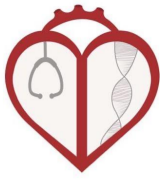




PATHOLOGY TEAM  
439



MED439  
KING SAUD UNIVERSITY

جامعة  
الملك سعود  
King Saud University



Revised & Approved  
by:

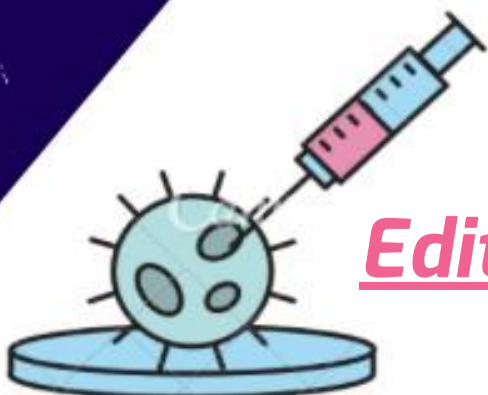


Shayma Abdullah Algharouni  
Yasuf Mohammad Alkhatib

# 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**]



**Editing File**

Index:  
**Important**  
NOTES  
Extra Information

# Inflammatory diseases of joints (Arthritis and Synovitis)

1

Degeneration, e.g.  
**OSTEOARTHRITIS**

2

Autoimmunity e.g.  
**RHEUMATOID  
ARTHRITIS**

3

Crystal deposition,  
e.g. Gout and other  
crystalline  
arthropathies.

4

Infection, e.g. Septic  
and Tuberculous  
arthritis

## Osteoarthritis



[click here For a better understanding](#)

It's not a inflammatory disease it's a degenerative disease, even though there is an inflammation, but it's a mild inflammation

also known as degenerative joint disease, it's the most common joint disease, and it's characterized by the progressive degeneration of articular cartilage in weight bearing joints.

## Types of Osteoarthritis

Osteo= Bone  
Arth= joint  
Itis= Inflammation

### Primary Osteoarthritis:

- appears insidiously with age and without apparent initiating cause.
- Usually affects only few joints

### Secondary Osteoarthritis:

- Some predisposing factors such as:
  1. Previous traumatic injury
  2. development deformity
  3. underlying systemic disease e.g. diabetes
  4. hemochromatosis
  5. obesity
- it's seen in less than 5% of the cases
- often involve one or several predisposed joints
- It affects young.

### Common sites

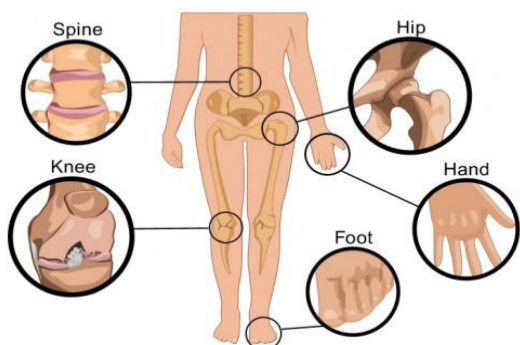
**Men:** Hips  
**Women:** Knee & Hands

Loss of articular cartilage

Friction

Inflammation

Pain



# Pathogenesis

## Articular cartilage:

bears the brunt of the degenerative changes in osteoarthritis and it has two functions:

01

Along with the synovial fluid, it provides virtually friction-free movement within the joint

02

In weight-bearing joints, it spreads the load across the joint surface

And these functions require the cartilage to be :

1. elastic (i.e., to regain normal architecture after compression)
2. have high tensile strength

These Attributes are provided by:

- Proteoglycans
  - Type II collagen
- Which are both produced by Chondrocytes

It's job is to maintain a healthy articular cartilage

**Chondrocytes** 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.

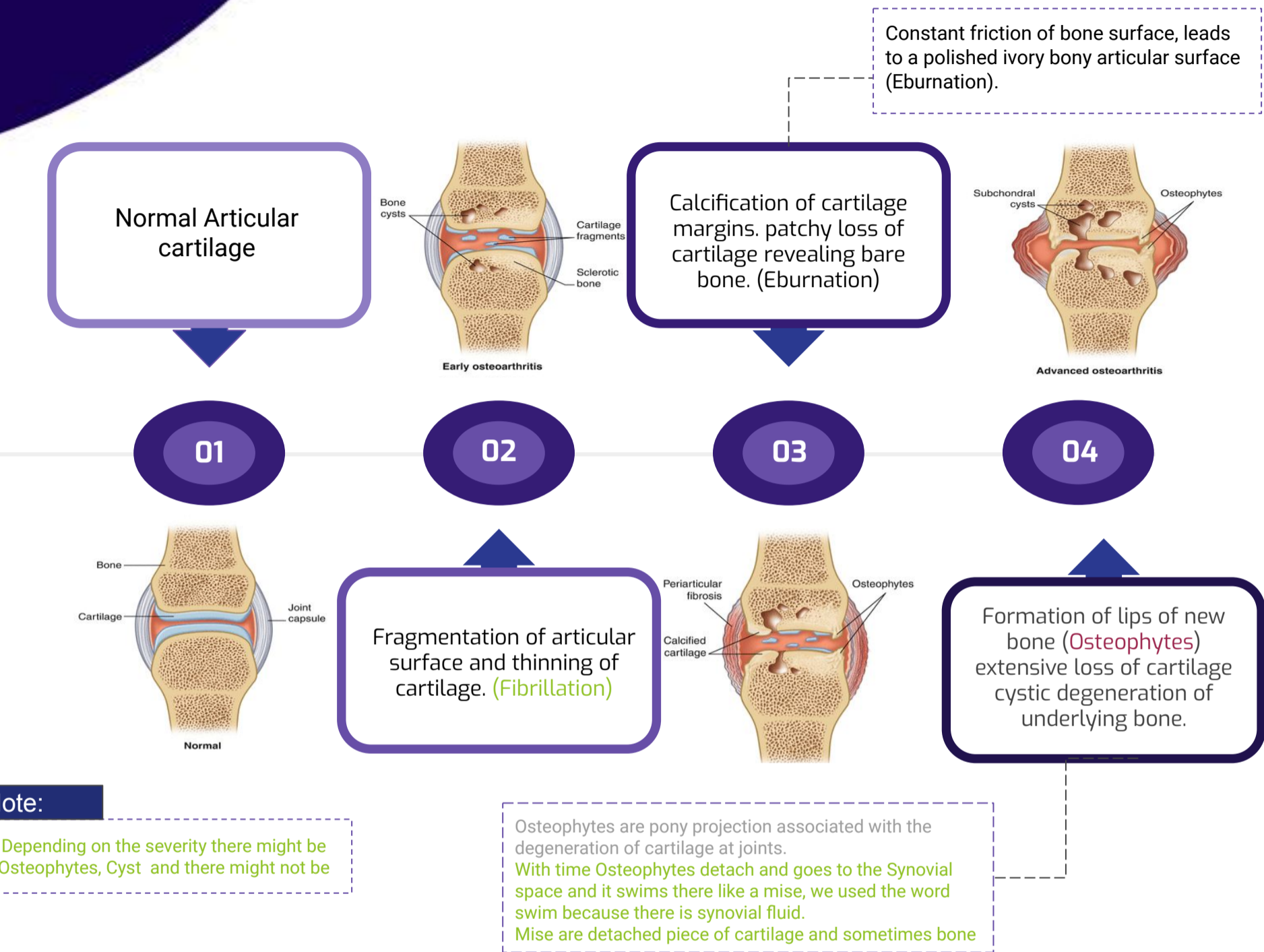
Early osteoarthritis is marked by degenerating cartilage containing more water and less proteoglycan.

The type II collagen network also is diminished, presumably as a result of decreased local synthesis and increased breakdown



Articular cartilage In osteoarthritis





**Heberden's node:** Osteophytes on the distal interphalangeal joints of the fingers

**Bouchard's node:** Osteophytes on the proximal interphalangeal joints of the fingers

# Cont. Osteoarthritis(OA)

## Morphology:

**1** fibrillation and cracking of the matrix occur as the superficial layers of the cartilage are **degraded**.

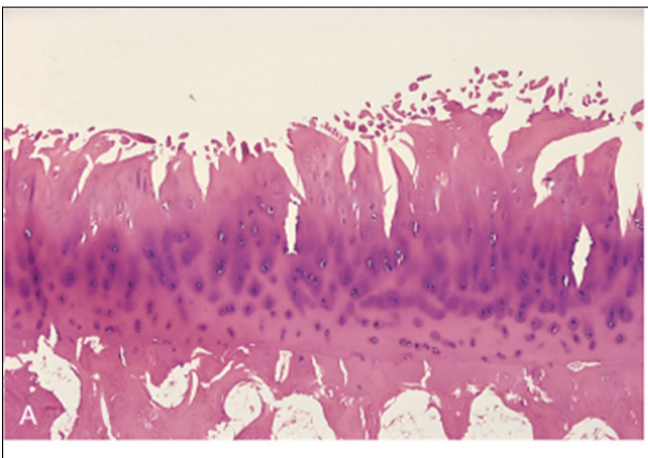
**2** Eventually, **full-thickness portions of the cartilage are lost**, and the subchondral bone plate is exposed and is smoothed by friction, giving it the appearance of polished ivory (**bone eburnation**)

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

**4** The fracture gaps allow synovial fluid to be forced into the subchondral regions to form fibrous walled **cysts**

**5** Mushroom-shaped **osteophytes** (bony outgrowths) develop at the margins of the articular surface

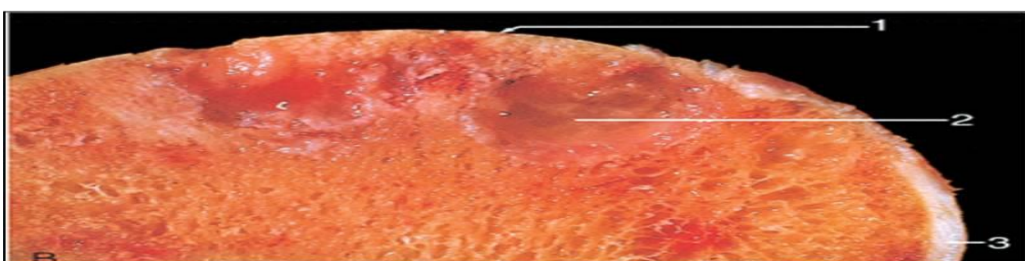
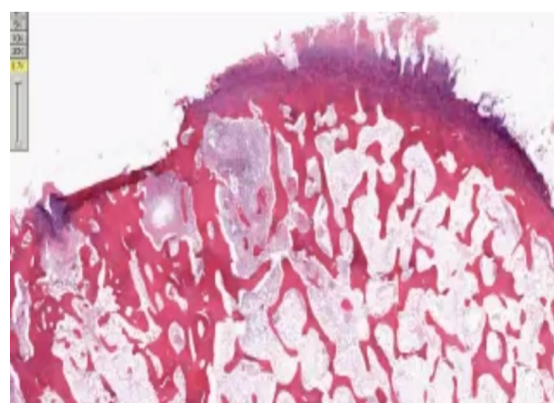
margins= طرف



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



Cracking and fibrillation of cartilage



1-Eburnated articular surface exposing subchondral bone.  
2-Subchondral cyst. 3-Residual articular cartilage



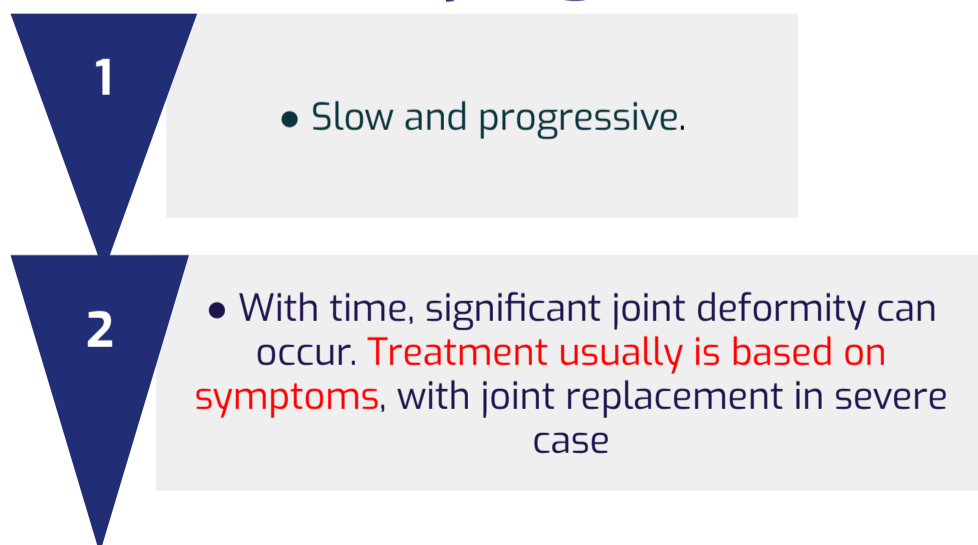
# Cont.

## Osteoarthritis(OA)

### Clinical Course

1	<p><b>Characteristic symptoms and signs include:</b></p> <ul style="list-style-type: none"> <li>- deep, aching pain exacerbated (worsened) by use</li> <li>- morning stiffness</li> <li>- crepitus (grating or popping sensation &amp; sounds in the joint)</li> <li>- limitation in range of movement</li> </ul>	
2	<p>Osteophyte impingement on spinal foramina can cause nerve root compression with radicular pain and neurologic deficits.:</p>	
3	<p>Osteophyte impingement on spinal foramina can cause nerve root compression with radicular pain and neurologic deficits. Commonly involves:</p>	1- Hips, knees
		2- Lower lumbar and cervical vertebrae
		3- Proximal and distal interphalangeal joints of the fingers
	<p>Heberden nodes in the fingers are characteristic in <b>women</b> (prominent osteophytes at the distal interphalangeal)</p>	<p>4- First carpometacarpal joints &amp; First tarsometatarsal joints</p>

### course and prognosis:



# Rheumatoid Arthritis ( RA )

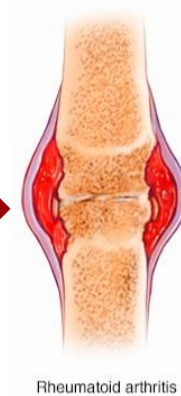


Check It !! 2 Minutes but very helpful :)

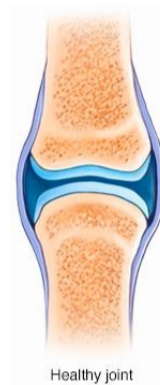
## Rheumatoid arthritis ( RA )

is a systemic, chronic inflammatory autoimmune disease affecting many tissues but principally attacking the joints.

مرض من أمراض المناعة الذاتية حيث تهاجم الخلايا المناعية للجسم الأنسجة المحيطة بالمفاصل



Virus



Rheumatoid arthritis

Healthy joint

## Characteristics

- 1 It causes a **nonsuppurative proliferative synovitis** that frequently progresses to destroy articular cartilage and underlying bone with resulting disabling arthritis.

**synovitis**: التهاب ال (Synovial membrane) حيث يحول دون تجديده , و وظيفته إفراز مواد تقلل احتكاك المفاصل , ويسبب الالتهاب تحطيم الغضاريف المفصالية

- 2 RA is a relatively common condition, with a prevalence of approximately 1% and it is three to five times more common in women than in men.

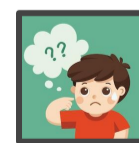
- 3 The peak incidence is in the second to fourth decades of life, but no age is immune.

## Pathogenesis

### Relationship between immune system and RA

1

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

# Cont.

## Rheumatoid Arthritis ( RA )

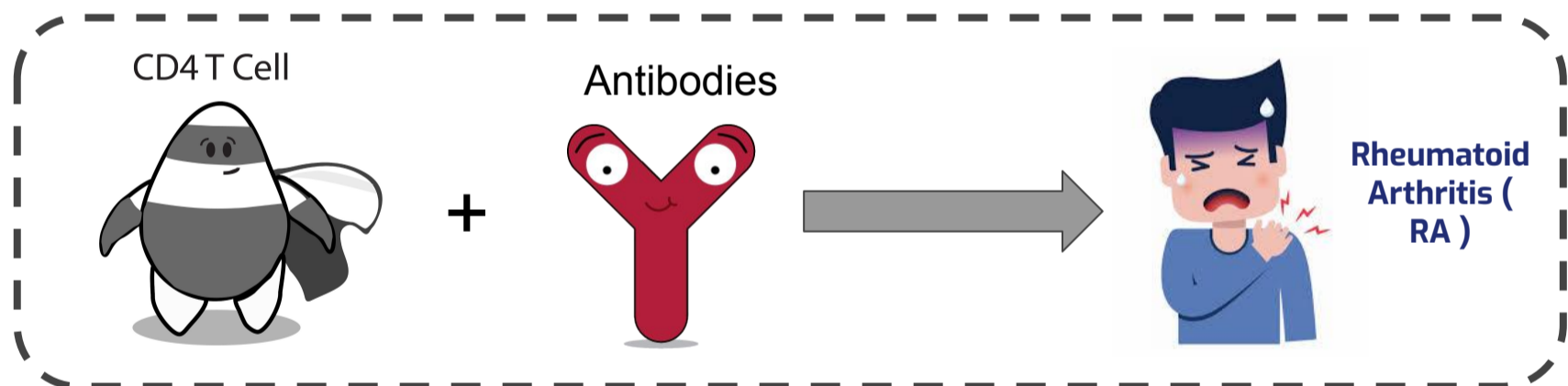
2

Many patients also produce **antibodies** against **cyclic citrullinated peptides** (CCPs), which may contribute to the joint lesions In RA.

CCPs : مجموعة ببتيدات تعمل كأهداف للأجسام المضادة ذات الاختيارية العالية جدا لالتهاب المفاصل الروماتويدي

antibodies to citrullinated fibrinogen, type II collagen,  $\alpha$ -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

#### Factors That cause The RA

01

#### 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.

HLA-DRB1 عبارة عن بروتينات MHC على سطح الخلية ( تذكر : MHC تحدد الأجسام الغريبة عن الأجسام الذاتية ) ففي حال حدوث طفرة في هذه البروتينات يبدأ الجهاز المناعي بمهاجمة هذه الخلايا مما يسبب التهاب المفاصل .

02

#### Environmental factors:

Many candidate infectious agents whose antigens may activate T or B cells have been considered, but none has been conclusively implicated.





# Cont. Rheumatoid Arthritis ( RA )

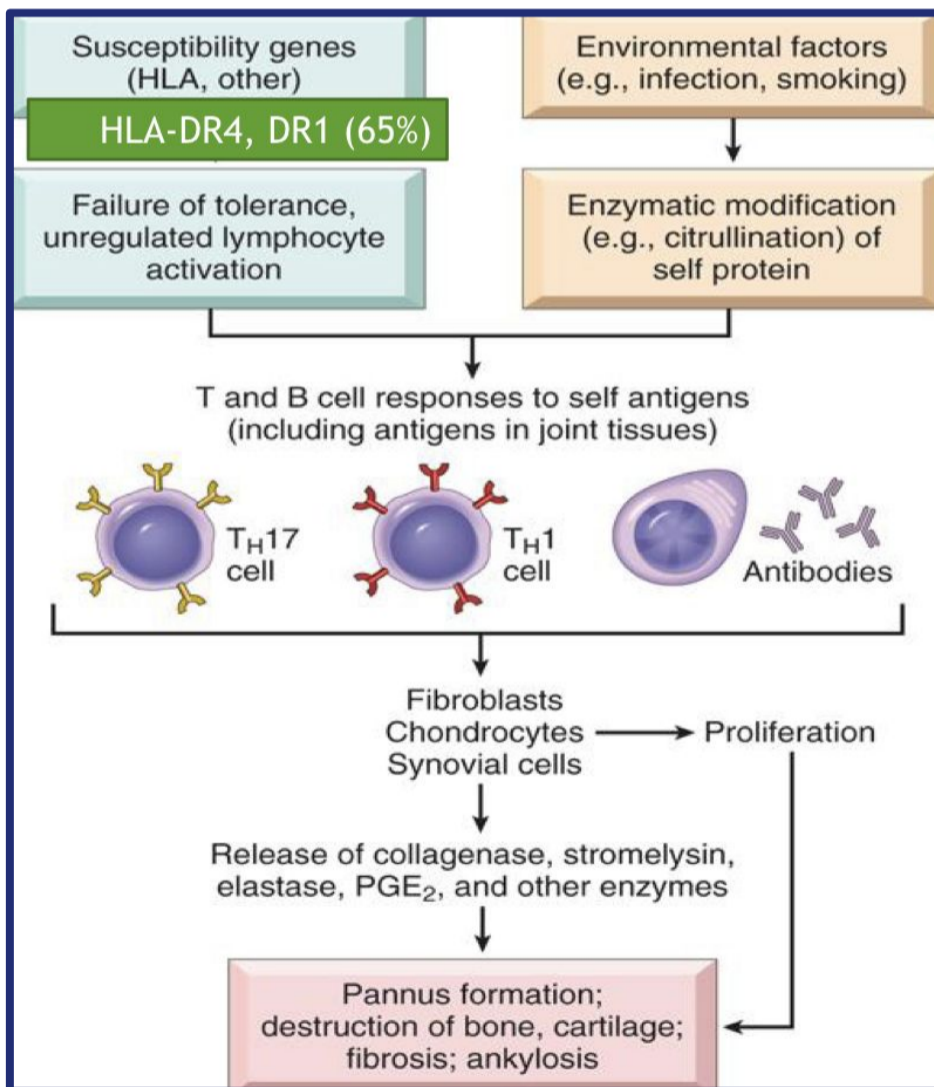
## Pathogenesis

### Relationship between immune globulins and RA

**1** About 80% of patients have serum immunoglobulin M (IgM) and, autoantibodies that bind to the Fc portions of their own (self) IgG.

**2** 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 extra articular lesions has not been established.

IgM will bind to FC portion in the IgG and that leads to form immune complex and



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

## Laboratory Findings:

- 1** Rheumatoid factor: **80% have IgM** autoantibodies to Fc portion of IgG -not sensitive or specific
- 2** Anti-CCP (cyclic citrullinated peptides) protein antibodies **most specific** for a diagnosis of rheumatoid arthritis
- 3** **ESR and C-reactive protein**

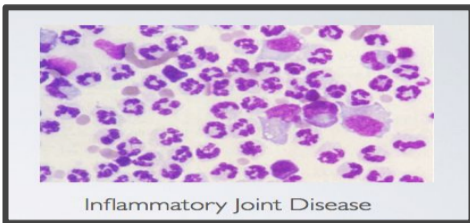


# Cont. Rheumatoid Arthritis ( RA )

## Pathologic Features

1

Synovial cell hyperplasia and proliferation .

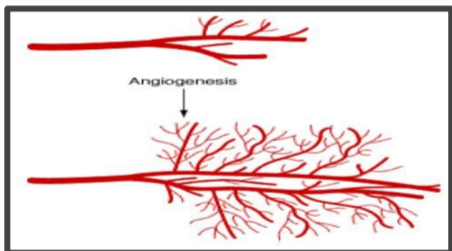


2

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.

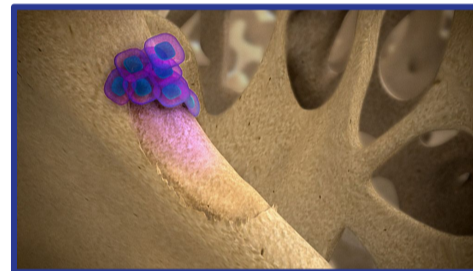


4

neutrophils and aggregates of organizing fibrin on the synovial surface

5

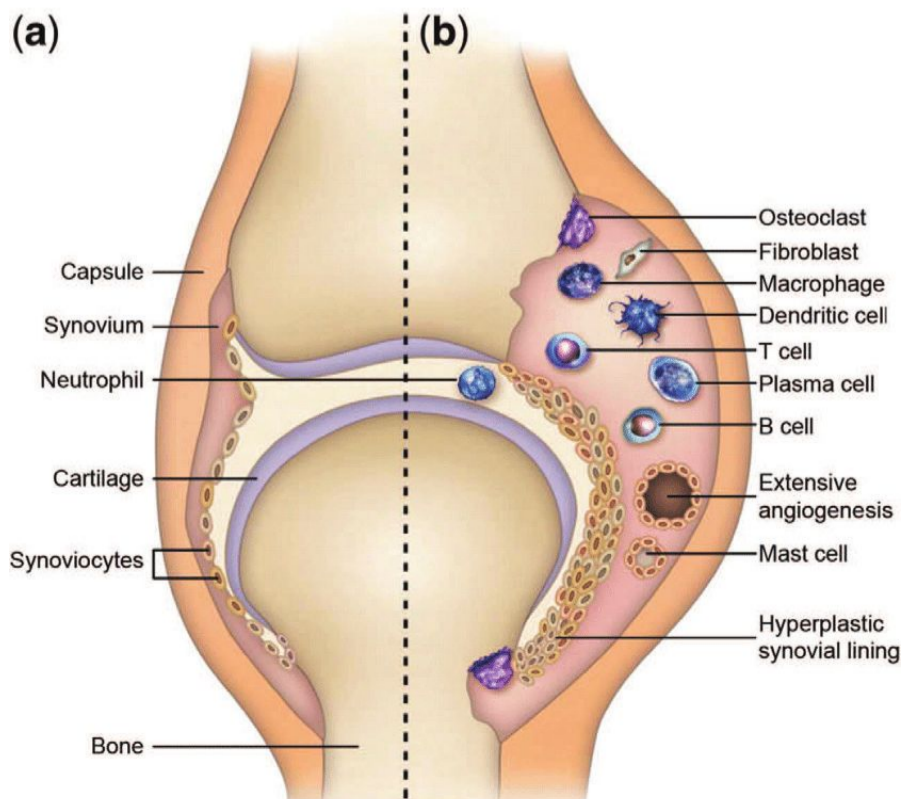
Increased osteoclast activity in the underlying bone → bone erosion.



Note :

The same topic Explained in **Immunology lectures**  
You can revise it for memorization and clarification

## Morphology of the affected joint (Extra information)



(A) shows a normal joint  
While  
(B) is a joint affected by RA



# Cont. Rheumatoid Arthritis ( RA )

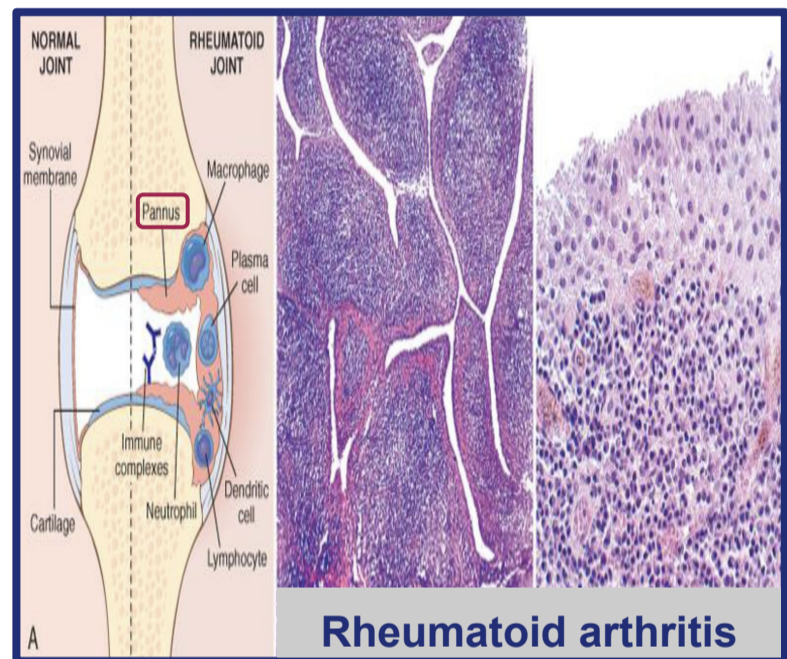
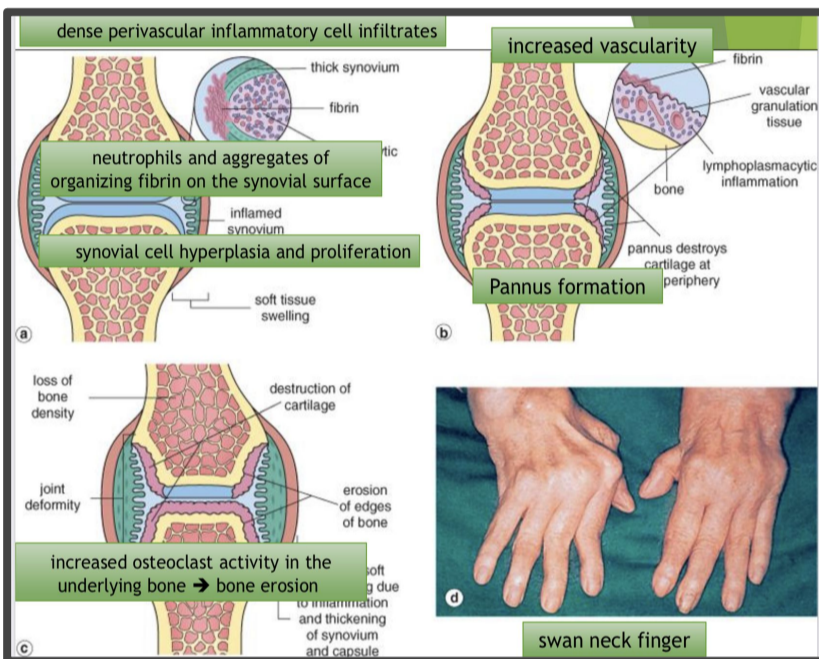
## Pathologic Features

### Pannus

#### Definition of pannus

It is an abnormal layer 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.

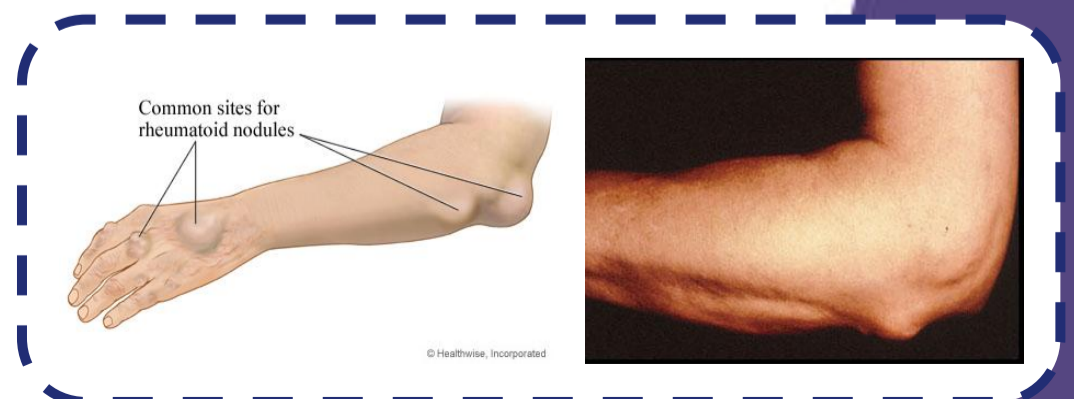
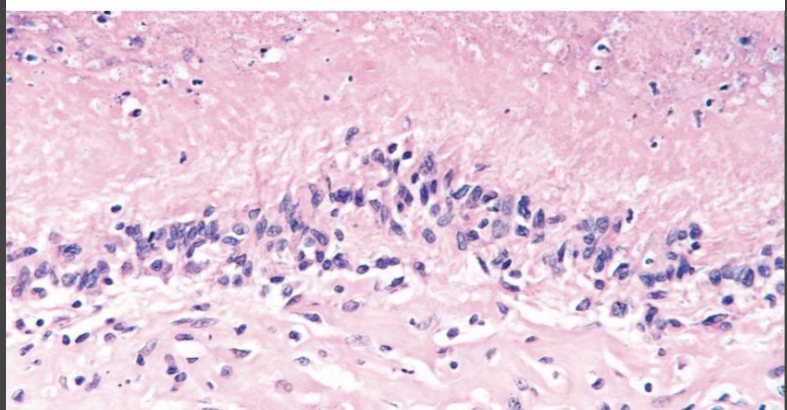


## Rheumatoid subcutaneous nodules

[Helpful video](#)

- 1 Develop in about one fourth of patients ( 25 % )
- 2 Occurring along the extensor surface of the forearm
- 3 Rheumatoid nodules are firm, nontender, oval or rounded masses as large as 2cm in diameter.
- 4 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

#### Morphology of : subcutaneous nodules





# Cont. Rheumatoid Arthritis ( RA )

## Clinical Features of Rheumatoid Arthritis

Clinical Features		
1	symmetric arthritis, principally affecting the small joints of the hands and feet, ankles, knees, wrists, elbows, and shoulders.	
2	Most often, the proximal interphalangeal and metacarpophalangeal joints are affected, but distal interphalangeal joints are spared.	
3	Axial involvement, when it occurs, is limited to the upper cervical spine; similarly, hip joint involvement is extremely uncommon.	
4	Weakness , low grade fever	
5	Aching and stiffness of the joints, particularly in the morning	
6	As the disease advances, the joints become enlarged, motion is limited	
7	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).

Extra Information

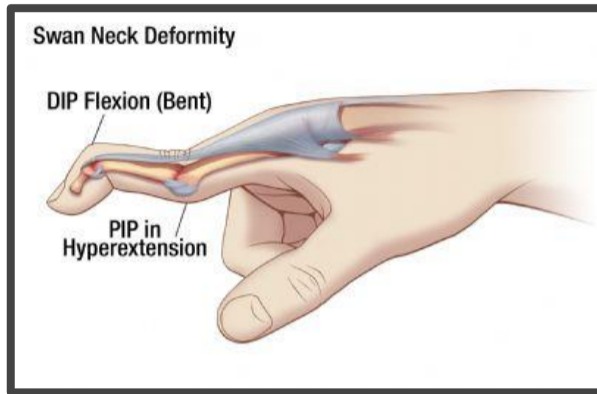
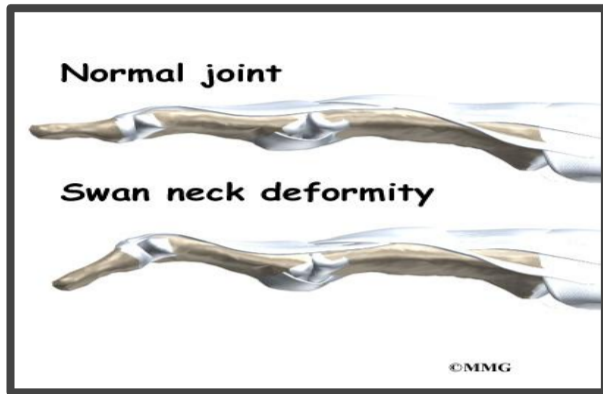
### Rheumatoid Arthritis

symptoms to **never** ignore

# Cont. Rheumatoid Arthritis ( RA )

## Swan neck deformity :

Swan neck deformity is a deformed position of the finger, in which the joint closest to the fingertip is permanently bent toward the palm while the nearest joint to the palm is bent away from it



## X-ray Scan to RA patients could show :

**01** Loss of articular cartilage leading to narrowing of the joint space.



**02** Joint effusions



**03** Erosions of the bone



## Prognosis Of Rheumatoid Arthritis ( RA )

1

The clinical course of RA is highly variable.

2

In a minority of patients, the disease may stabilize or even regress

3

in most patients it pursues a chronic, remitting-relapsing course.

4

progressive joint destruction leading to disability after 10 to 15 years. The outcome has been dramatically improved by recent advances in therapy.

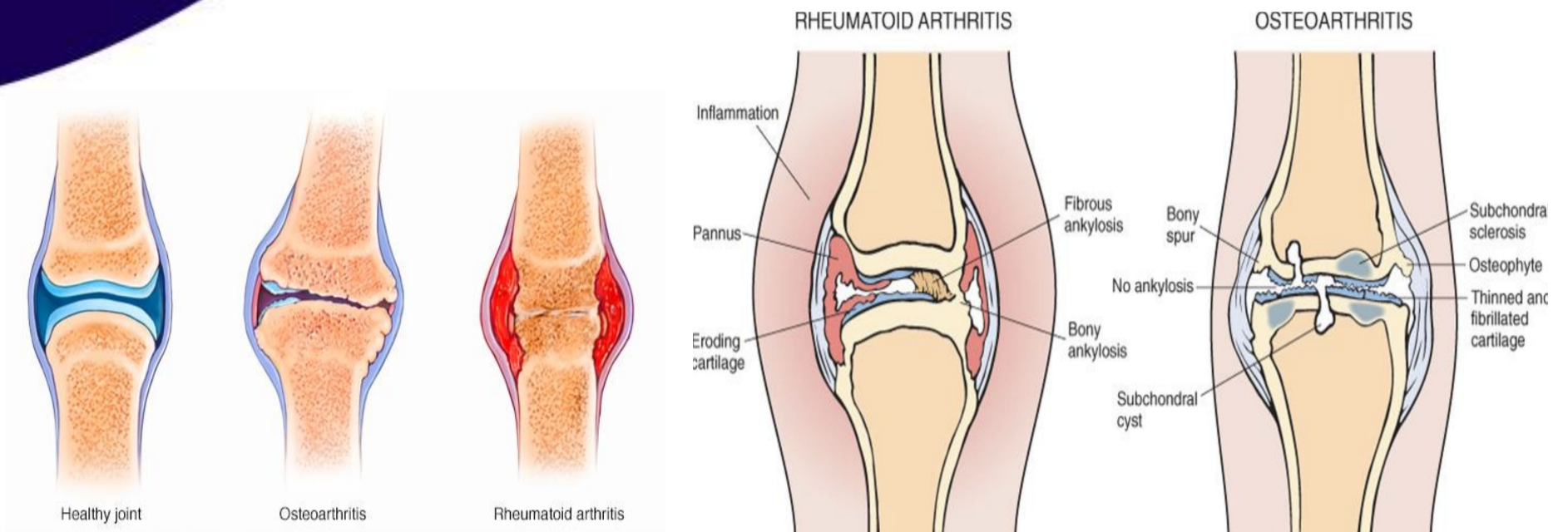
5

RA is an important cause of reactive amyloidosis, which develops in 5% to 10% of these patients, particularly those with long-standing severe disease



# Cont. Rheumatoid Arthritis ( RA )

## Comparison of the morphologic features of RA and osteoarthritis



	<b>Osteoarthrosis</b>	<b>Rheumatoid Arthritis</b>
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

### 438 Notes :

Osteoarthritis = Pain comes with movement

Rheumatoid arthritis = Pain in early morning (pain in rest)



# Gout (Podagra)

## Monosodium urate crystals

- ❑ Gout affects about 1% of the population, and shows a predilection for males.(affects men more than women,opposite in autoimmune diseases)
- ❑ It is caused by excessive amounts of *uric acid*
- ❑ **Monosodium urate crystals** precipitate from supersaturated body fluids and induce an acute inflammatory reaction.
- ❑ inflammatory disease of joints caused by crystal depositioning
- ❑ **Gout is marked by:**recurrent episodes of acute arthritis,sometimes accompanied by the formation of large crystalline aggregates called *tophi* (حصوات), and eventual permanent joint deformity.

### Risk factors for Gout :

Obesity

Excess alcohol intake

Consumption of purine-rich foods

diabetes

metabolic syndrome

Renal failure

### Types of Gout:

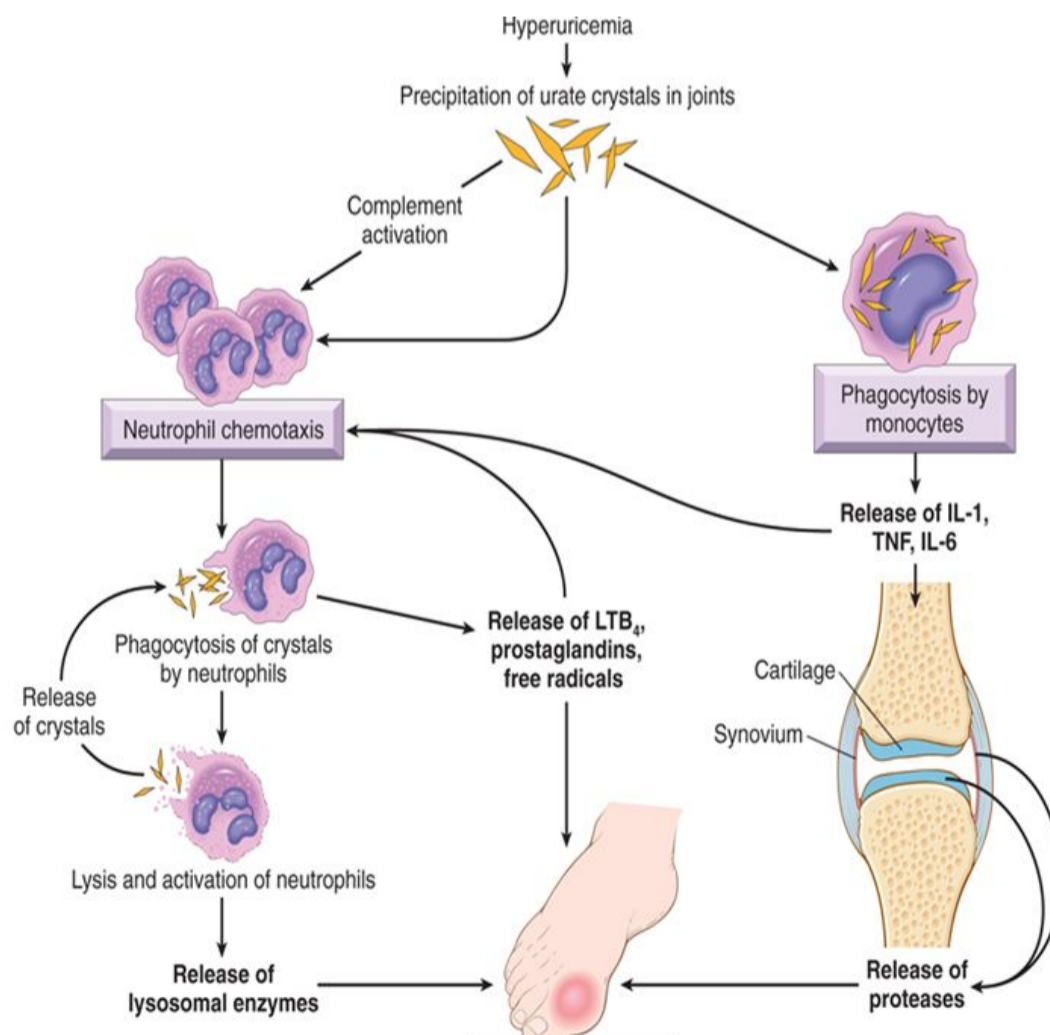
-primary 90%(more common)  
(due to mutation or hereditary)

-secondary 10%  
(e.g. abnormalities in the kidney , leukemia, etc)

# -Gout cont.

Clinical Category	Metabolic Defect
<b>Primary Gout (90% of cases)</b>	
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
<b>Secondary Gout (10% of cases)</b>	
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 :

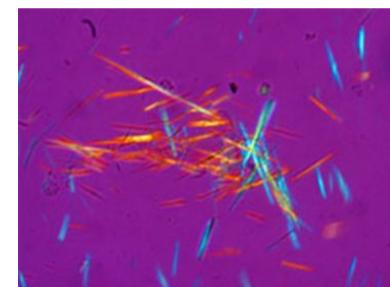
1)**Acute arthritis** is characterized by a dense neutrophilic infiltrate permeating the synovium and synovial fluid. **Long, slender, needle-shaped monosodium urate crystals** frequently

2)**Chronic tophaceous arthritis** evolves from repetitive precipitation of urate crystals during acute attacks.

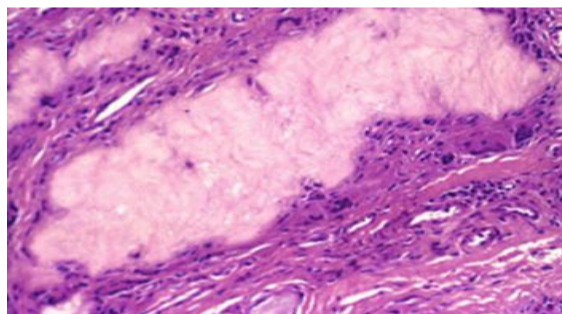
The synovium becomes hyperplastic, fibrotic, and thickened by inflammatory cells

3)**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 (picture on the left)

-Tophi can appear in the articular cartilage of joints and in the soft tissues, including the ear lobes & nasal cartilages (picture on the right)

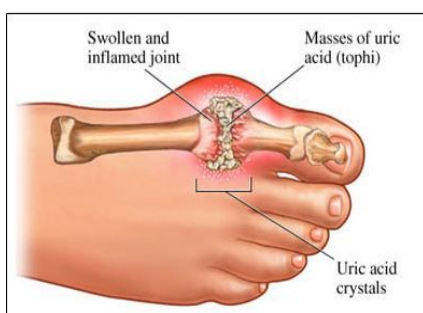


Uric acid crystals from a synovial fluid sample



## Clinical features of Gout:

- Renal manifestations of gout can appear as renal colic associated with the passage of gravel and stones




- The most commonly affected site is: **first metatarsophalangeal joint**. (the joints between the metatarsal and the phalanges in the foot)
- It is swollen, red, and very painful.





## 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:
  - 1) Sporadic (more common in the elderly).
  - 2) Hereditary.
  - 3) 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**.



GOUT	Pseudogout
monosodium urate crystals	calcium pyrophosphate crystals
The most commonly affected site is: <b>first metatarsophalangeal joint</b>	<b>The knee</b> is most commonly involved.(cause it's articular cartilage)
X-ray doesn't show the MSU	X-rays show the characteristic line of calcification of the articular cartilage.
Long, slender, <b>needle</b> -shaped <b>monosodium urate crystals</b>	The crystals look different under polarizing microscopy, they are <b>rhomboid</b> in shape .

# Quiz

**1- Which of the following best describes Osteophytes on the distal interphalangeal joints of the fingers?**

a- Heberden's node	b- Bouchard's node	c- joint mice	d- none
--------------------	--------------------	---------------	---------

**2- Which one bears the brunt of the degenerative changes in osteoarthritis?**

a- Articular cartilage	b- Elastic cartilage	c- fibrocartilage	d- Bone marrow
------------------------	----------------------	-------------------	----------------

**3- A systemic, chronic inflammatory autoimmune disease affecting many tissues but principally attacking the joints :**

a- Osteoarthritis	b- Rheumatoid Arthritis	c- Gout	d- None of them
-------------------	-------------------------	---------	-----------------

**4- 50% of the risk of developing RA is related to :**

a- Genetic Factors	b- Environmental Factors	c- Stress Factors	d- None of them
--------------------	--------------------------	-------------------	-----------------

**5- which of the following describes a bony outgrowths develop at the margins of the articular surface?**

a- osteophytes	b- joint mice	c- Chondrocytes	d- None
----------------	---------------	-----------------	---------

**6- This condition is also called calcium pyrophosphate crystals ?**

a- Gout	b- Rheumatoid arthritis	C- Pseudogout	d- osteoarthritis
---------	-------------------------	---------------	-------------------

## - SAQ

**2- What's the Results after X-ray Scan to RA patients ?** ( Answer Page 13 )

**4-what are the clinical features of gout ?** ( Answer page 18 )



## From Robben's



### SUMMARY

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#### Arthritis

- *Osteoarthritis (degenerative joint disease)* is by far the most common joint disease; it is primarily a degenerative disorder of articular cartilage in which matrix breakdown exceeds synthesis. Inflammation is secondary. The vast majority of cases occur without apparent precipitating cause except increasing age. Local production of pro-inflammatory cytokines and other mediators (IL-1, TNF, nitric oxide) may contribute to the progression of the joint degeneration.
- *Rheumatoid arthritis (RA)* is a chronic autoimmune inflammatory disease that affects mainly the joints, especially small joints, but can affect multiple tissues. RA is caused by an autoimmune response against self-antigen(s) such as citrullinated proteins, which 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 clinical benefit. Antibodies may also contribute to the disease.
- *Gout and pseudogout*. Increased circulating levels of uric acid (*gout*) or calcium pyrophosphate (*pseudogout*) can lead to crystal deposition in the joint space. Resulting inflammatory cell recruitment and activation lead to cartilage degradation, fibrosis, and arthritis.
- Either direct infection of a joint space (*suppurative arthritis*) or cross-reactive immune responses to systemic infections (e.g., in some cases of *Lyme arthritis*) can lead to joint inflammation and injury.



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