



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Clinical course

- ▶ Characteristic symptoms and signs include deep, aching pain exacerbated by use, morning stiffness, crepitus (grating or popping sensation in the joint), and limitation in range of movement.
- ▶ Osteophyte impingement on spinal foramina can cause nerve root compression with radicular pain and neurologic deficits.
- ▶ Hips, knees, lower lumbar and cervical vertebrae, proximal and distal interphalangeal joints of the fingers, first carpometacarpal joints, and first tarsometatarsal joints of the feet are commonly involved. **Heberden nodes** in the fingers, representing prominent osteophytes at the distal interphalangeal joints, are characteristic in women.

Course & Prognosis

- ▶ slowly progressive.
- ▶ With time, significant joint deformity can occur, Treatment usually is based on symptoms, with joint replacement in severe cases.

Rheumatoid arthritis

Rheumatoid arthritis

- ▶ *Rheumatoid arthritis (RA)* is a systemic, chronic inflammatory autoimmune disease affecting many tissues but principally attacking the joints.
- ▶ It causes a **nonsuppurative proliferative synovitis** that frequently progresses to destroy articular cartilage and underlying bone with resulting disabling arthritis.
- ▶ RA is a relatively common condition, with a prevalence of approximately 1%; it is three to five times more common in women than in men.
- ▶ The peak incidence is in the second to fourth decades of life, but no age is immune.

Pathogenesis (RA)

- ▶ RA is an autoimmune disease involving complex, and still poorly understood, interactions of genetic risk factors, environment, and the immune system. The pathologic changes are caused mainly by **cytokine-mediated inflammation, with CD4+ T cells being the principal source of the cytokines**
- ▶ Many patients also produce **antibodies against cyclic citrullinated peptides (CCPs)**, which may contribute to the joint lesions. In RA, antibodies to citrullinated fibrinogen, type II collagen, α -enolase, and vimentin are the most important and may form immune complexes that deposit in the joints. **These antibodies are a diagnostic marker for the disease and may be involved in tissue injury.**

Pathogenesis (RA)

- ▶ **Genetic factors:** It is estimated that 50% of the risk of developing RA is related to genetic factors. Susceptibility to rheumatoid arthritis is linked to the HLA-DRB1 locus.
- ▶ **Environmental factors:** Many candidate infectious agents whose antigens may activate T or B cells have been considered, but none has been conclusively implicated.

Pathogenesis (RA)

- ▶ About 80% of patients have serum immunoglobulin M (IgM) (and, autoantibodies that bind to the Fc portions of their own (self) IgG.
- ▶ These autoantibodies are called **rheumatoid factor**. They may form immune complexes with self-IgG that deposit in joints and other tissues, leading to inflammation and tissue damage. However, the role of rheumatoid factor in the pathogenesis of the joint or extraarticular lesions has not been established.

Susceptibility genes
(HLA, other)

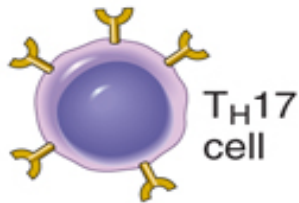
HLA-DR4, DR1 (65%)

Failure of tolerance,
unregulated lymphocyte
activation

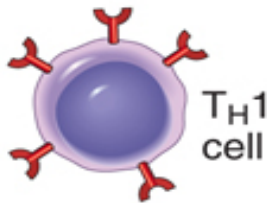
Environmental factors
(e.g., infection, smoking)

Enzymatic modification
(e.g., citrullination) of
self protein

T and B cell responses to self antigens
(including antigens in joint tissues)



T_H17
cell



T_H1
cell



Antibodies

Fibroblasts
Chondrocytes → Proliferation
Synovial cells

Release of collagenase, stromelysin,
elastase, PGE₂, and other enzymes

Pannus formation;
destruction of bone, cartilage;
fibrosis; ankylosis

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 protein**

Rheumatoid arthritis

Pathologic Features

1. synovial cell hyperplasia and proliferation
2. dense perivascular inflammatory cell infiltrates (Chronic synovitis) (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

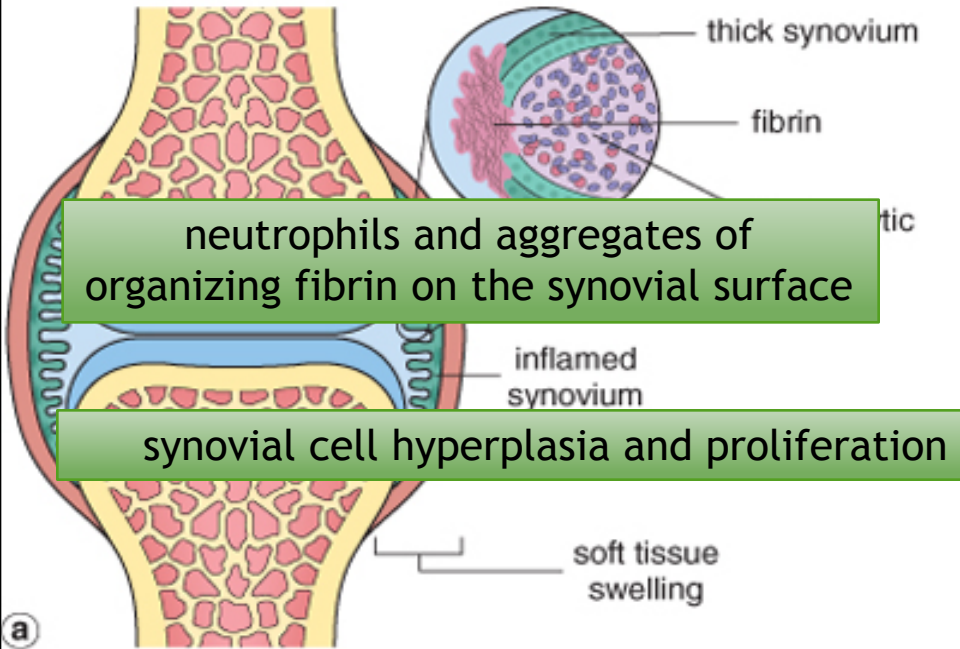
Pathologic Features

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**.

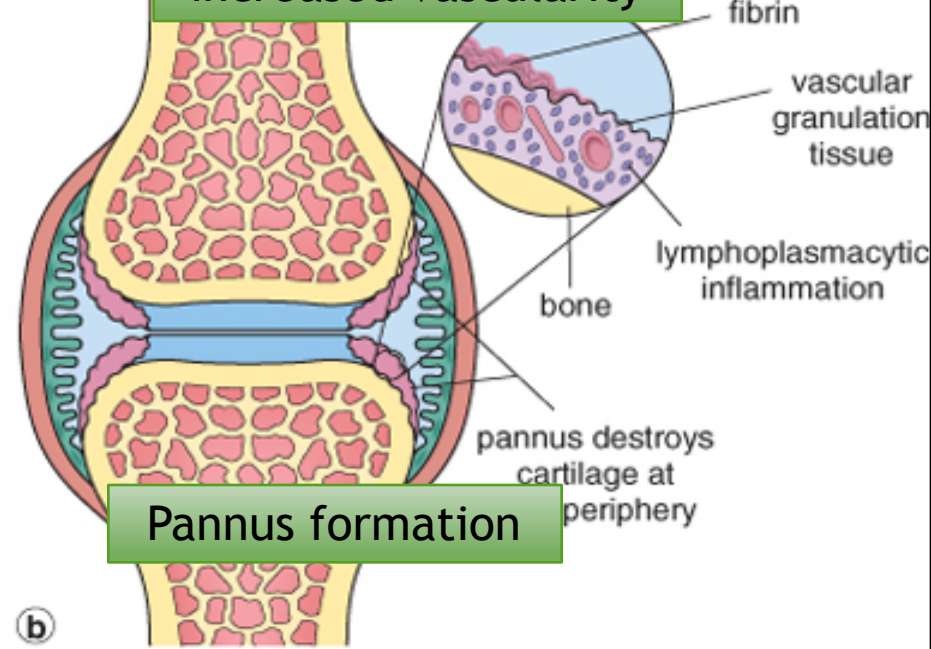
dense perivascular inflammatory cell infiltrates

increased vascularity

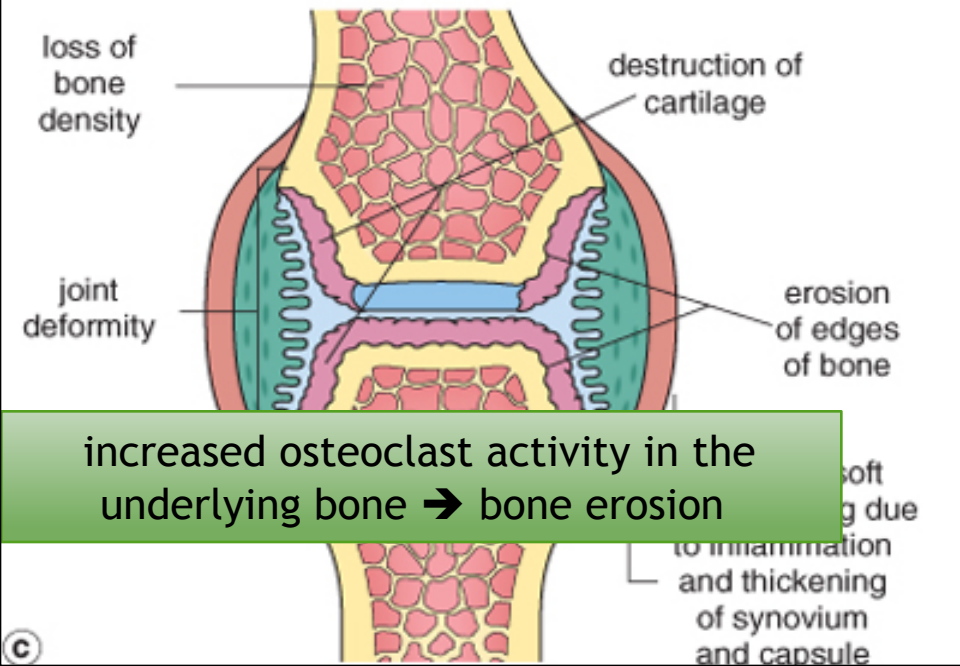


neutrophils and aggregates of organizing fibrin on the synovial surface

synovial cell hyperplasia and proliferation



Pannus formation



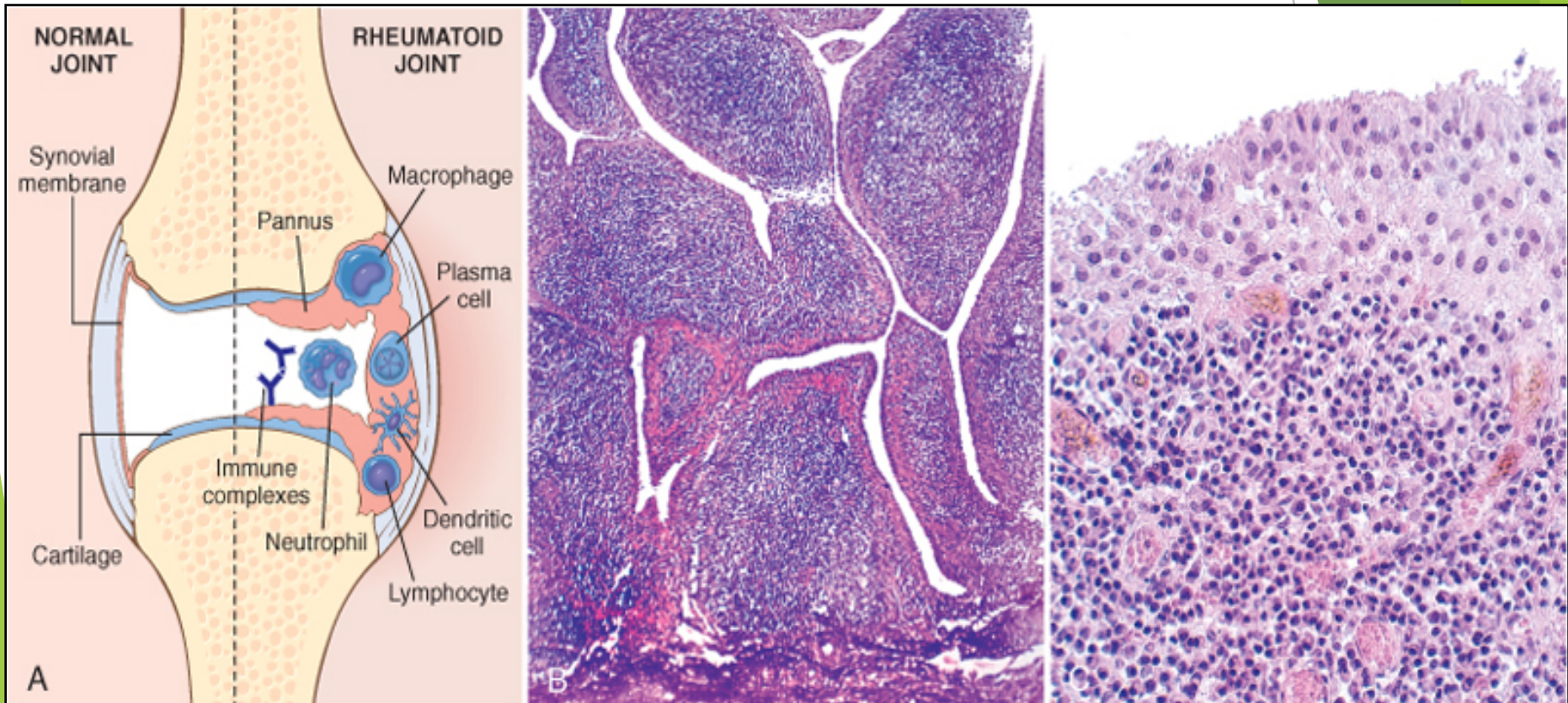
increased osteoclast activity in the underlying bone → bone erosion



swan neck finger

Rheumatoid arthritis

Pathologic Features

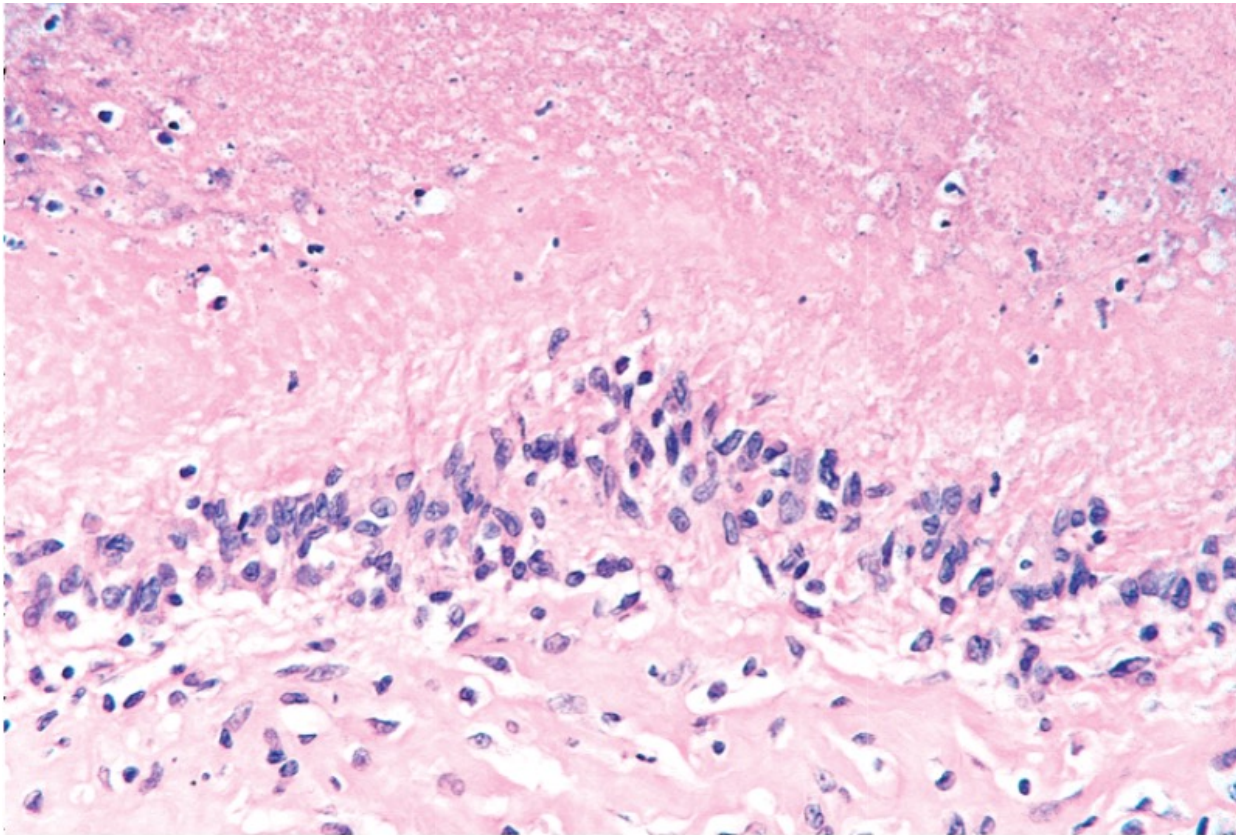


Rheumatoid subcutaneous nodules

- ▶ develop in about one fourth of patients
- ▶ occurring along the extensor surface of the forearm
- ▶ Rheumatoid nodules are firm, nontender, oval or rounded masses as large as 2 cm in diameter.
- ▶ They are characterized microscopically by a central focus of fibrinoid necrosis surrounded by a palisade of macrophages, which in turn is rimmed by granulation tissue and lymphocytes



Rheumatoid subcutaneous nodules



RA

Clinical features

- ▶ **symmetric arthritis, principally affecting the small joints** of the hands and feet, ankles, knees, wrists, elbows, and shoulders.
- ▶ Most often, the proximal interphalangeal and metacarpophalangeal joints are affected, but distal interphalangeal joints are spared.
- ▶ Axial involvement, when it occurs, is limited to the upper cervical spine; similarly, hip joint involvement is extremely uncommon.

RA

Clinical features

- ▶ Weakness , low grade fever
- ▶ aching and stiffness of the joints, particularly in the morning
- ▶ As the disease advances, the joints become enlarged, motion is limited
- ▶ characteristic deformities develop. These include:

Radial deviation at the wrists.

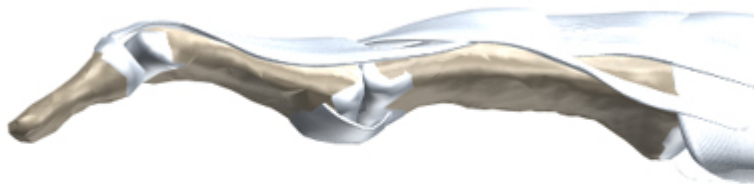
Ulnar deviation at the fingers.

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

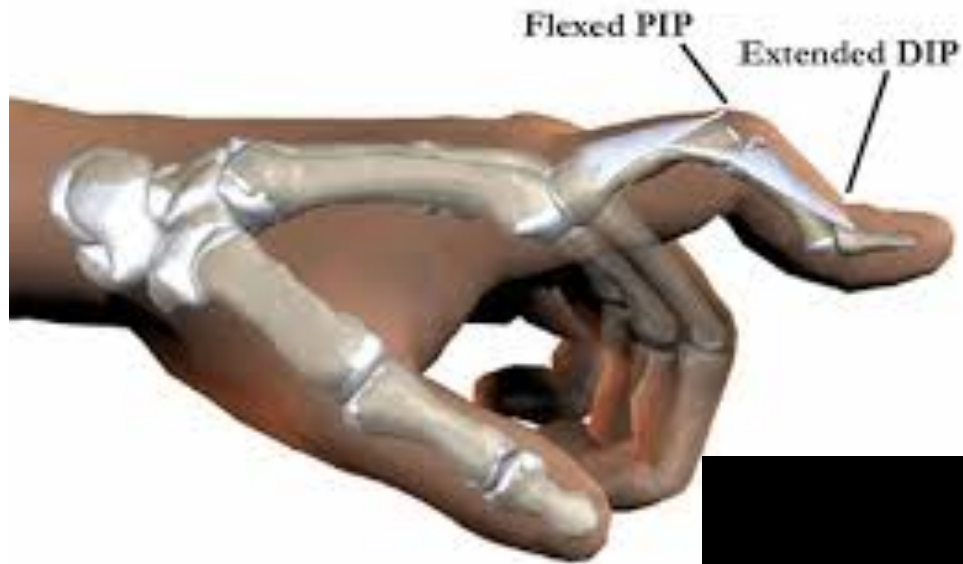
Normal joint



Swan neck deformity



Boutonniere Deformity



Rheumatoid arthritis

X-ray:

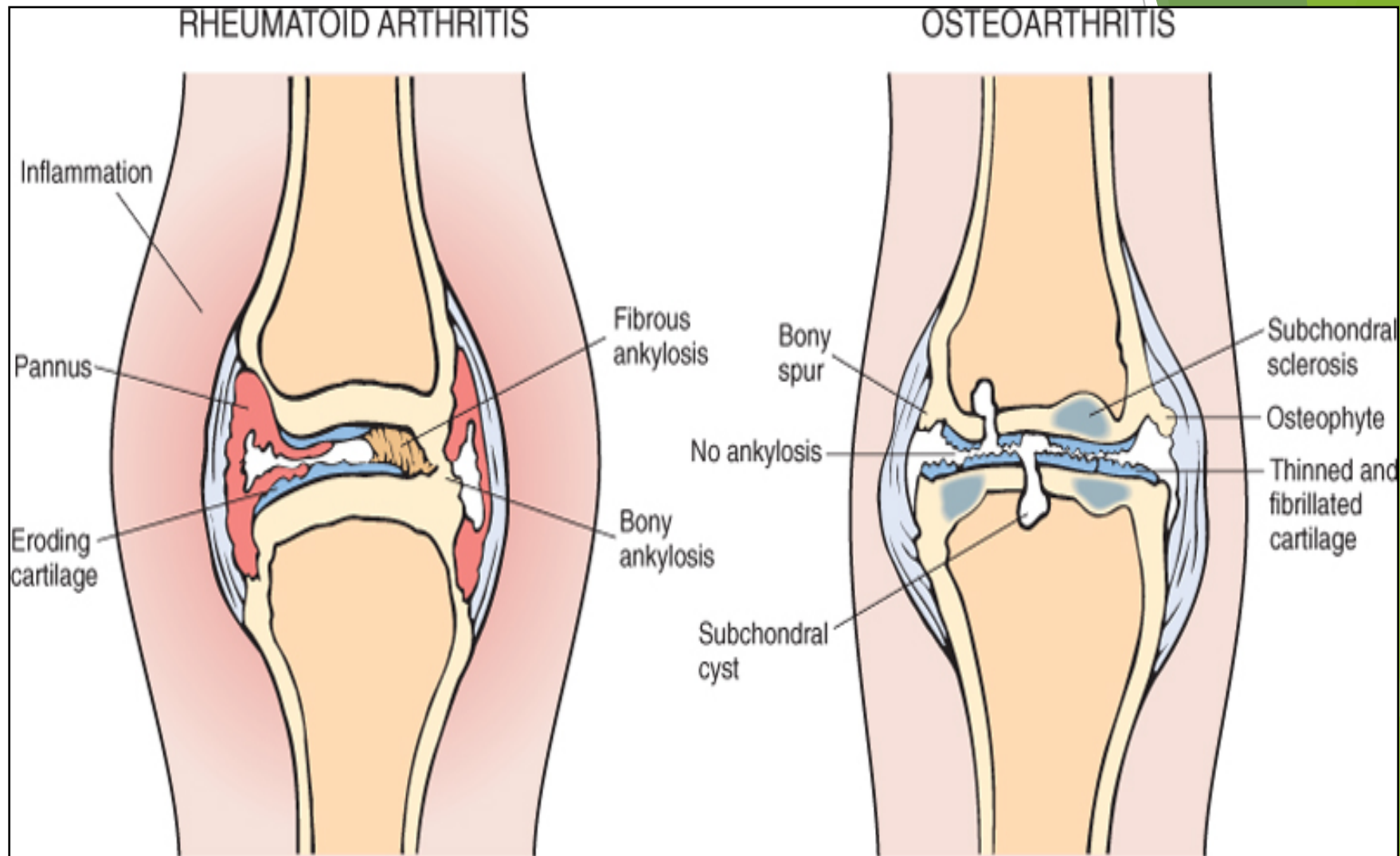
- ▶ Loss of articular cartilage leading to narrowing of the joint space.
- ▶ Joint effusions.
- ▶ Erosions.

Rheumatoid arthritis

Prognosis

- ▶ The clinical course of RA is highly variable.
- ▶ In a minority of patients, the disease may stabilize or even regress
- ▶ in most patients it pursues a chronic, remitting-relapsing course.
- ▶ progressive joint destruction leading to disability after 10 to 15 years. The outcome has been dramatically improved by recent advances in therapy.
- ▶ RA is an important cause of reactive amyloidosis, which develops in 5% to 10% of these patients, particularly those with long-standing severe disease

Comparison of the morphologic features of RA and osteoarthritis



Comparison of Osteoarthritis & Rheumatoid Arthritis

	Osteoarthritis	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 (Podagra)

- ▶ Gout affects about 1% of the population, and shows a predilection for males.
- ▶ It is caused by excessive amounts of *uric acid*,
- ▶ **Monosodium urate crystals** precipitate from supersaturated body fluids and induce an acute inflammatory reaction.
- ▶ Gout is marked by recurrent episodes of acute arthritis, sometimes accompanied by the formation of large crystalline aggregates called ***tophi***, and eventual permanent joint deformity.
- ▶ Risk factors for the disease include obesity, excess alcohol intake, consumption of purine-rich foods, diabetes, the metabolic syndrome, and renal failure.

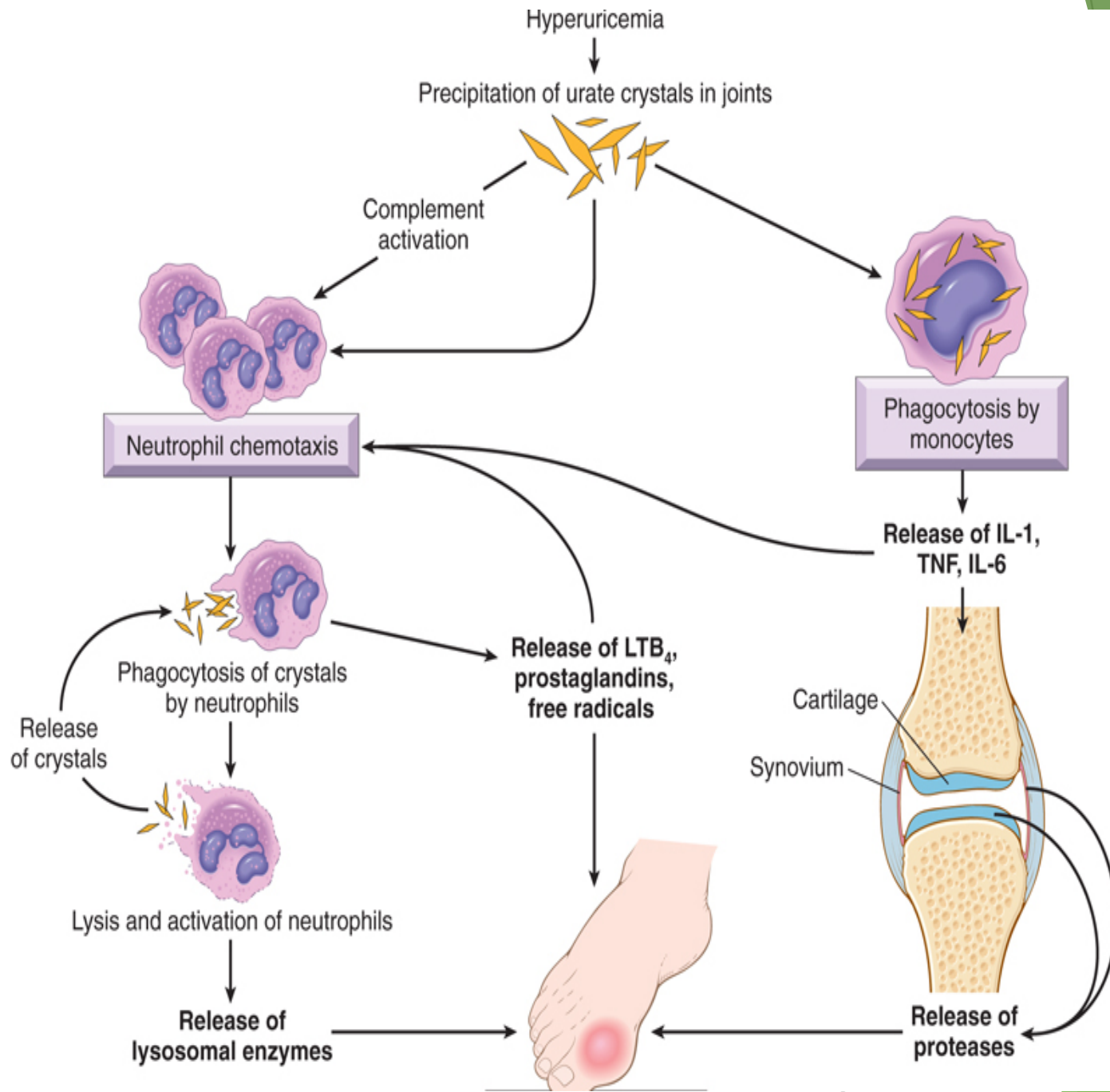
Gout is divided into :

- ▶ Primary 90%
- ▶ Secondary 10 %forms

Table 20–3 Classification of Gout

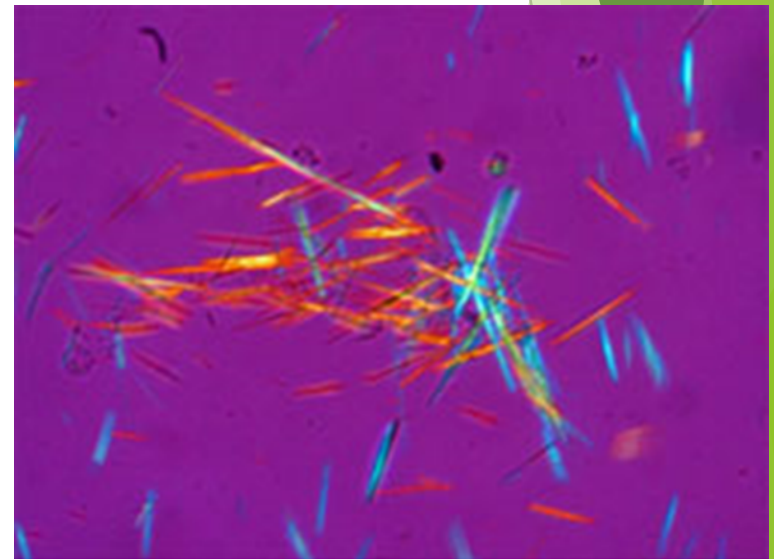
Clinical Category	Metabolic Defect
Primary Gout (90% of cases)	
Enzyme defects—unknown (85% to 90% of cases)	Overproduction of uric acid Normal excretion (majority) Increased excretion (minority) Underexcretion of uric acid with normal production
Known enzyme defects—e.g., partial HGPRT deficiency (rare)	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.



Gout Morphology

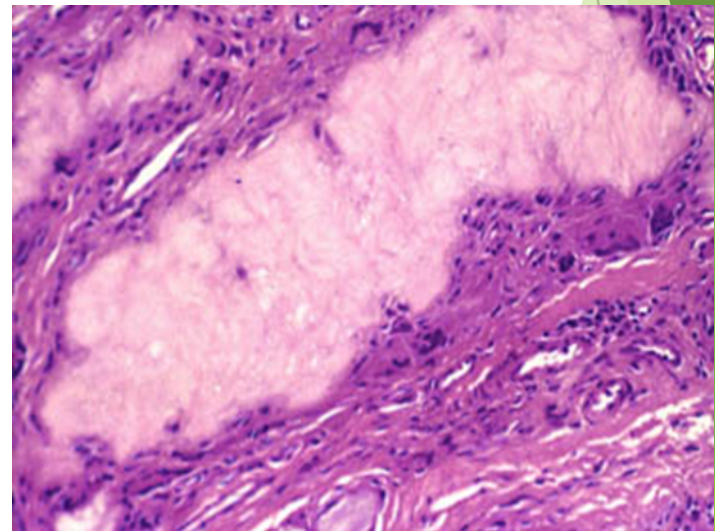
- ▶ **Acute arthritis** is characterized by a dense neutrophilic infiltrate permeating the synovium and synovial fluid. Long, slender, needle-shaped **monosodium urate crystals** frequently
- ▶ **Chronic tophaceous arthritis** evolves from repetitive precipitation of urate crystals during acute attacks. The synovium becomes hyperplastic, fibrotic, and thickened by inflammatory cells



Uric acid crystals from a synovial fluid sample

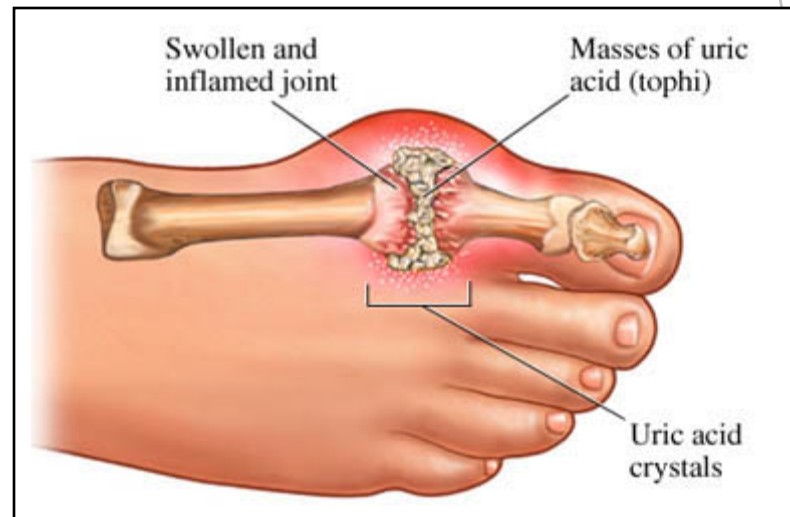
Gout Morphology

- ▶ **Tophi are pathognomonic for gout.** They are formed by large aggregations of urate crystals surrounded by an intense inflammatory reaction of lymphocytes, macrophages, and foreign-body giant cells
- ▶ Tophi can appear in the articular cartilage of joints and in the soft tissues, including the ear lobes & nasal cartilages



Gout, clinical features

- ▶ The most commonly affected site is: **first metatarsophalangeal joint**.
- ▶ It is swollen, red, and very painful.
- ▶ Renal manifestations of gout can appear as renal colic associated with the passage of gravel and stones



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 .