Joint diseases

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Osteoarthritis

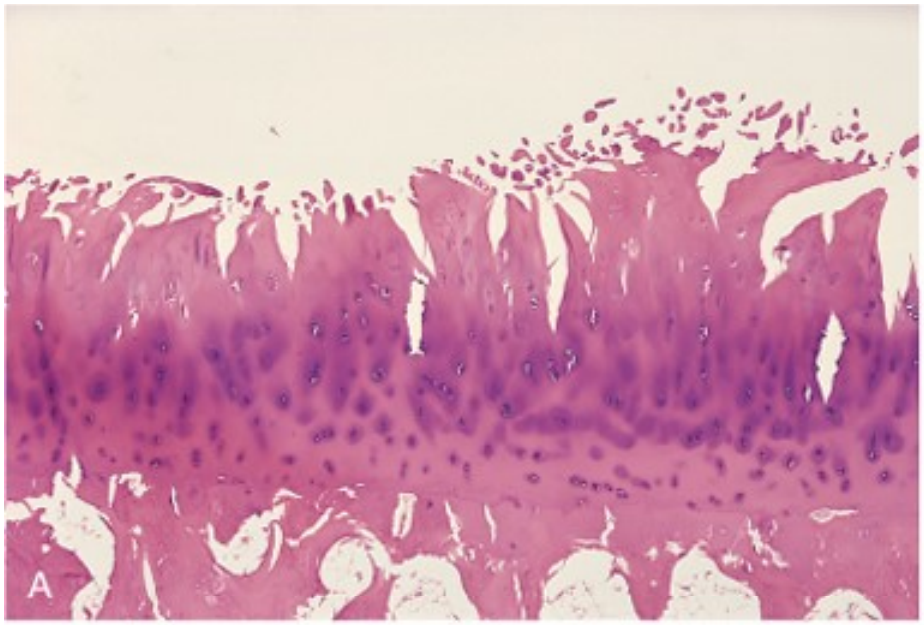
- Degenerative joint disease
- The most common joint disorder
- Important cause of physical disability in individuals over the age of 65
- Primary OA: most common, insidious onset, no initiating factor, oligoarticular
- Secondary OA: 5% of cases, young age, history of trauma, DM, hemochromatosis, marked obesity, one or many joints
- Gender has some influence; knees and hands are more commonly affected in women, whereas hips are more commonly affected in men

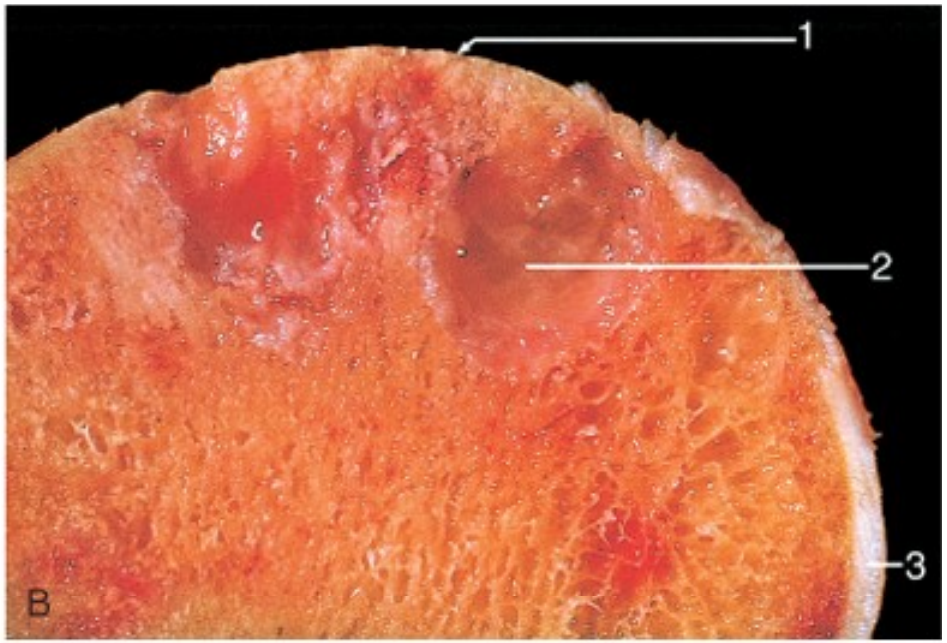
Pathogenesis

- The fundamental feature of osteoarthritis is degeneration of the articular cartilage
- Bone changes are secondary
- Inflammation can be present as a minor component
- Normal function of joint cartilage: prevents friction and spreads load across the joint to protect the underlying bone
- *Normal cartilage is elastic,* regain normal architecture after compression (proteoglycans), and to have high tensile strength (collagen II), both produced by chondrocytes
- Mechanical stresses and aging causes damage to chondrocytes
- Degenerating cartilage contains more water and less proteoglycan and collagen, its function is compromised

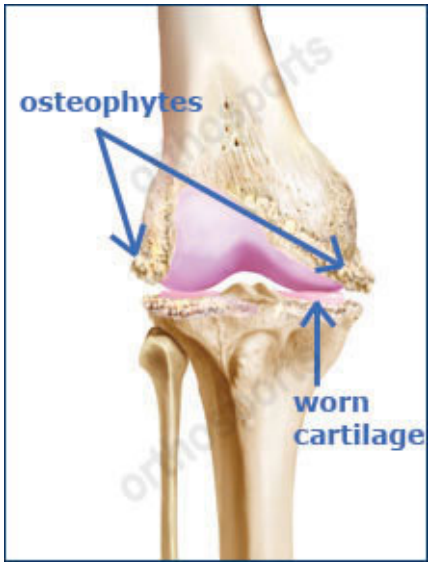
Morphology

- Early: proliferation and disorganization of the chondrocytes in the superficial part of the articular cartilage
- Later: vertical and horizontal **cracking of the matrix** occur as the superficial layers of the cartilage
- Small fractures can dislodge pieces of cartilage and subchondral bone into the joint, forming loose bodies **(joint mice)**
- With time, the subchondral bone plate is exposed
- Friction smooths and burnishes the exposed bone, giving it the appearance of polished ivory **(bone eburnation)** bone becomes sclerotic and thickened
- Mushroom-shaped **osteophytes** (bony outgrowths) develop at the margins of the articular surface
- Synovium moves into subchondral bone and forms cysts. In severe disease, a fibrous synovial **pannus** covers the peripheral portions of the articular surface





- Osteoarthritis. **A,** Histologic demonstration of the characteristic fibrillation of the articular cartilage. **B,** Severe osteoarthritis with 1, Eburnated articular surface exposing subchondral bone. 2, Subchondral cyst. 3, Residual articular cartilage



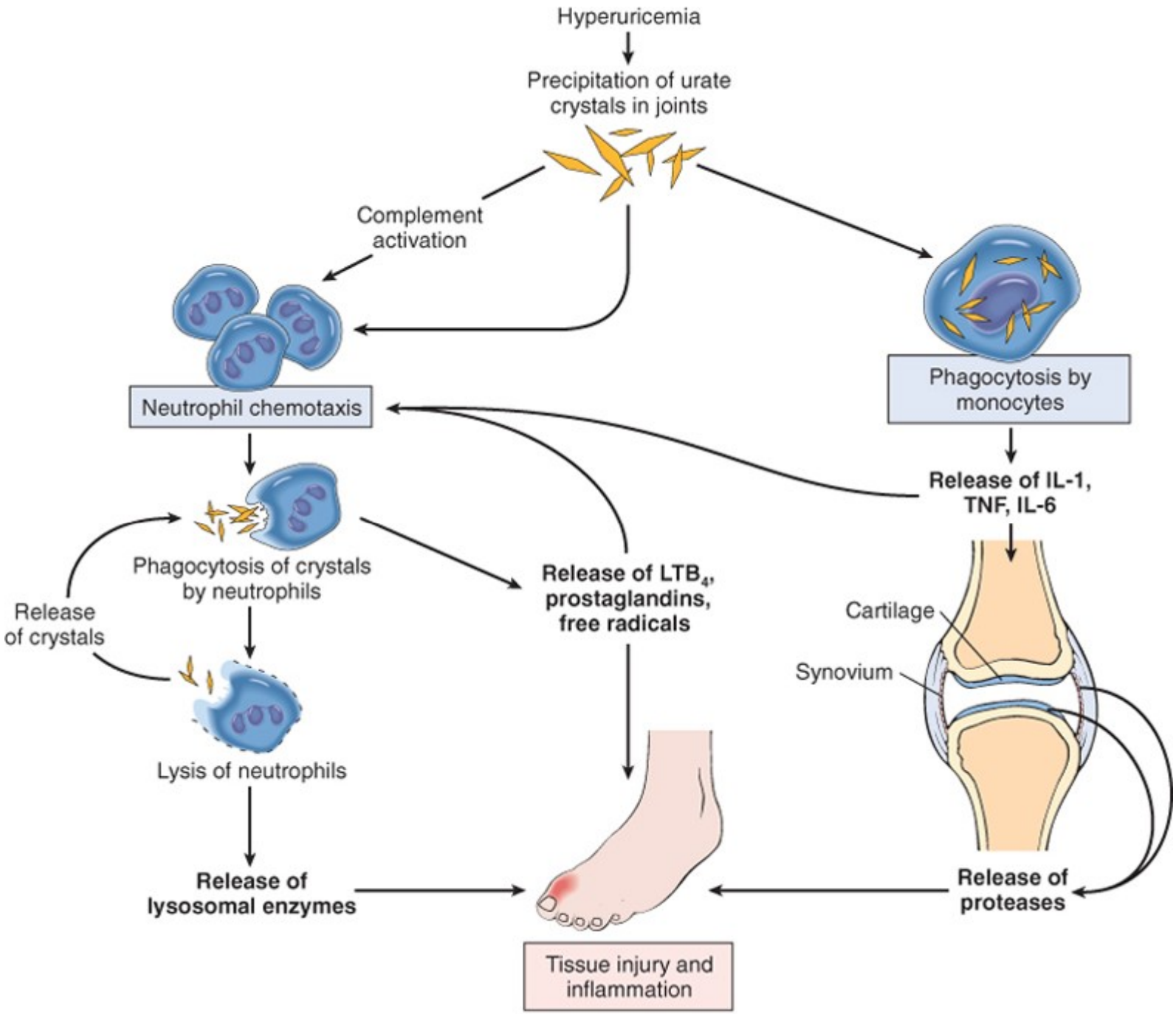
Clinical features

- Osteoarthritis is an insidious
- Patients, in their 50s and 60s
- Characteristic symptoms include deep, aching pain exacerbated by use, morning stiffness, crepitus, and limited range of movement
- *Heberden nodes* in the fingers, representing prominent osteophytes at the distal interphalangeal joints, are characteristic in women
- With time, significant joint deformity can occur, but unlike rheumatoid arthritis, fusion does not take place

Gout

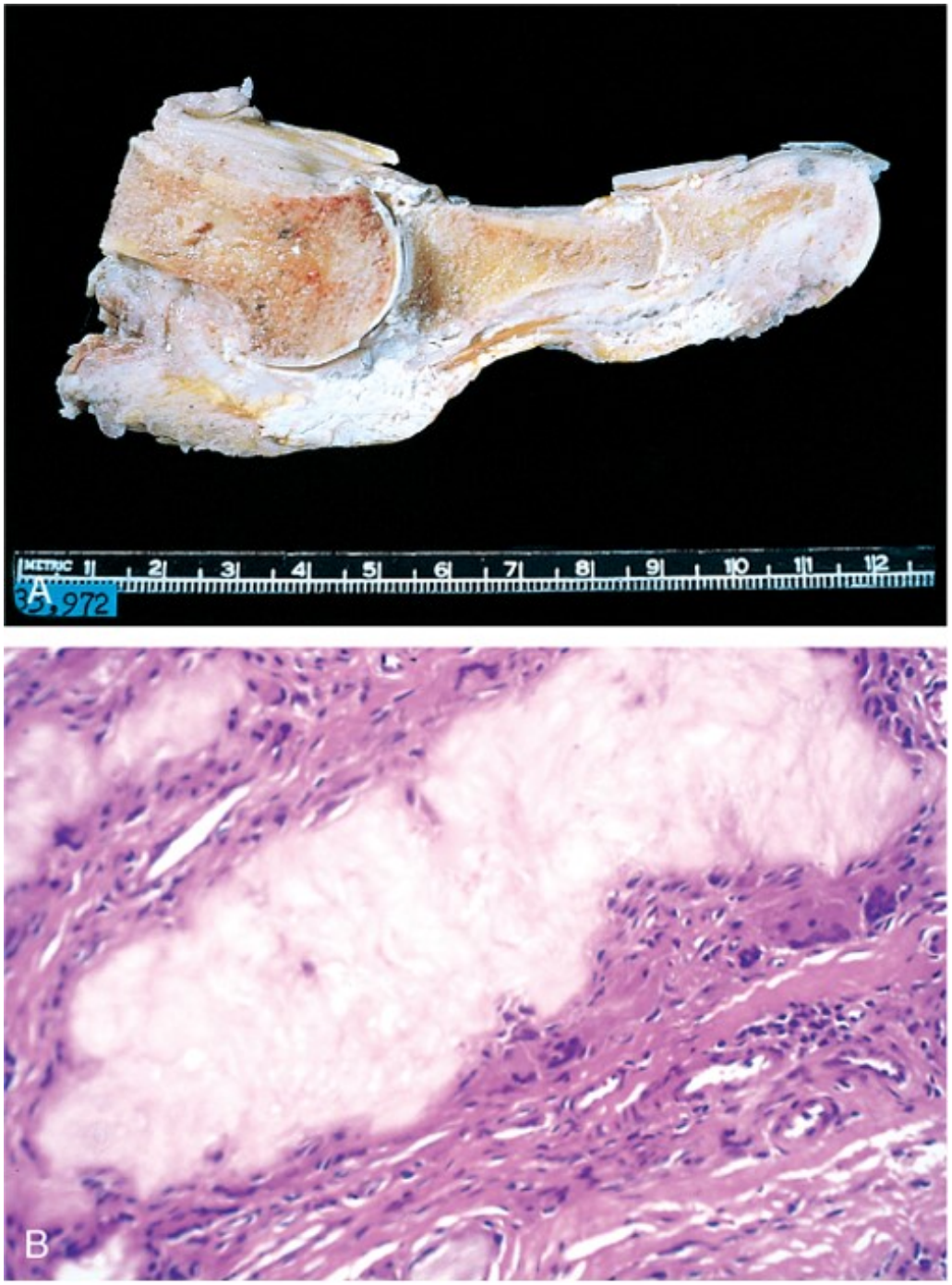
- Metabolic disease
- Accumulation of excessive amounts of *uric acid (end product of purine metabolism)* and form monosodium urate crystals
- *Primary gout (90%),* basic cause is unknown or (less commonly) when it is due to an inborn metabolic defect that causes hyperuricemia
- S*econdary gout (10%)* the cause is known, but gout is not necessarily the main or even dominant clinical disorder

Clinical Category	Metabolic Defect
Primary Gout (90% of cases)	
Enzyme defects unknown (85% to 90% of primary gout)	Overproduction of uric acid Normal excretion (majority) Increased excretion (minority) Underexcretion of uric acid with normal production
Known enzyme defects-e.g., partial HGPRT deficiency (rare)	Overproduction of uric acid
Secondary Gout (10% of cases)	
Associated with increased nucleic acid turnover-e.g., leukemias Chronic renal disease Inborn errors of metabolism	Overproduction of uric acid with increased urinary excretionReduced excretion of uric acid with normal productionOverproduction of uric acid with increased urinary excretion e.g., complete HGPRT deficiency (Lesch-Nyhan syndrome)



Clinical

- **Acute arthritis**: dense neutrophilic infiltrate permeating the **synovium** and synovial fluid. Long, slender, needle-shaped **monosodium urate crystals** are frequently found in the cytoplasm of the neutrophils and in the synovium. Big-toe is a common site.
- **Chronic tophaceous arthritis**: repetitive acute attacks. Synovium forms a pannus that destroys the underlying cartilage, and leading to bone erosions. In severe cases: ankylosis (bone fusion)
- **Tophi:** large aggregations of urate crystals surrounded by an intense inflammatory reaction of lymphocytes, macrophages, and foreign-body giant cells. Tophi appear in cartilage of joints, ligaments, tendons, and soft tissues, including the ear lobes, nasal cartilages, and skin of the fingertips
- **Gouty nephropathy:** medullary tophi, intratubular precipitations, or free uric acid crystals and renal stones (radiolucent), can cause obstruction,



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- Gout. **A,** Amputated great toe with white tophi involving the joint and soft tissues. **B,** Photomicrograph of a gouty tophus. An aggregate of dissolved urate crystals is surrounded by reactive fibroblasts, mononuclear inflammatory cells, and giant cells.

Pseudogout

- AKA chondrocalcinosis
- Calcium pyrophosphate crystal deposition disease
- Pseudogout typically first occurs in those age 50 or older
- Accumulation and crystallization with calcium
- Recruitment and activation of inflammatory cells
- Joint involvement can last from several days to weeks (subacute)
- may be monoarticular or polyarticular; the knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected
- Ultimately, approximately 50% of patients experience significant joint damage
- Therapy is supportive; no known treatment prevents or retards crystal formation

Infectious arthritis

- Hematogenous, or complication of osteomyelitis
- Rapid destruction of joint structures and permanent deformity (sudden pain, fever)
- *Haemophilus influenzae* <2 years
- *S. aureus* is the main causative agent in older children and adults
- *gonococcus* is prevalent during late adolescence and young adulthood
- Individuals with sickle cell disease are prone to infection with *Salmonella* at any age

Lyme disease

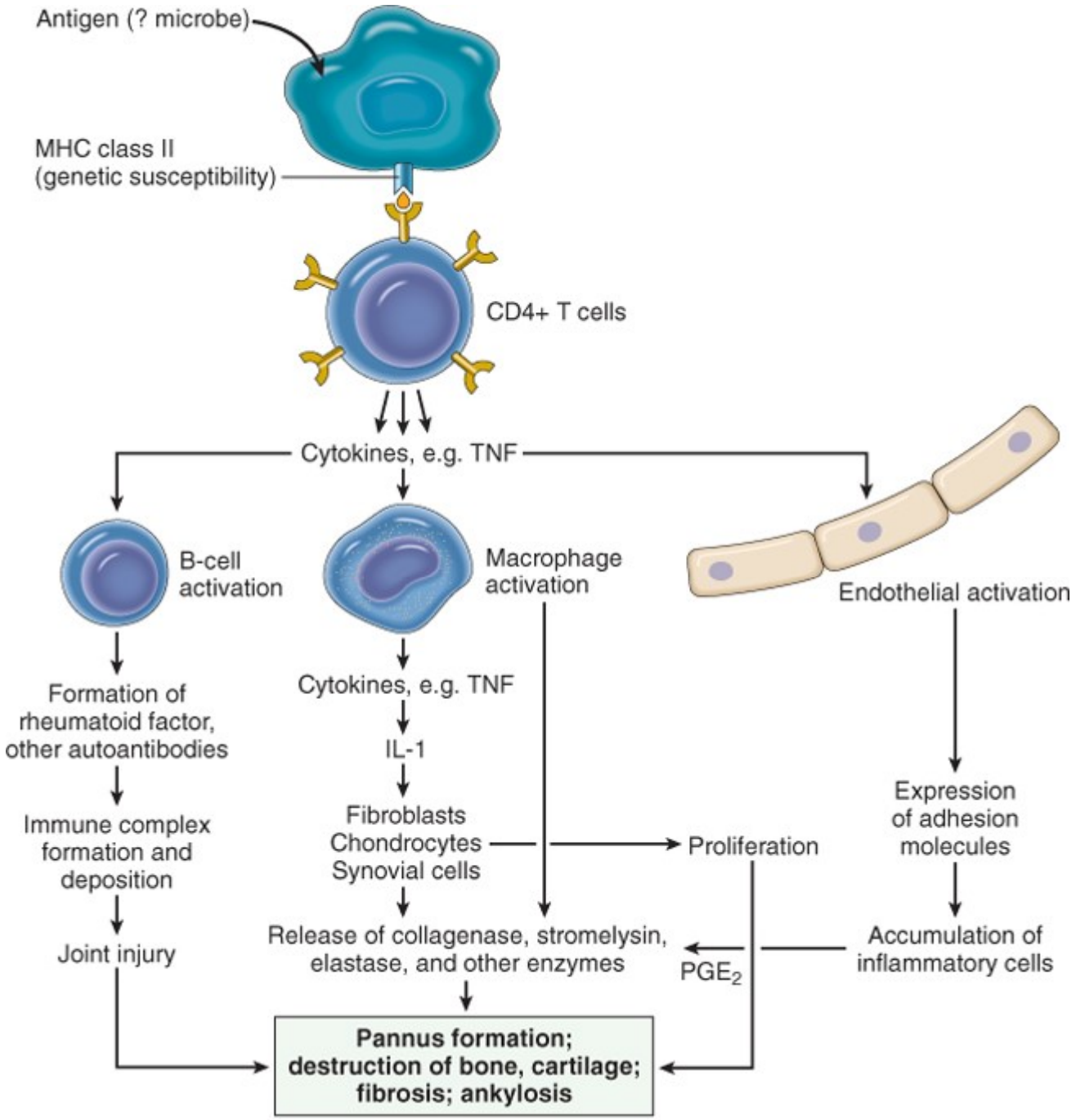
- *Borrelia burgdorferi,* transmitted by deer ticks, common in the United States
- Involves multiple organ systems and is usually divided into three stages
- In *stage 1 Borrelia* spirochetes multiply at the site of the tick bite and cause an expanding area of redness (*erythema chronicum migrans)* + fever and lymphadenopathy but usually disappears in a few weeks' time
- In *stage 2,* the *early disseminated stage,* spirochetes spread hematogenously and cause secondary annular skin lesions, lymphadenopathy, **migratory arthritis (large joints)** and muscle pain, cardiac arrhythmias, and meningitis, often with cranial nerve involvement
- In *stage 3,* the *late disseminated stage,* which occurs 2 or 3 years after the initial bite, Lyme *Borrelia* organisms cause a **chronic arthritis** and joint deformity
- Histologically, there is a chronic papillary synovitis with synovial hyperplasia, fibrin deposition, mononuclear cell infiltrates, pannus formation
- In only 25% of cases do silver stains reveal organisms

Rheumatoid arthritis

- Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease affecting many tissues
- Affects 1% of population, 2^{nd}-4^{th} decade, F:M 5:1
- Principally attacking the joints to produce a *nonsuppurative proliferative synovitis that frequently progresses to destroy articular cartilage and underlying bone with resulting disabling arthritis*
- Extra-articular inflammation can occur: skin, heart, blood vessels, muscles, and lungs

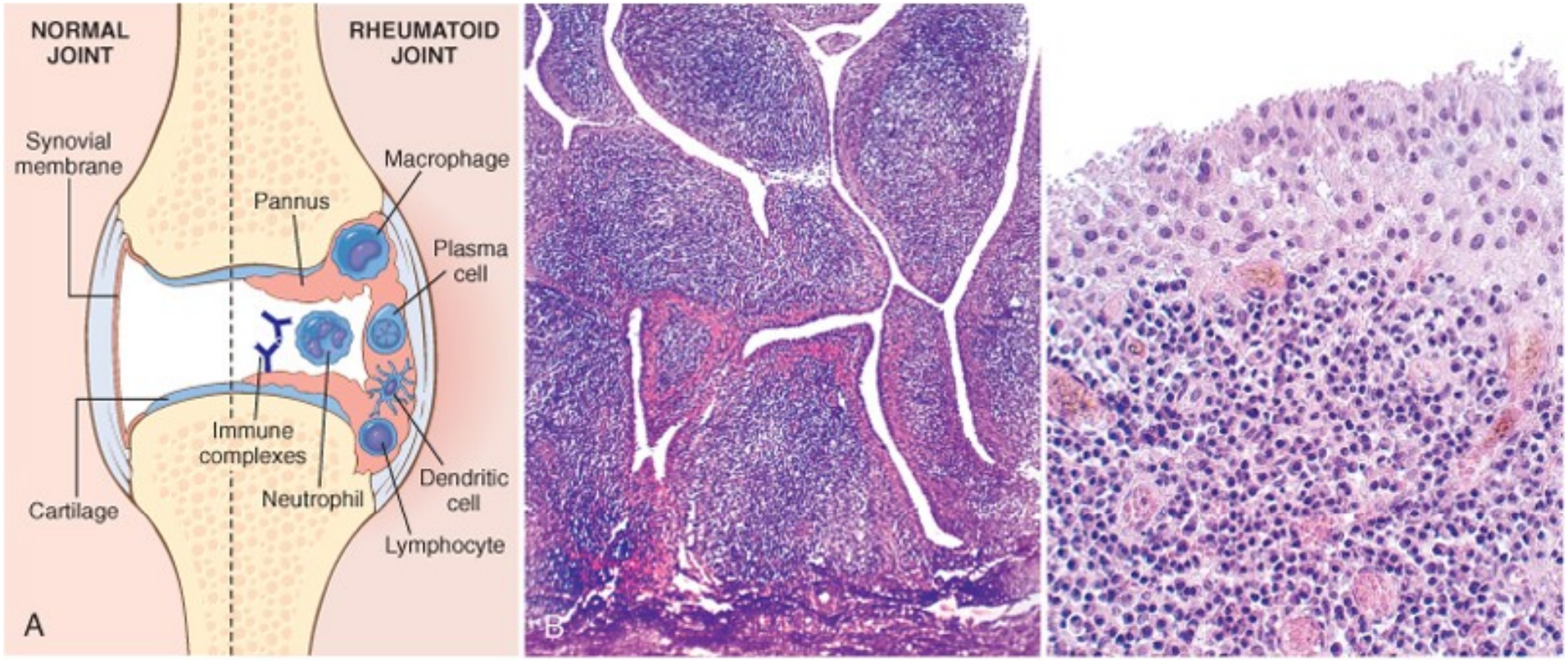
Pathogenesis

- Genetic predisposition
- Abnormal activation of *CD4+ helper T cells* responding to local antigens
- Activated T cells produce *cytokines* (TNF) that activate macrophages, B-lymphocytes and endothelium
- Activate B and plasma cells produce IgM antibodies (called rheumatoid factor) that bind normal IgG, forming immune complexes that deposit in joint and cause inflammation and damage
- Macrophages secret IL-1, cause proliferation of synovial cells and fibroblasts, producing pannus and fibrosis
- The cytokines also stimulate secretion of proteinase (collagenase, elastase) causing severe damage to cartilage and bone
- Activated T-cells secrete large amount of RANK ligand, causing bone resorption



Morphology

- (1) synovial cell hyperplasia and proliferation
- (2) dense inflammatory cell infiltrates (frequently forming lymphoid follicles) in the synovium composed of CD4+ T cells, plasma cells, and macrophages;
- (3) increased vascularity due to angiogenesis
- (4) neutrophils and aggregates of organizing fibrin on the synovial surface and in the joint space
- (5) increased osteoclast activity in the underlying bone
- Joint edema causes swelling, mostly prominent in the interphalangeal joints
- With progression cartilage and bone are destroyed
- Pannus fill the joint space, show fibrosis and calcification, leading to joint fusion (ankylosis)



- Rheumatoid arthritis. **A,** A joint lesion. **B,** Low magnification reveals marked synovial hypertrophy with formation of villi. **C,** At higher magnification, dense lymphoid aggregates are seen in the synovium

Radiology

- joint effusions
- osteopenia with erosions
- narrowing of the joint space
- loss of articular cartilage

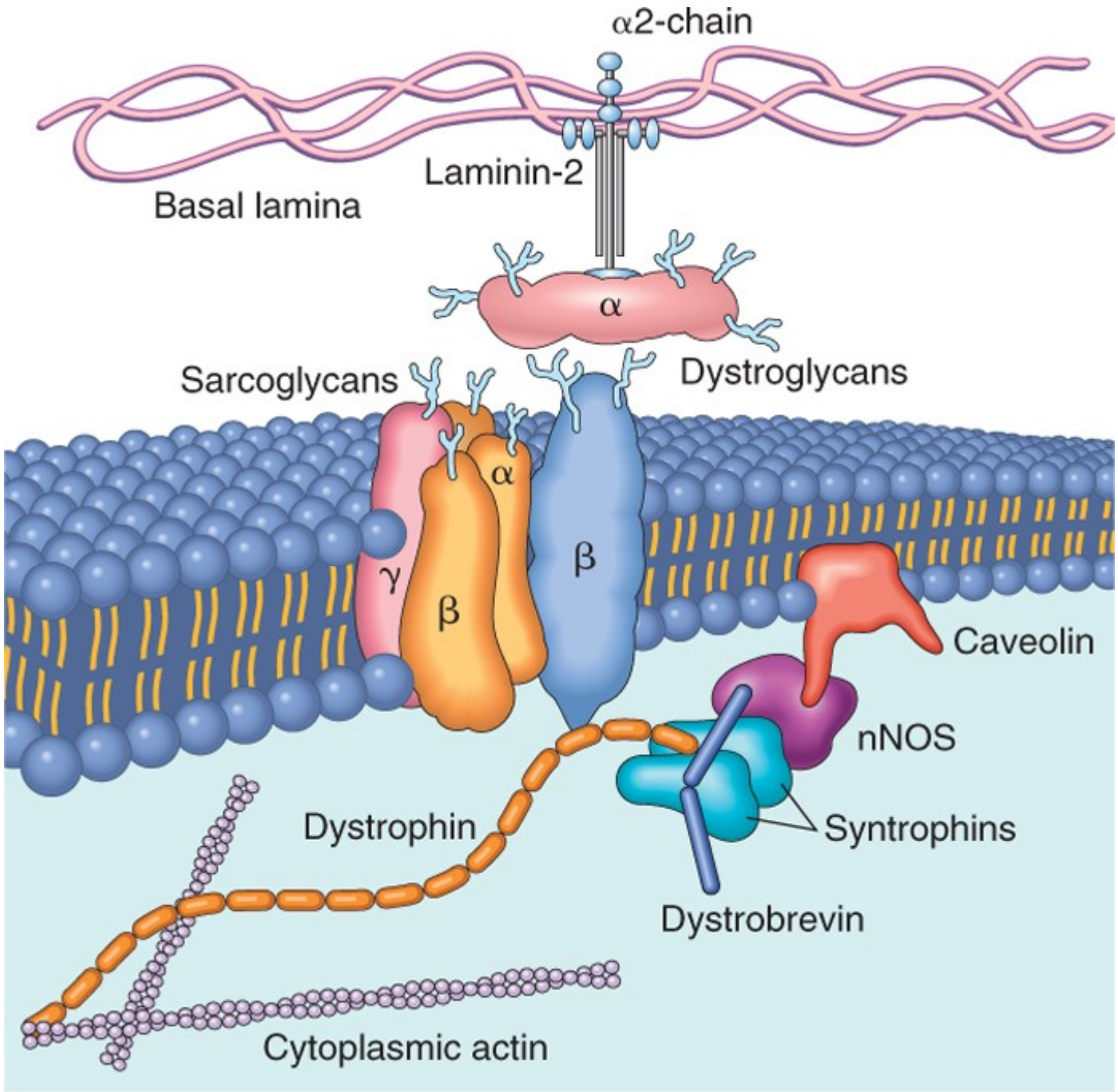
Muscle diseases

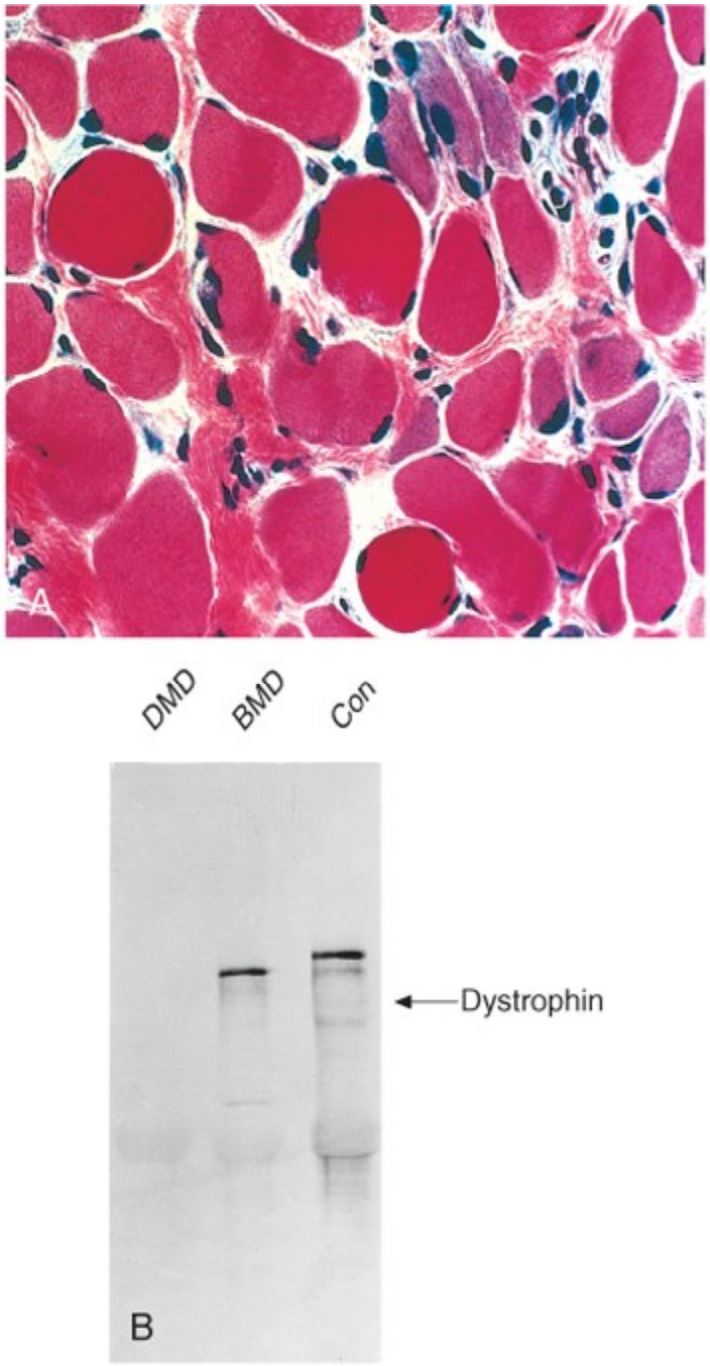
Duchenne & Becker Muscular Dystrophy

- X-linked inheritance
- 1:3500 boys
- Becomes evident at age of 5
- Progressive muscle weakness
- Muscles are replaced by fat
- Death by the early 20s

Pathogenesis

- abnormalities in the dystrophin gene located on the short arm of the X chromosome (Xp21)
- Dystrophin is a large protein (427 kD) that is expressed in a wide variety of tissues, including muscles of all types, brain, and peripheral nerves
- dystrophin attaches portions of the sarcomere to the cell membrane, maintaining the structural and functional integrity of skeletal and cardiac myocytes
- When decreased (Beker) or absent (Duchenne), it cannot transfer force of contraction to connective tissue, leading to muscle degeneration
- Approximately two-thirds of the cases are familial, with the remainder representing new mutations
- In affected families, females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase and can show mild histologic abnormalities on muscle biopsy. Female carriers, however, are at risk for developing dilated cardiomyopathy





- **A,** Duchenne muscular dystrophy (DMD) showing variation in muscle fiber size, and regenerating fibers *(blue hue).* **B,** Western blot showing absence of dystrophin in DMD and altered dystrophin size in Becker muscular dystrophy (BMD) compared with control (Con)

Clinical

- Normal at birth
- Delayed walking
- Weakness begins in muscles in pelvic girdle, then shoulder girdle
- Pseudohypertrophy: enlarged muscles caused by fat infiltration within fibers
- Wheelchair dependence at age of 10
- Heart failure, arrythmia
- Respiratory muscle failure
- Some patients have cognitive impairments

Myotonic Dystrophy

- AD
- CTG trinucleotide repeat (thousands) expansion on chromosome 19
- affects the mRNA for the dystrophila myotonia-protein kinase
- Becomes more severe in next generation (anticipation)
- Muscles have abnormal function, excessive involuntary contraction
- Manifest in late childhood with gate abnormality, and muscle atrophy

Malignant skin tumors

Squamous Cell Carcinoma

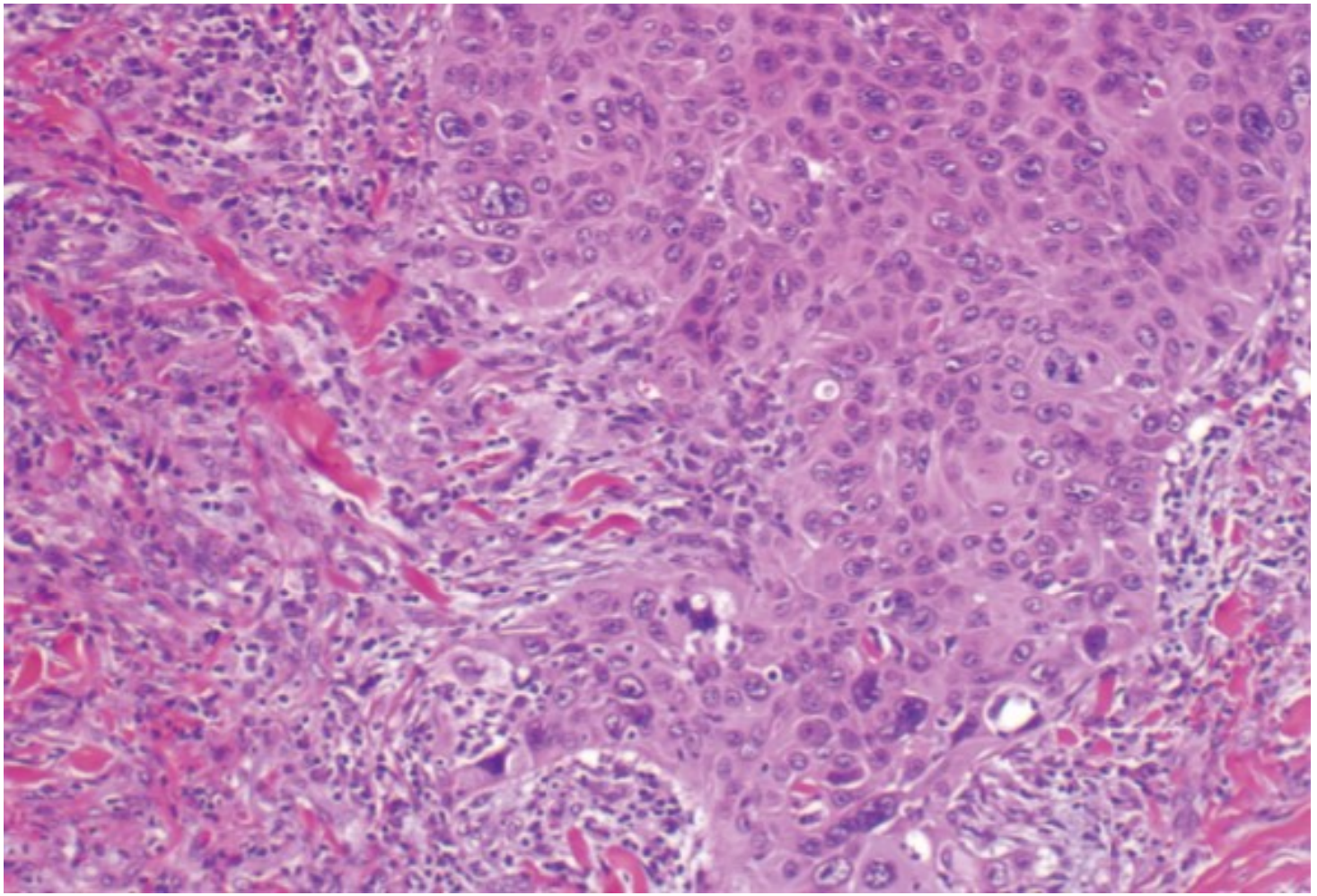
- is *a common tumor arising on sun-exposed sites in older people.*
- Incidence: men >>women.
- Predisposing factors include: sunlight, industrial carcinogens (tars and oils), chronic ulcers, old burn scars and ionizing radiation, immune suppression
- may be preceded by carcinoma in-situ lesions

Pathogenesis

- *TP53* mutations caused by UV light-induced DNA damage
- UV light (UVB in particular) →a transient immunosuppressive effect on skin by impairing antigen presentation by Langerhans cells

Morphology

- in-situ: highly atypical cells at **all levels** of the epidermis, with nuclear crowding and disorganization.
- Invasive SCC: breaching the basement membrane by neoplastic cells; variable degrees of differentiation (ranging from well-differentiated tumors that exhibit extensive keratinization, to neoplasms consisting of anaplastic cells with necrosis)



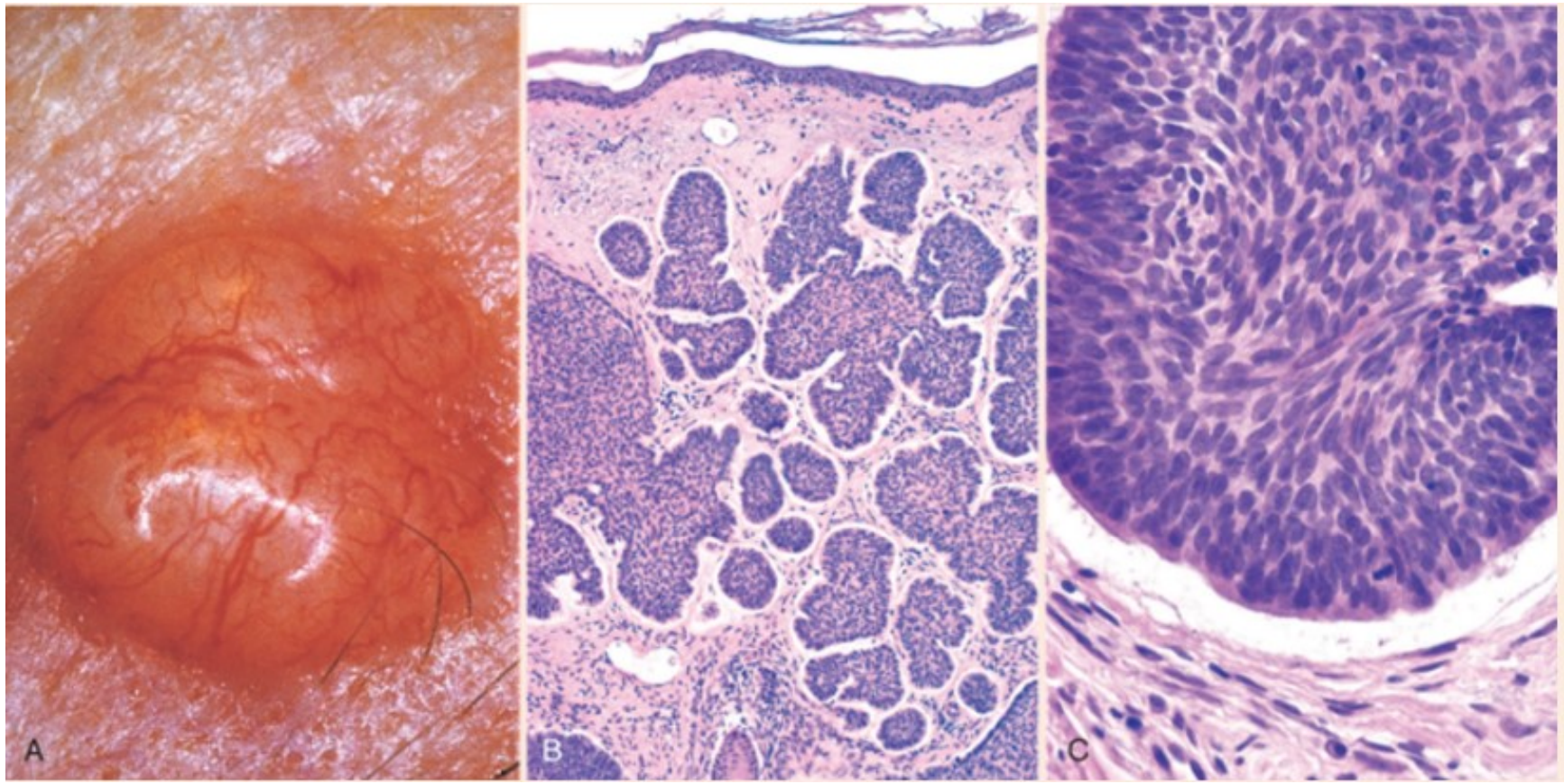
- SCC: irregular projections of atypical squamous cells in the dermis, which in this case exhibit acantholysis

Basal Cell Carcinoma

- **common *slow-growing cancer that rarely metastasizes.***
- It tends to occur at sites of chronic sun exposure and in lightly pigmented individuals
- Familial (Gorlin syndrome), or sporadic
- PATHOGENESIS:
- **associated with dysregulation of the Hedgehog pathway (**It controls cell division of adult stem cells and has been implicated in development of some cancers**)**
- Mutations in *TP53* are also common in both familial and sporadic tumors.
- **Clinical Features of BCC:**
- usually cured by local excision
- < 40% of patients will develop another BCC within 5 years.
- Advanced lesions may ulcerate, and extensive local invasion of bone or facial sinuses may occur if the lesions are neglected for many years

Morphology

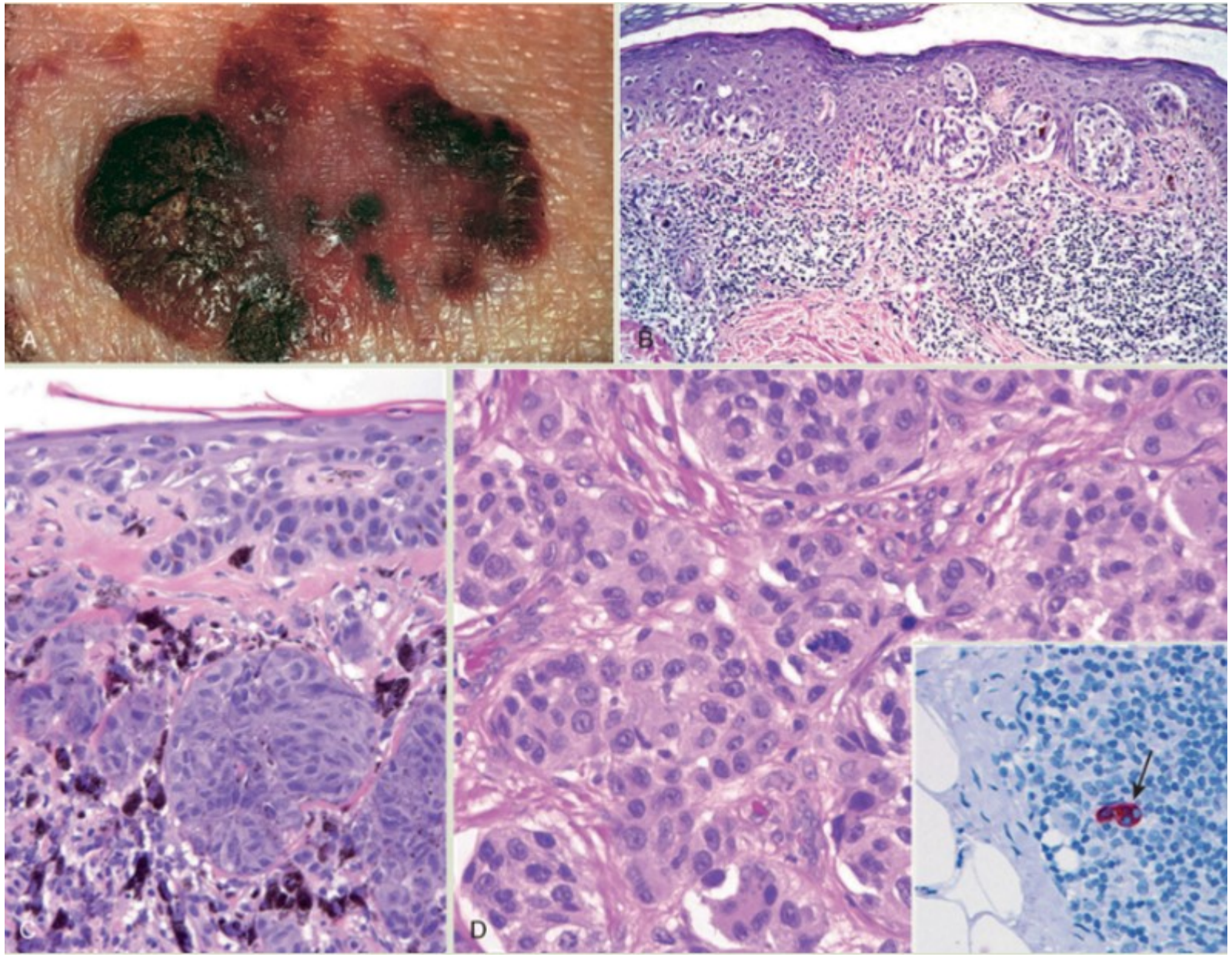
- Grossly: papule, with dilated blood vessels
- Micro: cords and islands of hyperchromatic cells (resemble normal basal layer of epidermis), peripheral palisades, retraction artifact


A
B
C

Melanocytic tumors

- Either benign or malignant
- Benign lesions are called nevi (pleural of **nevus**)
- Most ***melanocytic nevi*** have activating mutations in *BRAF* or less often *NRAS*, but the vast majority never undergo malignant transformation.
- ***dysplastic nevi*** are best regarded as markers of melanoma risk. They are characterized by cytologic atypia
- ***Melanoma*** is a highly aggressive malignancy; tumors only a few millimeters in thickness can give rise to deadly metastases.
- In most cases, it progresses from an (in situ) to an invasive (dermal) form.
- Characteristics of the dermal tumor such as depth of invasion and mitotic activity correlate with survival

- Melanoma with irregular contours and pigmentation. Melanoma cells have hyperchromatic nuclei of irregular size and shape with prominent nucleoli. Mitoses, including atypical forms often are encountered.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