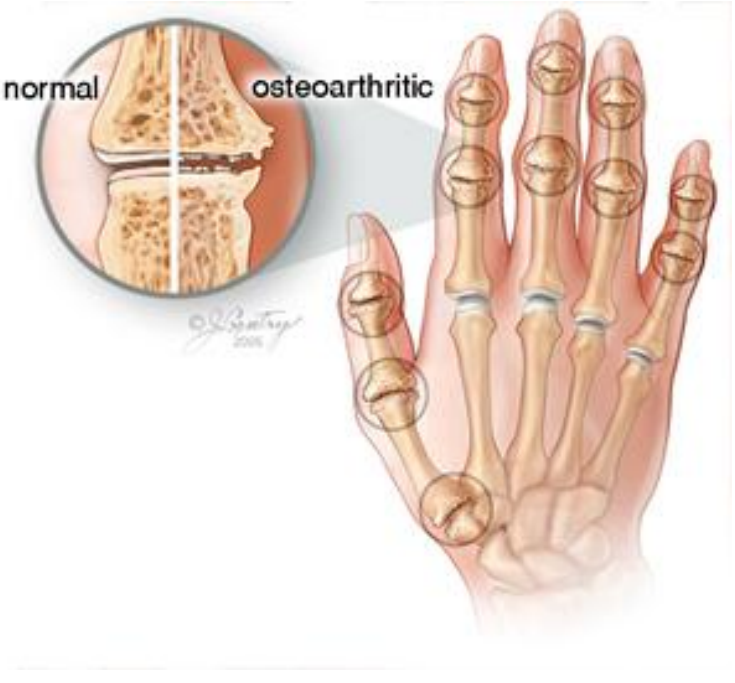
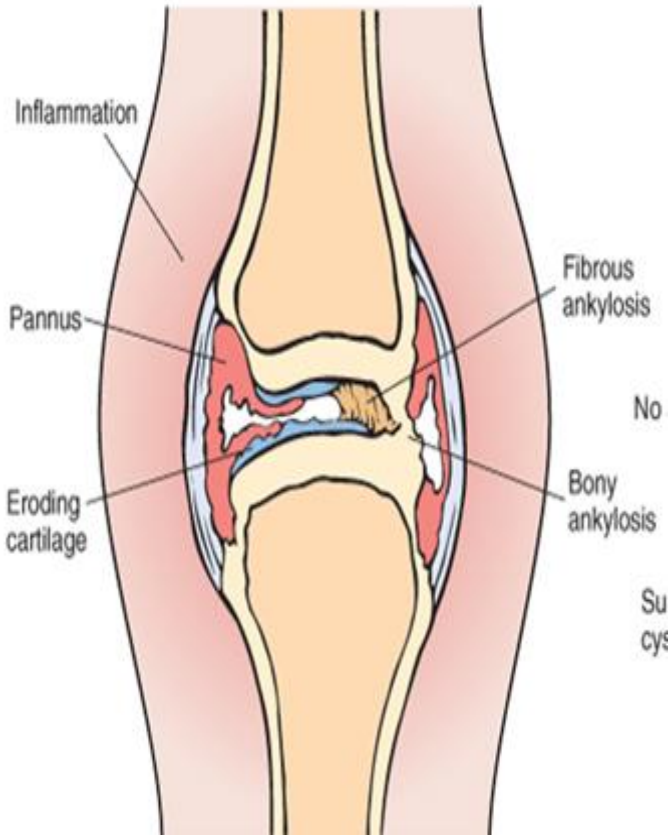
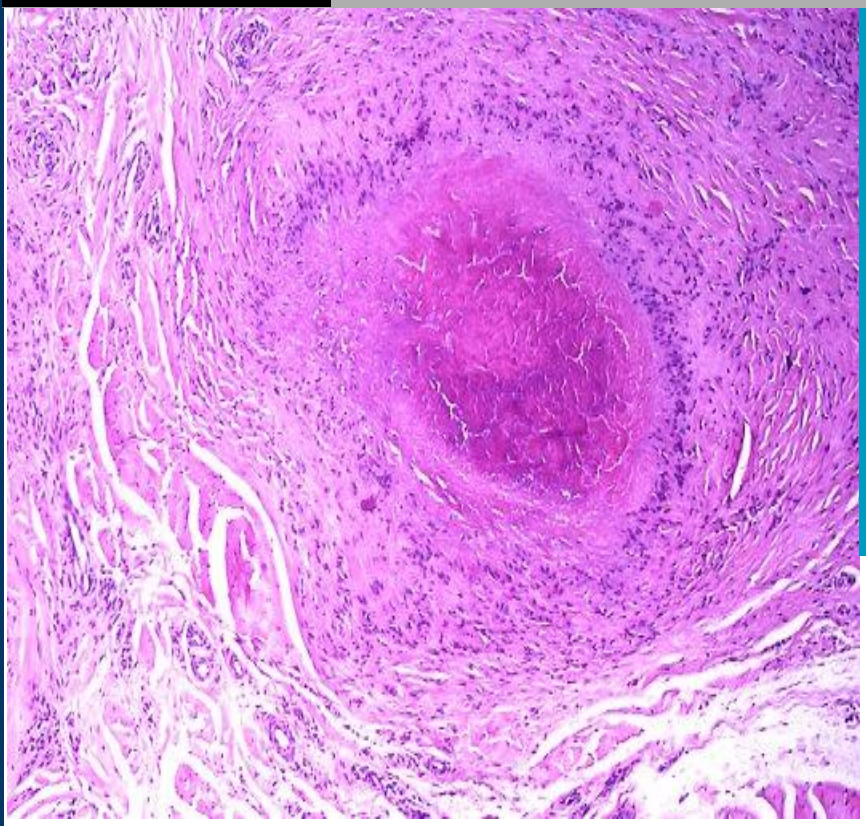




LECTURE FOUR

NON-INFECTIOUS ARTHTRITIS



BY:

PATHOLOGY TEAM 432

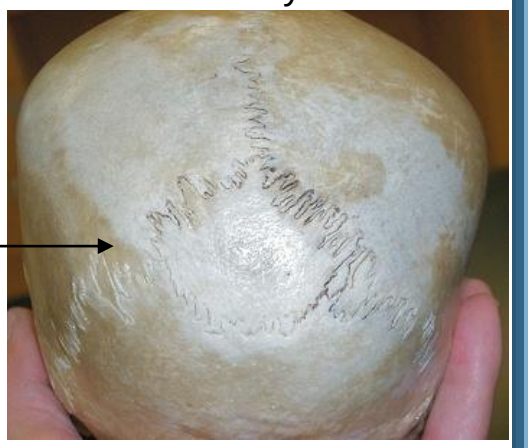
STRUCTURE AND FUNCTION OF JOINTS

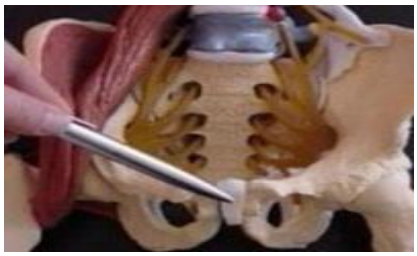
Joints are of two types:

- **Solid joints** – these joints are fixed and rigid and allow only minimal movement.

  Examples:

  - the skull sutures (where the skull bones are bridged by fibrous tissue)
  - symphysis pubis (where the bones are joined by cartilage).

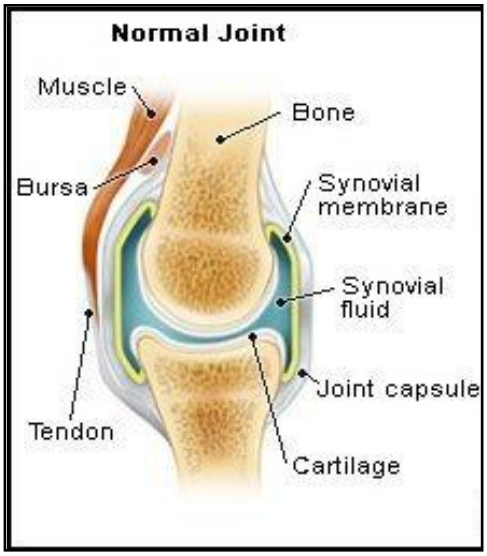




- **Synovial joints** – these joints have:

  1- A joint space, which allows a wide range of movement.

  2- Articular cartilage : The articular cartilage in synovial joints is a specialized hyaline cartilage which is an excellent shock absorber. It covers the ends of articulating bones.



  3- Synovial membrane (synovium)

  4- Synovial fluid (1-2 ml) : The synovial membrane secretes synovial fluid into the joint space. Synovial fluid acts as lubricant and provides(helps the joint to move) nutrients for the reticular hyaline cartilage.

Non-infectious arthritis ⟶ **No bacteria**

1- Osteo arthritis
2- Rheumatoid arthritis
3- Gout arthritis
4- Pseudo-Gout arthritis

Thos diseases affect either: the synovium, the cartilage or both.

They can even erode تتلف the subchondral bone.

1- OSTEOARTHIRITS (DEGENERATIVE[1] JOINT DISEASE)

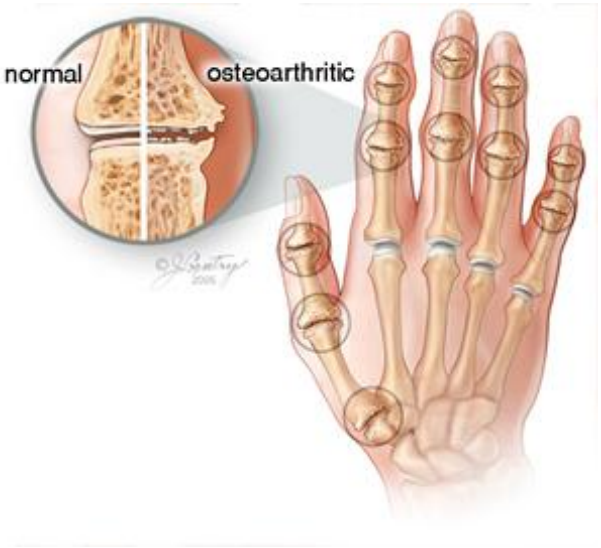
OsteoArthritis ⟶ **degenerative**

Cartilage

This is the **most common type** of non-infectious joint diseases. It is characterized by the progressive erosion تلف of **articular cartilage** in weight-bearing joints (knee, hip …).

Causes:

1- Age: The incidence increases with age.
2- Systemic diseases such as diabetes.
3- A congenital or developmental deformity of a joint.
4- Previous trauma including repetitive minor trauma.



REMEMBER: Osteoarthritis can be primary or secondary to other bone or joint disease, systematic disease or congenital disease.

(1)**Degeneration is the loss** of function, and the changing of tissue or cell structure due to aging.

PATHOLOGY AND PATHOGENESIS:

Main signs:

eburnation and fibrillation → increased subchondral plate→ Small fractures → joint mice formation → osteophytes

eburnation and fibrillation → loss of cartilage →increased subchondral plate→ Small fractures → joint mice formation → osteophytes

1- In the early stages of osteoarthritis the articular cartilage becomes eroded متحلل وتالف and fragmented (**fibrillated**) and portions of the cartilage flake off. **There is eventual full thickness of loss of cartilage**, with the underlying bone becoming exposed and developing a polished ivory appearance (**eburnation** تعري).

eburnation and fibrillation → **increased subchondral plate**→ Reduction of joint space → Bone friction → and limited movement→ Small fractures → joint mice formation → osteophytes formation

2- Loss of articular cartilage stimulates **thickening of the subchondral plate** and the adjacent cancellous bone which impairs the ability of the joint to move and act as a shock absorber. This results in increased damage to the residual (remaining) cartilage.

eburnation and fibrillation → increased subchondral plate→ **Small fractures** → **Pseudocysts** → joint mice formation → osteophytes

3- **Small fractures** develop in the now articulating bone, allowing synovial fluid to enter the subchondral regions forming subchondral **pseudo cysts**.

eburnation and fibrillation → increased subchondral plate→ Small fractures → **joint mice formation** → osteophytes

4- Fragments of cartilage and bone fall into the joint space forming loose bodies (**joint mice**).

eburnation and fibrillation → increased subchondral plate→ Small fractures → joint mice formation → **osteophytes** →heberdene's nodes

5- Bony outgrowths, known as **osteophytes**, form at the margin of the articular cartilage. These osteophytes take an important role in limiting joint movement. **They can also press on nearby nerves causing neurological pain (especially vertebral osteophytes.)**

X-ray of the knee joint showing:

F1: Normal knee joint with normal joint space and articular ends.

F2: Osteoarthritis of a knee joint showing narrowed joint space, and osteophytes (spurs).

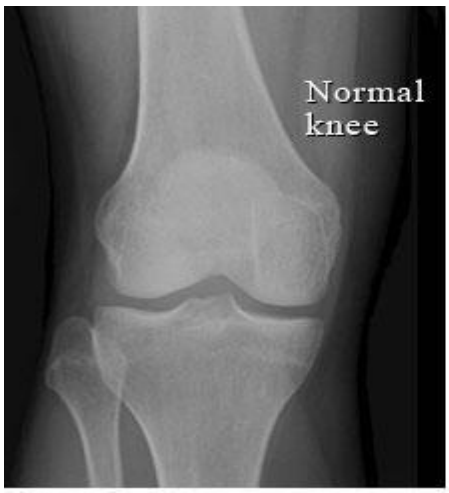


Figure 1

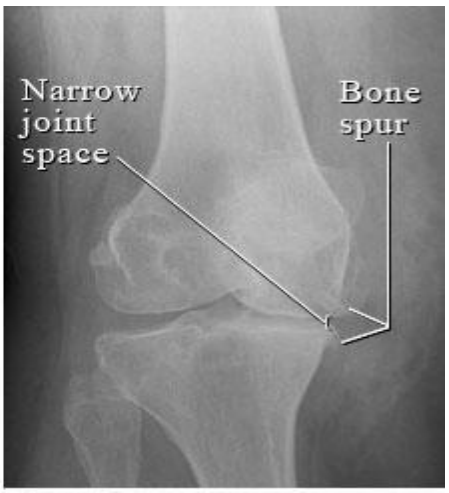
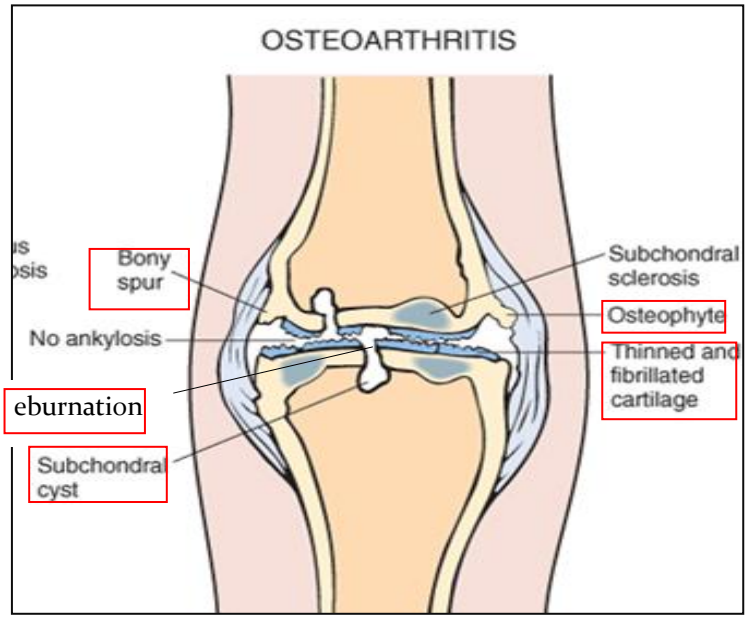


Figure 2

A diagram of typical osteoarthritis showing:

- Fibrillation and eburnation
- Subchondral cysts
- Osteophytes (spurs)



HOW is osteoarthritis formed?

REMEMBER:

1- Osteoarthritis is a degenerative process caused mainly due to AGE + WEGHT + BIOCHEMICAL AGENTS – All these three combine together causing degeneration in **articular cartilage.**

2- In osteoarthritis the inflammation is either mild or absent.

BUT, why does articular cartilage degenerate?

The reason why the articular cartilage becomes predispose to this damage appears to be related to biochemical alterations in the hyaline. In hyaline cartilage affected by osteoarthritis

1- the water content is increased

2- 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 تكاثر of chondroblasts, and it

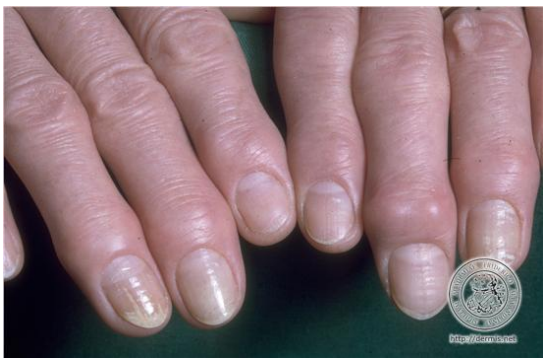
has been proposed that these cells produce enzymes that induce these biochemical changes in the hyaline cartilage.

Clinical Presentation:

A. With increasing deformity of the joint the typical symptoms develop, which are
    a. **pain** (which is worse with use)
    b. **morning stiffness**
    c. **Limitation in joint movement.**

B. The most frequently affected joints are:
    a. **The weight bearing joints**: hips, the knees, the cervical and lumbar vertebrae and ankle joint.
    b. **The proximal and distal interphalangeal** (PIP and DIP) joint of the hands
    c. The **first metacarpophalangeal** joint and the **first metatarsophalangeal** joint.

C. Osteophytes at the Distal Inter Phalangeal joints produce nodular swellings called Heberden's nodes (the joint is sometimes called heberden's joint). Osteophytes at proximal inter phalangeal joints are called Bouchard's nodes. **The presence of the**



nodes is usually accompanied by pain and limited movement (but it may not) .

D. With involvement of the cervical and lumbar spine, osteophytes may compress on the nerve roots causing symptoms such as pain and "pins and needles" in the arms or legs. The overall result is disability. The process cannot be stopped.

Summary:

Osteoarthritis is a degenerative disease, affecting mainly the articular cartilage where by it is eroded, ebernated and fibrillated. The disease is usually accompanied with mild inflammation of the synovium, pain and limited movement (which can be very severe) of the effected joint. It likes weight bearing joints, prefers females and can be primary or secondary . The patient can present with pain or limited movement or both, he/she can also be asymptomatic.

2-RHEUMATOID ARTHRITIS

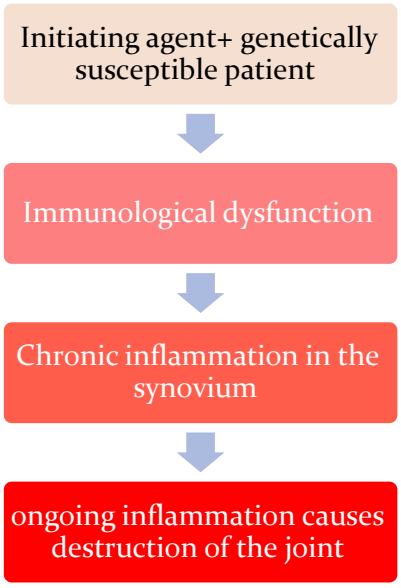
Rheumatoid arthritis ⟶ Autoimmune Disease (Synovium)

Rheumatoid arthritis is a chronic inflammatory multisystem disorder (hence rheumatoid disease), but the joints are invariably 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.

Rheumatoid arthritis is a **SYNOVIAL DISEASE**. Thus, if the synovium is not inflamed it is **NOT** Rheumatoid arthritis. The changes affecting bone & cartilage in Rheumatoid arthritis are **secondary** changes.

PATHOGENESIS:

In Rheumatoid arthritis it is thought that an initiating agent, possibly an organism, triggers immunological dysfunction resulting in persistent chronic inflammation **in genetically susceptible individuals** (genetic predisposition). This chronic inflammation attacks the synovium causing inflammation, destruction and may also cause ankylosis in advanced cases.



Genetic predisposition

HLA-DRB1 antigens are present on the patient's leukocytes

Immunological dysfunction (Auto Immune reactions):

a. **Rheumatoid Factor:**

It was found that RA patients develop IgM immunoglobulins against FC segment of IgG immunoglobulins, forming an immunocomplex called Rheumatoid factor (hypersensitivity type III). Circulating (rheumatoid factors) which are directed against autologous IgG immunoglobulins, can be detected in the serum of around 80% of affected individuals. The exact role of these autoantibodies is uncertain.

b. **CCP (Crystallinated Cyclic Protein/Peptide):**

CCP are proteins derived from arginine . RA patients develop anti-bodies against CCP forming an antigen- antibody reaction (hypersensitivity type II)

Activation of CD4:

The immunocomplexes accumulate in synovial joints causing an inflammatory reaction that activates CD4 lymphocytes and transforms them into **TH1** lymphocytes.

TH1 lymphocytes secrete cytokines (IFNϒ, IL-1, IL-8, IL17, TNF) which are chemical mediators of inflammation, thus causing **chronic inflammation** in affected joints. **The ongoing inflammation causes destruction of the articular cartilage, bone and ligaments resulting in severe deformities in advanced cases.**

SUMMARY:

Initiating agent+ genetically susceptible patient (جينيا) شخص مهيأ →Antigen – antibody reaction against CCP + Immuncomplex formation → deposition in joints → Inflammatory reaction → Activation of **CD4** lymphocyte to **TH1** → secretion of lymphokines (IFNϒ, IL-1, IL-8, IL17, TNF) → Cytokines act on the joint causing inflammation → ongoing inflammation results in destruction of the joint

PATHOLOGICAL FEATURES:

Rheumatoid arthritis is a systemic disease, it affects the joints, skin, heart, lungs…But, the most severe morphological changes of rheumatoid arthritis manifest in the joints.

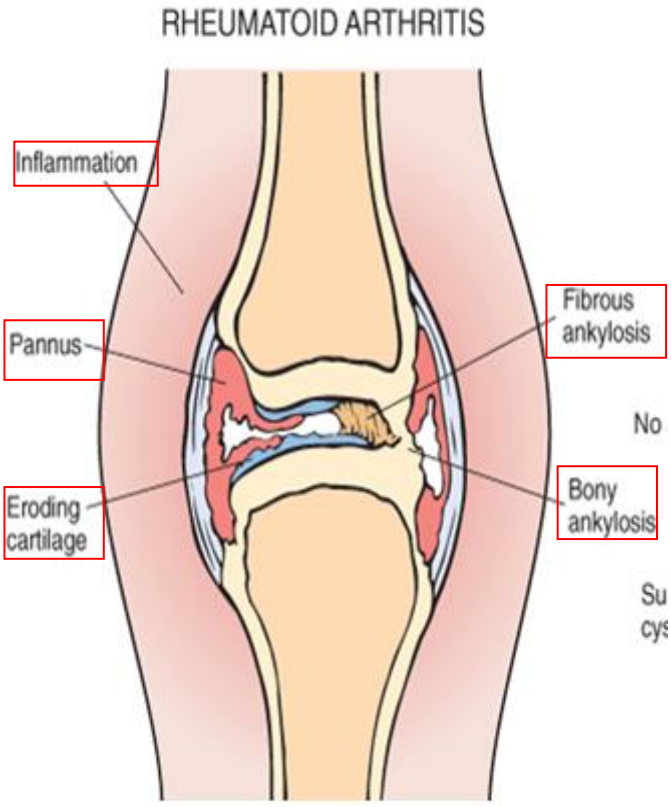
ALWAYS REMEMBER : The main site affected in rheumatoid arthritis is the **synovium**. The synovium is inflamed due to the antigen-antibody reaction that lead to an immune mediated injury in the joint that causes an inflammatory reaction, all the deformities in bone and cartilage are SECONDARY.

Synovial changes → hyperplasia →inflammation →edema→Pannus formation → Fbrosis & Ankylosis → Pannus spread

1- Synovium becomes :
   a. Hyperplasic Infiltrated by chronic inflammatory cells
   b. The joint becomes edematous.

We also notice that the whole joint becomes swollen.

Synovial changes → Pannus formation → Fbrosis & Ankylosis → Pannus spreads



2- With ongoing inflammation the synovium becomes eroded and forms a **pannus**. A pannus is a piece of an inflamed, necrotic and detached synovium which was initially covering the synovium.

Synovial changes → Pannus formation → Fbrosis of pannus→Pannus Adherance → Ossification→ Ankylosis → Pannus spreads →

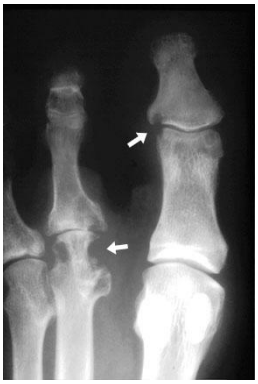
2- After detachment of the pannus it goes to the joint space, and with time it develops fibrosis. The fibrous pannus eventually bridges the opposing bones causing limitation of movement, and ossification of this fibrous tissue leads to bony ANKYLOSIS. The ankylosis limits the joint's movement while also causing severe pain

Synovial changes → Pannus formation → Fbrosis & Ankylosis → Pannus spreads →secondary osteoporosis + sublaxations + Bone deformities→ lucent areas

3- As the pannus slowly spreads:

a. It degrades the underlying cartilage + erosions and subchondral cysts develop in the underlying bone.

b. The inflammatory process stimulates the activity of Osteoclasts resulting in **secondary osteoporosis** which may form what is called **lucent (transparent) areas** (Picture). **These areas are common sites for fractures**. We also see **sublaxations** خلعin some of the joints.

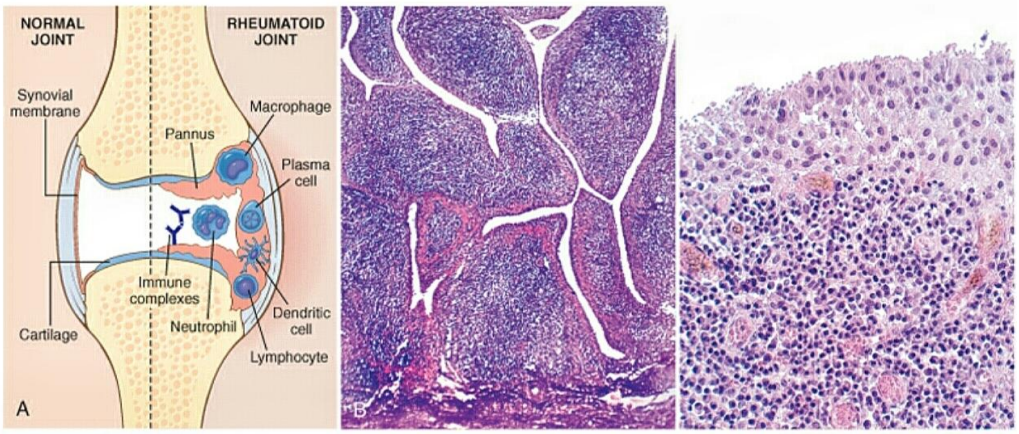


c. The inflammation also affects the bone, joint capsule,

tendons and ligaments causing characteristic **deformities** (in his hands, legs...etc).

In severe cases , the cartilage totally disappears + ankylosis and loss of movement are clear .

Note: Small detached fragments fall into the joint space and are called **rice bodies**.



Here we can see:

A. Comparison between a normal joint and a joint affected by RA.
B. Low magnification shows marked synovial hypertrophy.
C. In high magnification we see very heavy and dense chronic inflammatory infiltration (Lymphoid aggregates).

MOSTLY AFFECTED JOINTS:

- Cervical spine
- Shoulder joint.
- Hip joint.
- Hand (It likes to affect the wrist and interphalangeal joints)
- Knee joint.

- Sometimes foot joints.

CLINICAL PRESENTATION:

The clinical course of rheumatoid arthritis is very variable. Some patients have mild disease, whereas others have severe progressive disease quickly leading to disability. Initially, patients may suffer constitutional symptoms and only after a few weeks or months do the joints become involved. Generally, the small joints (especially those in the hands) are affected before the large joints. The affected joints are swollen, painful and stiff following a period of inactivity. Symptoms may improve with the administration of anti-inflammatory drugs or immunosuppressants. As a result of the pathological processes within the articular and periarticular tissues, characteristic deformities develop. These include:

1- Symptoms;

- The patient is usually present because of pain and stiffness in some of his joints (especially in the morning)
- He/she may also be present with some systematic symptoms (fever, anemia, ulcerations, skin nodules)
- Sometime the patient is present without any joint symptoms, instead he complains about other symptoms, and later on joint problems appear.

2- Signs

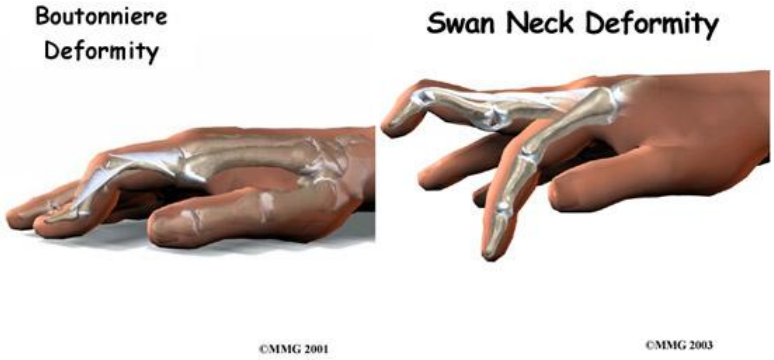
- Radial deviation at the wrists.

  A disposition of the wrist in which it is displaced toward the radial side.

- Ulnar deviation at the fingers.

  A deformity of the hand in which the swelling of metacarpophalangeal joints causes displacement of the fingers toward the ulnar side.

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



  - Rheumatoid nodules:

CASE:

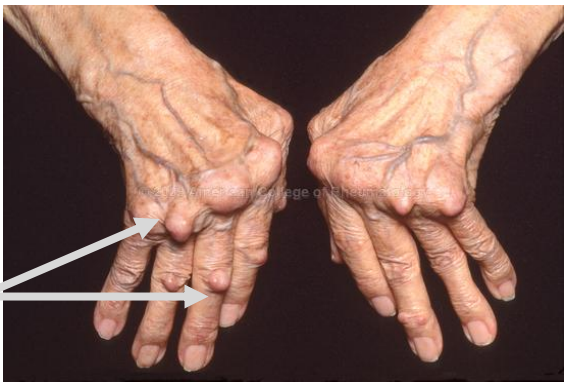
Patient's hands are showing:

1- Ulnar deviation

2- Metacarpophalangeal **sublaxations**

3- **Secondary muscle atrophy**

4- **Rheumatoid nodules** are seen over the proximal interphalangeal joints of the patient's right hand, metacrpophalangeal joints bilaterally في كلتا اليدين and the third distal interphalangeal joint of the left hand.



Source: images.rheumatology.org

Typical X-ray changes include:

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

- Localized osteoporosis.
- Erosions.
  - Fatalities الوفيات are usually the result of complications such as amyloidosis, vasculitis or the iatrogenic effects of therapy (e.g. gastrointestinal bleed secondary to non-steroidal anti-inflammatory drugs (NSAIDs), infections secondary to steroids).

DETECTING THE DISEASE:

There are several methods to detect RA:

1- Rheumatoid factor serology:

- RA patients develop (IgM) immunoglobulins against the FC segment of IgG forming what is called **RHEUMATOID FACTOR**.
- This factor can be detected in the serum
- The problem is that this test is not 100% accurate. It was found that almost 20% of the normal population (not affected by the disease) have rheumatoid factor (these people may develop RA later on).

2- Crystallinated Cyclic Protein/Peptide CCP serology:

It was found that most of RA patients (more than 70-80%) have anti-bodies against this protein, thus this test is **more accurate** and sophisticated than rheumatoid factor test.

3- Synovial Biopsy

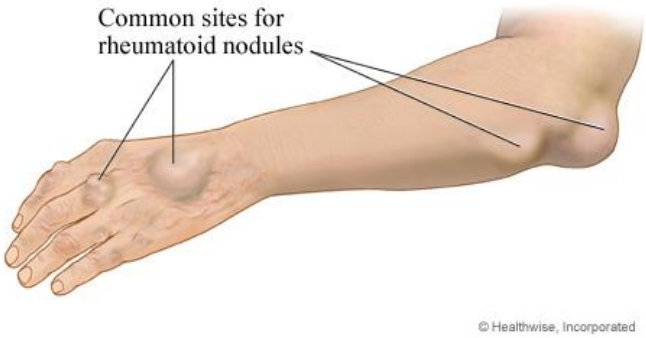
4- Imaging

SYSTEMIC MANIFESTATIONS:

As we already know, there are lots of manifestations that appear in addition to joint problems in RA patients. Here we will take a look at the most common manifestation categorized according to their organ.

Skin

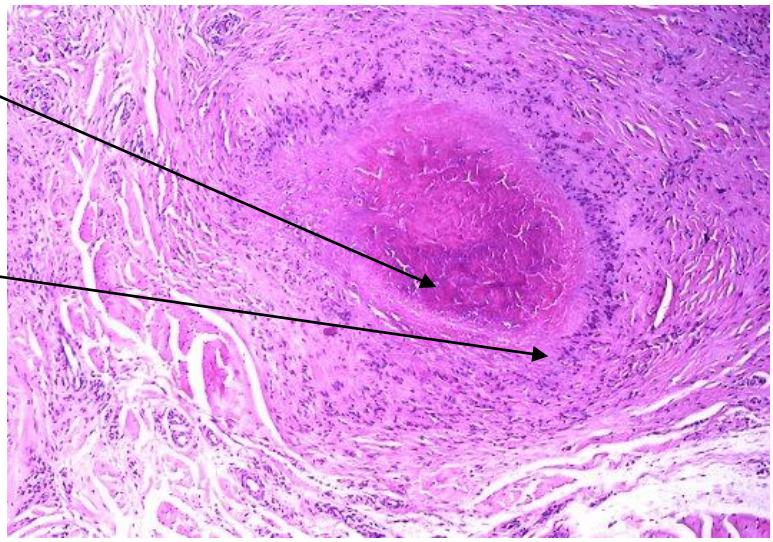
The most common cutaneous lesions are **rheumatoid nodules** which arise in areas exposed to pressure, e.g. the **extensor surfaces of the hands and feet**, and the arm. They are seen in -30% of patients.



They arise in the subcutaneous tissue and manifest as **firm, non-tender skin nodules**. A central area of fibrinoid necrosis surrounded by a palisade of histiocytes and fibroblasts.

Microscopically, they consist of:

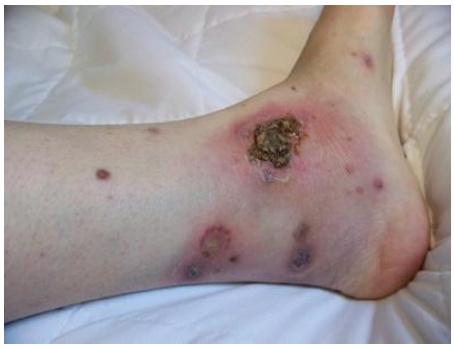
1- Central area of fibrinoid necrosis
2- Histiocytes surrounding the necrotic areas.



Blood vessels

Patients with severe disease may develop a rheumatoid **vasculitis**.

The vasculitis causes decreased blood flow to the affected areas. Thus, necrosis peripheral neuropathy, skin ulceration, gangrene and nail-bed infarcts may develop.



Impairment of blood supply to vital organs can be fatal.

Curing the affected area is very hard, and sometimes part of the organ or limb must be amputated.

Lungs

RA can cause interstitial lung diseases.

Parenchymal rheumatoid nodules (usually asymptomatic), chronic interstitial fibrosis and pleurisy can occur.

Eyes

Scleritis (inflammation of the sclera) and **uveitis** (inflammation of the connective tissue above the sclera) can develop.

Heart الكلام الملون بالرصاصي لم يذكره الدكتور عمار الركابي في المحاضرة

The development of rheumatoid nodules in the conduction system may occur and coronary artery vasculitis may result in myocardial ischemia. Pericarditis can also be a feature.

Bones

Patients are at increased risk of localized and generalized osteoporosis

Lymphoreticular

Patients may develop lymphadenopathy with or without splenomegaly. The combination of rheumatoid arthritis, splenomegaly and neutropenia is called **Felty's syndrome**. Approximately, 50% of patients with Felty's syndrome develop secondary Sjogren's syndrome. Patients may have a normocytic normochromic anaemia.

Miscellaneous

Because RA is a chronic inflammatory disorder, patients are at an increased risk of developing secondary **amyloidosis AA** which can cause other problems such as **sudden renal failure**.

SUMMARY:

The clinical course of rheumatoid arthritis is very variable. Some patients have mild disease, whereas others have severe progressive disease quickly leading to disability. Initially, patients may sufer constitutional symptoms and only after a few weeks or months do the joints become involved. Generally, the small joints (especially those in the hands) are affected before the large joints. The affected joints are swollen, painful and stiff following a period of inactivity.

Summary of complications:

1- Joint deformities
2- Effects on other organs
3- Amyloidosis AA

CRYSTAL ARTHROPATHIES

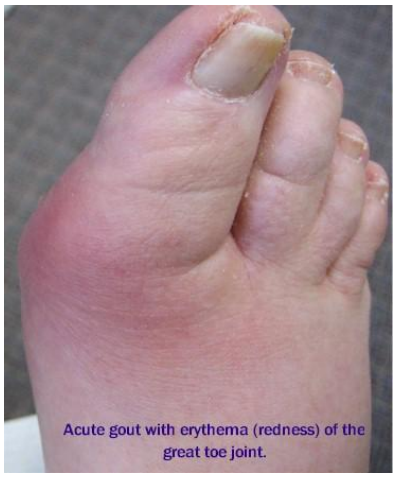
Crystal arthorpathies are a group of disorders caused by the deposition of crystals within the joint resulting in an acute and chronic arthritis.

Such crystals may be endogenous or exogenous. The most common crystal arthropathies, gout and calcium pyrophosphate arthropathy (pseudogout), are due to endogenous crystal deposition.

3-GOUT

GOUT ⟶ Uric crystals deposition

Gout occurs due to the crystallization of monosodium urate within a joint, resulting in an acute (gouty) arthritis


Acute gout with erythema (redness) of the great toe joint.

Characteristics of the affected joint:

- extreme localized pain,
- erythema
- exquisite tenderness.

The most commonly affected joints:

- metatarsophalangeal joint of the great toe
- followed in decreasing frequency by the ankle and the knee.

The disorder is due primarily **to raised serum uric acid** levels, but only around 3% of people with hyperuricaemia will develop gout.

Uric acid is the end product of purine metabolism and is excreted by the kidneys. Purines can either be derived from the breakdown of nucleic acid or synthesized de novo

Hyperuricaemia has several causes:

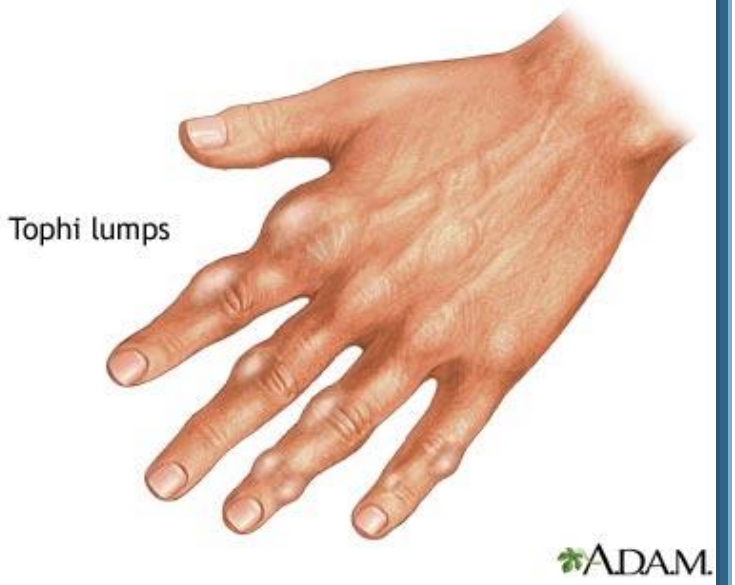
1. **Idiopathic** (80% of cases).
2. Any disease that causes **Quick cell turn over** (Cancers mainly): When there is a tumor and there is quick turnover of the cells, large amounts of purine is produced due to DNA production.

   EX:

   In Leukemia, there is very high amount of turnover in the cells, thus lots of production and metabolism of DNA resulting in large amounts of purine. So, in leukemia patients especially who are treated with cytotoxics they are also treated with anti-uric acid drugs to prevent the accumulation of uric acid resulting from purine metabolism.
3. **Decreased excretion of uric acid** (e.g chronic renal failure, thiazide diuretics).
4. **DIET:**
   - **Red meat**
   - **Alchohol**
   - **High dietary purine intake**
5. **Congenital:**

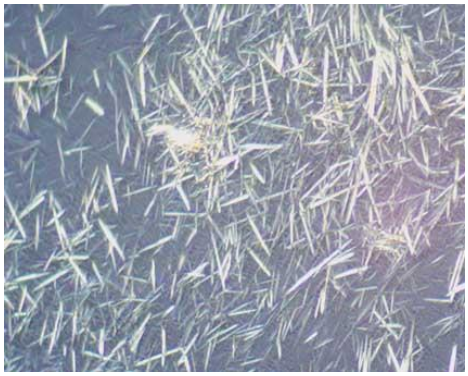
   Lesh-Nyhand syndrome → Congenital absence of HGPRT (an enzyme that takes a role in purine metabolism)

GOUT LESIONS are called **Tophi (singular is tophus)** and they 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.



Urate crystals can also in become deposited the kidney, resulting in acute uric acid nephropathy, chronic renal disease, or uric acid stones causing renal colic.

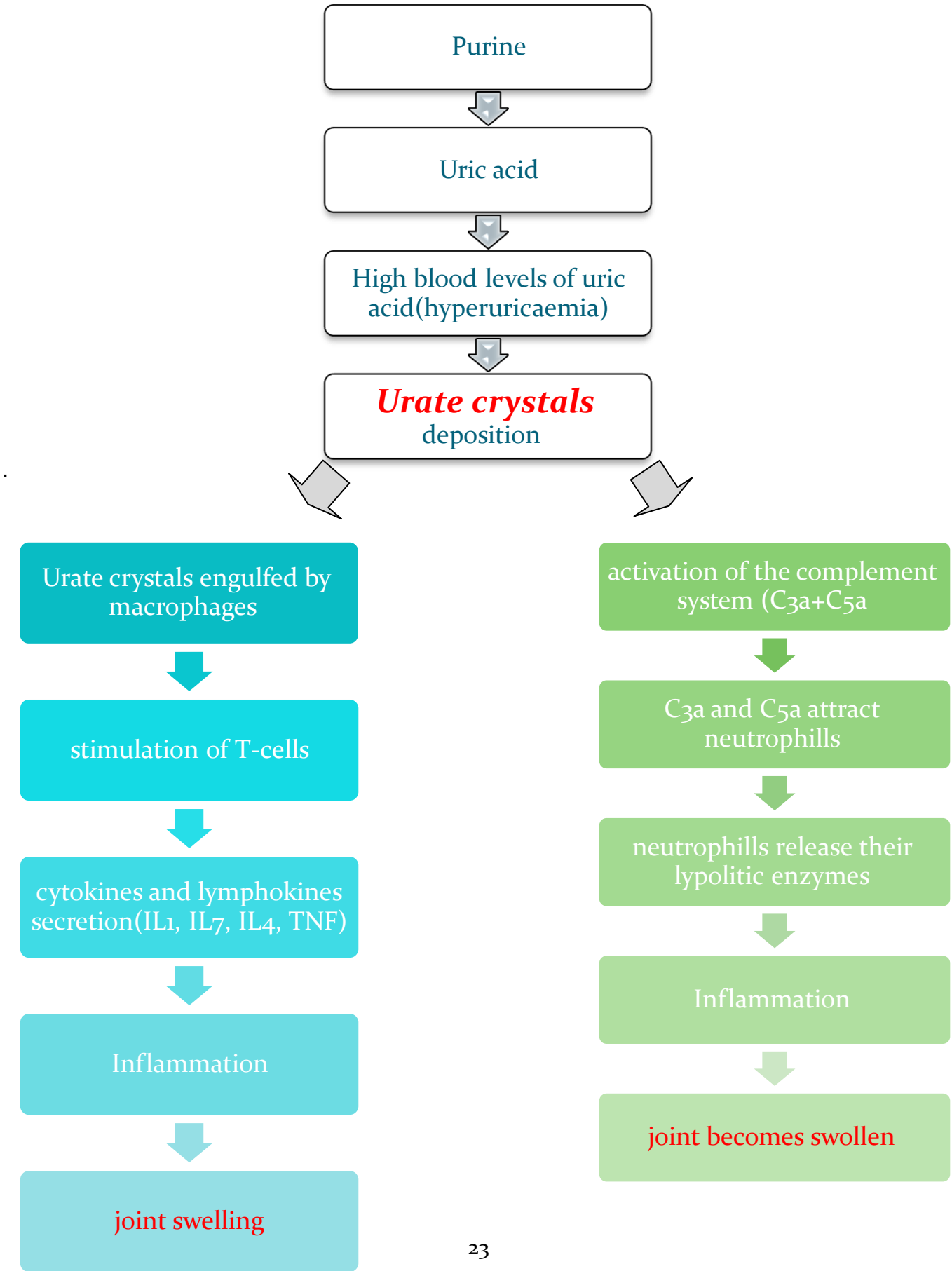
The diagnosis can be confirmed by aspirating the joint fluid and using polarizing microscopy to detect the **needle-shaped crystals**, which exhibit negative birefringence red with a filter.



N.B

- Repeated attacks of acute gouty arthritis eventually lead to chronic tophaceous gouty arthritis. where the affected joint is damaged and function is impaired.

-Urate crystals can also become deposited in the kidney, resulting in acute uric acid nephropathy, chronic renal disease, or uric acid stones causing renal colic.


Purine
Uric acid
High blood levels of uric acid(hyperuricaemia)
Urate crystals deposition
Urate crystals engulfed by macrophages
stimulation of T-cells
cytokines and lymphokines secretion(IL1, IL7, IL4, TNF)
Inflammation
joint swelling
activation of the complement system (C3a+C5a
C3a and C5a attract neutrophills
neutrophills release their lypolitic enzymes
Inflammation
joint becomes swollen

4-CALCIUM PYROPHOSPHATE ATHROPATHY

(PSEUDOGOUT, CHONDROCALCINOSIS)

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:

Uric acid	**Calcium pyrophosphate athropathy**
needle-shaped crystals and exhibit negative birefringence with a red filter	crystals are rhomboid in shape and exhibit positive birefringence with a red filter
The knee is not commonly involved	The knee is most commonly involved
	X-rays show the characteristic line of calcification of the articular cartilage