ARTHRITIS

Kenneth Alonso, MD, FACP

Joint anatomy

- Non-synovial joints (synarthrosis)
- Lack a joint space as are tightly connected to provide structural strength
- Sutures (cranial)
- Syndesmosis
- Links bones by ligaments or thick membranes
- Connects radius and ulna, tibia and fibula
- Gomphosis (peg and socket)
- Connects tooth to jaw

Joint anatomy

- Amphiarthrosis joints are slightly movable
- Cartilaginous
- Fibrocartilage
- Intervertebral discs and pubic symphysis
- Hyaline cartilage
- Ribs

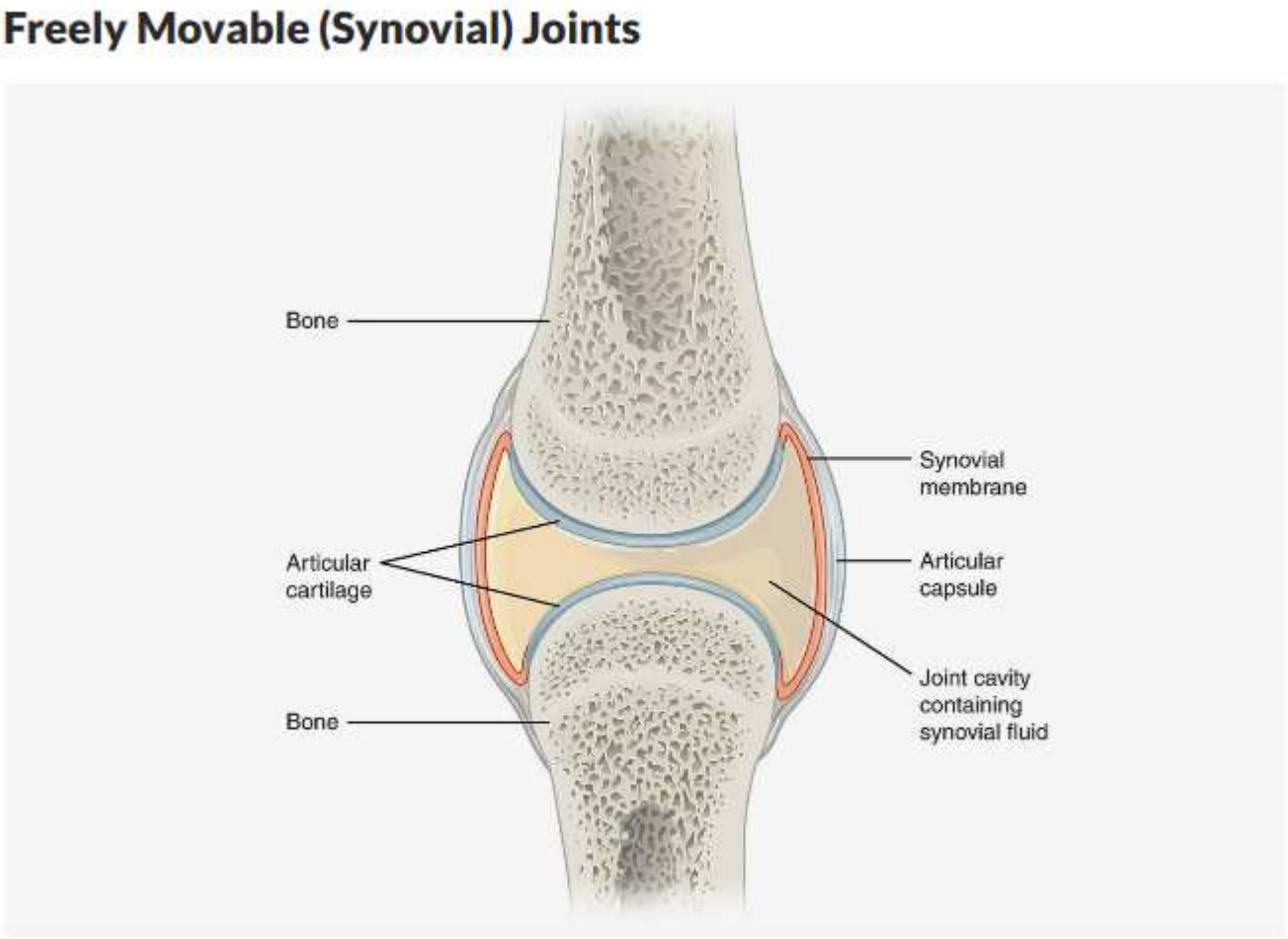
Joint anatomy

- Synovial joints (diarthrosis)
- Joint space permits motion
- Pivot, hinge, condyloid, saddle, plane, and ball-and-socket joints.
- Articular surface is made of hyaline cartilage (type II collagen)
- Synovium lines the joint capsule
- No basement membrane
- Synoviocytes secrete hyaluronic rich fluid that bathes the articular surface

Synovium

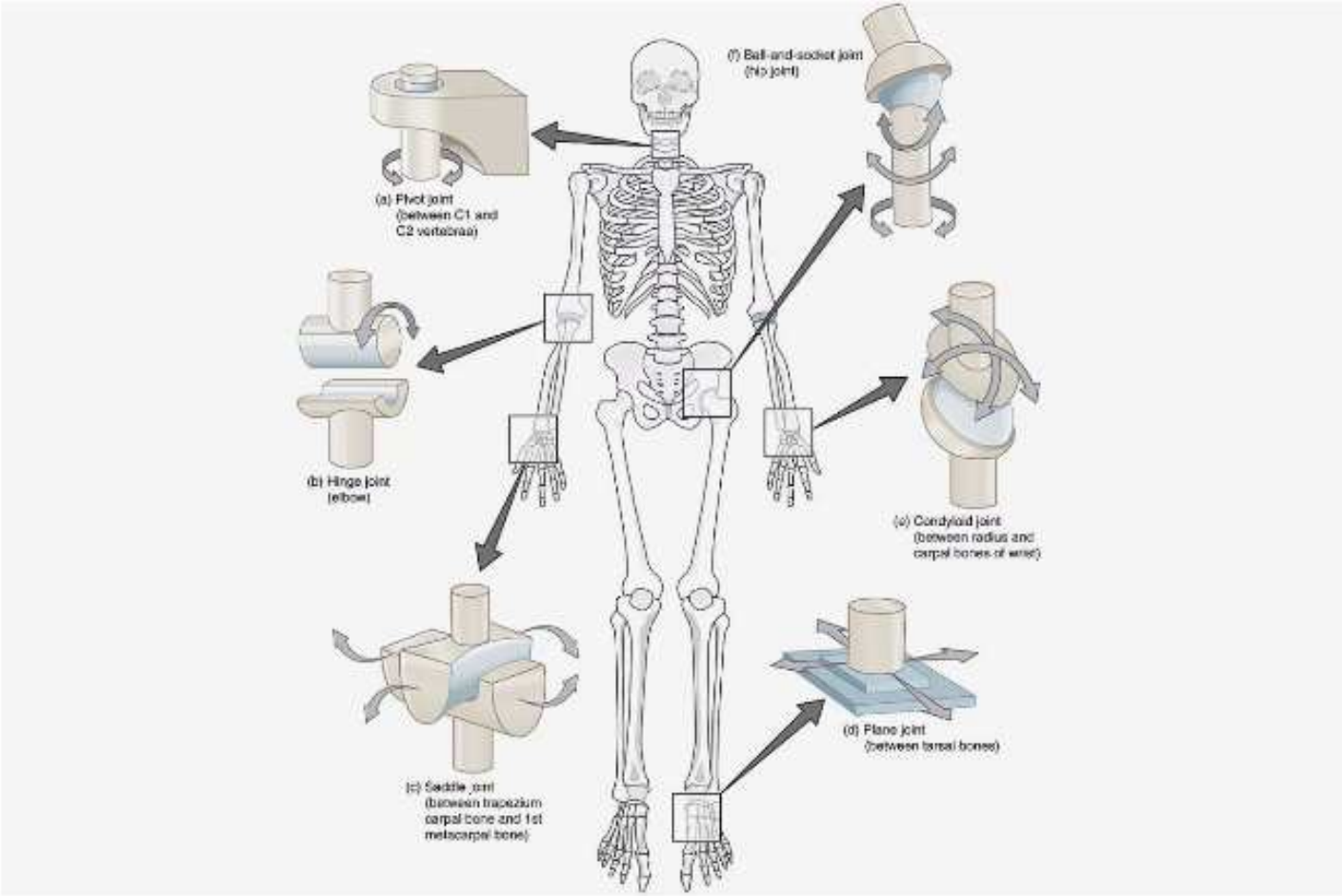
- Synovial membrane anchored to underlying capsule and does not cover the articular surface of the joint
- The synovial membrane is lined by
- Type A synoviocytes (specialized macrophages)
- Type B synoviocytes synthesize hyaluronic acid
- Similar to fibroblasts
- Synovial membrane lacks a basement membrane
- Permits efficient exchange between blood and, synovial fluid
- Synovial fluid is a hyaluronic acid containing plasma filtrate

Synovial joint



Synovial joints are freely movable and provide the greatest degree of mobility. OpenStax College/Wikimedia Commons/CC BY 3.0

Types of Synovial Joints in the Body



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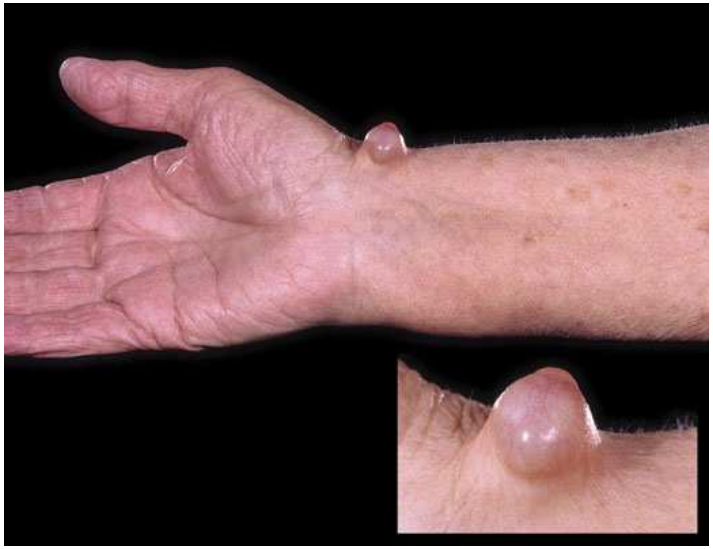
Ganglion cyst

- Outpouching of synovium.
- Occurs adjacent to joints or tendons.
- Most frequently found on back of the wrist the palm side of the wrist, the base of the finger on the palm side, and the top of the end joint of the finger .
- Filled with a clear, gel-like fluid and resemble a water balloon on a stalk . They may fluctuate in size, and some may eventually disappear completely.
- The origin is not known.
- Carpal tunnel syndrome as a complication.



Baker's cyst

- Swelling of bursa behind the knee
- Increased intra-articular pressure
- Trauma and gout are two common causes
- May be confused with popliteal artery aneurysm
- If cyst ruptures, fluid may flow into calf; mimics thrombophlebitis

Differential diagnosis of fever and arthritis

- Active infection
- Systemic lupus erythematosus
- Gout
- Pseduogout
- Acute rheumatic fever
- Sarcoidosis
- Inflammatory bowel disease

Common causes

	Osteoarthritis	Rheumatoid arthritis	Gout	Pseudo-gout	Infection
Age and sex	**Older adults**	**Women, 25-40 years old**	**Older men**	**Older adults**	**Any age**
Joints (classic)	**DIP, PIP, hip, knee**	**PIP, MCP, wrist**	**Big toe**	**Knee, elbow**	**Knee**
WBC in joint fluid	**<2000 <25% polys**	**>2000 >50% polys**	**>2000 >50% polys**	**>2000 >50% polys**	**>50,000 >75% polys**

Acute monoarticular arthritis

- 90% of cases of monoarticular arthritis are infectious in origin
- The concern is septic arthritis
- May not be febrile
- 10% of monoarticular arthritis caes represent crystal deposition disease
- A single, acutely inlamed joint should be assumed infected until proved otherwise

Acute monoarticular arthritis

- Monoarticular arthritis in an adolescent or young adult should trigger a search for Neisseria gonorrheae.
- May also present as tenosynovitis, pustular skin lesions, and polyarthralgia
- Represents high grade bacteremia

Acute oligoarticular arthritis

- Oligoarticular arthritis is usually infection
- Neiserria gonorrheae common.
- Look for bacterial endocarditis.
- Spondyloarthropathies may also present with oligoarticular arthritis.
- Are usually asymmetric.

Acute polyarticular arthritis

- Viral arthritis usually involves multiple small joints
- Evanescent and migratory arthritis
- Consider Lyme disease
- Consider rheumatoid arthritis
- Extreme pain and limited range of motion, but minimal effusion or swelling is associated with rheumatic fever.

Acute polyarticular arthritis

- Bacterial infections are more common in neonates
- Consider:
- Group B Stretpococcus
- Neisseria meningitidis
- Neisseria gonorrhoeae
- Staphylococcus aureus

Infectious arthritis

- Arthritis due to Hemophilus influenza type B, Streptococcus pneumoniae, hepatitis B virus, measles, or mumps may occur in unimmunized children
- Hemophilus influenza arthritis predominates in children younger than 2 years of age
- Staphylococcus aureus is the main causative agent in older children and adults.
- Streptococcus pneumoniae may also be found in adults.
- May enter due to direct inoculation or spread hematogenously.

Infectious arthritis

- N. gonorrhea is prevalent during late adolescence and young adulthood.
- 90% monoarticular
- Knee is the common site.
- Hip, shoulder, elbow, wrist, sternoclavicular
- Principally in sexually active women
- Deficiencies of components of the complement membrane attack complex (C5, C6, C7) are associated with disseminated gonococcal infections.
- Individuals with sickle cell disease are prone to infection with Salmonella at any age.

Infectious arthritis

- Mycobacterium tuberculosis.
- Monoarticular
- Extension from adjacent osteomyelitis or hematogenous spread from lung.
- Immunocompromised host.
- Mycobacterial seeding of the joint induces the formation of confluent granulomas with central caseous necrosis.

Infectious arthritis

- The affected synovium may grow as a pannus over the articular cartilage and erode the bone along the joint margins.
- Chronic disease results in fibrous ankylosis and obliteration of the joint space.
- The weight-bearing joints are usually affected, especially the hips, knees, and ankles in descending order of frequency.
- Associated rash may suggest Lyme disease, Neisseria infection, or Varicella.

Infectious arthritis

- Borrelia (Deer tick).
- The initial infection of the skin (target lesion) is followed within several days or weeks by dissemination of the organism to other sites, especially the joints.
- 60%-80% of untreated individuals with the disease develop arthritis during the late stage.
- Large joints
- Knees, shoulders, elbows, and ankles
- Spirochetes identified in 25%
- 10% refractory cases where Borrelia is not identified.
- Histologically resembles rheumatoid arthritis.

Infectious arthritis

- Following:
- Respiratory infection
- Group A streptococcus, N. meningitidis
- Gastrointestinal infection
- Shigella, Salmonella, Campylobacter
- Genitourinary infection
- Most common cause of reactive arthritis
- Chlamydia trachomatis
- Chlamydia responds to antibiotic therapy with remission of arthritis; gastrointestinal organisms do not respond

Infectious arthritis

- Genitourinary manipulation
- Mycoplasma hominis
- Ureaplasma urealyticum
- Up to 50% of sexually active women and men
- Prostatitis or bacterial vaginosis
- Pneumonia and meningitis if newborn colonized at vaginal delivery
- Septic arthritis and lung infection in adults
- May lead to infertility in both men and women
- Confirm by PCR
- Macrolides, quinolones, tetracycline therapy

Infectious arthritis

- Candida.
- May occur in neonates or immunocompromised host.
- Histoplasma, Coccioides, Blastomyces
- Inoculated or inhaled.
- Immunocompromised host.
- Sporotrichum schenkii.
- Inoculated or inhaled.
- Immunocompromised host.
- Joint aspiration diagnostic in cases of infectious arthritis. May well be therapeutic.

Infectious arthritis

- Varicella zoster virus may cause primary arthritis within several days of the onset of rash
- Monoarticular knee involvement is most common
- Varicella also may cause secondary bacterial arthritis by providing a portal of entry for Staphylococci or Streptococci.
- Hepatitis B virus.
- 10-25% develop arthritis
- Usually during the prodromal stage
- Joints of hands and knees most often affected
- May be associated with urticarial and maculopapular eruption.

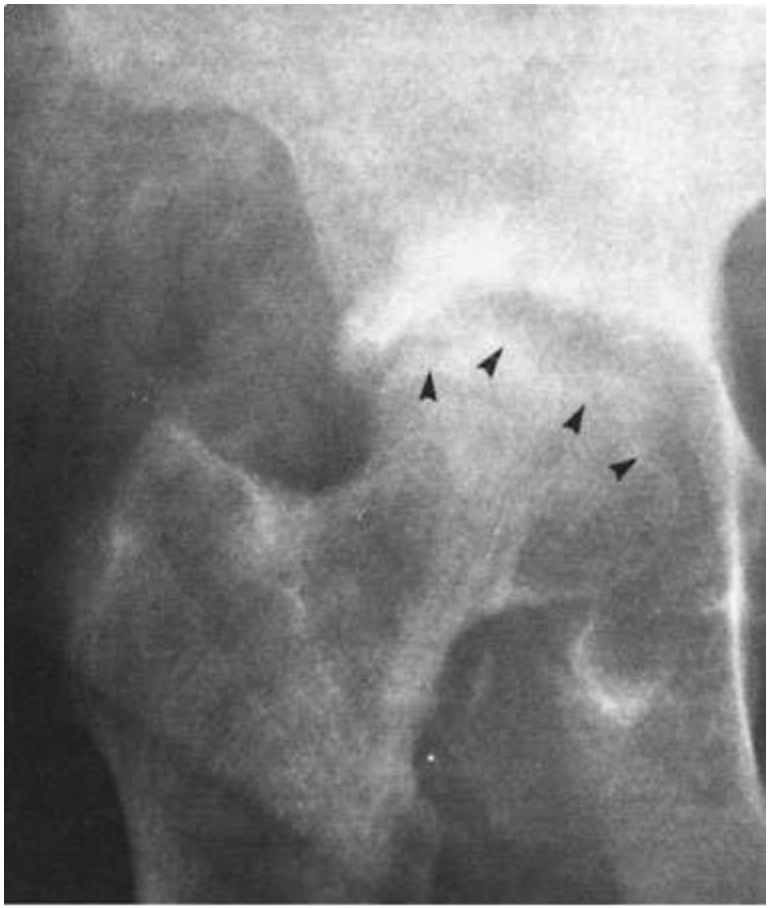
Infectious arthritis

- Hepatitis C virus.
- 2-20% of patients develop arthritis
- Evanescent arthritis or oligoarthritis
- Parvovirus.
- Arthralgia or symmetric arthritis may accompany or follow the skin eruption
- The knee is the most commonly affected joint.
- Presents 10 days after flu-like syndrome.

Infectious arthritis

- Rubella virus.
- Joint symptoms develop within one week before or after the rash.
- Rubella vaccine virus.
- Joint symptoms develop approximately two weeks after vaccination.
- Mumps virus.
- Joint symptoms develop after the onset of parotitis.

Infectious arthritis



The radiograph of the right hip shows articular space narrowing, bony erosion in the acetabulum and femoral head (arrowheads), and irregular bony sclerosis.

Fig. 7-36 Accessed 07/01/2010

Chen, MYM, Pope Jr., TL, Ott DJ: *Basic Radiology*: http://www.accessmedicine.com

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Differential diagnosis of rash and arthritis

- Erythematous maculopapular rash
- Viral illness
- Secondary syphilis
- Drug reaction
- Uriticaria
- Systemic lupus erythematosus
- Hepatitis B
- Palpable purpura
- Vasculitides
- Subacute bacterial endocarditis

Differential diagnosis of rash and arthritis

- Papulosquamous lesions
- Psoriatic arthritis
- Secondary syphilis
- Systemic lupus erythematosus
- Annular lesions
- Systemic lupus erythematosus
- Lyme disease
- Acute rheumatic fever

Differential diagnosis of rash and arthritis

- Pustular lesions
- Pustular psoriasis
- Beçhet's syndrome
- Sweet's syndrome

Differential diagnosis of rash and arthritis

- Subcutaneous nodules
- Sarcoidosis
- Inflammatory bowel disease
- Beçhet's syndrome
- Systemic lupus erythematosus
- Polyarteritis nodosa
- OsleWeber-Christian disease

Non-infectious arthritis

- Hemarthrosis.
- May be the first presentation of bleeding disorder.
- Crohn's disease.
- Ankylosing spondylitis
- Extra-articular manifestations include abdominal pain, diarrhea, rectal bleeding, and aphthous ulcers

Non-infectious arthritis

- Kawasaki disease.
- 80% occur in those <4 years of age
- Fever
- Conjunctivitis
- Erythema of the lips and oral mucosa ("strawberry"tongue)
- Rash
- Lymphadenopathy.
- Sarcoid.
- Periarthritis about ankle joint.

Non-infectious arthritis

- Serum sickness.
- Rash (usually urticarial)
- Fever; lymphadenopathy
- Polyarthralgias or polyarthritis
- Begin one to two weeks after exposure to the inciting agent
- Usually involves the metacarpophalangeal joints, knees, wrists, ankles, and shoulders
- Swelling and erythema are uncommon.

Non-infectious arthritis

- Hoenich-Schoenlein Purpura.
- Palpable purpura
- Arthritis/arthralgia
- Renal disease.

Gout

- 80% monoarticular
- Characteristically associated with a tophus of the metatarsal-phalangeal joint of the great toe.
- Frequently involves the knee
- Recurrent disease may present with other joint (or plantar arch) involvement.
- May see as olecranon or patellar bursitis.

Gout

- Gout is marked by transient attacks of acute arthritis initiated by crystallization of monosodium urate within and around joints
- Macrophages phagocytose the monosodium urate and the intracellular sensor, the inflammasome recognizes the crystals.
- The NALP3 inflammasome is activated once the crystals are phagocytosed.
- Inflammasome activated capsase 1 leads to activation of IL-1β
- Triggers the expression of adhesion molecules as well as the chemokine CXCL8.
- IL-18 is also produced.

Gout

- Complement cascade activated as well
- Acute pain due to the deposition of urate crystals.
- 90% of causes are not known
- Hyperuricemia a common finding
- It is thought that release of crystals from micro-tophi form the nucleus that permits precipitation of uric acid in synovial fluid (or urine).
- The nucleus is uric acid coated with immunoglobulin.

Gout

- Acute attacks may be precipitated by alcohol consumption as well as foods rich in purines (meat, seafood, dried peas, beer)
- Risk factors include obesity, diabetes mellitus, and hypertriglyceridemia.
- Uric acid solubility is 7 mg/dl at body temperature.
- Solubility diminishes at lower temperatures.
- Solubility also diminishes at acid pH
- Crystals are precipitated preferentially in sites of lower temperature (digits, ear, joints, kidneys)
- Uric acid crystals are taken up in tissues.

Gout

- Known causes:
- Impaired reabsorption of filtered urate
- Chronic renal disease
- Thiazide diuretics
- Excess production if disease of increased nucleic acid turnover
- Myeloproliferative disorders
- Lymphoproliferative disorders
- Tumor lysis syndrome

Gout

- The urate transporter gene (URAT1) is abnormal in 90% of cases of primary gout.
- Reabsorption of filtered urate is impaired.
- HPRGT deficiency blocks the salvage pathway of purine base recovery and leads to purine synthesis from non-purine precursors by a de novo pathway.
- Purine degraded to uric acid
- Severe deficiency noted in Lesch-Nyhan syndrome.
- Dystonia, chorea, ballismus
- HPRT1 gene at Xq26.2-3

Table 26-7 Classification of Gout

Clinical Category	Uric Acid Production	Uric Acid Excretion
Primary Gout (90%)		
Unknown enzyme defects (85%-90%)	↑ (majority) ↑↑ (minority) Normal	Normal ↑ ↓
Known enzyme defects (e.g., partial HGPRT deficiency)	↑	Normal
Secondary Gout (10%)		
Increased nucleic acid turnover (e.g., leukemia)	↑↑	↑
Chronic renal disease	Normal	↓
Congenital (e.g., Lesch-Nyhan syndrome HGPRT deficiency)	↑↑	↑

HGPRT, Hypoxanthine guanine phosphoribosyl transferase.

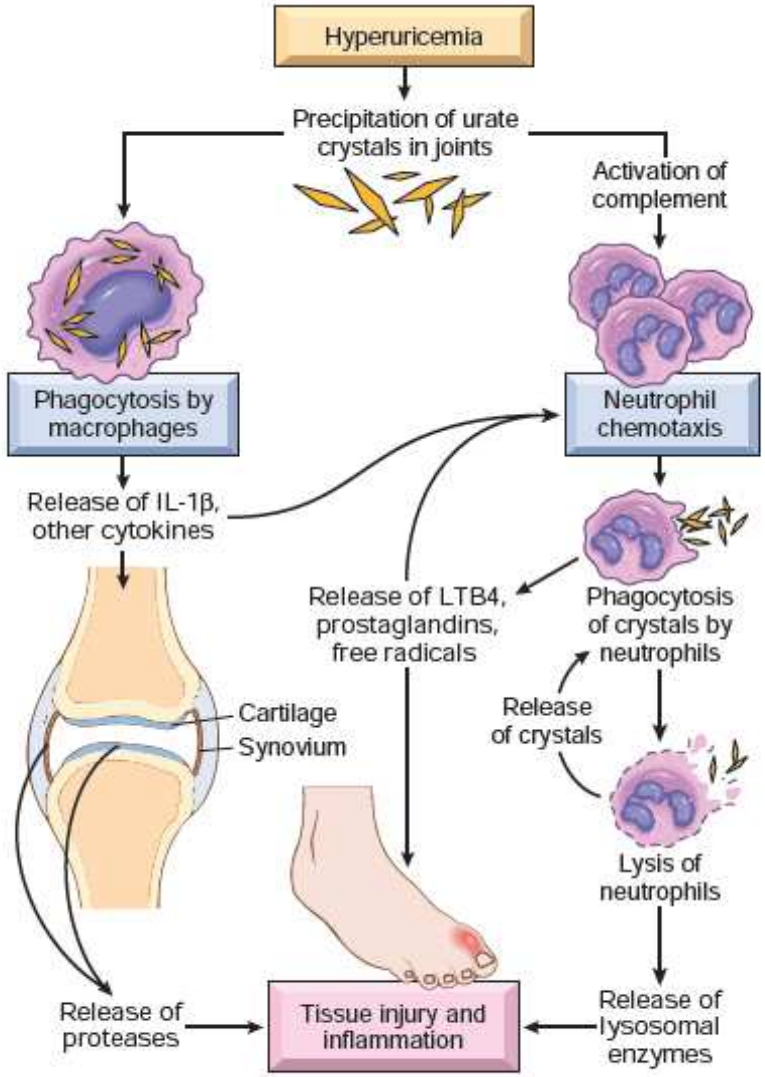

Figure 26-46 Pathogenesis of acute gouty arthritis. LTB4, Leukotriene B4; IL-1β, interleukin 1β.

Gout

- Joint fluid will show >10,000 leukocytes/ml
- 90% are neutrophils.
- Needle shaped negatively bi-refringent crystals are present in the joint aspirate.
- Indomethacin is the drug of choice for pain relief
- Blocks prostaglandin synthesis
- Colchicine is useful in acute attacks
- Inhibitor of tyrosine kinase as well as tubulin
- Alkalinization of the urine increases uric acid excretion.

Gout

- Aspirin is counterproductive as its metabolites compete with α-ketogenic compounds and with lactate for the UART1 receptor in proximal tubules used by uric acid
- Intra-articular cortiocsteroids may provide immediate relief.
- Oral corticosteroids may aggravate hyperglycemia in diabetics.
- Allopurinol is a xanthine oxidase inhibitor that is used as maintenance therapy.
- When beginning probenecid or allopurinol, administer colchicine to prevent acute attack.

Gout

- Podagra refers to involvement of great toe.

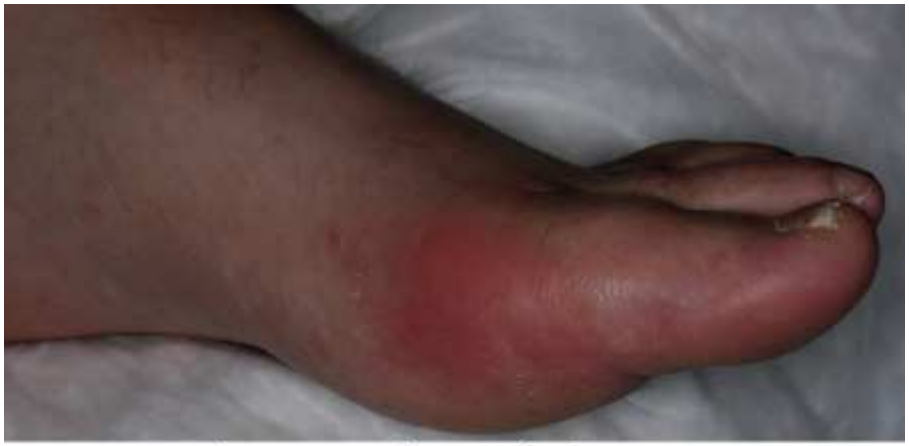

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Fig. 12-10 Accessed 07/01/2010

- Swelling and erosion at the first metatarso-phalangeal joint

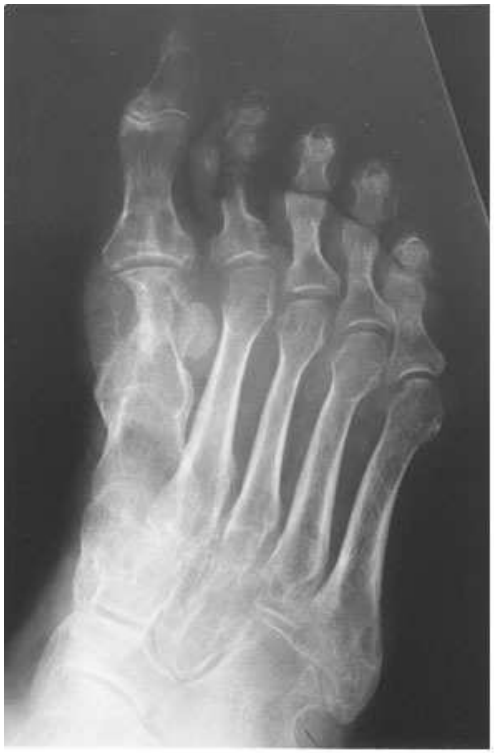

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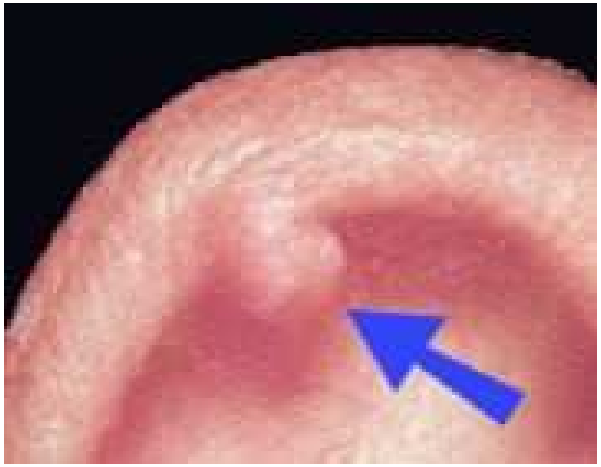
Fig. 7-37 Accessed 07/01/2010

Gout

- Acute arthritis is characterized by a dense neutrophilic infiltrate that permeates the synovium and synovial fluid.
- Long, slender, needle-shaped, and negatively birefringent urate crystals are frequently found in the cytoplasm of the neutrophils and are arranged in small clusters in the synovium.
- The synovium is edematous and congested, and also contains scattered lymphocytes, plasma cells, and macrophages.
- Chronic changes may develop over years.

Gout

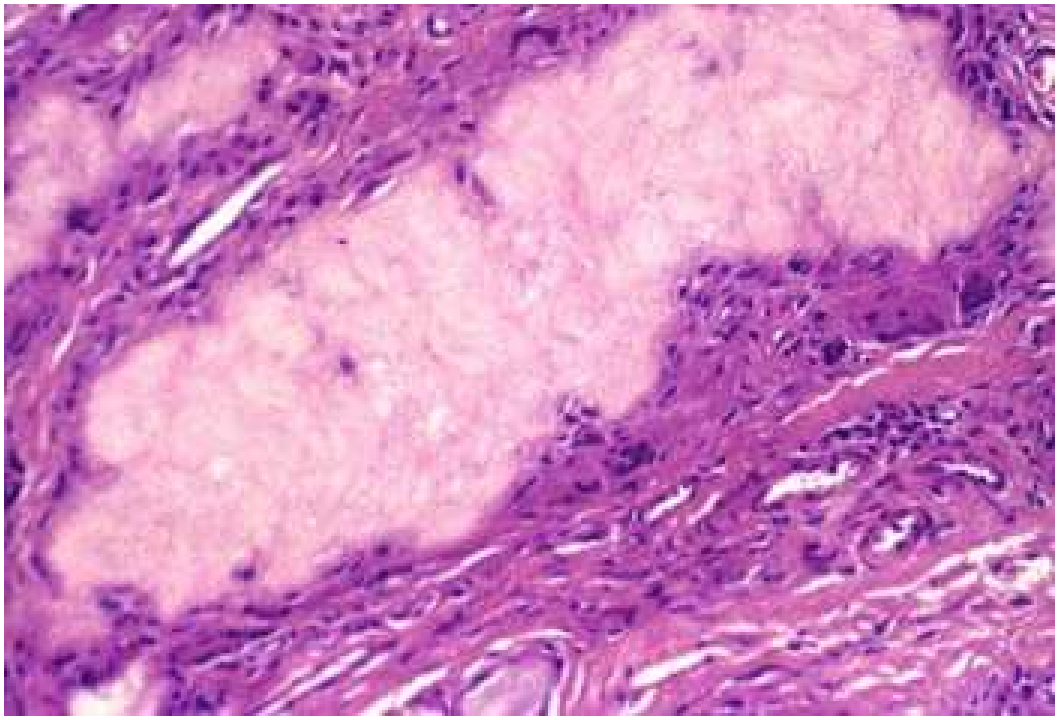
- **Chronic tophaceous arthritis** evolves from the repetitive precipitation of urate crystals during acute attacks.
- Urates encrusts the articular surface and forms visible deposits in the synovium surrounded by an intense inflammatory reaction of foreign body giant cells.
- The synovium becomes hyperplastic, fibrotic, and thickened by inflammatory cells and forms a pannus that destroys the underlying cartilage and lead to juxta articular bone erosions.
- In severe cases, fibrous or bony ankylosis ensues, resulting in loss of joint function.



Tophus frequently deposited in ear cartilage. (Arrow)

Tophus

Urate crystals surrounded by inflammatory cells and foreign body giant cells

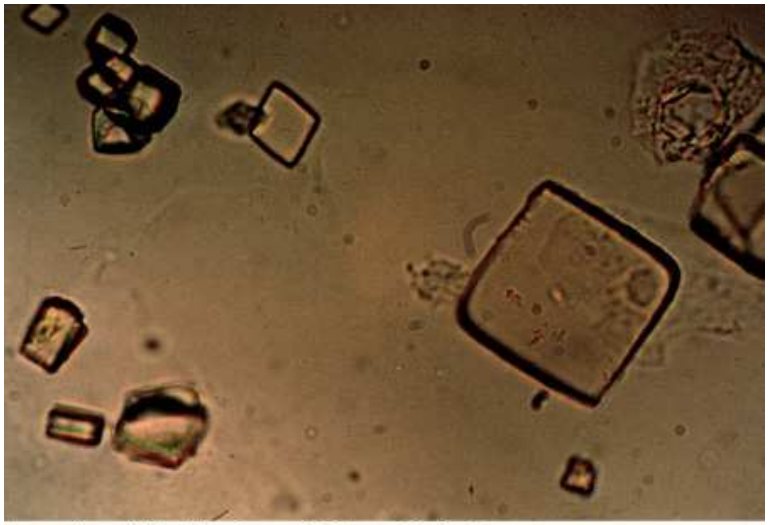


Crystals

<u>Found in acid urine.</u>

Uric acid

- Rhomboid



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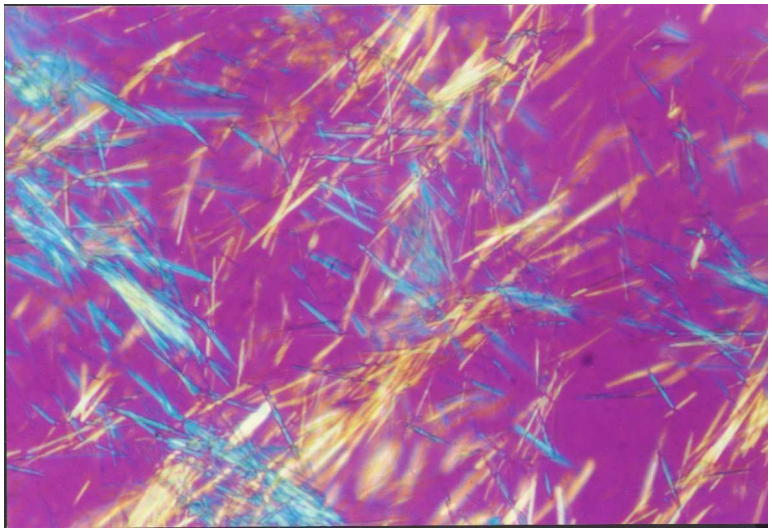
<u>Found in joint fluid</u>

Monosodium urate crystals

- Needles, rods
- Negative birefringence



Calcium pyrophosphate crystal deposition disease

- Pseudo-gout.
- More common after age 50.
- Usually knee.
- Bilateral wrist involvement common in older adults (or the symphisis pubis).
- Usually presents on an x-ray as an incidental finding. (May see calcified ligament).
- Chondrocalcinosis is a reflection of impaired calcium/phosphate metabolism and may be seen in gout, hyperthyroid states, and hypomagnesemia.

Calcium pyrophosphate crystal deposition disease

- Articular cartilage proteoglycans, which normally inhibit mineralization, are degraded allowing crystallization around chondrocytes.
- As in gout, inflammation is caused by activation of the inflammasome in macrophages.
- Associated with deposition of calcium pyro-phosphate dihydrate crystals.
- Excess tripyrophosphate production.

Calcium pyrophosphate crystal deposition disease

- ANKH mutation at 5p15.2 may be present in primary disease
- Defect in intracellular phosphate transport
- Joint aspirate shows monoclinic or biclinic , weakly bi-refringent intracellular crystals.
- NSAIDs or intra-articular corticosteroids utilized for pain relief.

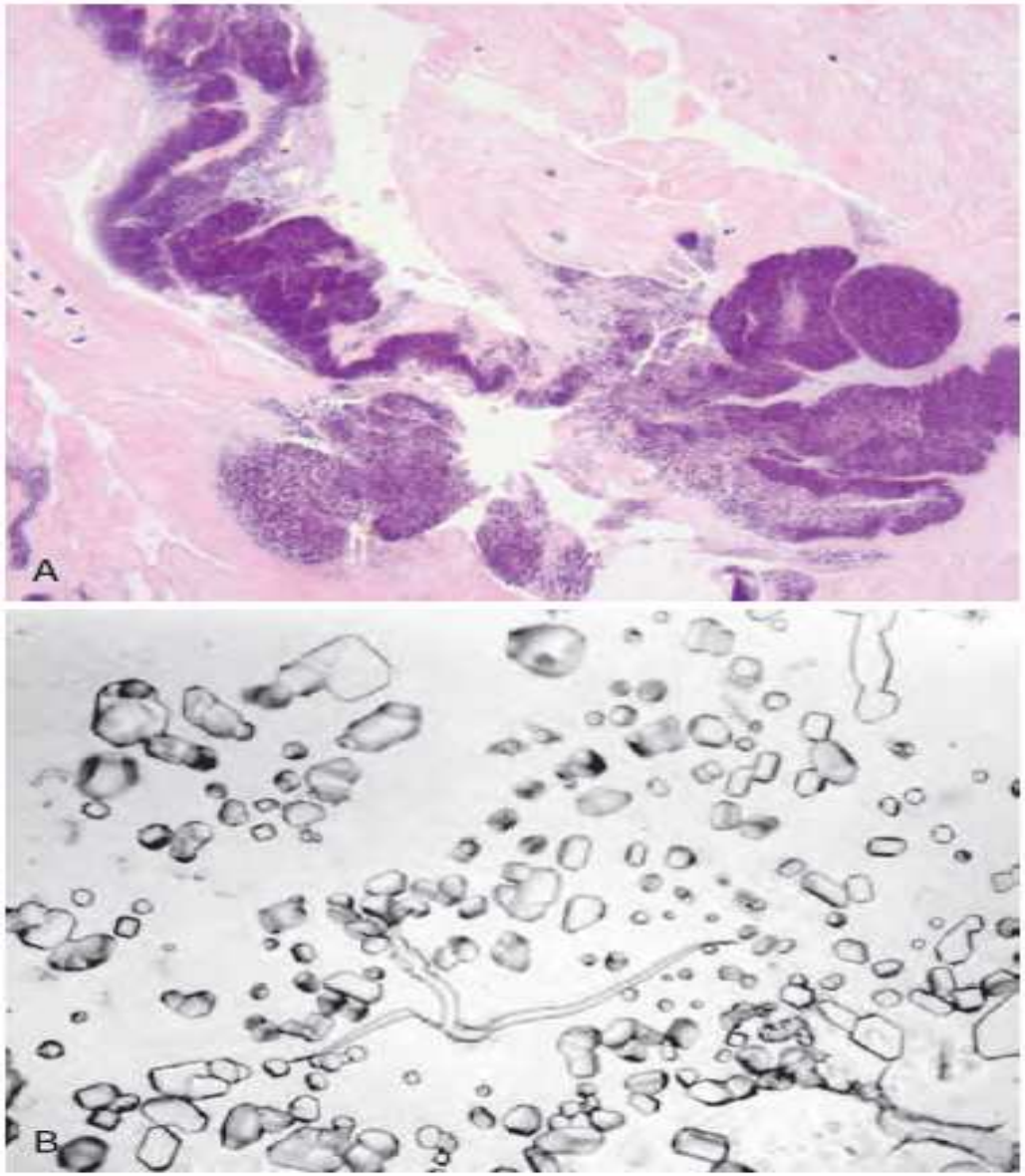
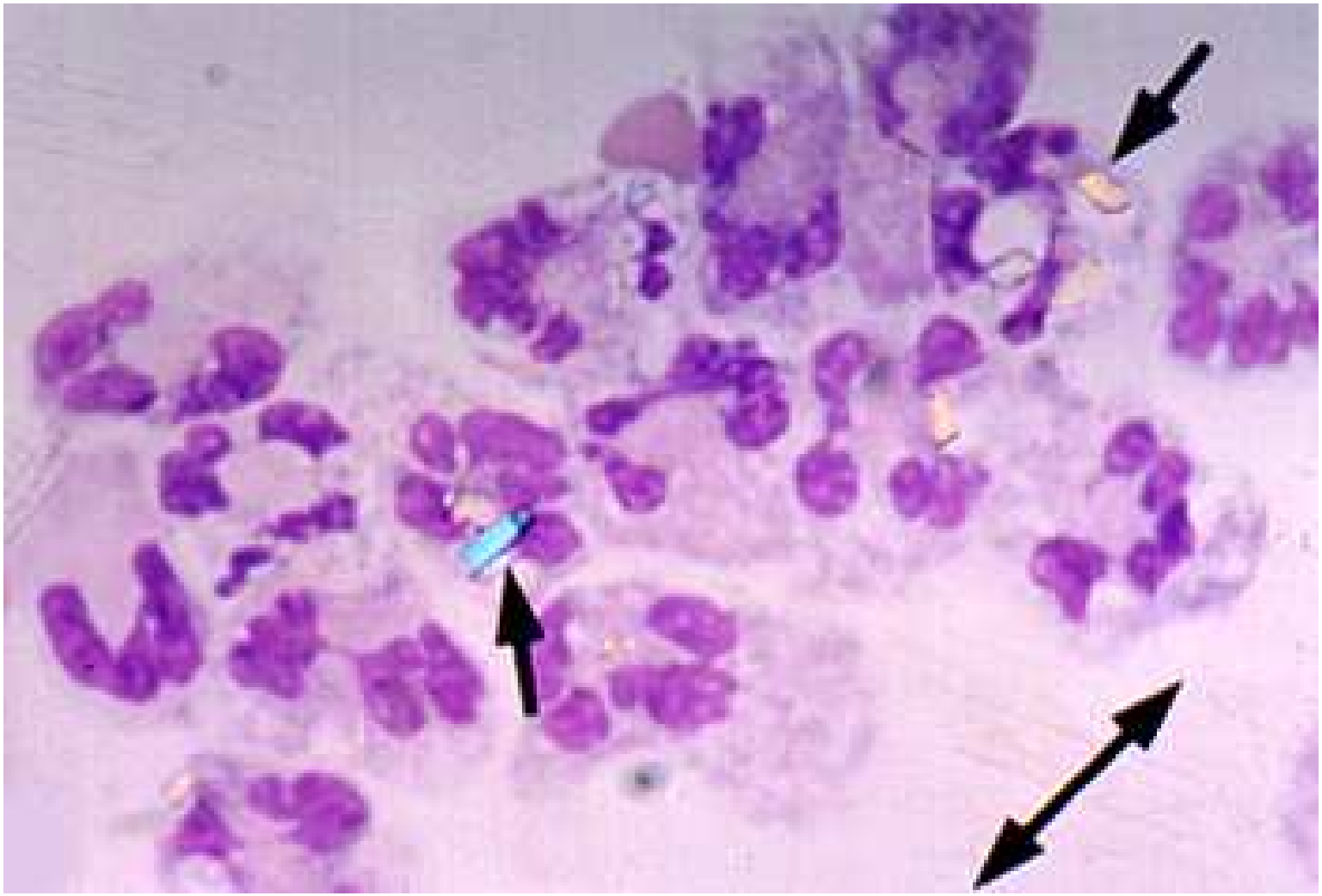


Figure 26-48 Pseudogout. **A,** Deposits are present in cartilage and consist of amorphous basophilic material. **B,** Smear preparation of calcium pyrophosphate crystals.



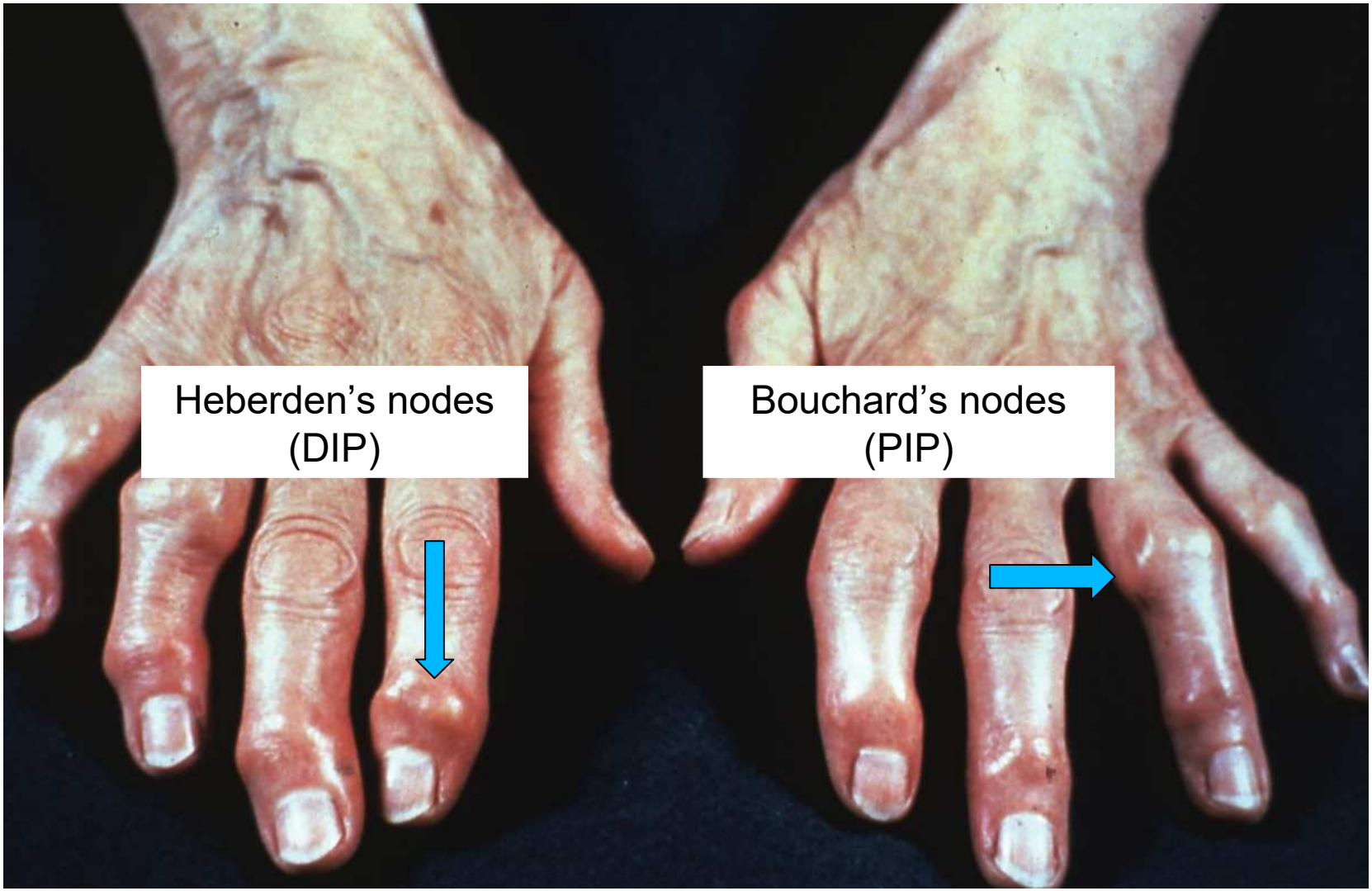
Note the colors parallel and perpendicular to the light

Degenerative joint disease

- Osteoarthritis is characterized by degeneration of cartilage that results in structural and functional failure of synovial joints.
- It is the most common type of joint disease
- Causes are aging and biomechanical stress.
- Women more likely to be affected
- Pain worsens as the day progresses.
- Relief with rest.
- Polyarticular.
- Not associated with inflammation.

Degenerative joint disease

- Periarticular tenderness
- Characteristic hand deformities include Heberden's and Bouchard's nodes in the interphalageal joints of the hand.
- Hips and knees commonly affected.
- Clinical diagnosis only.


Heberden’s nodes
(DIP)
Bouchard’s nodes
(PIP)

Degenerative joint disease

- In the early stages of osteoarthritis, the chondrocytes proliferate, forming clusters (“cloning).
- Concurrently, the water content of the matrix increases and the concentration of proteoglycans decreases.
- The normally horizontally arranged collagen type II fibers in the superficial zone are cleaved, yielding fissures and clefts at the articular surface.

Degenerative joint disease

- Collagen type II is degraded by matrix metalloproteinases.
- The composition of proteoglycans changes.
- Inflammatory cells are sparse
- WNT signaling and prostaglandin metabolism upregulated.
- Inflammatory cytokines and other diffusible factors, particularly TGF-β (which induces matrix metalloproteinases), TNF, prostaglandins and nitric oxide, have been implicated in progression.

Degenerative joint disease

- Eventually, following repetetive injury, chondrocytes die and full-thickness portions of the cartilage are sloughed.
- There is erosion with fraying and loss of cartilage
- Fragments in joint (joint mice, loose bodies)
- The exposed subchondral bone plate becomes the new articular surface
- Friction with the opposing surface smooths and burnishes the exposed bone, giving it the appearance of polished ivory (bone eburnation)
- There is rebuttressing and sclerosis of the underlying cancellous bone.

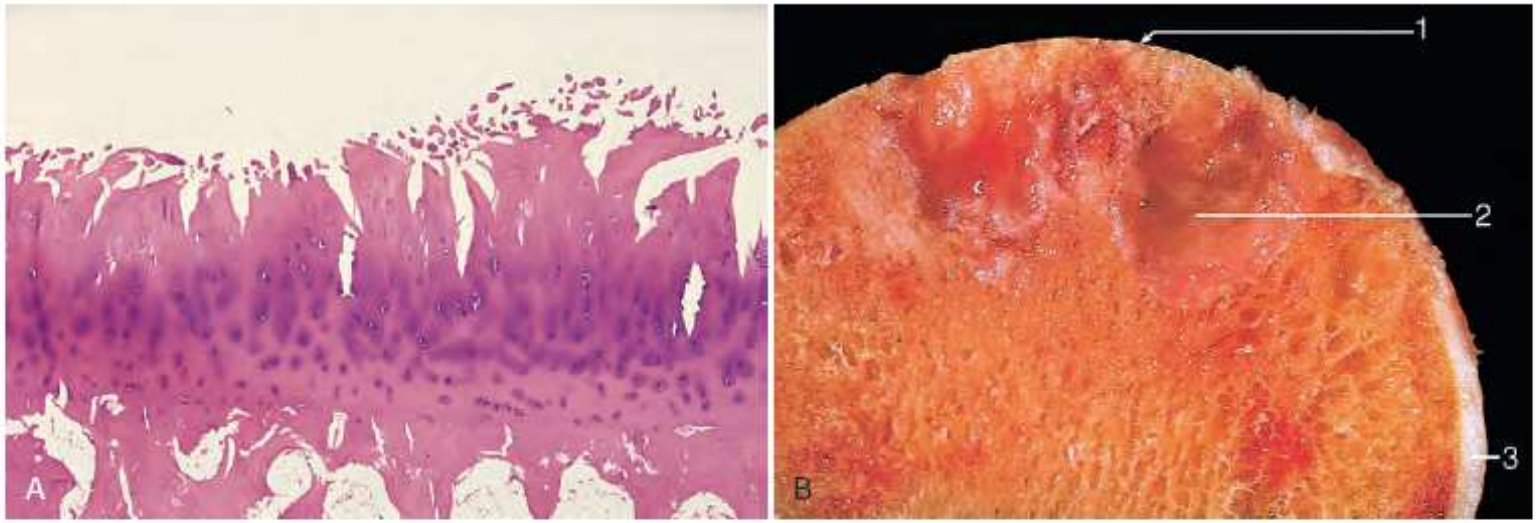


Figure 26-39 Osteoarthritis. **A,** Histologic demonstration of the characteristic fibrillation of the articular cartilage. **B,** Eburnated articular surface exposing subchondral bone (1), subchondral cyst (2) and residual articular cartilage (3).

Degenerative joint disease

- Small fractures through the articulating bone are common
- The fracture gaps allow synovial fluid to be forced into the subchondral regions in a one-way, ball valve-like mechanism.
- Form fibrous-walled (subchondral) cysts.
- Mushroom-shaped osteophytes (bony outgrowths) develop at the margins of the articular surface
- Are capped by fibrocartilage and hyaline cartilage that gradually ossify.
- The synovium is usually only mildly congested and fibrotic. Little inflammation.

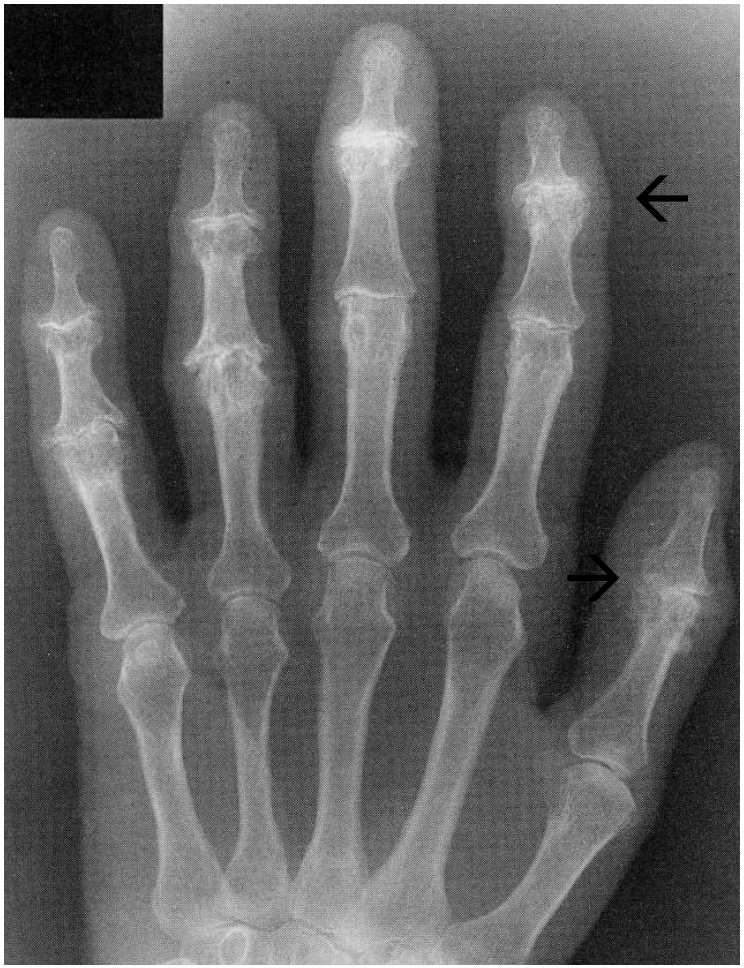
Degenerative joint disease

- Clinical diagnosis only.
- HAND:
- Hard tissue enlargement of 2 or more of 10 selected joints.
- The 10 selected joints are the second and third distal inter-phalangeal (DIP) joints, the second and third proximal inter-phalangeal (PIP) joints, and the first carpo-metacarpal (CMC) of both hands.
- Hard enlargement of two or more DIP joints.
- Fewer than three swollen metacarpo-phalangeal (MCP) joints.
- Deformity of at least 1 of the 10 selected joints.

Degenerative joint disease

- KNEE:
- Greater than 50 years of age
- Morning stiffness for less than 30 minutes
- Crepitus on active motion of the knee
- Bony tenderness, bony enlargement, no palpable warmth
- HIP:
- Osteophytes on x-ray (femoral or acetabular)
- Joint space narrowing on radiography (superior, axial or medial)
- In contrast to changes in rheumatoid arthritis, there is joint narrowing but no erosions or juxtacortical osteoporosis.

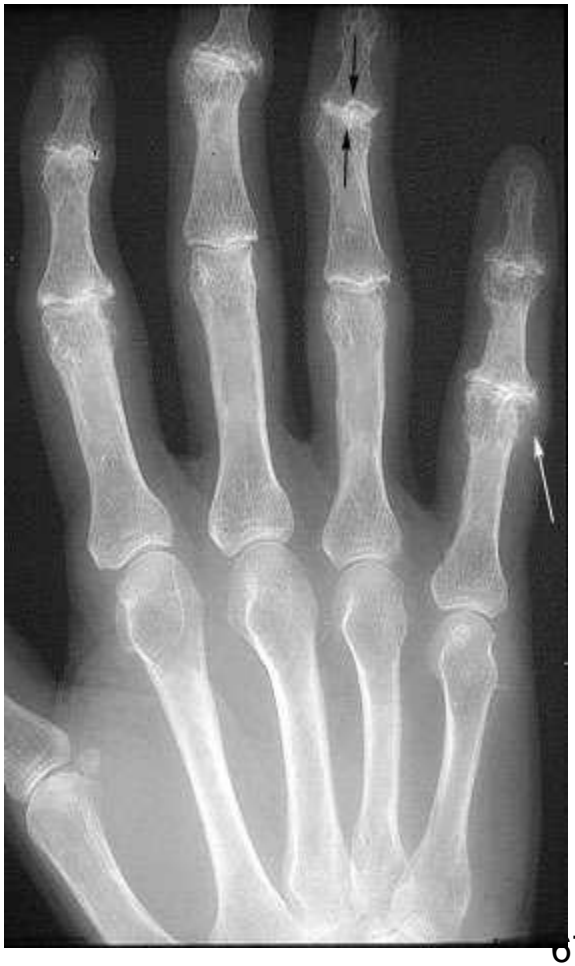
Degenerative joint disease



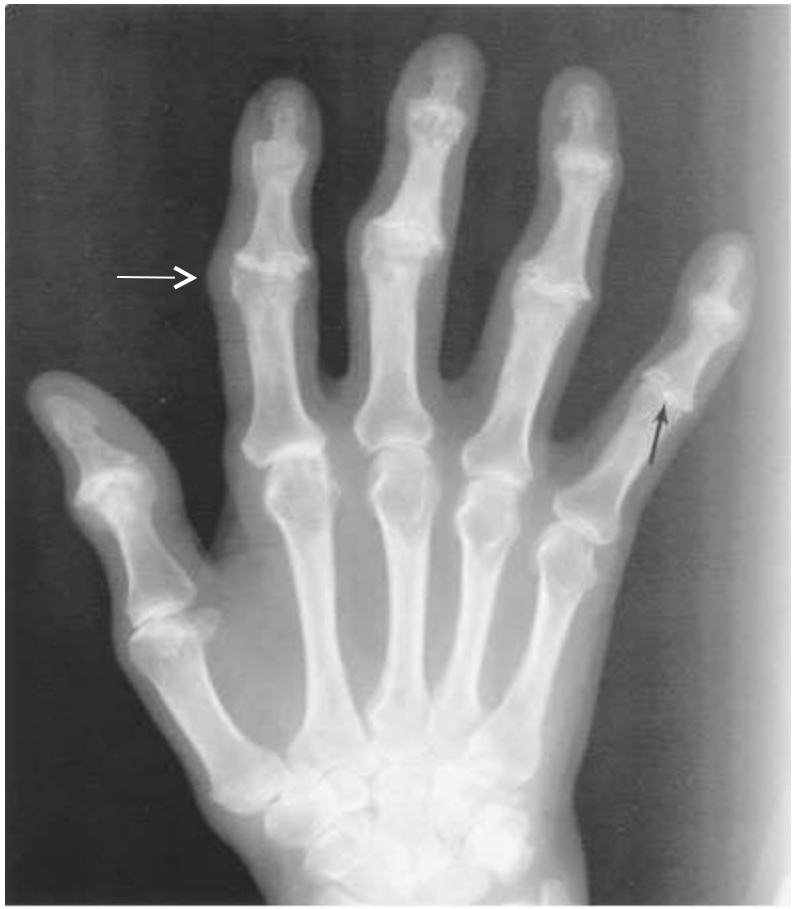
Joint narrowing (small black arrows)

Heberden nodes (large black arrows)

Osteophytes (white arrow)



Degenerative joint disease



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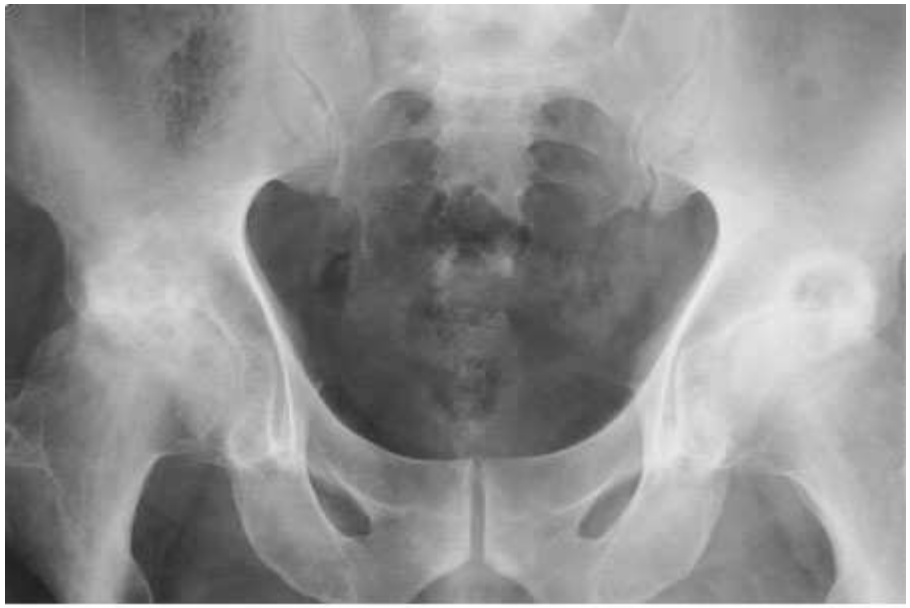
Frontal radiograph of the right hand in a 56-year-old woman shows the classic changes of erosive osteoarthritis.

Note the "gull-wing" appearance (black arrow) of the PIP joint of the fifth digit.

A Heberden's node is shown with the white arrow.

Fig. 7-41 Accessed 08/01/2010

Degenerative joint disease



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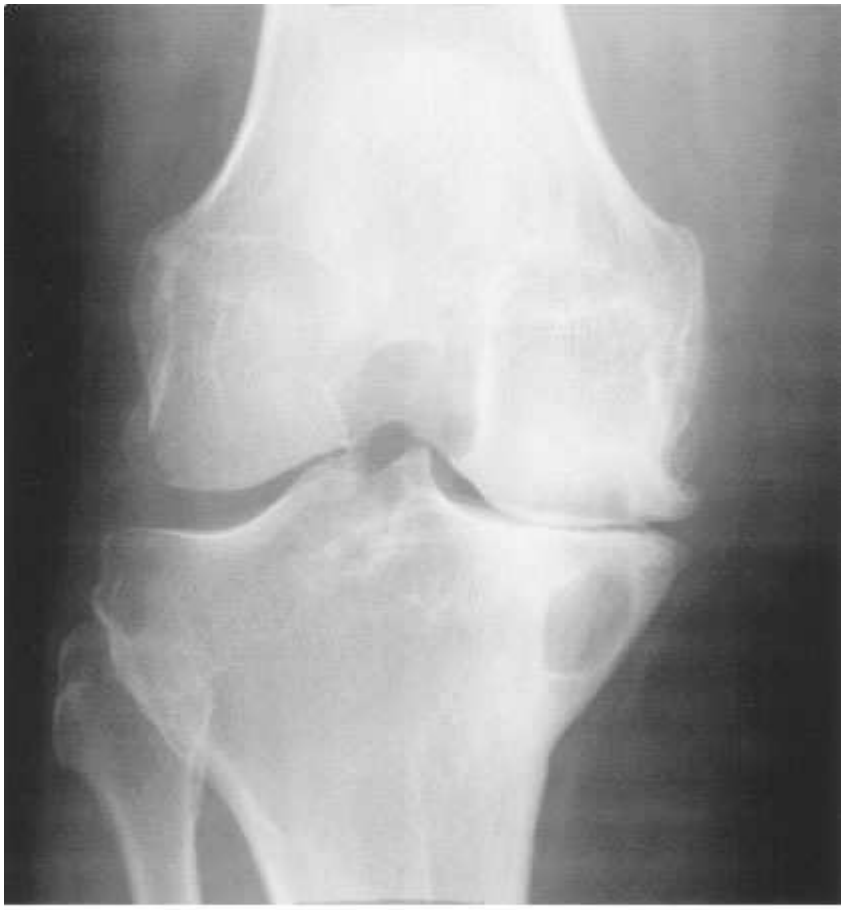
There is articular space narrowing, sclerosis, and subchondral cyst formation (also called geodes) bilaterally.

There is no significant juxta-articular osteopenia.

The findings of osteoarthritis are similar regardless of the joint in which they occur.

Fig. 7-34 Accessed 07/01/2010

Degenerative joint disease



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Frontal view of a 65-year-old man shows the classic features of osteoarthritis of the knee with medial articular space narrowing, subchondral cyst formation, sclerosis, and osteophyte formation.

Osteoarthritis of the knee initially involves the medial compartment but may, over time, progress to involve the lateral and patellofemoral compartments.

Fig. 7-40 Accessed 08/01/2010

Degenerative joint disease treatment

- NSAIDS or acetaminophen for pain relief equally effective
- Serotonin and Norepinehprine Receptor uptake Inhibitors (SNRI) may provide short term pain relief but are associated with greater complications over long term
- Heat
- Weight bearing exercise.
- Surgery may be necessary to correct deformities.
- May also be present in ochronosis (homogentisic acid deposition) and hemochromatosis (iron overload) deposition

Rheumatoid arthritis

- Most common form of chronic inflammatory arthritis.
- Autoimmune origin that may affect many tissues and organs but principally attacks the joints, producing a non-suppurative proliferative and inflammatory synovitis.
- RA often progresses to destruction of the articularcartilage and ankylosis of the joints.
- Polyarticular arthritis of the small joints
- Particularly the metacarpo-phalangeal and wrist joints.
- Bouchard's nodes (PIP joints)
- Heberden's nodes (MP joints)

Rheumatoid arthritis

- “Swan neck” (proximal inter-phalangeal flexion) and “boutonnièrre” (distal inter-phalangeal extension) deformities characteristic.
- C1-C2 instability can occur secondary to associated tenosynovitis.
- The hip is rarely involved.
- Also associated with interstitial lung disease with pleural effusions, pericarditis with effusion, and splenomegaly.

Rheumatoid arthritis

- Certain Native American populations have the highest prevalence (5-6%).
- Asian populations have the lowest prevalence (less than 1%).
- Women are 2-3 times more likely to develop rheumatoid arthritis than men.
- The peak of age of disease onset for adult rheumatoid arthritis is 30-50 years of age.
- Within 6 years of onset, half of the patients show a severe loss of functional ability and joint destruction.

Rheumatoid arthritis

- Erythrocyte sedimentation rate is elevated.
- Joint fluid shows >10,000 leukocytes/ml with a predominance of neutrophils.
- Symptoms include four of the following for >6 weeks:
- Rheumatoid nodules on extensor tendons
- Rheumatoid factor
- Radiographic changes of joint erosion
- Symmetric joint involvement
- Hand joint arthritis arthritis >3 joints
- Morning stiffness

Rheumatoid arthritis

- Instigator event is unknown.
- Mycoplasma often found in patients.
- Cartilage antigen, Type II collagen, and glycoprotein 39 are antigens commonly found to react with rheumatoid factor (IgM that binds to Fc of own IgG or IgA)
- These antibodies may self-associate to form immune complexes.
- 80% of patients will demonstrate rheumatoid factor

Rheumatoid arthritis

- High-affinity self-reactive T cells are found in tissue.
- There is a large expansion of T cell clones with large numbers of HLA-DR surface receptors, principally HLA-DRB1
- Co-modulating conformation of antigen presented to T cells as it shares an epitope located in the antigen-binding cleft of the DR molecule. This location is presumably the specific binding site of the arthritogen that initiates the inflammatory synovitis.
- Augment B cell antibody production.
- CD4+ and memory T-cells are found in affected joints.

Rheumatoid arthritis

- The synovium of RA contains germinal centers with secondary follicles and abundant plasma cells which produce antibodies specific for citrullinated peptides (post-translation conversion of arginine residues to Citrulline)
- Anti-citrulline antibodies are pathognomonic. Positive likelihood ratio (LR+) of 12.5 with an LR-, 0.3.

Rheumatoid arthritis

- IL-17 and IFN-γ secreted
- Stimulate production of pro-inflammatory materials in synovial cells and macrophages.
- Endothelial cells are then activated, facilitating leukocyte binding.
- Matrix metalloproteinase production increases.
- Osteoclast activity upregulated.

Rheumatoid arthritis

- PTPN22 involved in rheumatoid arthritis
- Encodes a protein tyrosine phosphatase that participates in activation of inflammatory cells.
- IL-1 production is marked.
- TNF-α production is induced
- Both IL-1 and TNF-α are capable of inducing the production of the other.
- Angiogenesis accompanies the acute inflammatory response.
- TNF-α is secreted.

Rheumatoid arthritis

- With RANKL activation, osteoclasts are activated and may contribute to cartilage loss.
- Immunosenescent lesions contain CD4 cells that are CD28-; these are essentially NK cells that do not respond to co-stimulation.

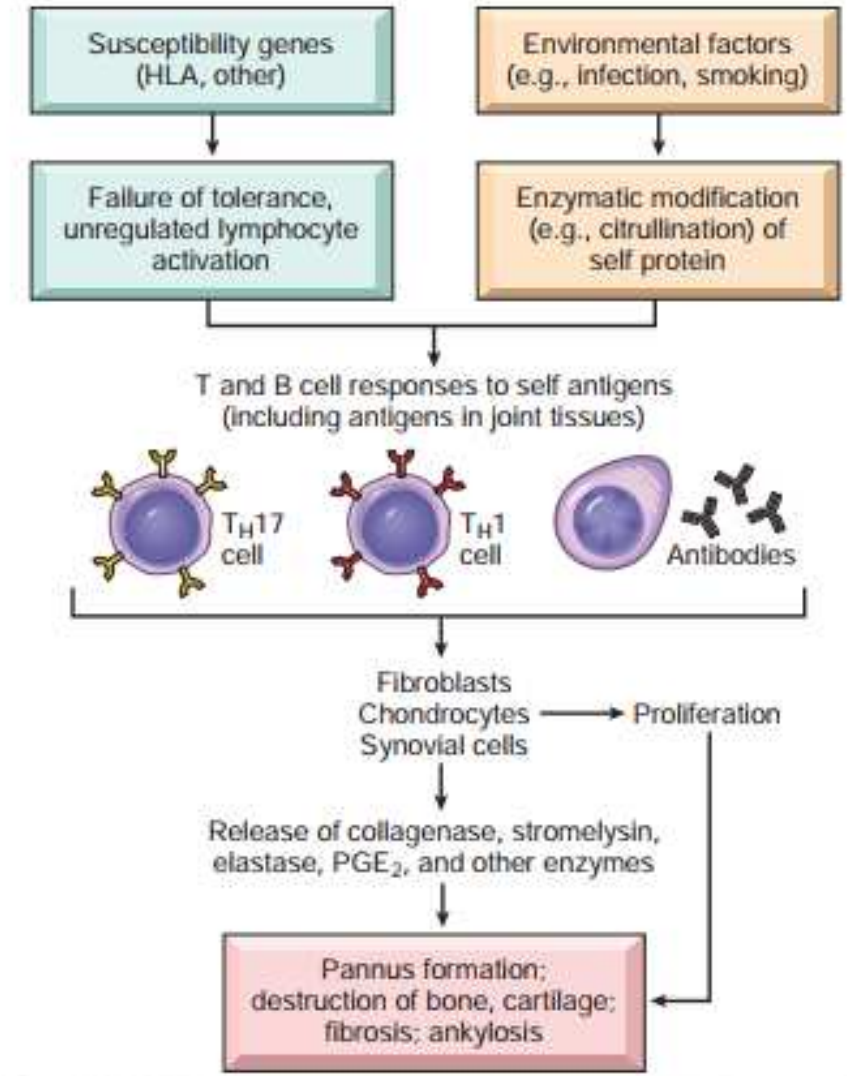


Figure 26-42 Major processes involved in the pathogenesis of rheumatoid arthritis.

Rheumatoid arthritis

- The characteristic histologic features include:
- (1) synovial cell hyperplasia and proliferation;
- (2) dense inflammatory infiltrates (frequently forming lymphoid follicles) of CD4+ helper T cells, B cells, plasma cells, dendritic cells, and macrophages
- (3) increased vascularity due to angiogenesis
- (4) fibrinopurulent exudate on the synovial and joint surfaces
- (5) osteoclastic activity in underlying bone, allowing the synovium to penetrate into the bone and cause periarticular erosions and subchondral cysts.

Rheumatoid arthritis

- Pannus is characterized by synovial cell proliferation associated with focal collections of lymphocytes and a reactive fibrosis that grows over the articular cartilage and causes its erosion.
- In time, after the cartilage has been destroyed, the pannus bridges the apposing bones to form a fibrous ankylosis, which eventually ossifies and results in fusion of the bones (ankylosis)

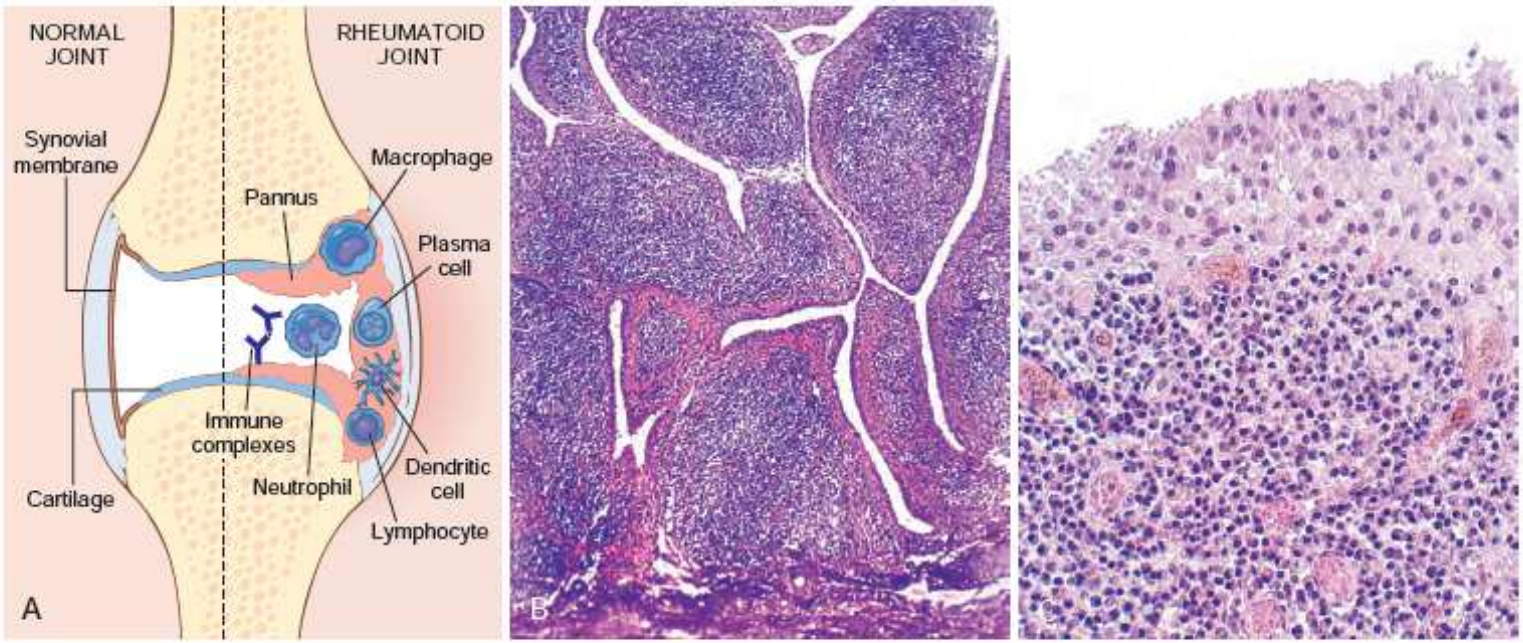
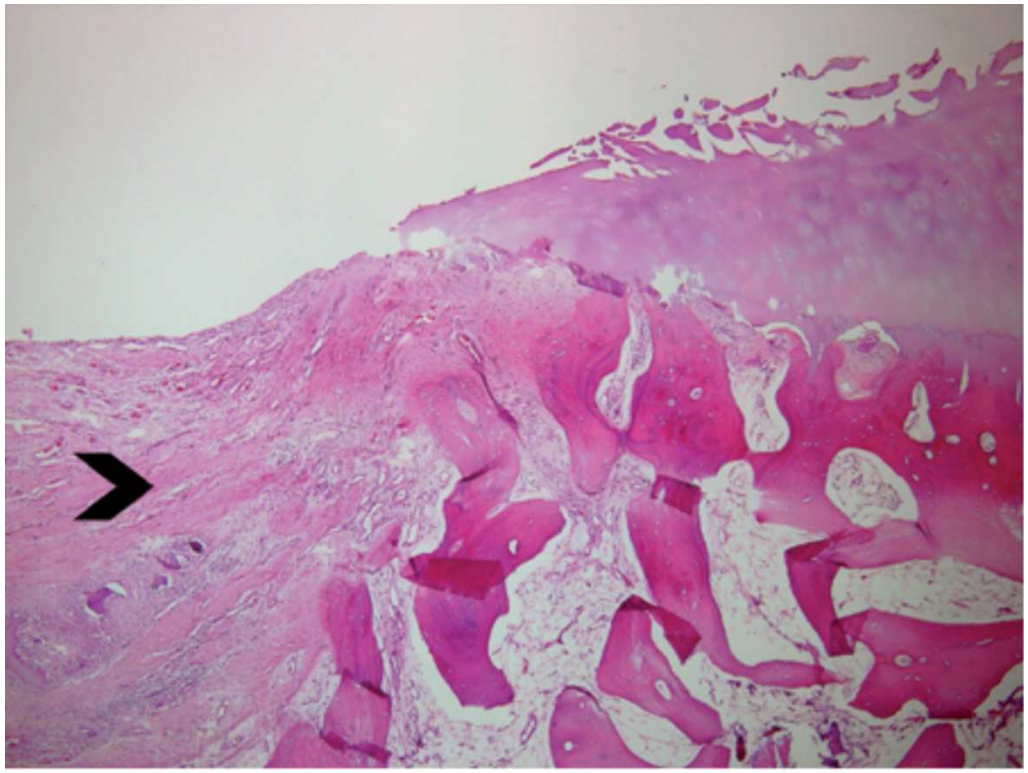


Figure 26-43 Rheumatoid arthritis. **A,** Schematic view of the joint lesion. **B,** Low magnification reveals marked synovial hypertrophy with formation of villi. **C,** At higher magnification, subsynovial tissue containing a dense lymphoid aggregate. (**A,** Modified from Feldmann M: Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2:364, 2002.)

Pannus



Source: Kemp WL, Burns DK, Brown TG: *Pathology: The Big Picture*: www.accessmedicine.com

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Figure 19-10 **Accessed 02/03/2016**

The inflammation associated with rheumatoid arthritis can lead to fibrosis of synovial tissues (arrowhead) and fusion of the joint (ankylosis). Hematoxylin and eosin, 40×.

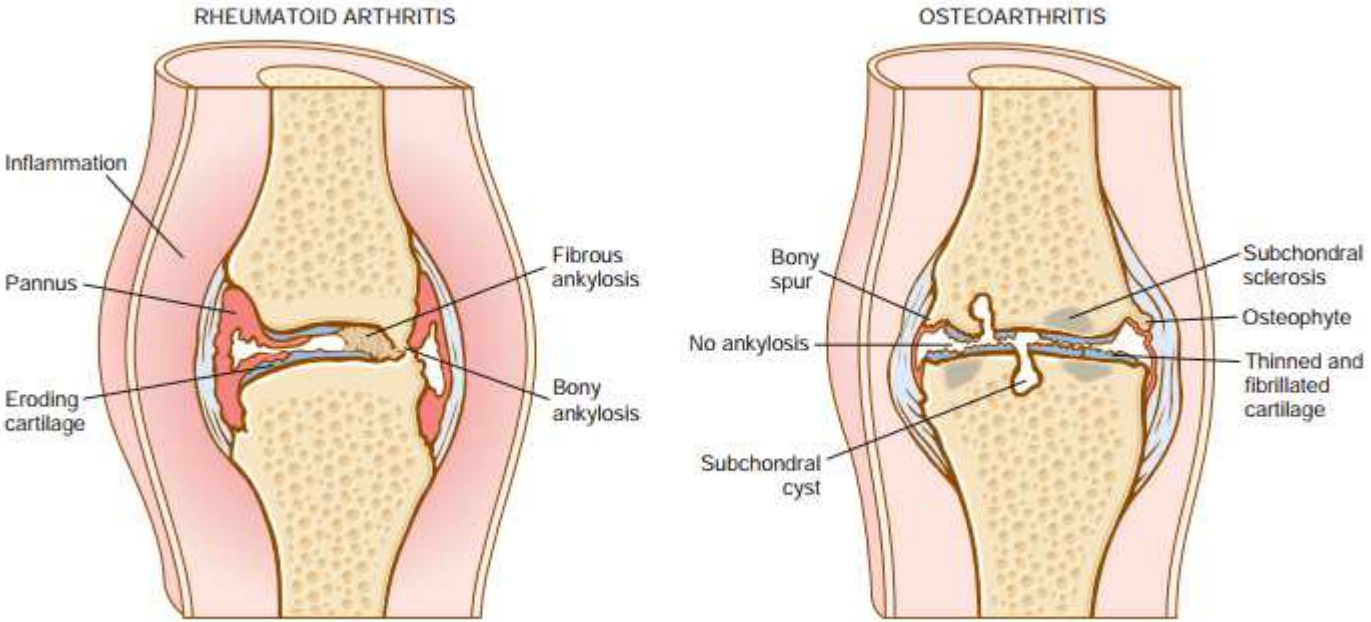
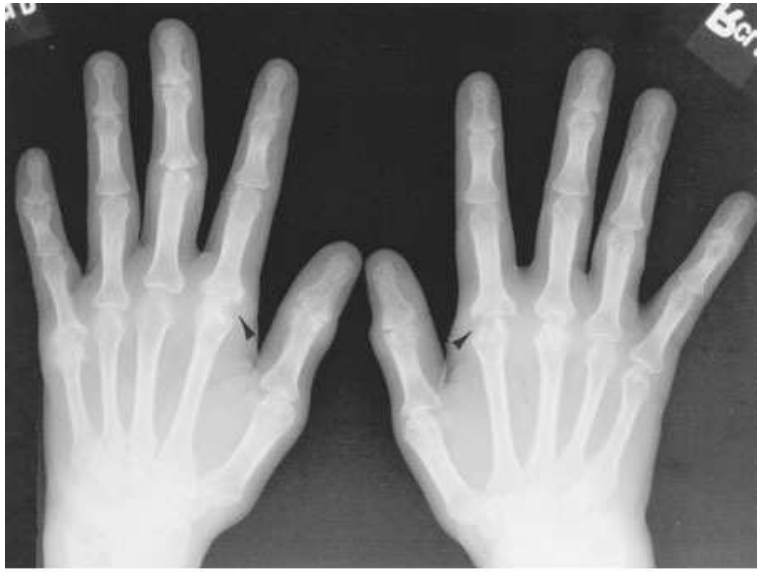


Figure 26-41 Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.

Rheumatoid arthritis



Chen, MYM, Pope Jr., TL, Ott DJ: *Basic Radiology*: http://www.accessmedicine.com

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Frontal view of both hands in a patient with long-standing rheumatoid arthritis showing marked carpal destruction and radiocarpal joint narrowing with substantial erosive change as well as the characteristic "bare area" erosions best exhibited at the second metacarpo-phalangeal joint (arrowheads). Also note the soft-tissue swelling at multiple joints. Deviation of digits is a late change.

Fig. 7-42 Accessed 08/01/2010

Rheumatoid nodule

- Major extra-articular manifestation of rheumatoid arthiritis.
- Present in 25% of patients.
- Lesions are found in areas of skin subject to pressure. They are firm subcutaneous non-tender nodules.
- Positive likelihood ratio (LR+) >30.

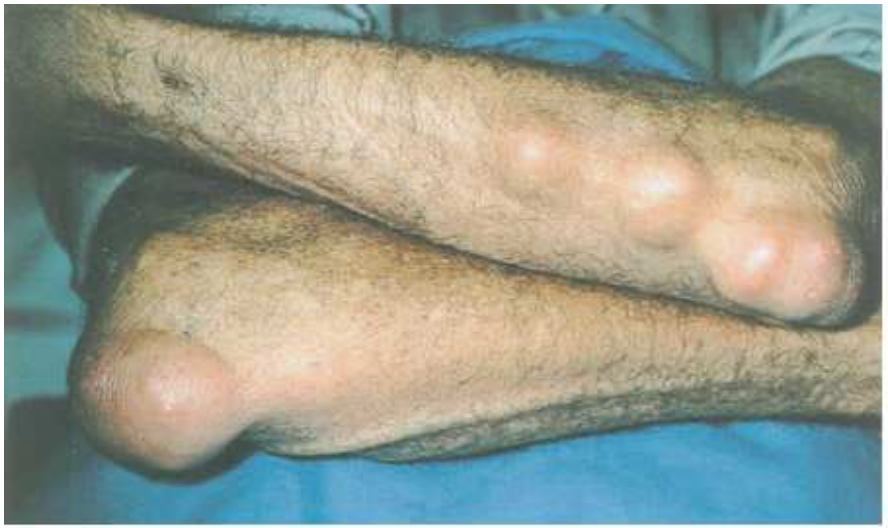

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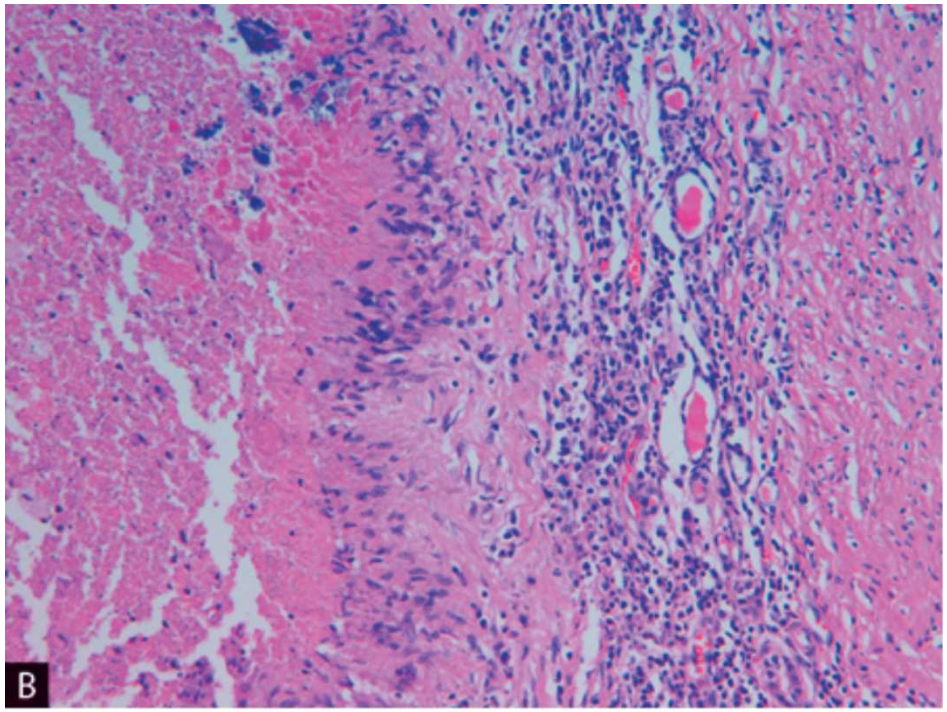
Fig. e10-75 Accessed 07/01/2010

Rheumatoid nodule



Source: Kemp WL, Burns DK, Brown TG: *Pathology: The Big Picture*: www.accessmedicine.com

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Figure 3-3B Accessed 02/03/2016

Subcutaneous rheumatoid nodule with a central area of fibrinoid necrosis (top) surrounded by a palisade of epithelioid histiocytes, macrophages, and lymphocytes (B, CD4 Th1, and CD28- T cells).
H&E 400x

Rheumatoid arthritis vasculitis

- Affected individuals with severe erosive disease, rheumatoid nodules, and high titers of rheumatoid factor are at risk of developing vasculitis.
- The acute necrotizing vasculitis involves small and large arteries. It may involve the pleura, pericardium or lung evolving into chronic fibrosing processes.
- Frequently, segments of small arteries such as vasa nervorum and the digital arteries are obstructed by an obliterating endarteritis resulting in peripheral neuropathy, ulcers, and gangrene.

Rheumatoid arthritis vasculitis

- Leukocytoclastic vasculitis produces purpura, cutaneous ulcers, and nail bed infarction.
- Ocular changes such as uveitis and keratoconjunctivitis may be prominent.
- 5-10% of rheumatoid arthritis patients will develop amyloidosis.

Rheumatoid lung disease

- Once referred to as Hamman-Rich syndrome.
- Diffuse alveolar damage resulting from "repeated cycles" of acute lung injury (alveolitis).
- There is damage to alveolar epithelial cells (with secondary microvascular injury) and Type II pneumocyte hyperplasia.
- Reparative changes at these sites give rise to exuberant fibroblastic proliferation and fibrous nodules.
- Both non-caseating granulomata and vasculitis are found in active rheumatoid arthritis involving the lung.

Rheumatoid lung disease

- Mediators of repair such as TGF-β are expressed at these sites.
- The inflammatory response is thought to be of the T_{H2} type.
- Thus, eosinophils, mast cells, and IL-4 and IL-13 are found in the lesions.
- Pulmonary capillary hydrostatic pressure is usually not elevated
- Hemodynamic factors play a secondary role.

Indicators of poor prognosis in rheumatoid arthritis

- Female sex
- Functional disability
- Number of joints involved
- Older age at onset
- High titer of rheumatoid factor
- HLA-D4, particularly if homozygous
- Extra-articular manifestations, particularly if vasculitis or skin nodules
- Structural damage or deformity
- Uncontrolled polyarthritis

Management of rheumatoid arthritis

- NSAIDs remain an important component of pharmacotherapy because of their analgesic and anti-inflammatory properties.
- Early aggressive therapy with disease modifying anti-rheumatic drugs (DMARDs) has become the standard of care.
- Methotrexate is the drug of choice for monotherapy.
- Gold and antimalarial agents inhibit the induction of TNF-α and IL-1
- Methotrexate acts as general immuno-suppressant.

Management of rheumatoid arthritis

- Etanercept reduces circulating TNF.
- Treatment-naïve patents, those with DMARD-refractory RA, and those with moderately to severe active RA
- Not recommended in patients with congestive heart failure or with demyelinating disease
- Fever and chills with intravenous infusion are common (cytokine release).
- Sarucimab (IL-6 inhibitor) in DMARD failure.
- They may be used in combination with methotrexate.

Juvenile idiopathic arthritis

- Six types
- Develops in those younger than16 years of age.
- Affects four or fewer joints during the first 6 months of disease.
- Oligoarthritis: Affects four or fewer joints, typically knees, ankles, elbows.
- 60% of JIA.
- 4:1 girls
- Peak incidence at age 3
- 20% with iridiocyclitis (uveitis)
- 80% have positive ANA (titer correlates with uveitis)

Juvenile idiopathic arthritis

- Polyarthritis (RF negative): Affects five or more joints, often on both sides of the body
- May affect large and small joints.
- Affects about 25% of children with JIA.
- 4:1 girls
- Peak incidence at age 3
- Uveitis if positive ANA
- 25% of patients are ANA positive

Juvenile idiopathic arthritis

- Polyarthritis (RF positive): Affects five or more joints, often on both sides of the body
- May affect large and small joints.
- Affects about 25% of children with JIA.
- 9:1 girls
- Peak incidence in adolescence
- Rheumatoid nodules present
- 75% ANA positive

Juvenile idiopathic arthritis

- Systemic: Affects joints, skin and internal organs.
- Symptoms may include a high spiking fever (103°F or higher) that lasts at least two weeks, and a migratory salmon-pink macular skin rash.
- Macrophage activation syndrome (cytokine storm) may occur in a subset of patients
- Will have frequent flares over a lifetime.
- Affects about 10-20% of children with JIA.
- Both sexes equally affected
- RF and ANA negative

Juvenile idiopathic arthritis

- Psoriatic arthritis: Asymmetric joint involvement of small and large joints, particularly hips and DIP joints
- Scaly rash behind the ears and/or on the eyelids, elbows, knees, umbilicus, and scalp.
- Nail pitting.
- Skin symptoms may occur before or after joint symptoms appear.
- 10% uveitis
- Age 5-15 years
- 3:2 girls

Juvenile idiopathic arthritis

- Enthesitis-related (spondyloarthritis): Affects where the muscles, ligaments or tendons attach to the bone (entheses).
- Commonly affects the hips, knees and feet, but may also affect the fingers, elbows, pelvis, chest
- Sacroilitis and inflammatory bowel disease
- Ankylosing spondylitis.
- Uveitis in 20%
- More common in boys
- Typically appears in adolescence
- HLA B27 positive

Other cartilage disorders

- Alkaptonuria
- Brown-black discoloration of cartilage
- Deposition of homogentisic acid
- Hardening of tendons, ligaments, heart valves
- Prone to rupture
- Chronic inflammation
- Brown pigment spots on corneal limbus; hyperpigmentation of sclerae

Charcot joint

- Peripheral nerve neuropathy, usually ankle and foot
- Diabetes, Sarcoid, Syphilis, Psoriatic arthritis as causes
- Soft tissue swelling and microfractures destroy joint
- Rocker-bottom feet, bony protrusions noted
- Reparative phase may not correct deformity

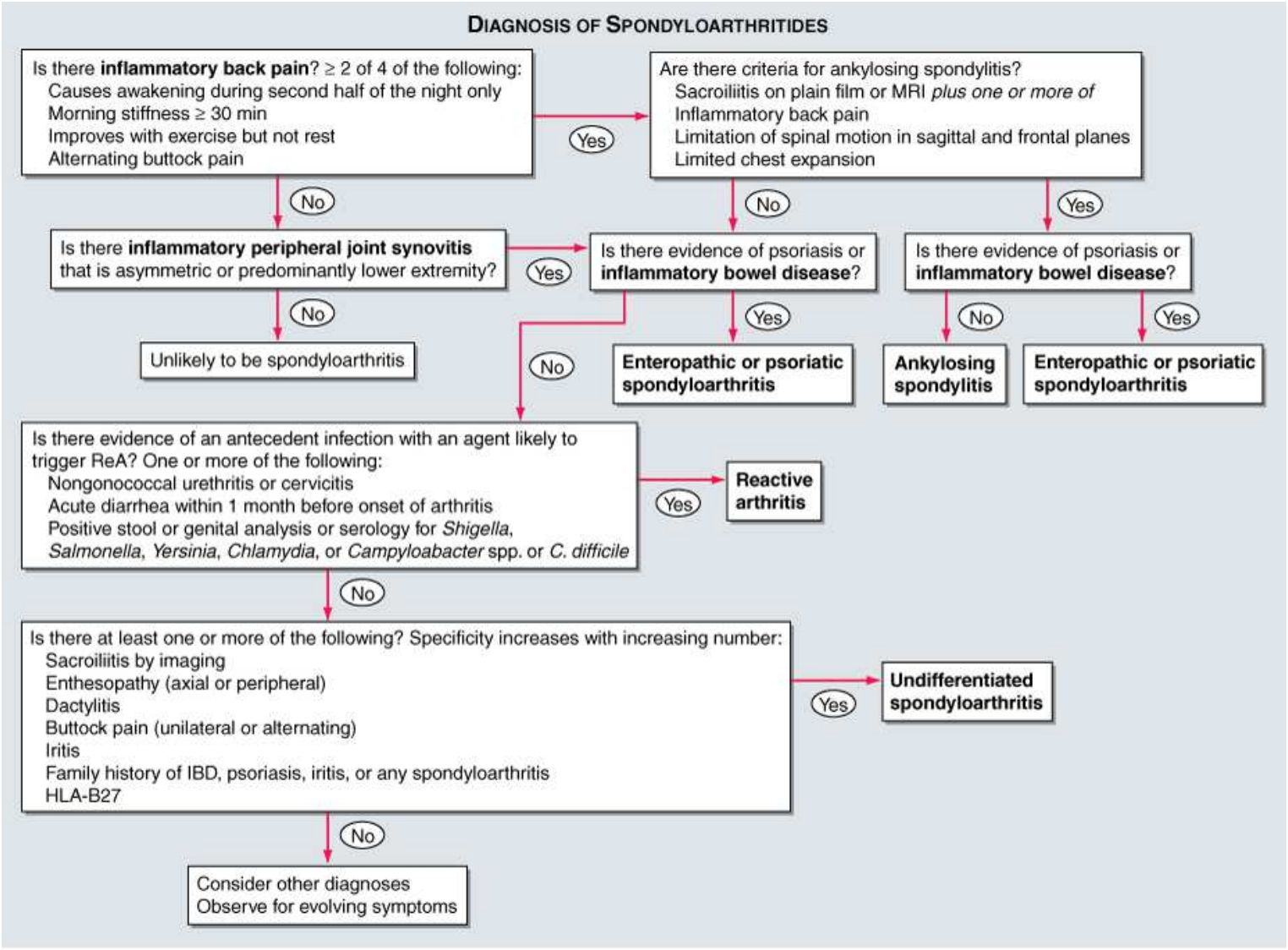

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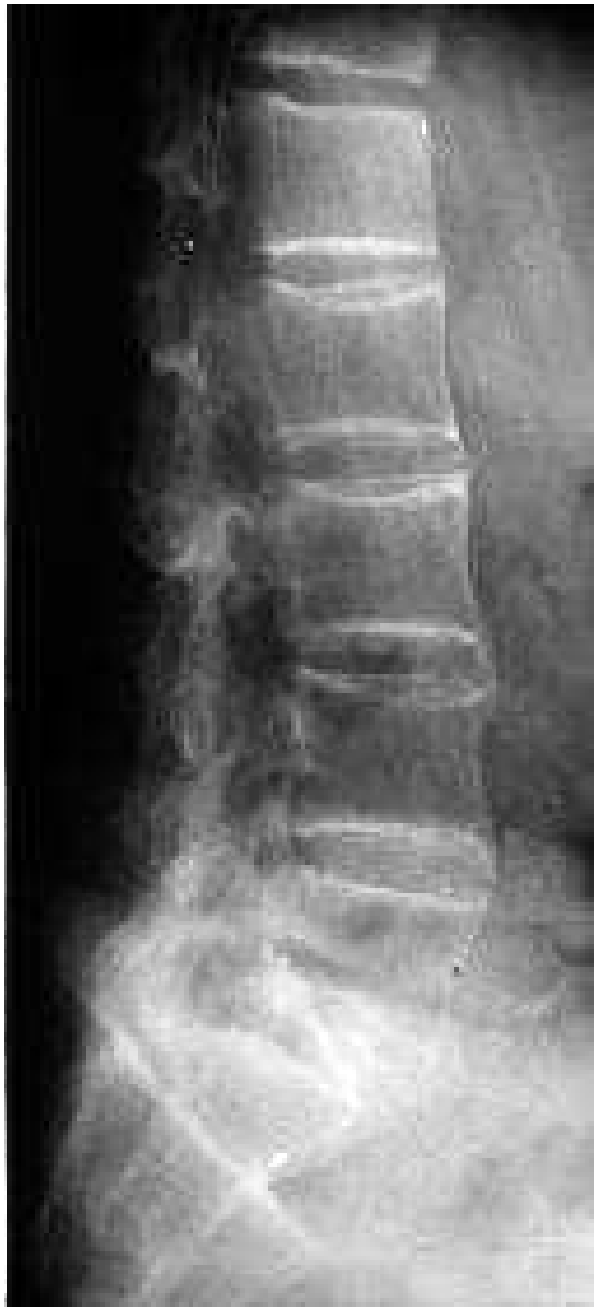
Fig. 318-4 Accessed 08/01/2010

Ankylosing spondylitis

- Gradual onset of intermittent bouts of lower back pain and stiffness.
- Worse in the morning
- Improves with heat and exercise.
- May have tenderness at the costochondral junctions, spinous processes, scapulae, iliac crests, and heels which are indicative of sacroiliitis and spondylitis.
- Acute anterior uveitis can cause blurred vision, lacrimation, and photophobia.
- Aortic insufficiency is another potential complication.

Ankylosing spondylitis

- Causes destruction of articular cartilage and bony ankylosis, especially of the sacroiliac and apophyseal joints (between tuberosities and processes)
- 90% are HLAB27 associated
- Sacroiliitis of inflammatory bowel disease as well
- X-rays of the hip will show sacroiliac joint erosions and sclerosis.
- X-rays of the spine shows calcification of the spinal ligaments and a “bamboo spine”.
- Treatment includes NSAIDS and physical therapy.
- Sulfasalazine used in treatment of sacroiliitis of inflammatory bowel disease.



Bamboo spine

Reactive arthritis

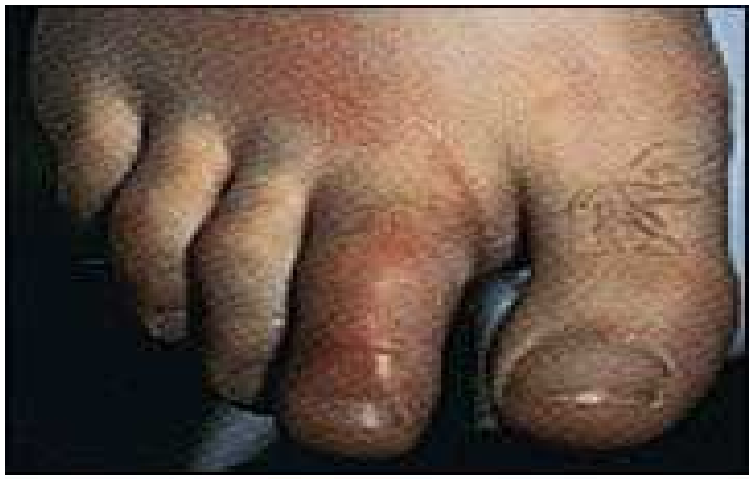
- Once known as Reiter's syndrome.
- Triad of arthritis, non-gonococcal urethritis or cervicitis, and conjunctivitis.
- Most affected individuals are men in their 20s or 30s
- >80% are HLA-B27 positive.
- This form of arthritis also affects HIV infected individuals
- An autoimmune reaction initiated by prior infection of the genitourinary system (Chlamydia) or the gastrointestinal tract (Shigella, Salmonella, Yersinia, Campylobacter).

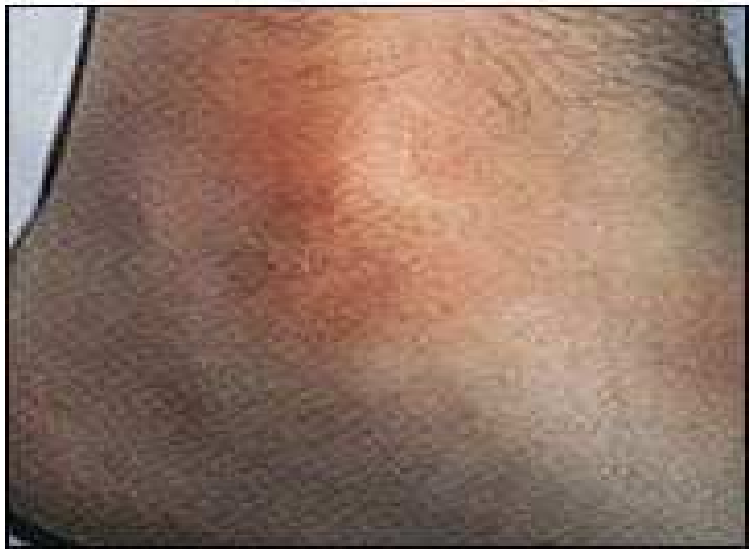
Reactive arthritis

- The ankles, knees, and feet are affected most often, frequently in an asymmetric pattern.
- Synovitis of a digital tendon sheath produces the sausage finger or toe
- Ossification of tendoligamentous insertion sites leads to calcaneal spurs and bony outgrowths.
- May have involvement of the spine that is indistinguishable from ankylosing spondylitis.
- Extraarticular involvement manifests as inflammatory balanitis, conjunctivitis, cardiac conduction abnormalities, and aortic regurgitation.

Reactive arthritis

- The episodes of arthritis usually wax and wane over several weeks to 6 months.
- Almost 50% of affected individuals have recurrent arthritis, tendonitis and lumbosacral pain.
- If obtained, synovial fluid WBC usually is <50,000 cells/μL





Swollen “sausage” toe (top) and inflamed ankle (bottom) in a patient with reactive arthritis

Barth,W, and Segal, K, “Reactive arthritis,” Am Fam Physician 1999; 60(2):499-503
Fig. 1
Accessed 03/20/2020

Enteritis associated arthritis

- The outer cell membranes of Yersinia, Salmonella, Shigella, and Campylobacter have lipopolysaccharides as a major component
- Stimulate a range of immunological responses.
- Usually arises abruptly
- Usually involves wrists and ankles
- May last a year, then clear
- Rarely accompanied by ankylosing spondylitis.

Psoriatic arthritis

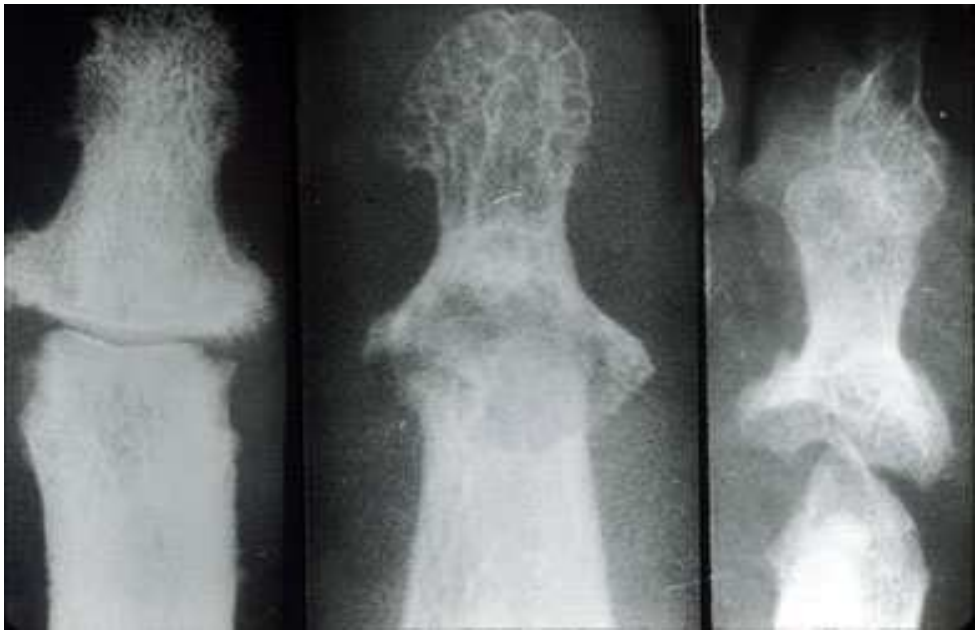
- Psoriatic arthritis is a chronic inflammatory arthropathy associated with psoriasis that affects peripheral and axial joints and entheses (ligaments and tendons).
- Susceptibility to the disease is related to HLA-B27 and HLA-Cw6 alleles.
- 30-50 years of age
- 10% of psoriatic population
- HLA-B27 association in 50% of patients
- 20% of patients will have sacroilitis

Psoriatic arthritis

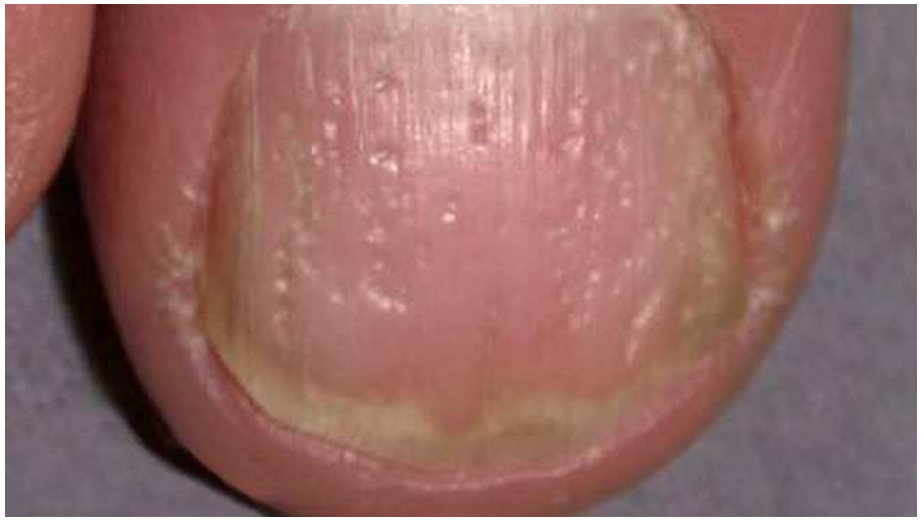
- Positive family history.
- Pruritic red rash with white scales
- Affects back, scalp, forearms and shins principally
- Nail pitting
- Painful tendon or ligament insertions (enthesitis).
- Achilles tendon involvement is common
- 70% have asymmetric oligoarthritis
- Sausage digits (dactylitis)
- Joints of fingers and wrist usually affected
- DIP joint involvement of fingers and toes distinguishes from rheumatoid arthritis

Psoriatic arthritis

At right: “pencil in cup” appearance on x-ray



Below: pitted nails



Psoriatic arthritis

- Treat with NSAIDs, physical therapy, local corticosteroid injections.
- Methotrexate may be monotherapy.
- Slow-acting DMARDs such as intramuscular gold injections and oral hydroxychloroquine may also be utilized.

Tempero-mandibular joint disease

- Anterior dislocation may be noted as a result of excessive contraction of the lateral pterygoids.
- Traumatic arthritis
- Oral appliance may relieve pressure on joint
- Bruxation or grinding of teeth while asleep
- NSAIDs or intra-articular corticosteroids for pain relief.

Movement of the tempero-mandibular joint

- Temporalis and masseter muscles are superficial. Involved with mastication.
- Lateral pterygoid assisted by medial pterygoid contols protrusion of the mandible.
- Posterior fibers of the temporalis, deep part of masseter, geniohyoid, and digastric muscles control retraction of mandible.
- Temporalis, masseter, and medial pterygoid elevate mandible.
- Digastric, geniohyoid, and mylohyoid muscles depress mandible.

Muscles acting on the tempero- mandibular joint

- The temporal muscle elevates the mandible, closing the jaws.
- Posteriorly, more horizontal fibers retract the mandible.
- The masseter elevates the mandible, closing the jaws
- Acts in synergy with the medial pterygoid
- Both are innervated by CN V.

Muscles acting on the tempero- mandibular joint

- The lateral pterygoid muscles (bilateral) protract the mandible and depress the chin.
- Acting unilaterally, it swings the jaw toward the contralateral side.
- Alternate unilateral contraction produces chewing movements.
- The medial pterygoid contributes to jaw protrusion
- Alternate unilateral contraction produces grinding movements
- Both muscles are innervated by CN V.

Muscles acting on the tempero- mandibular joint

- The digastric depresses the mandible against resitance when infrahyoid muscles fix or depress the hyoid bone.
- Innervated by CN V and VII.
- The omohyoid fixes or depresses the hyoid bone.
- Innervation from C1-3.
- The platysma depresses the mandible against resistance.
- Innervated by CN VII.

Tempero-mandibular joint disease

- The latral temero-mandibular ligament strengthens the lateral aspect of the joint.
- The spheno-mandibular ligament descends from near the spine of the sphenoid to the lingula of the mandible and is the hinge on which the mandible is suspended.
- The stylo-mandibular ligament is part of the parotid sheath that inserts on the angle of the mandible.
- Both superior and inferior potions of the joint are lined by synovium.

Tempero-mandibular joint disease

Anterior dislocation may be noted as a result of excessive contraction of the lateral pterygoids.

Traumatic arthritis

Oral appliance may relieve pressure on joint (bruxation or grinding of teeth while asleep).

NSAIDs or intra-articular corticosteroids for pain relief.

Tenosynovial giant cell tumor

- It usually arises in patients in their twenties to forties.
- Monoarticular
- 80% of cases involve the knee.
- Hip, ankle and calcaneocuboid may also be involved.
- Once known as giant cell tumor of tendon sheath (localized) and as pigmented villonodular synovitis (diffuse)
- Nodular proliferation of synovial tissue
- Hyperplastic

Tenosynovial giant cell tumor

- Red-brown
- Composed of uniform oval mononuclear cells (CD68+) that have indistinct cell membranes and appear to grow in a syncytium.
- Mitoses are frequent.
- Scattered within this background are numerous giant cells (CD68+) believed to form via fusion of the mononuclear cells.
- RANKL present on cells
- Necrosis, hemorrhage, hemosiderin deposition, and reactive bone formation are common secondary features.

Tenosynovial giant cell tumors

- Recur
- Localized tumors are well circumscribed.
- May be locally invasive with bone cyst formation and loss of bone and cartilage
- In nodular tumors, the cells grow in a solid aggregate that may be attached to the synovium by a pedicle.
- In diffuse tumors the normally smooth joint synovium is converted into a tangled mat by red-brown folds, finger-like projections, and nodules.
- In the diffuse variant they spread along the surface and infiltrate the sub-synovial issue.

Tenosynovial giant cell tumors

- t(1;2)(p13;q37), resulting in fusion of the type VI collagen α-3 promoter upstream of the monocyte colony-stimulating factor (M-CSF) gene.
- Stimulates proliferation of macrophages

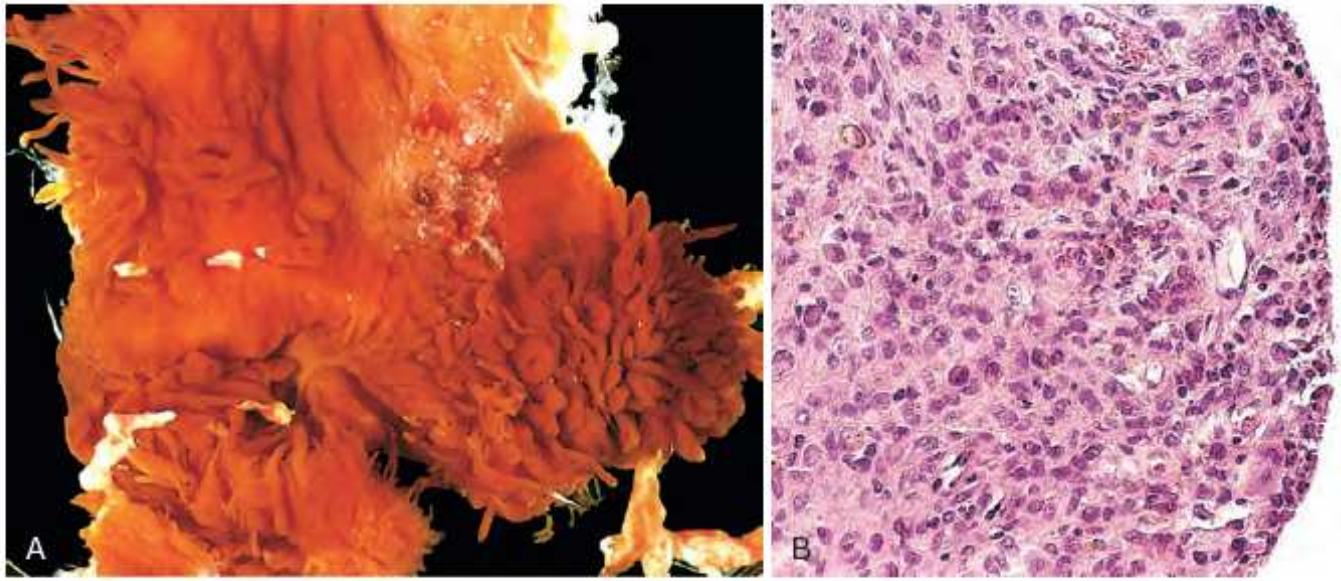


Figure 26-49 Tenosynovial giant cell tumor, diffuse type. **A,** Excised synovium with fronds and nodules typical of pigmented villonodular synovitis *(arrow)*. **B,** Sheets of proliferating cells in tenosynovial giant cell tumor bulging the synovial lining.

Tenosynovial giant cell tumor

Fig. 9-3 Kempson, Richard L., Fletcher, Christophr DM,