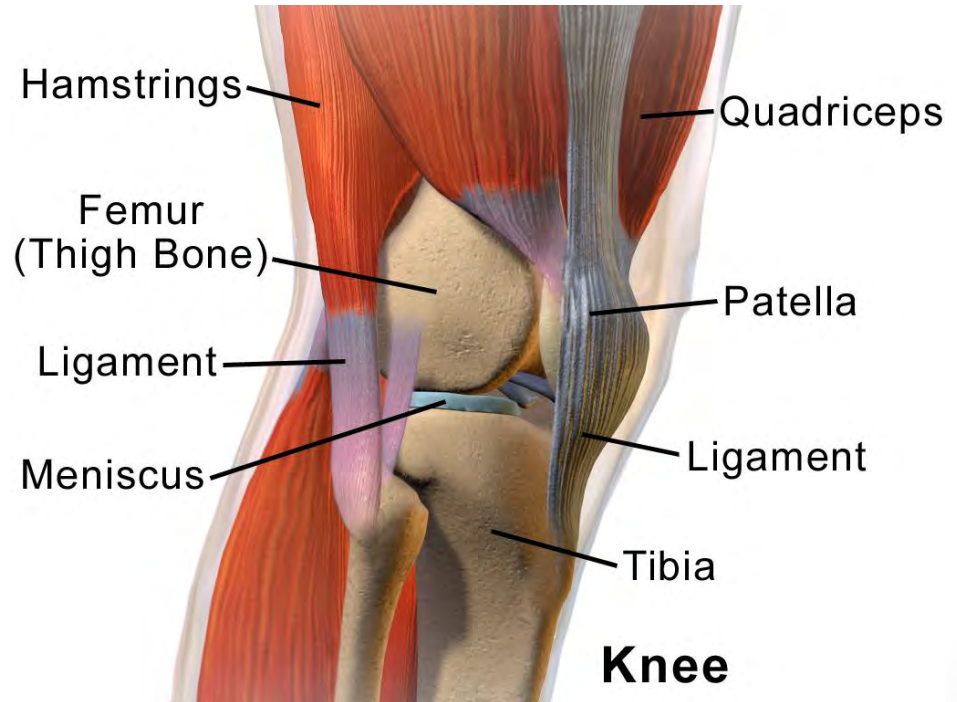


Knee

Jason Ryan, MD, MPH

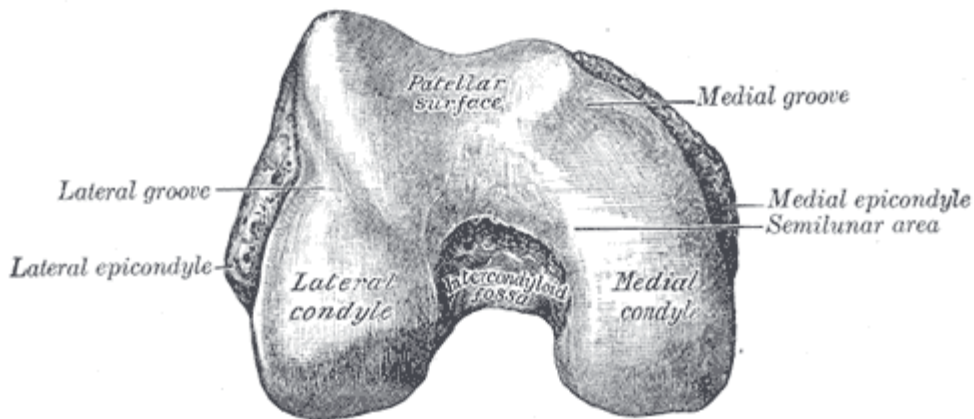
Knee

- Four bones
 - Femur, tibia, fibula, patella
- Four ligaments
 - Anterior cruciate
 - Posterior cruciate
 - Medial collateral
 - Lateral collateral
- Two menisci
 - Medial
 - Lateral

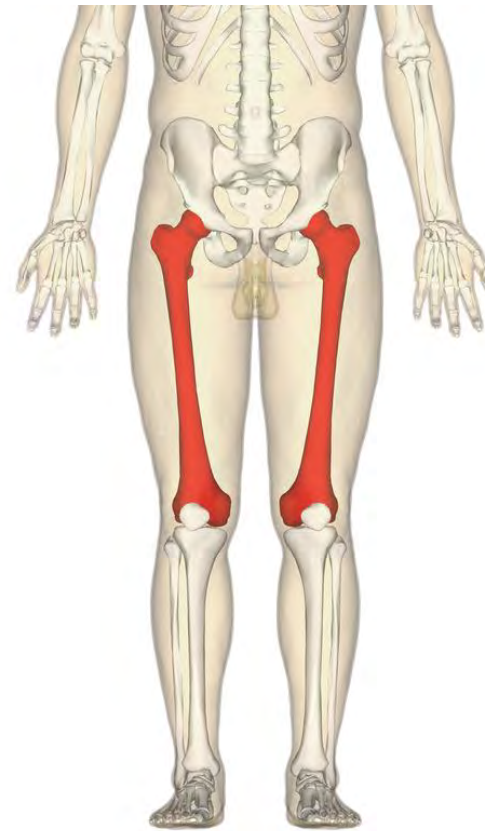


BruceBlaus/Wikipedia

Femur

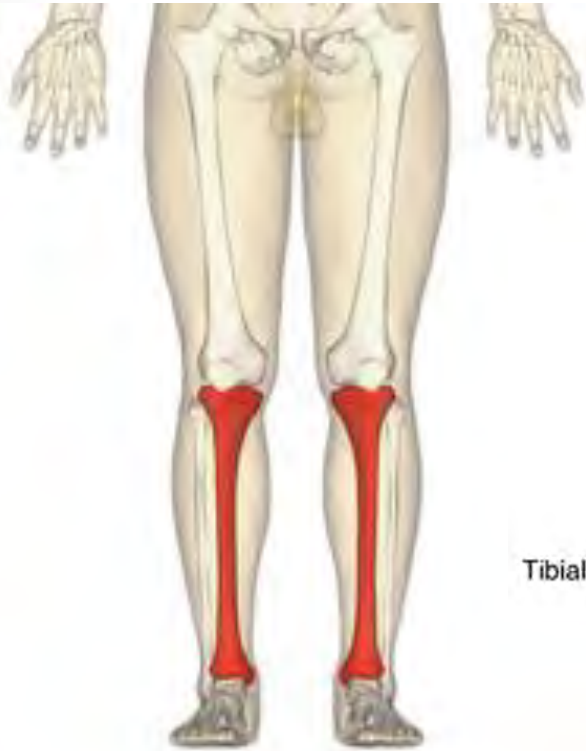


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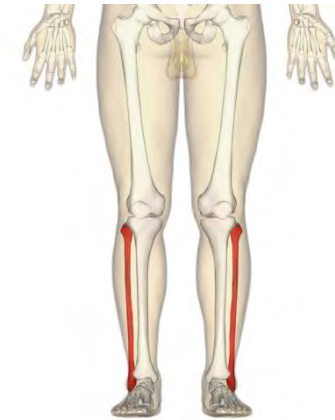
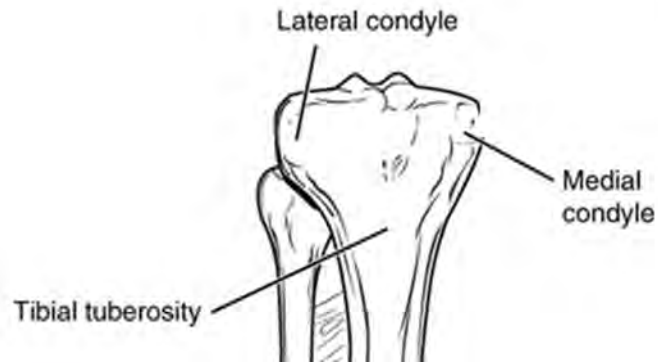


Anatomography/Wikipedia

Tibia, Fibula, Patella



Tibia



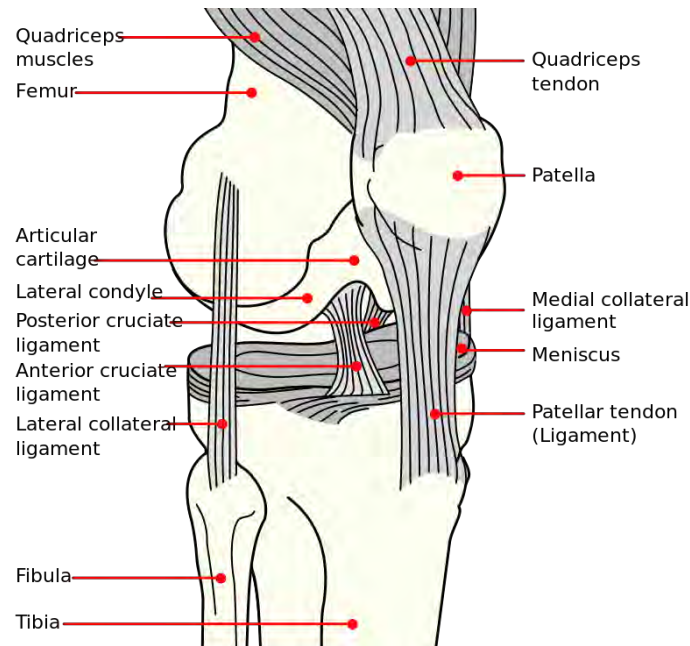
Fibula



Patella

Cruciate Ligaments

- Cruciate = cross shaped
- Two ligaments (ACL/PCL)
- Form X

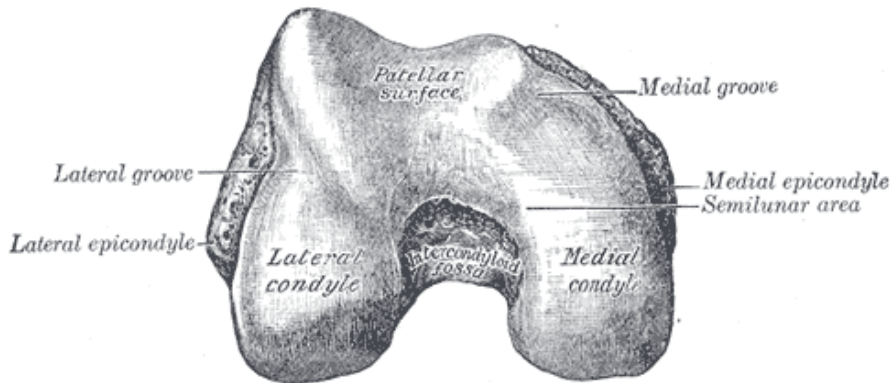


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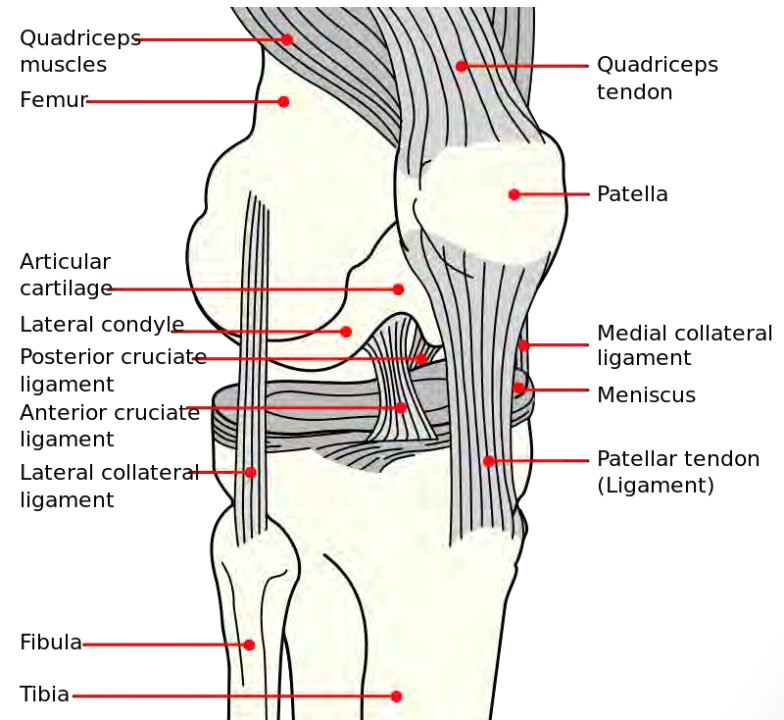
Anterior Cruciate Ligament

ACL

- Lateral femoral condyle → **anterior** tibia
- Resists anterior movement of tibia



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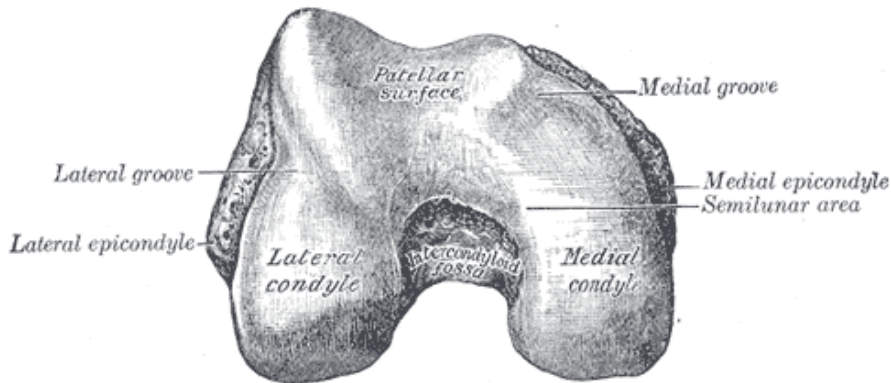


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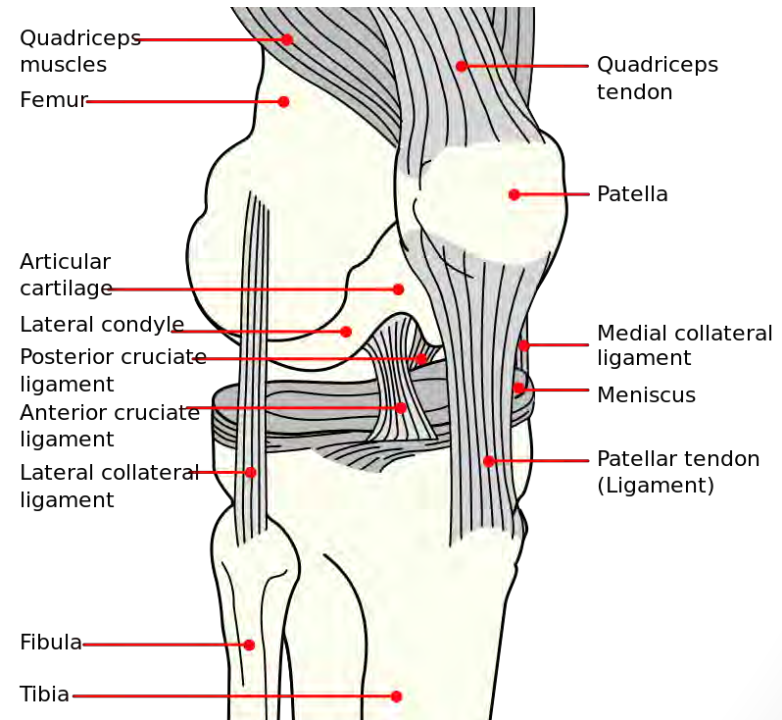
Posterior Cruciate Ligament

PCL

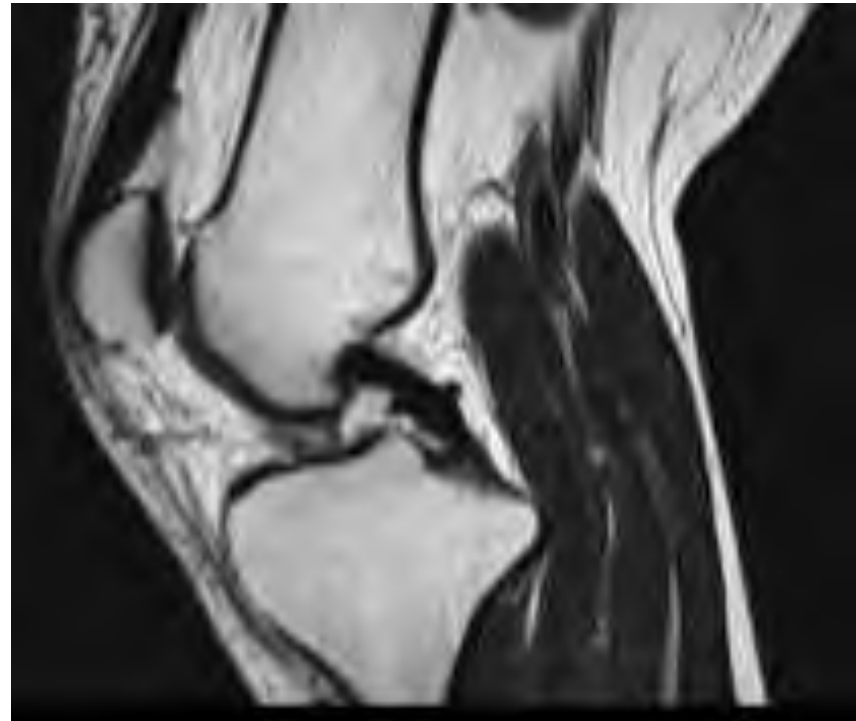
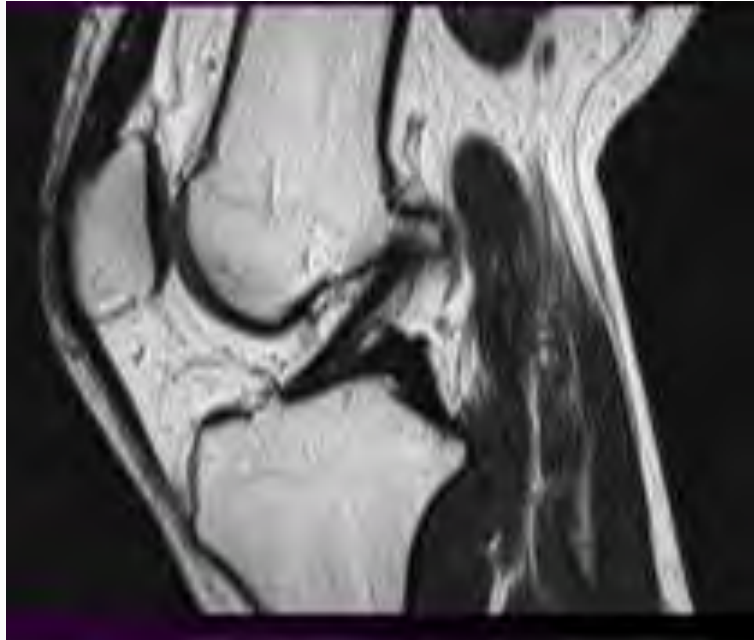
- Medial femoral condyle → **posterior** tibia
- Resists posterior movement of tibia

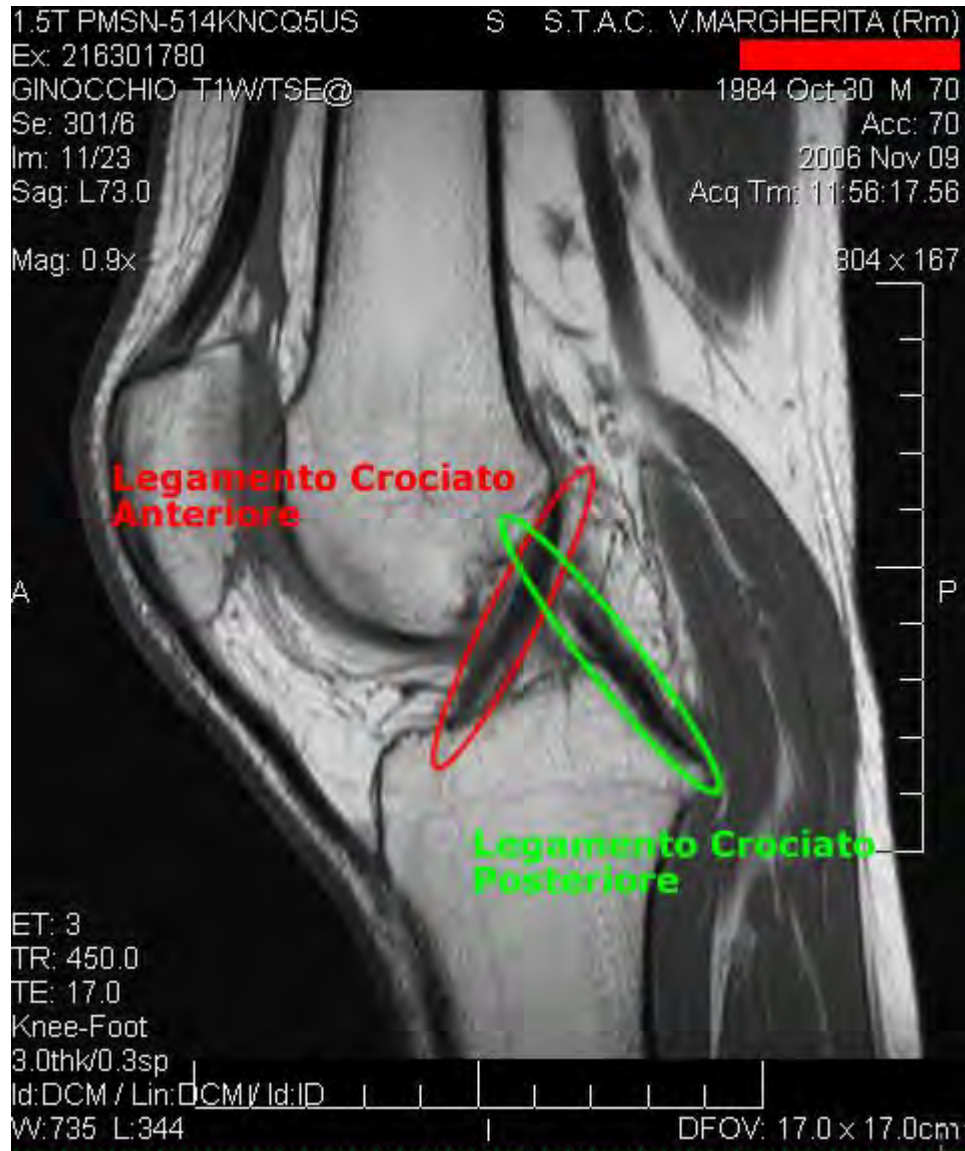


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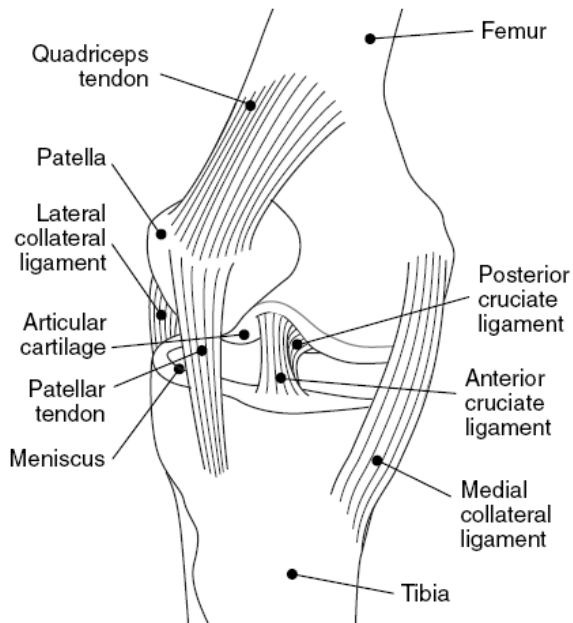




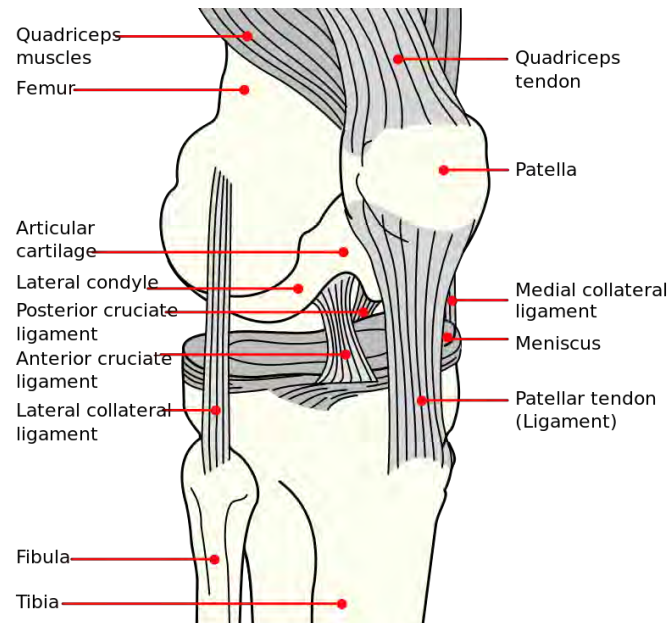
Wikipedia/Public Domain

Collateral Ligaments

- Lateral and medial bands
- Resist **valgus and varus** deformity



Wikipedia/Public Domain



Wikipedia/Public Domain

Collateral Ligaments

- Valgus
 - Knock kneed
 - Lower leg abducted
- Varus
 - Bow legged
 - Lower leg adducted

Valgus Deformity

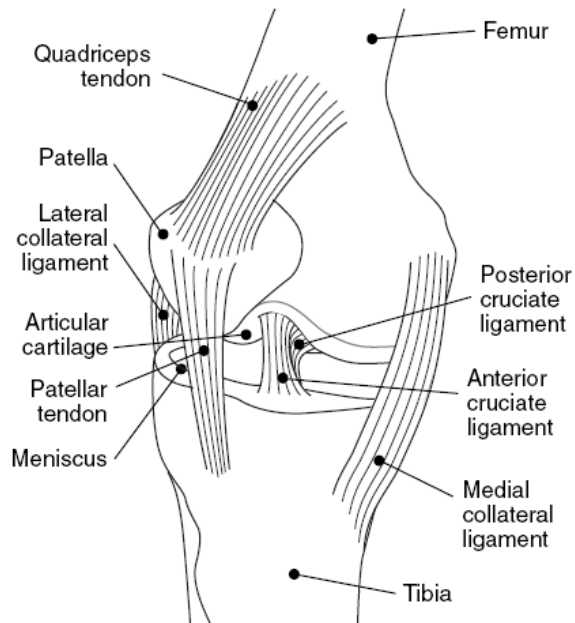


BioMed Central/Wikipedia

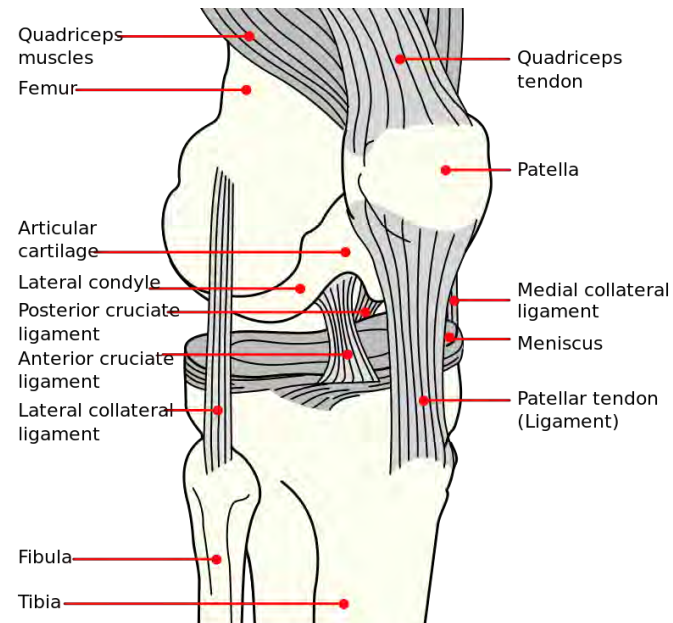
Medial Collateral Ligament

MCL

- Medial epicondyle of femur
- Medial condyle of tibia
- Resist valgus (knock knee) stress



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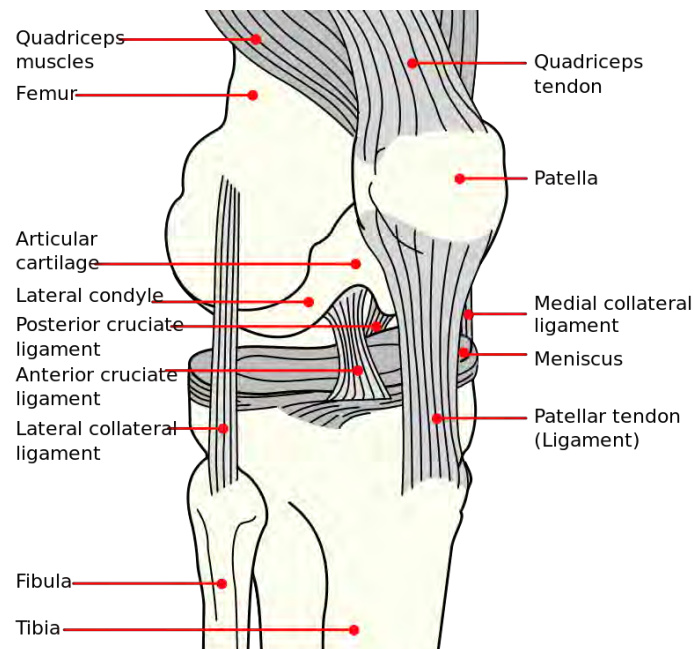


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Lateral Collateral Ligament

LCL

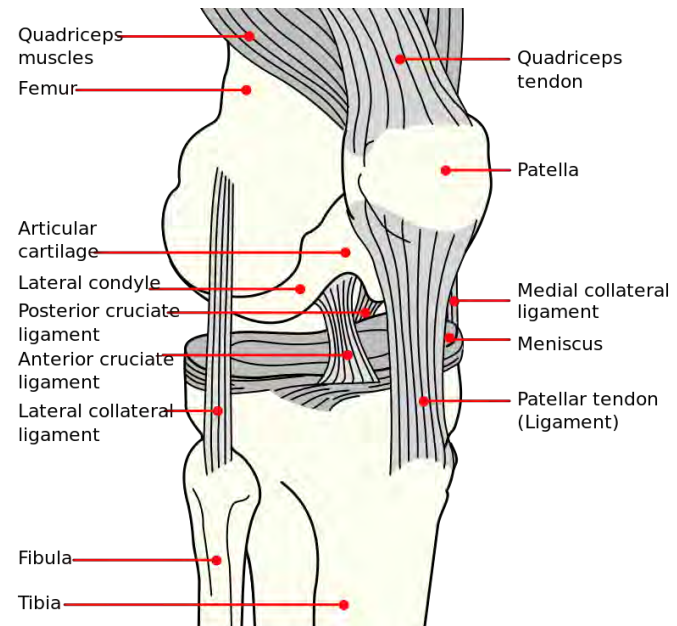
- Lateral epicondyle of femur
- Head of fibula
- Resists varus (bow leg) stress



Wikipedia/Public Domain

Menisci

- Two crescent-shaped pads (medial and lateral)
- Fibrous tissue and cartilage
- Between tibia and femoral condyles



Wikipedia/Public Domain

Knee Injuries

- Often involve tears of ligaments or menisci
- Swelling
- Instability
- Sensation that knee will “give out”



[James Heilman, MD/Wikipedia](#)

ACL Injury

Anterior Cruciate Ligament

- Most commonly injured knee ligament
- Often a **noncontact** athletic injury
 - Running/jumping
 - Sudden change of direction (cutting/pivot)
- Classically senses as a “pop” in knee

ACL Injury

Anterior Cruciate Ligament

- Patient supine
- **Anterior drawer sign**
 - Bend knee 90° angle
 - Tibia drawn forward
 - Forward movement greater than normal in ACL tear
- Lachman test
 - Same as drawer sign but 30° angle

PCL Injury

Posterior Cruciate Ligament

- Often from trauma
 - Force directed posteriorly at knee
 - Classic cause: **“dashboard injury”** – knee into dashboard
- Posterior drawer sign
 - Patient supine
 - Knee bent at at 90° angle
 - Tibia moves backwards more than normal

MCL Injury

Medial Collateral Ligament

- Damaged by valgus stress
 - Contact
 - Non-contact (twisting)
- **Abnormal passive abduction**
 - Force from lateral side (valgus)
 - Lower leg away from midline (abduction)
 - Medial space widens

Valgus Deformity



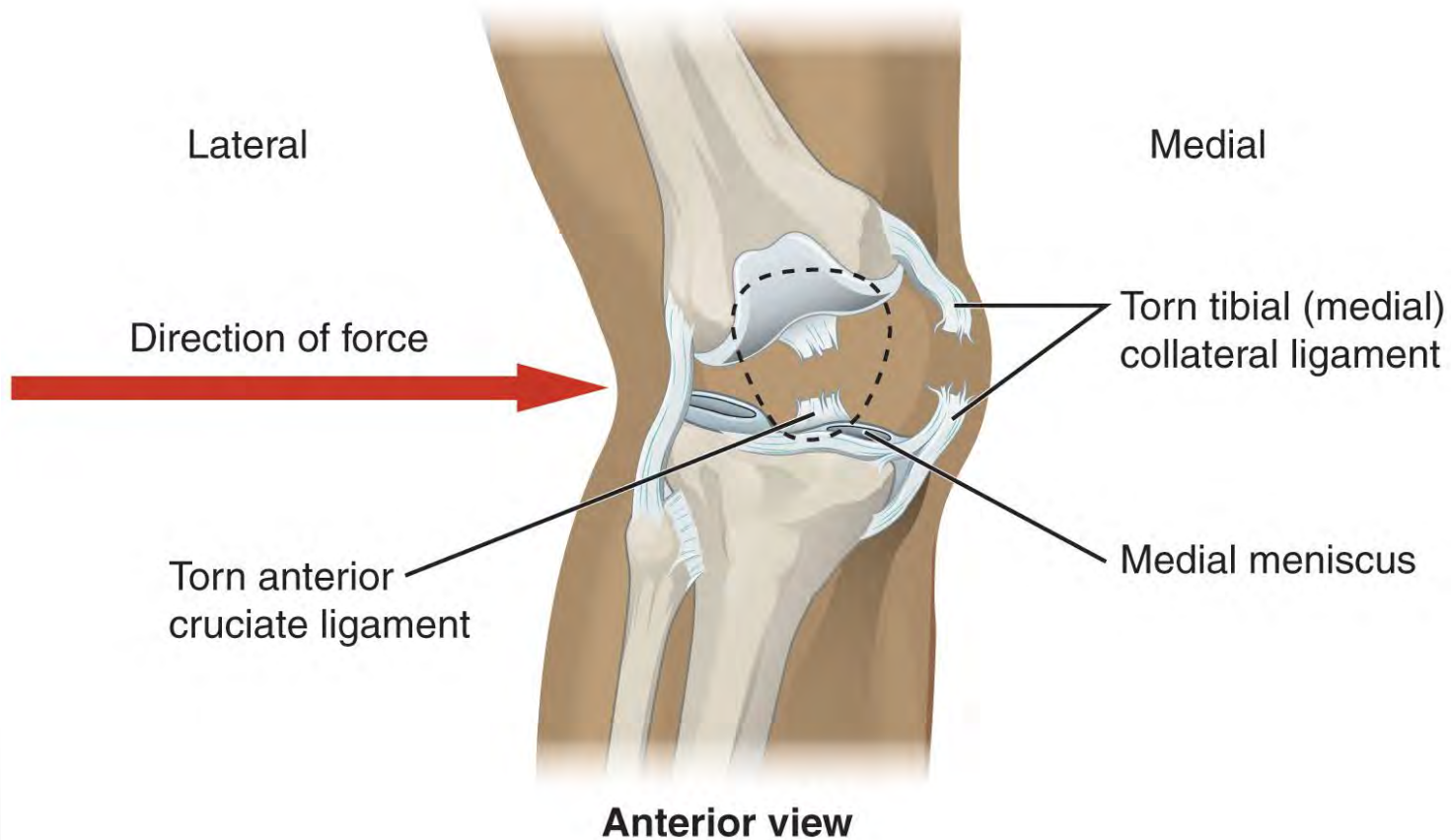
BioMed Central/Wikipedia

Unhappy Triad

- Triad of injury common in contact sports
- Lateral force applied to knee when foot planted
- Original triad description:
 - Anterior cruciate ligament (ACL) tear
 - Medial collateral ligament (MCL) tear/sprain
 - Medial meniscal tear
- Modern studies: lateral meniscus more common

Shelborune KD, Nitz PA. Am J Sports Med **The O'Donoghue triad revisited. Combined knee injuries involving anterior cruciate and medial collateral ligament tears.** 1991 19(5): 474-7

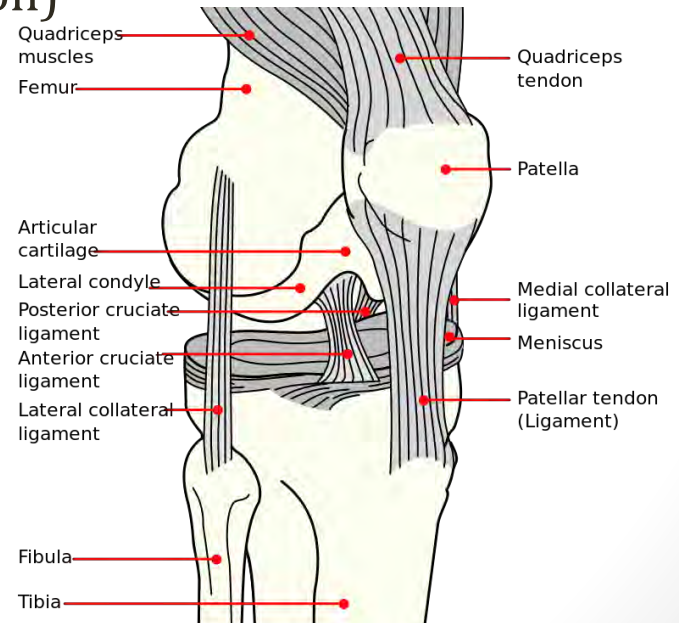
Unhappy Triad



LCL Injury

Lateral Collateral Ligament

- Rarely injured in isolation
- Often trauma to medial knee
- **Abnormal passive adduction**
 - Force from medial side (varus)
 - Lower leg toward midline (adduction)
 - Lateral space widens



Wikipedia/Public Domain

Meniscal Tear

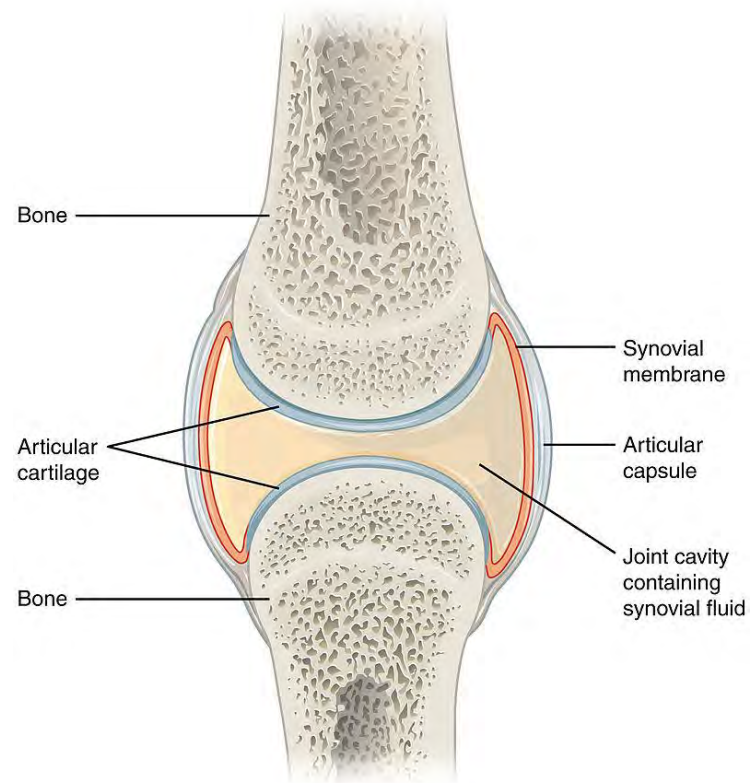
- Often occurs when foot is planted
- Sudden change in direction → twisting of knee
- Often occurs in sports (soccer, basketball)
- Pain and swelling following injury
- Pain worse with twisting or pivoting

McMurray Test

- Patient supine
- Flexed (bent) knee held by examiner's hand
- Foot held by examiner's other hand
- Extend knee while rotating foot
- Pain or “pop” = positive McMurray test
- Internal rotation tibia → tests lateral meniscus
 - Foot toward midline
- External rotation → tests medial meniscus
 - Foot away midline

Knee

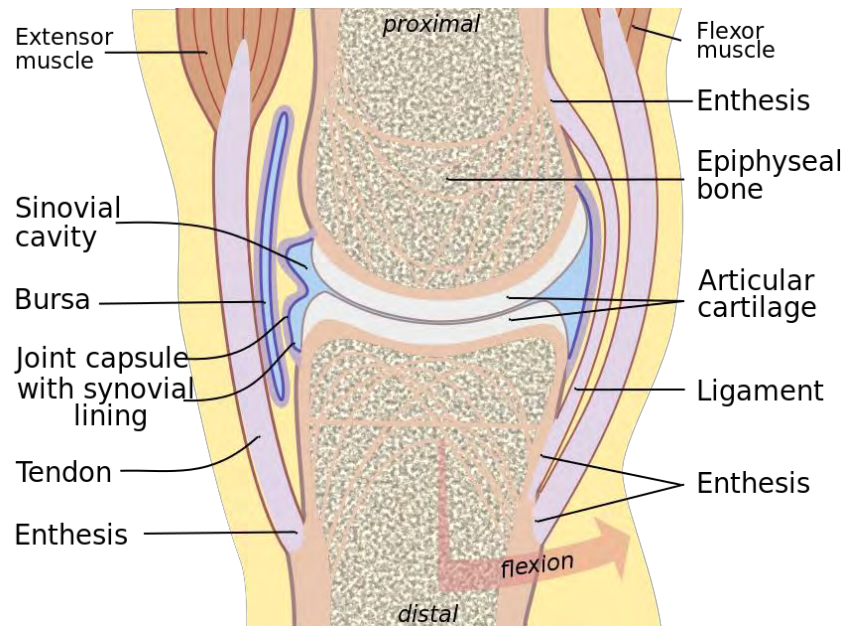
- Synovial joint
 - Connects bones
 - Synovial membrane
 - Synovial fluid



OpenStax College/Wikipedia

Bursitis

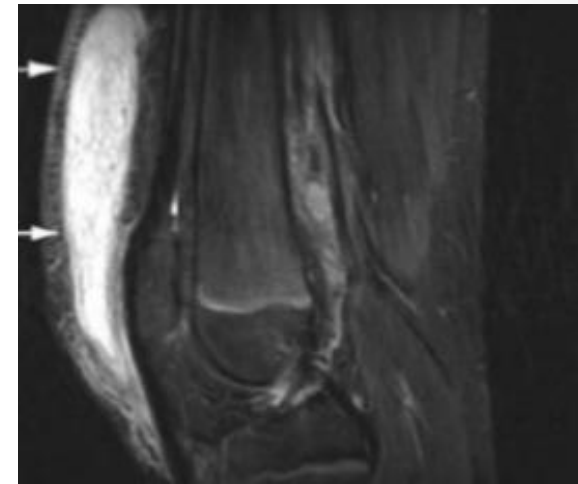
- Bursa = synovial-lined sac
- Cushion between bones and tendons/muscles
- Four bursa near knee



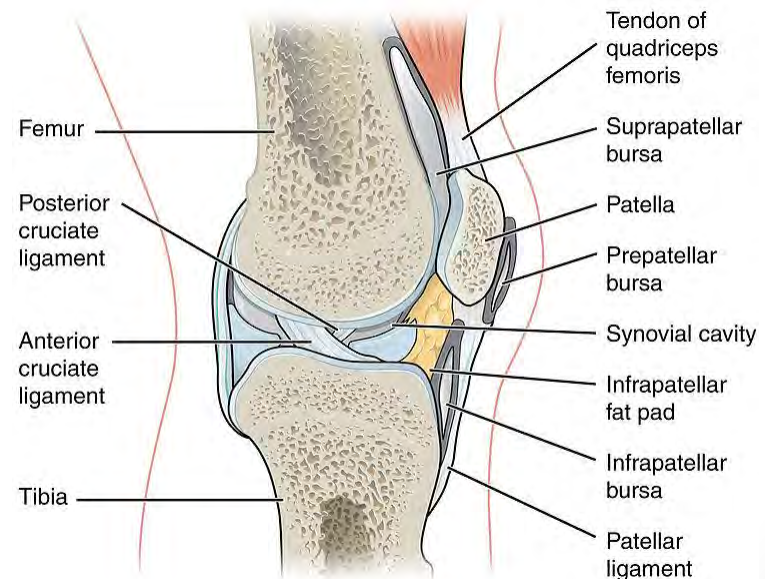
Madhero88/Wikipedia

Prepatellar Bursitis

- Inflammation of prepatellar bursa
- Often caused by repeated kneeling
 - “Housemaid’s knee”
- Other causes: infection, gout
- Pain with activity
- Swelling anterior to patella
- Warmth



Anish Choudhary



Baker's Cyst

Popliteal Cyst

- Popliteal fluid collection
- Gastrocnemius-semimembranosus bursa
 - Bursa between two muscle tendons
 - Found in back of the knee
- Often communicates with synovial space
- Often related to chronic joint disease
 - Degenerative
 - Inflammatory
 - Joint injury



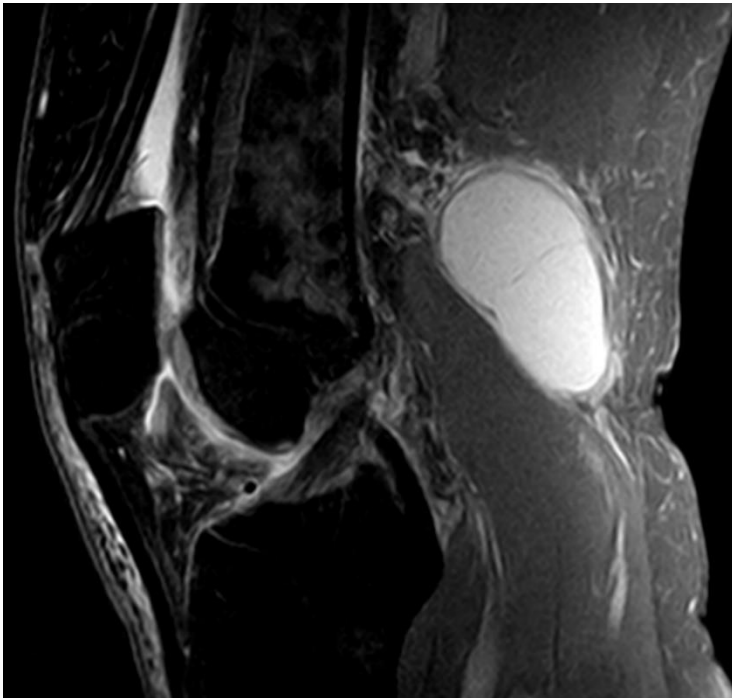
Dr. Johannes Sobotta/Public Domain

Baker's Cyst

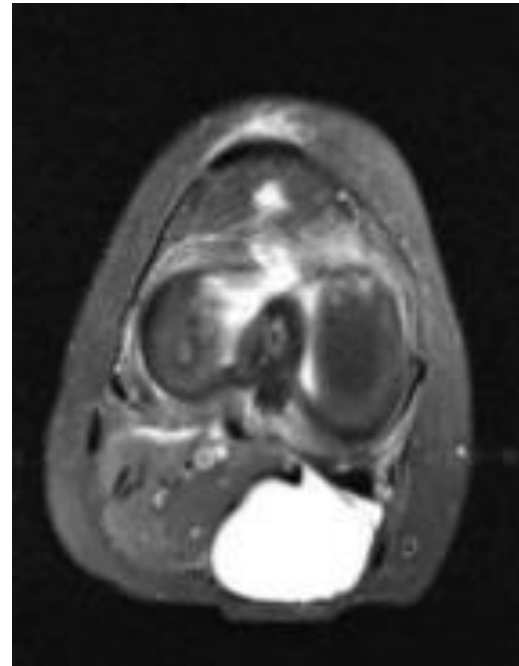
Popliteal Cyst

- Often small, asymptomatic
 - Detected by imaging for unrelated joint symptoms
- May cause posterior knee pain
- Pain with prolonged standing
- Symptoms/swelling worse with activity
- Rupture may cause acute pain (mimics DVT)
- Common in patients with rheumatoid arthritis

Baker's Cyst



Hellerhoff/Wikipedia

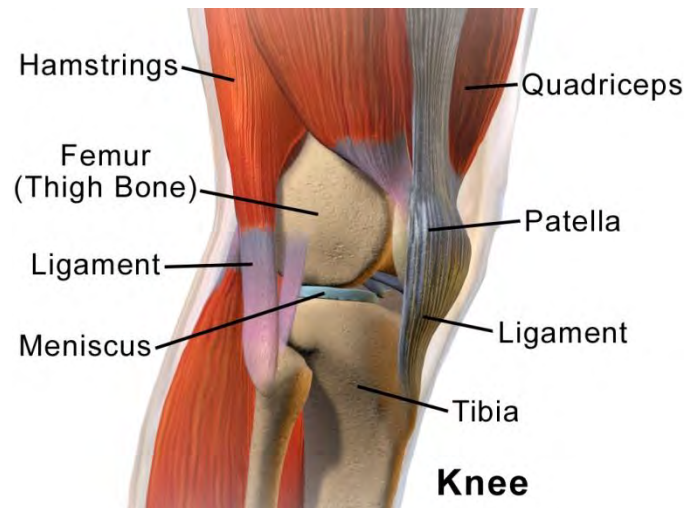


Siwaporn Khureerung

Osgood-Schlatter Disease

Tibial tuberosity avulsion

- Occurs in children
- Pain/swelling at tibial tubercle from overuse
 - Insertion point of patellar tendon
- **Secondary ossification center of tibia**
- Usually benign, self-limited condition



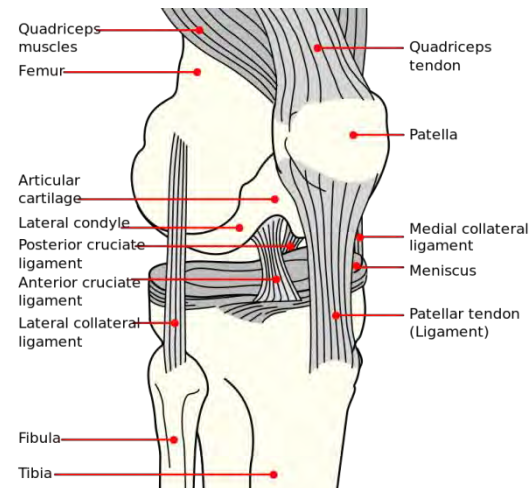
BruceBlaus/Wikipedia

Patellar Fracture

- Results from trauma to knee
- Swollen, painful knee
- Cannot **extend knee against gravity**
 - Indicates loss of knee extension
 - Classic cause: patellar fracture
 - Quadriceps tendon tear
 - Injury to patellar tendon
- Diagnosis: X-ray



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Shoulder and Elbow

Jason Ryan, MD, MPH

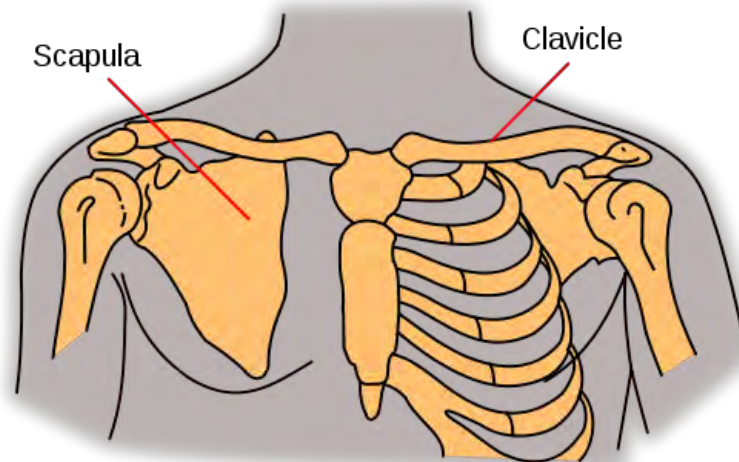
Shoulder

- Ball and socket joint
 - “Glenohumeral joint”
 - Glenoid = fossa of scapula bone
- Three bones
 - Clavicle, scapula, humerus

Glenoid cavity

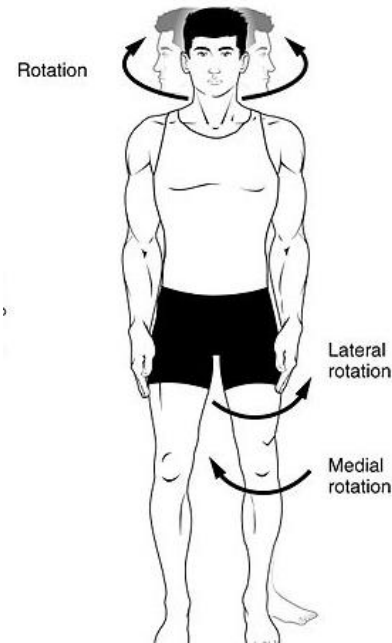
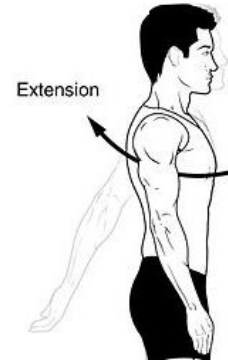
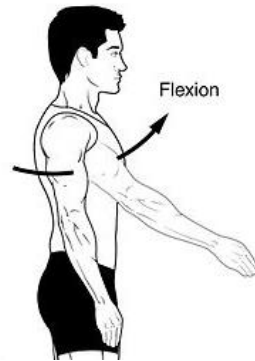


BodyParts3D/Wikipedia



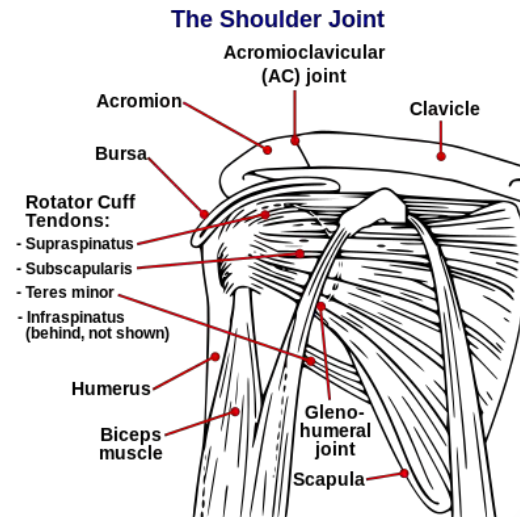
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Shoulder Movements



Rotator Cuff

- Rotator cuff
 - Four muscles surrounding joint → conjoint tendon
 - Supraspinatus, infraspinatus, subscapularis, teres minor
 - Draws humerus head into glenoid during **abduction**
- Tendonitis: common cause of shoulder pain
 - **Pain with abduction**
- Tears: inability to abduct



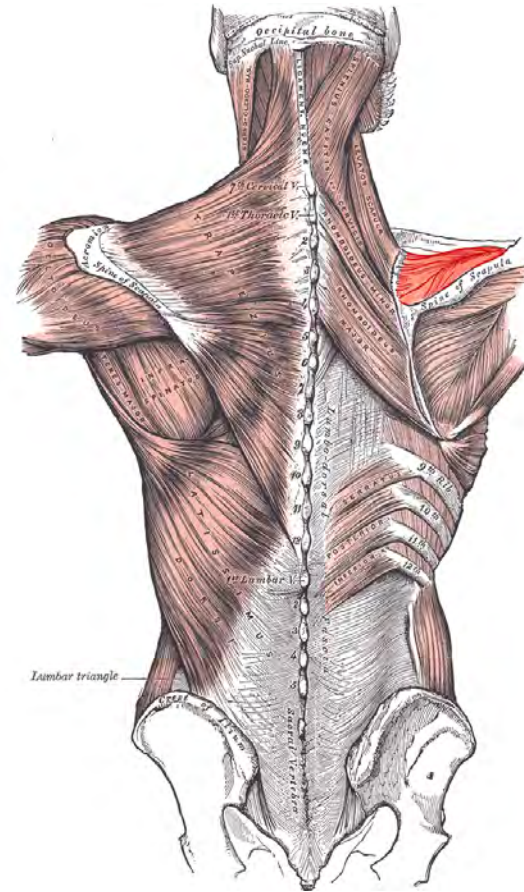
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Supraspinatus

- Above spine of scapula
- Initial abduction (0-15°)
 - Main abductor: deltoid (15-100°)
- Innervation: suprascapular nerve
 - Also infraspinatus muscle
- Most common rotator cuff injury



BodyParts3D/Wikipedia



Mikael Häggström/Wikipedia

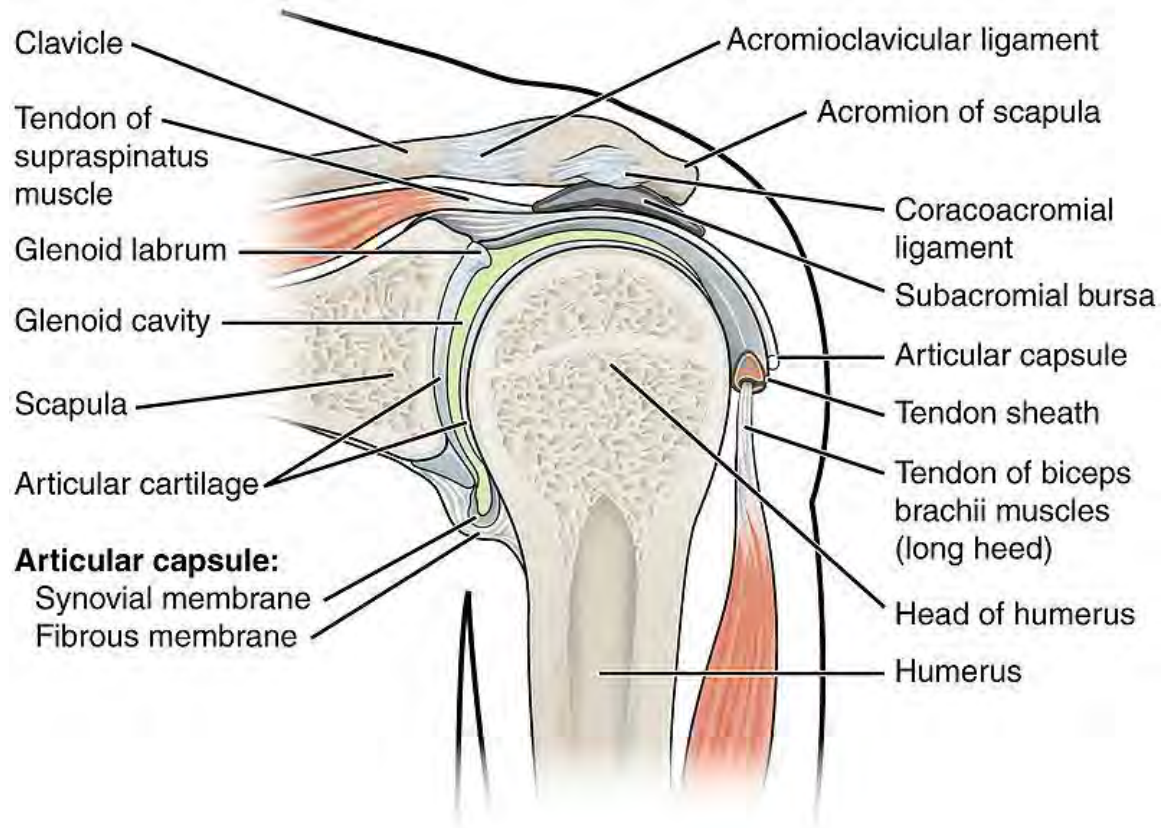
Supraspinatus



BodyParts3D/Wikipedia

- Common cause of rotator cuff injury
- **Impingement**
 - Compression of tendon
 - Between humeral head and acromion process of scapula
 - Impingement in the subacromial space
- Leads to tendinopathy (inflammation) or tear
- Occurs in swimmers and throwers
 - “Swimmer’s shoulder”
 - “Thrower’s shoulder”

Supraspinatus



OpenStax College/Wikipedia

Empty/Full Can Tests

- Identify supraspinatus injury
- Empty Can Test
 - Arms out (90° abduct; 30° in front)
 - Thumbs down
 - Examiner pushes arms down
 - Positive if pain
- Full Can Test
 - Thumbs up



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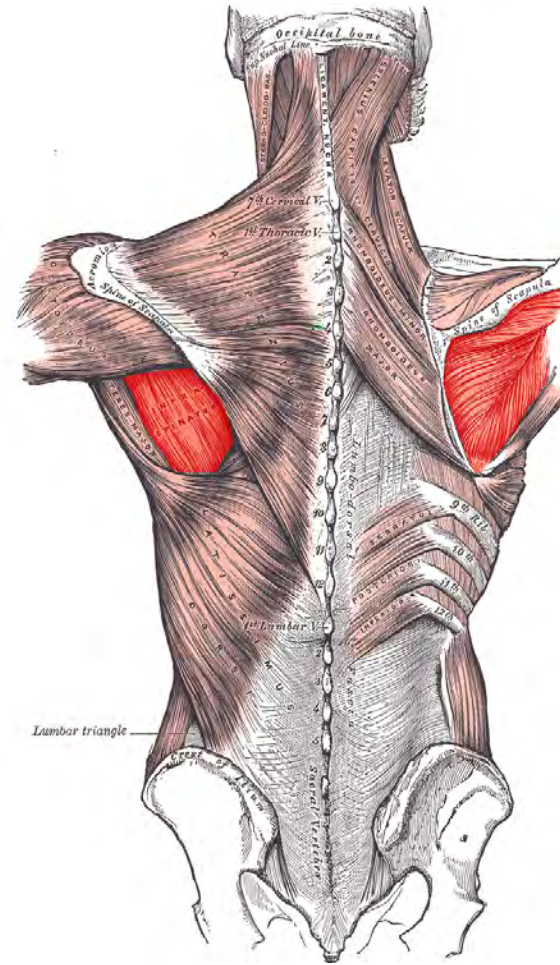
Infraspinatus

- Below spine of scapula

Spine of Scapula



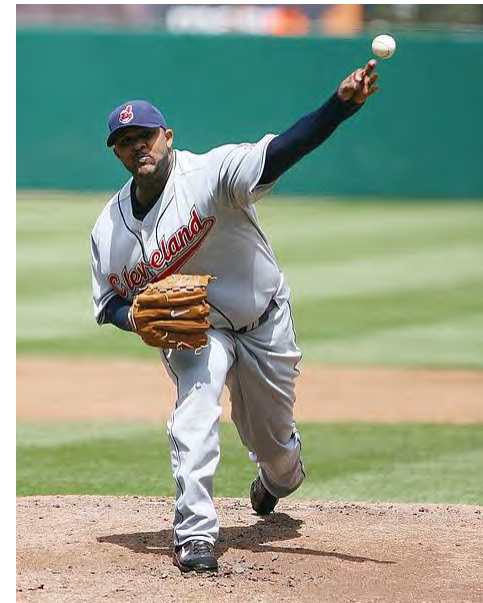
BodyParts3D/Wikipedia



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Infraspinatus

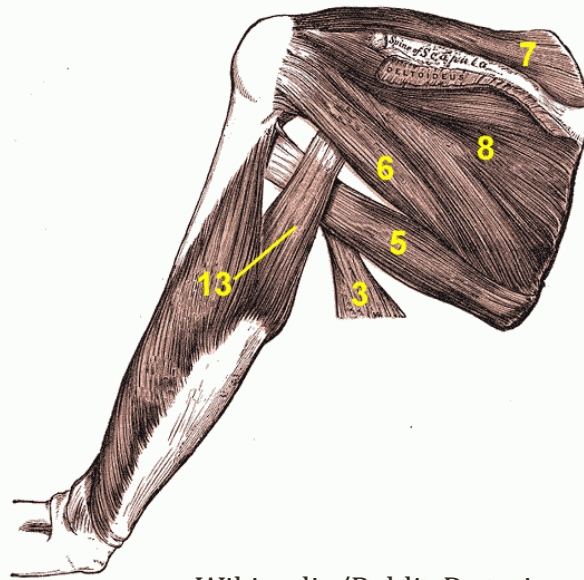
- Assists in external rotation/abduction of shoulder
- Innervation: suprascapular nerve
- Commonly injured in overhead throwers (**pitchers**)
 - Most common rotator cuff injuries: supra/infraspinatus
- Difficult to assess in isolation



Keith Allison/Wikipedia

Teres Minor

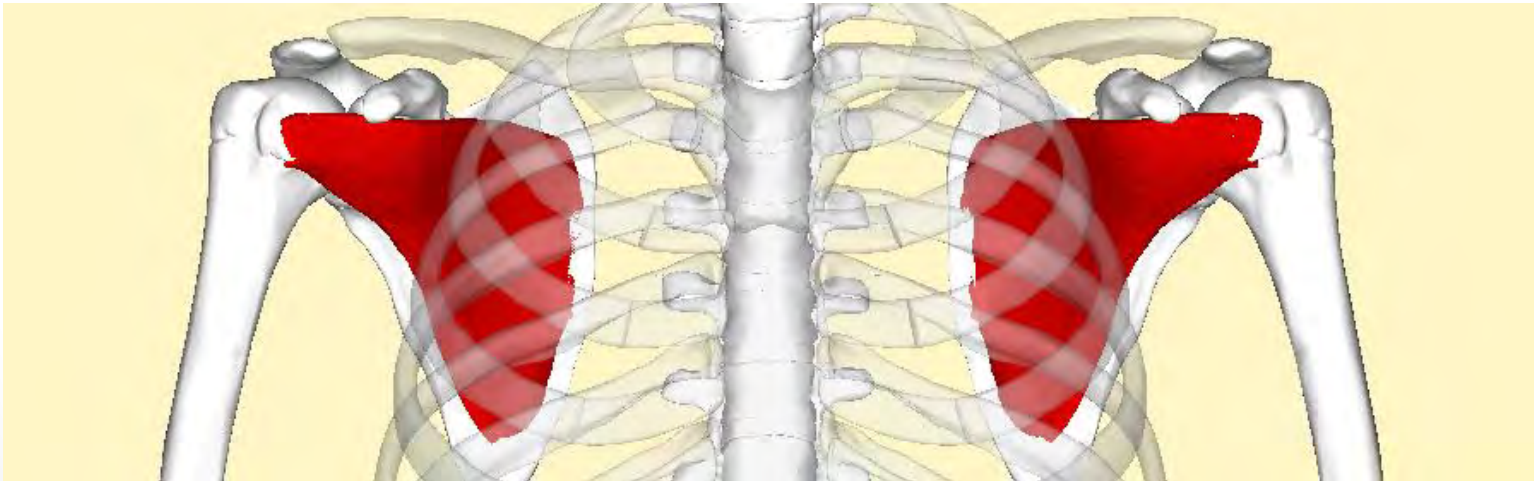
- Assists in external rotation/adduction of shoulder
- Innervation: axillary nerve



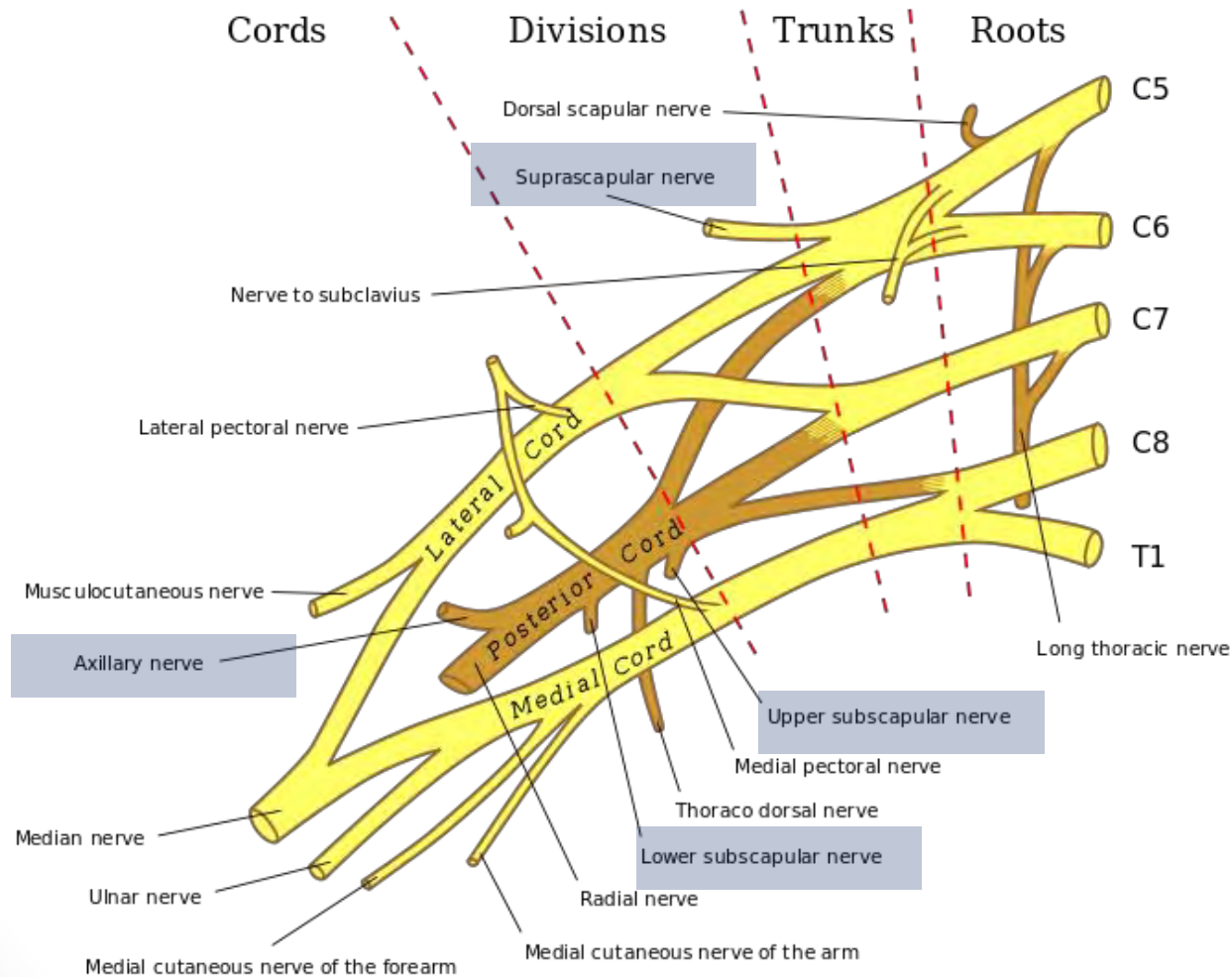
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Subscapularis

- Internal rotation of shoulder/arm
- Innervation: Upper/lower subscapular nerves



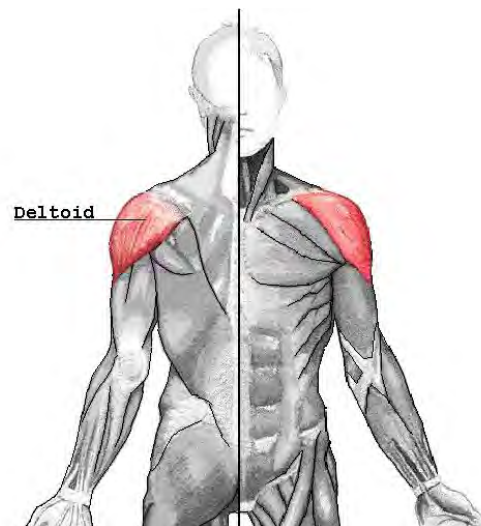
Brachial Plexus



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Shoulder Movement

- **Deltoid:** primary shoulder abductor up to 90°
 - Innervated by axillary nerve
- Other muscles
 - Supraspinatus: initiates abduction; first 15°
 - Trapezius/serratus anterior: abduction beyond 90°



Användare:Chrizz

Shoulder Dislocation

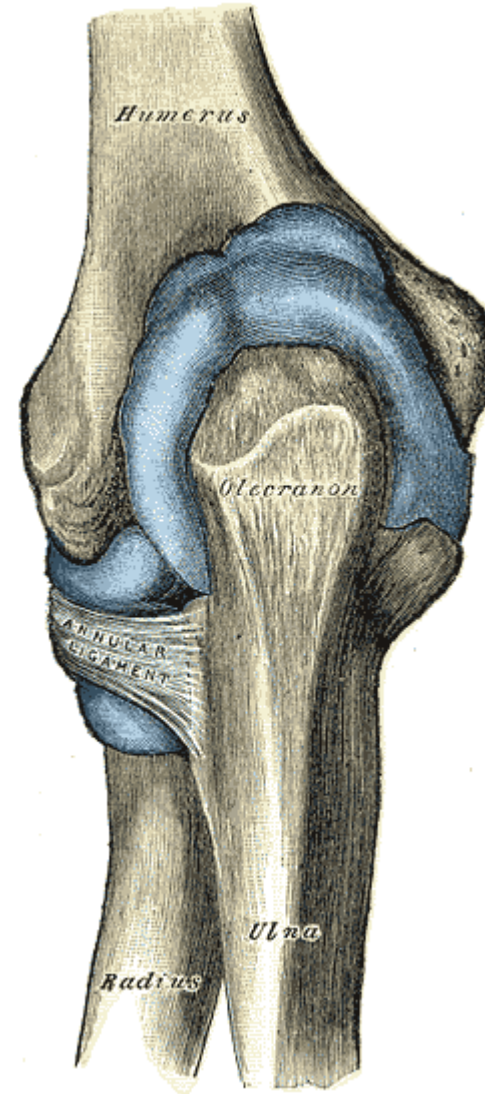
- Trauma → anterior dislocation of humeral head
 - Vulnerable arm: abducted, externally rotated, extended
 - Blocking a basketball shot
 - Tackle while throwing a football
- Commonly injures **axillary nerve**
 - Runs below humeral head
 - Wraps around neck
 - Sensory loss of deltoid
 - Weak abduction (shoulder usually too painful to move)

Humerus Fracture

- Common in elderly (falls)
- Often occur in the **proximal humerus**
 - Blood supply: branches of axillary artery
 - Fractures may disrupt blood supply
 - Avascular necrosis of head
- Proximal humerus nerves
 - Brachial plexus
 - Axillary nerve → loss of arm abduction (deltoid)

Elbow

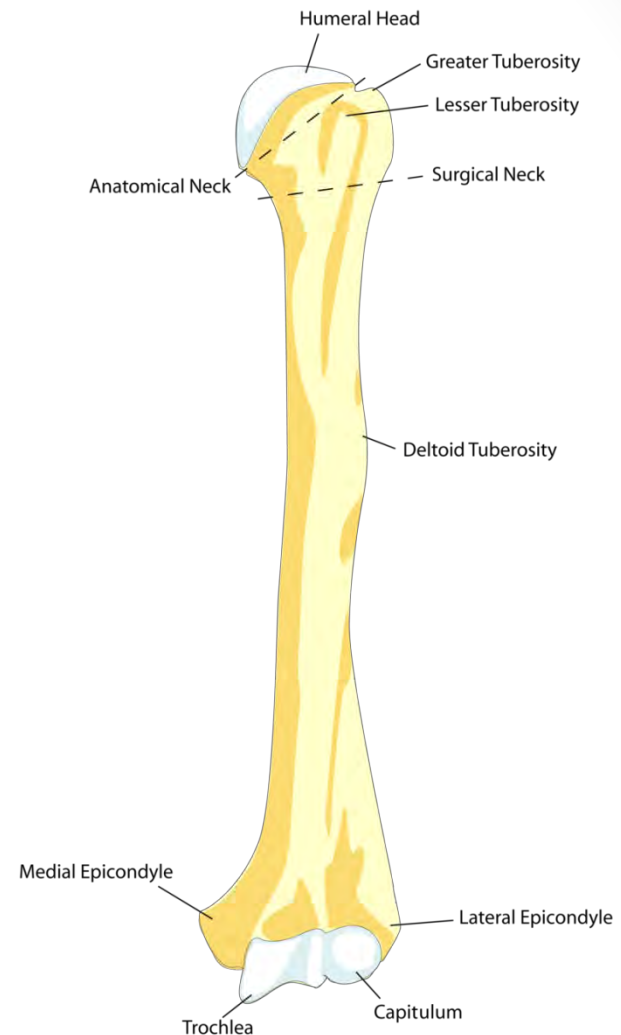
- Three bones
 - Humerus (upper arm)
 - Radius/ulna (lower arm)
- Prone to overuse injuries
 - Golfers, tennis players



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Epicondylitis

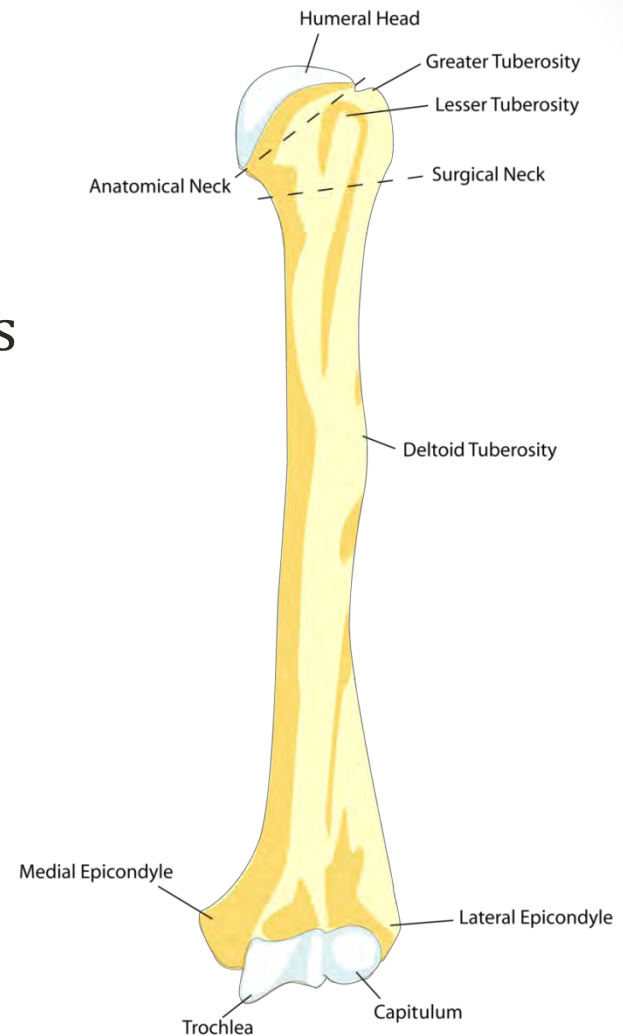
- Lateral epicondyle
 - Bone origin of wrist extensors
- Medial epicondyle
 - Bone origin of wrist flexors
- Epicondylitis
 - Pain at epicondyle from overuse
 - Form of “chronic tendinosis”
 - Few inflammatory cells
 - Disorganized tissue/vessels



Wikipedia/Public Domain

Epicondylitis

- Pain in medial or lateral elbow
- Worse with repetitive movements



Wikipedia/Public Domain

Epicondylitis

- Lateral epicondylitis (tennis elbow)
 - Tenderness: lateral epicondyle and proximal wrist extensors
 - Elbow pain with resisted wrist **extension**



François GOGLINS

Epicondylitis

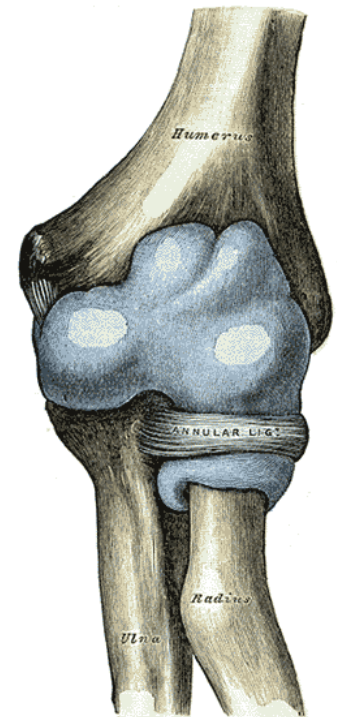
- Medial epicondylitis (golfer's elbow)
 - Tenderness: medial epicondyle
 - Pain with resisted **wrist flexion**



Pixabay/Public Domain

Nursemaid's Elbow

- **Radial head subluxation**
 - Subluxation = partial dislocation
- Caused by “axial traction” on pronated forearm
 - Arm pulled when extended at elbow
- **Annular ligament** slips over head of radius
 - Trapped in radiohumeral joint



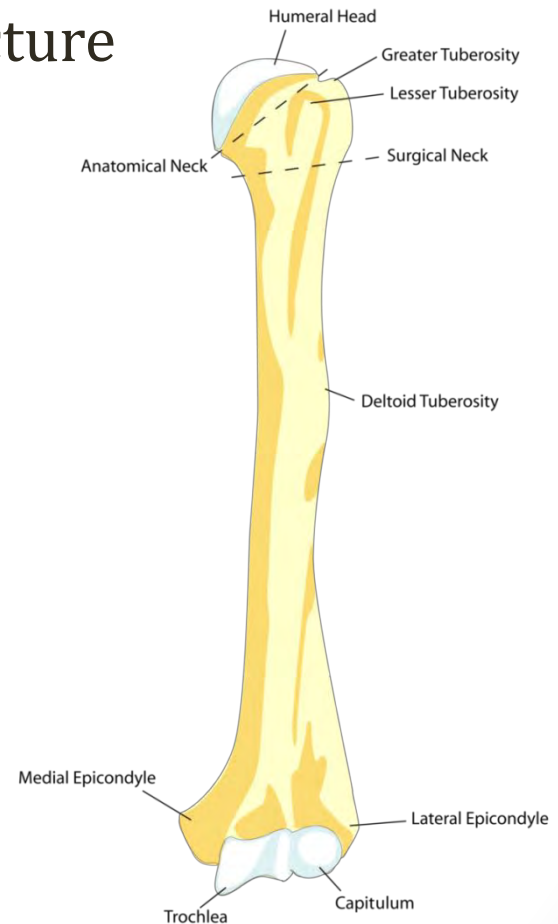
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Supracondylar Fracture

- Most common **pediatric** elbow fracture
- Often from fall on outstretched arm



James Heilman, MD/Wikipedia

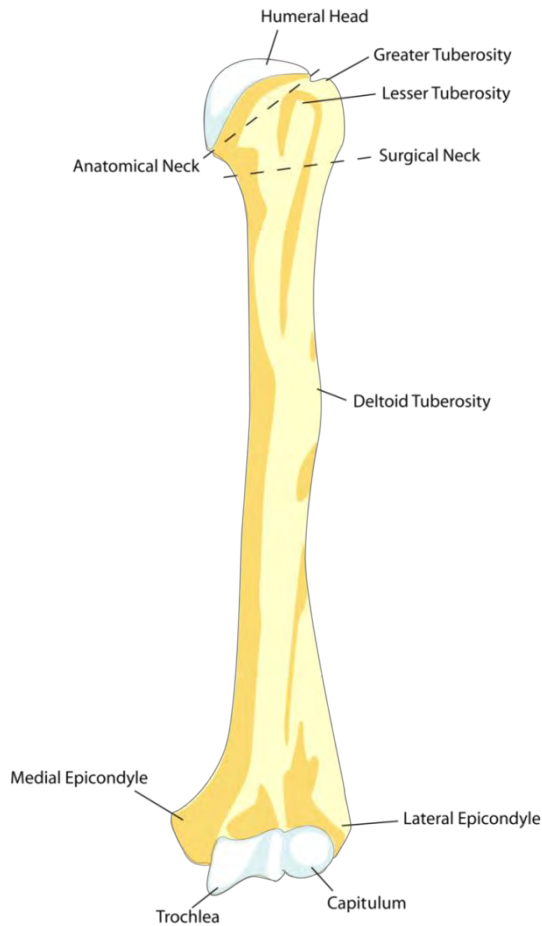


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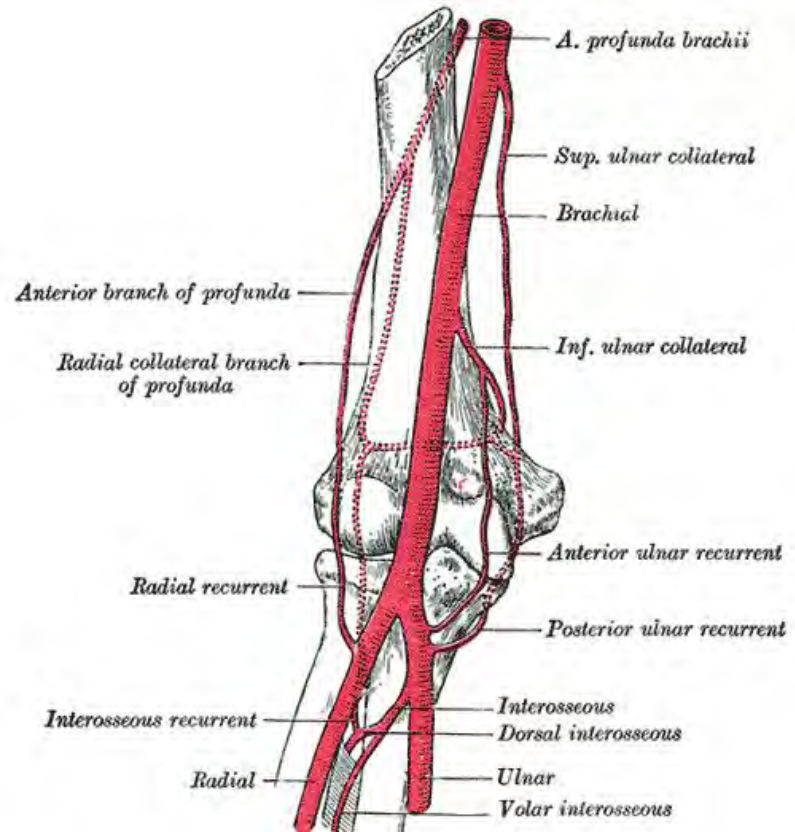
Supracondylar Fracture

- **Brachial artery** may be injured
- **Median nerve** travels with brachial artery
- Injury to both: most common neurovascular injury
- Radial or ulnar nerves may also be injured
 - Ulnar nerve travels under medial epicondyle
 - Radial nerve wraps around humerus laterally

Supracondylar Fracture



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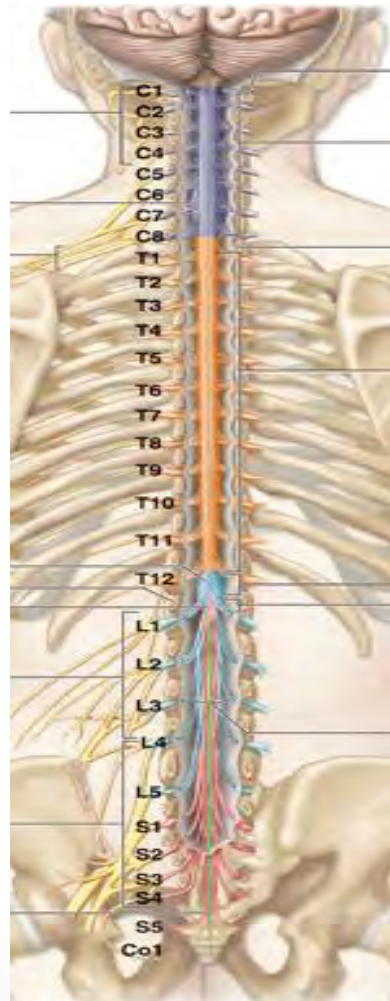
Brachial Plexus

Jason Ryan, MD, MPH

Brachial Plexus

- Network of nerves
- Motor and sensory innervation of arm
- Damage to plexus elements → nerve syndromes

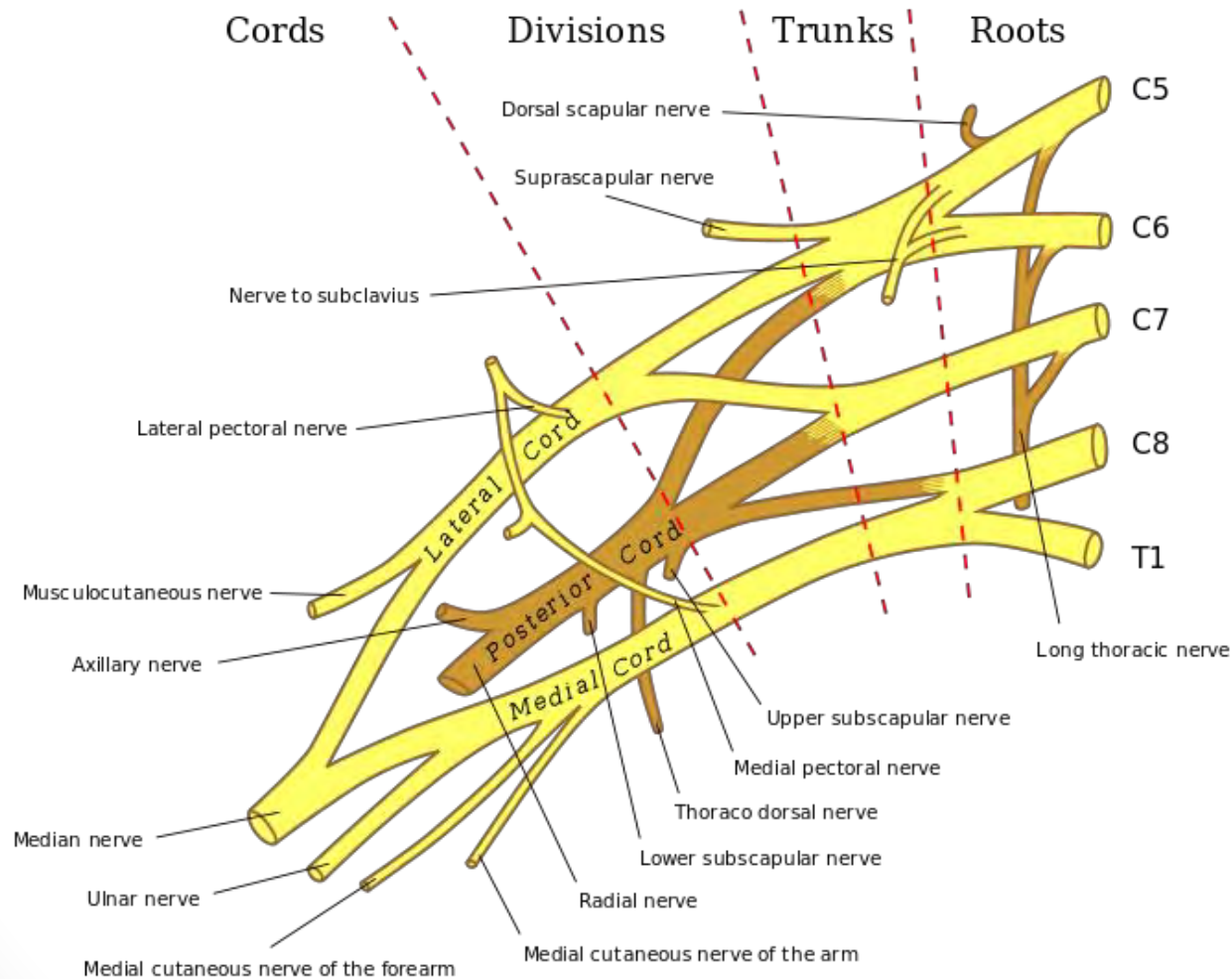
Spinal Nerve Roots



- Cervical (8)
- Thoracic (12)
- Lumbar (5)
- Sacral (5)

guest334add

Brachial Plexus



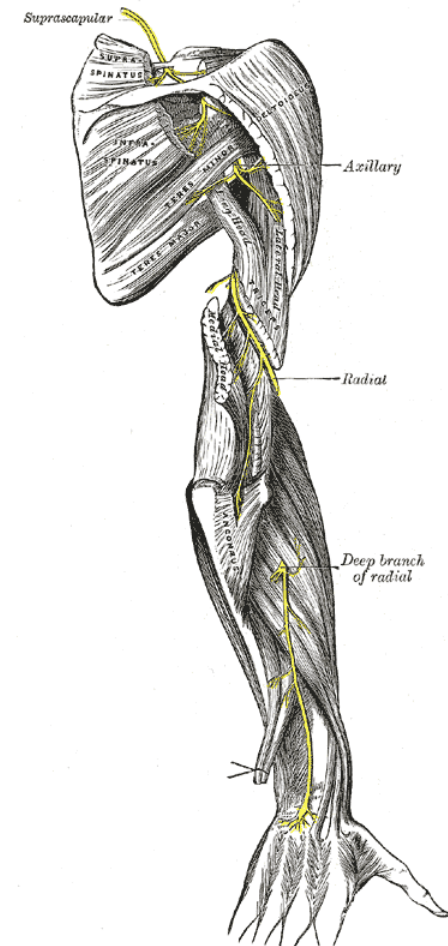
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Brachial Plexus Lesions

- Nerves
 - Axillary
 - Radial
 - Median
 - Ulnar
 - Musculocutaneous
- Trunks
 - Upper: C5-C6
 - Lower: C8-T1
- Long thoracic nerve

Axillary Nerve

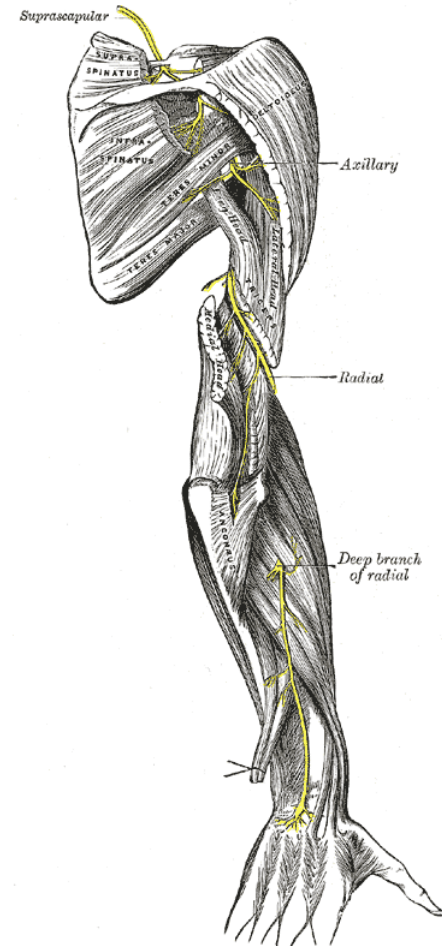
- **Deltoid muscle**
 - Abduction 15° to 90°
- Loss of sensation over deltoid
- **Proximal humerus fracture**
 - Elderly patient with fall
- **Dislocated shoulder**
 - Anterior displacement of humerus



Wikipedia/Public Domain

Radial Nerve

- **Extensor** to arm, wrist, fingers
- Triceps (**extends** at the elbow)
- Extensor muscles in forearm
 - **Extends** wrist and fingers
 - Supinates the forearm
- Sensory to back of hand/forearm



Wikipedia/Public Domain

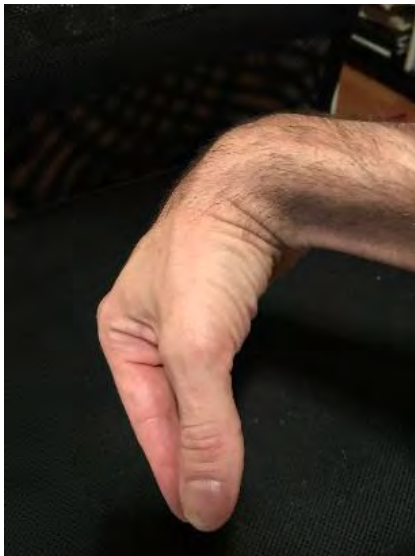
Wrist Flexion and Extension

Major Flexors

Median and Ulnar Nerves

Flexor carpi radialis

Flexor carpi ulnaris



Public Domain

Major Extensors

Radial Nerve

Extensor carpi radialis longus

Extensor carpi radialis brevis

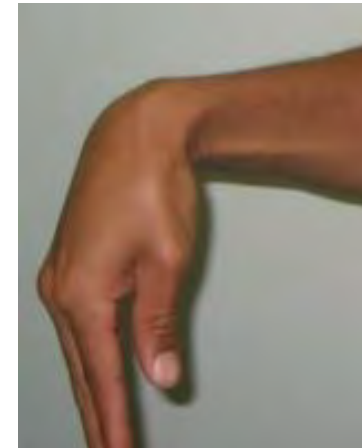
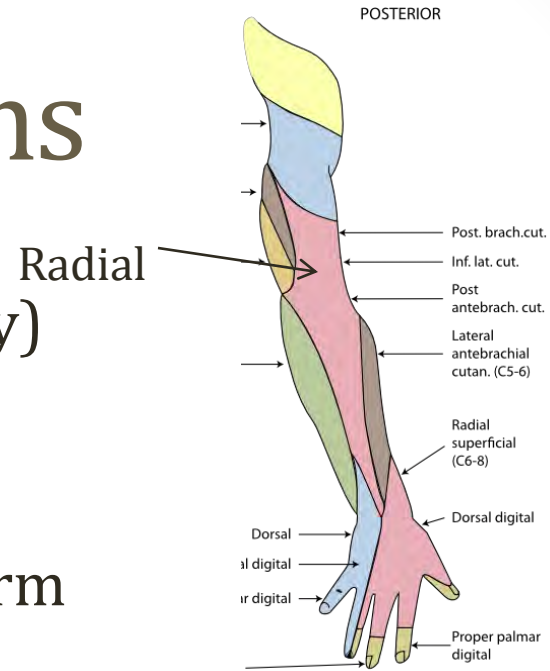
Extensor carpi ulnaris



Public Domain

Radial Nerve Lesions

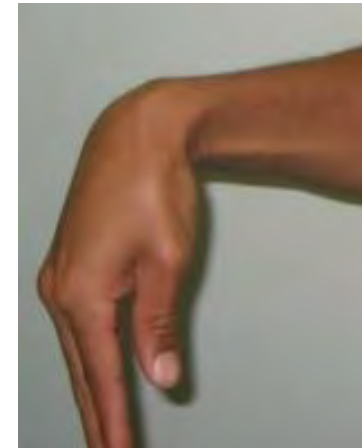
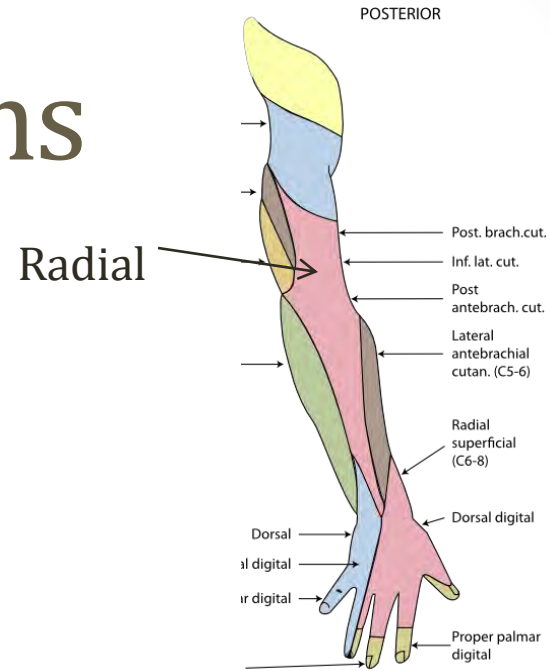
- Triceps weakness (axillary injury)
- **Wrist drop**
 - Weakness wrist/finger extensors
- Sensory loss back of hand/forearm



Wikipedia/Public Domain

Radial Nerve Lesions

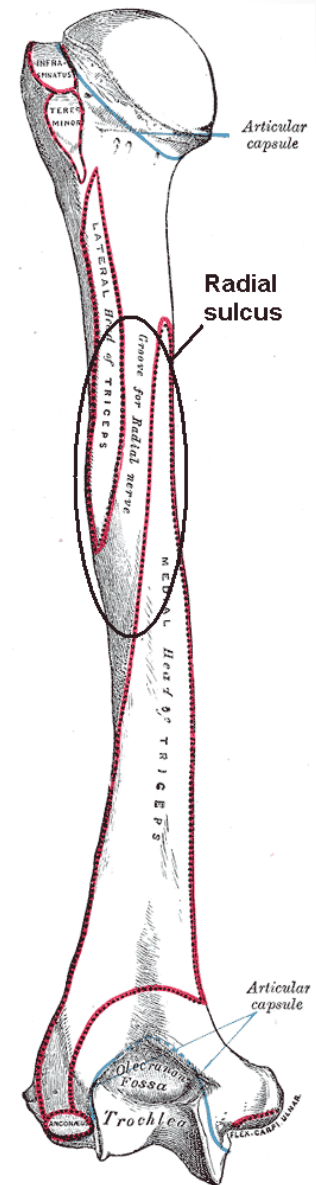
- Causes
 - Humeral fracture (midshaft)
 - Crutches (compression)
 - Sleeping with arms out over chair
 - **“Saturday night palsy”**



Wikipedia/Public Domain

Radial Nerve

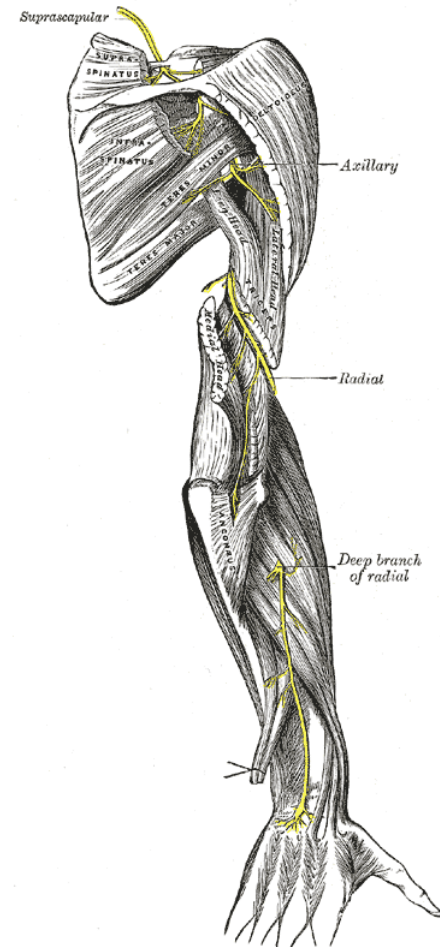
- Runs adjacent to humerus
 - In **spiral/radial groove**
 - Vulnerable to compression against bone



Mikael Häggström/Wikipedia

Radial Nerve Lesions

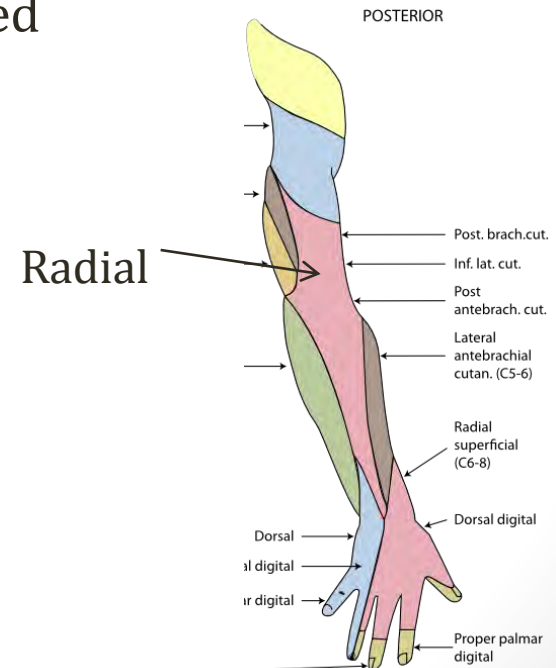
- Axilla level damage
 - Triceps weakness
 - Weakness wrist/finger extensors
 - Sensory loss back of hand/forearm



Wikipedia/Public Domain

Radial Nerve Lesions

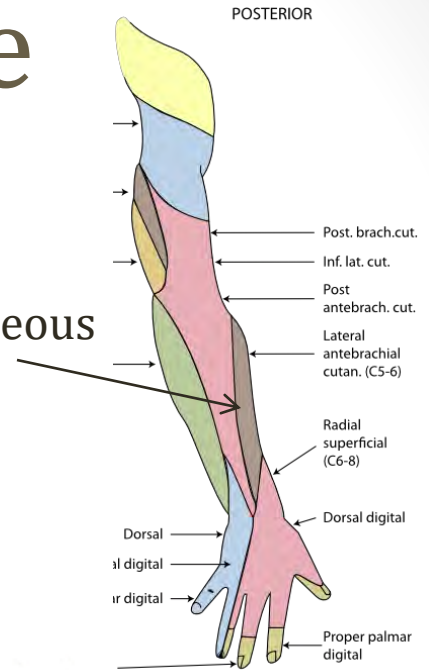
- Radial groove damage
 - **Triceps spared**
 - Weakness wrist/finger extensors
 - Most sensory nerves (arm/forearm) unaffected
 - Superficial branch of radial nerve damaged
 - **Sensory loss dorsal surface**



Musculocutaneous Nerve

- Lateral cord of brachial plexus
 - C5, C6, and C7
- Innervates **biceps** and other muscles
- Sensation to **lateral forearm**
- Nerve lesion (rare)
 - Weakness of elbow flexion
 - Sensory loss lateral forearm

Musculocutaneous



Everkinetic/Wikipedia

C5-C6 Trunk

Erb's Palsy/Upper Plexus Injury

- Caused by excessive angle at neck/shoulder
- Stretches/tears nerve roots → nerve damage
- Classic cause: **birth trauma**
 - “Shoulder dystocia:” shoulder impedes delivery
 - Stretching of angle between neck/shoulder



MaxPixel/FreeGreatPicture.com

C5-C6 Trunk

Erb's Palsy/Upper Plexus Injury

- Axillary nerve
 - Deltoid → abduction
 - Shoulder flat at side
- Musculocutaneous
 - Biceps → elbow flexion
 - Forearm down
- Suprascapular
 - Infraspinatus → external rotation
 - Arm internally rotated

C5-C6 Trunk

Erb's Palsy/Upper Plexus Injury

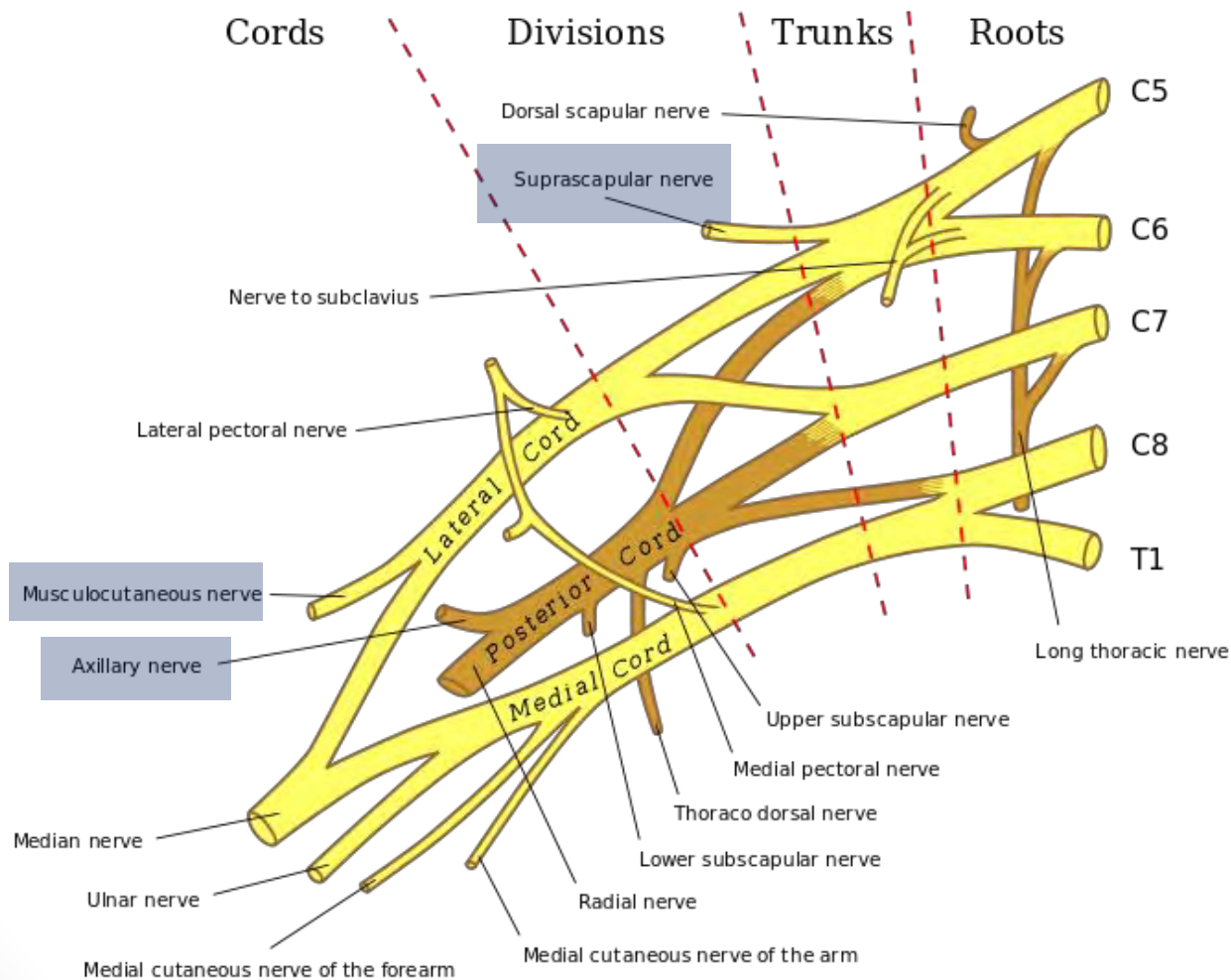
- **Arm straight at side**
- **Internally rotated (hand facing out)**
- “Waiter’s tip”



Caryl Subion

Brachial Plexus

Erb's Palsy/Upper Plexus Injury



Wikipedia/Public Domain

C8-T1 Trunk

Klumpke Palsy/Lower Plexus Injury

- Caused by excessive abduction of arm
- **Catching a tree branch while falling**
- Rarely occurs from birth trauma



Pixabay/Public Domain

C8-T1 Trunk

Klumpke Palsy/Lower Plexus Injury

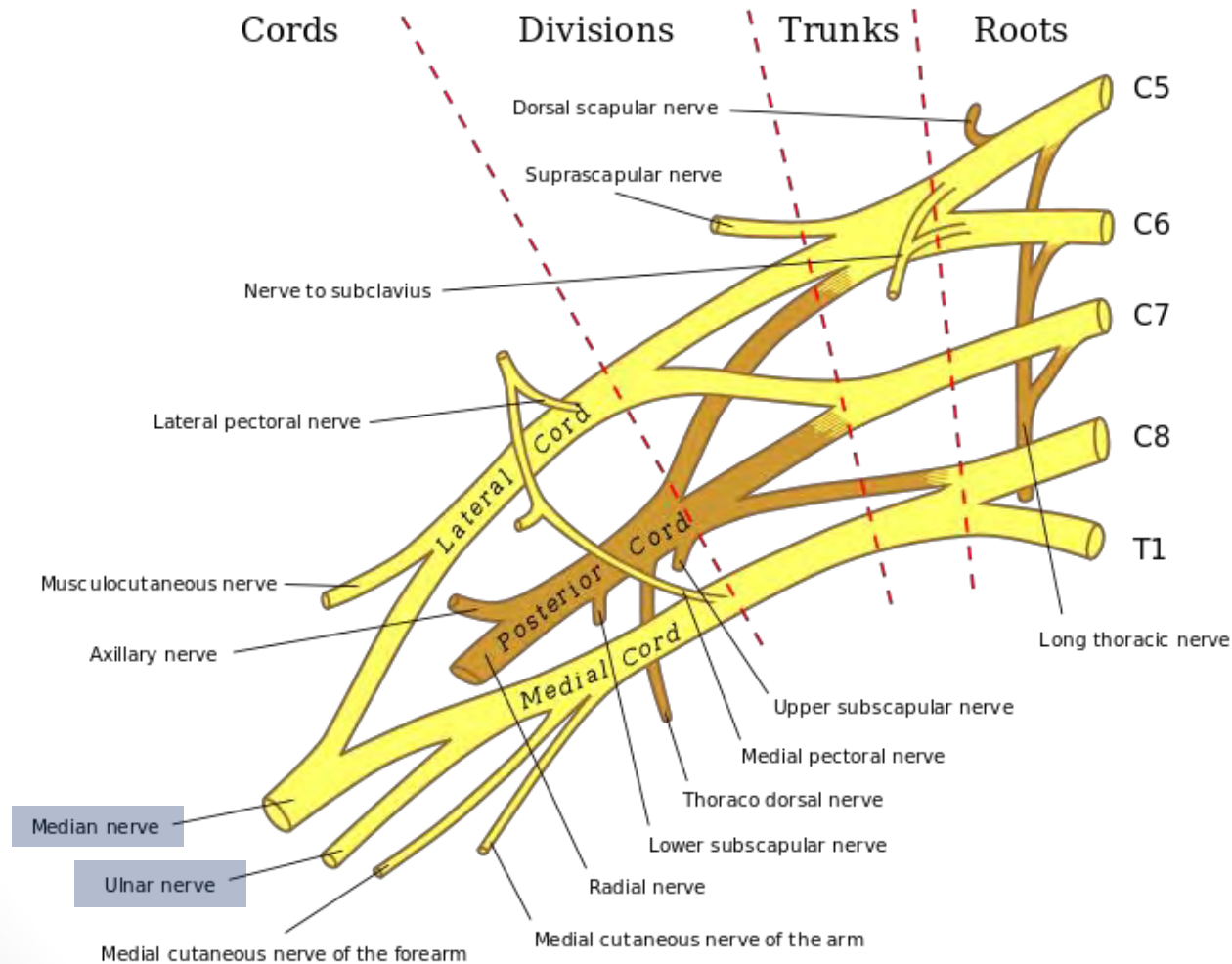
- **Ulnar and median nerves**
- Affects intrinsic hand muscles
- Flexors at wrist arm spared
 - Also supplied by ulna and median nerves
 - Innervated by different roots
- Metacarpophalangeal joints hyperextended
- Interphalangeal joints flexed
- Result: **clawed hand**



Wikipedia/Public Domain

Brachial Plexus

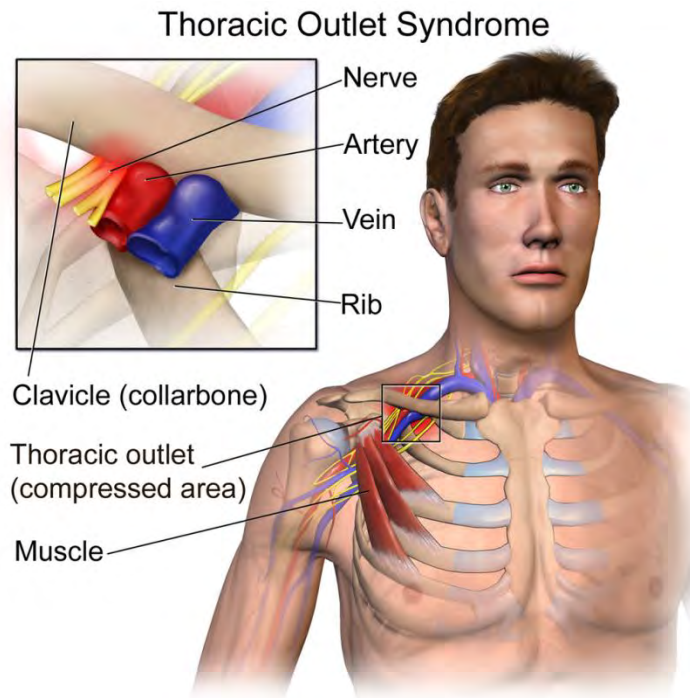
Klumpke Palsy/Lower Plexus Injury



Wikipedia/Public Domain

Thoracic Outlet Syndrome

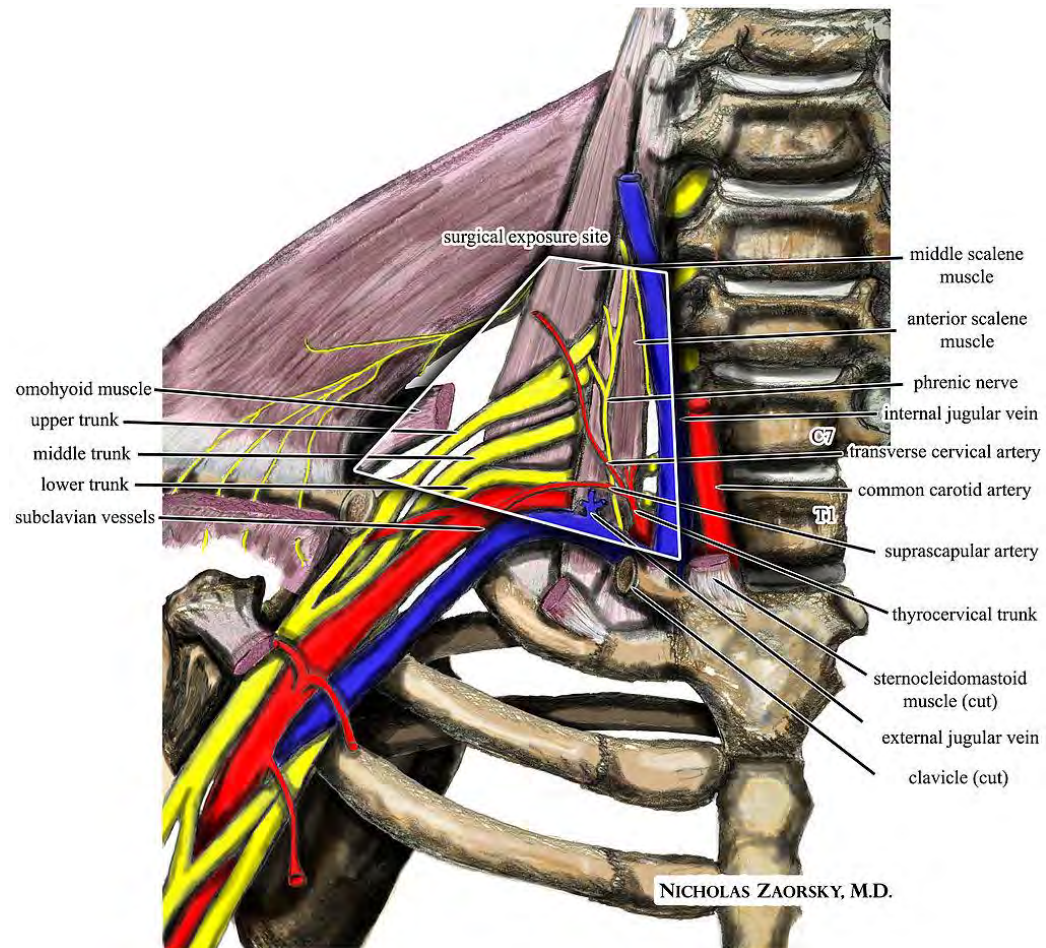
- Compression of nerves/vessels leaving thorax
- Occurs above first rib and behind clavicle
 - “Thoracic outlet”



BruceBlaus/Wikipedia

Thoracic Outlet Syndrome

- Scalene triangle
 - Anterior scalene
 - Middle scalene
 - Above first rib

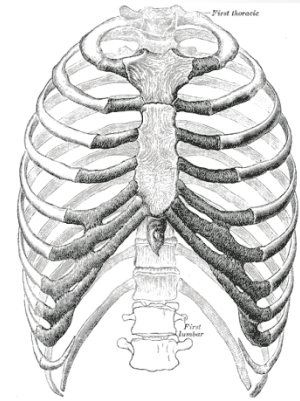


Nicholas Zaorsky/Wikipedia

Thoracic Outlet Syndrome

Causes

- **Cervical rib**
 - Anomalous extra rib from 7th cervical vertebrae
 - Predisposes to outlet syndrome
 - Often occurs after hyperextension-flexion (whiplash)



Thoracic Outlet Syndrome

Clinical Features

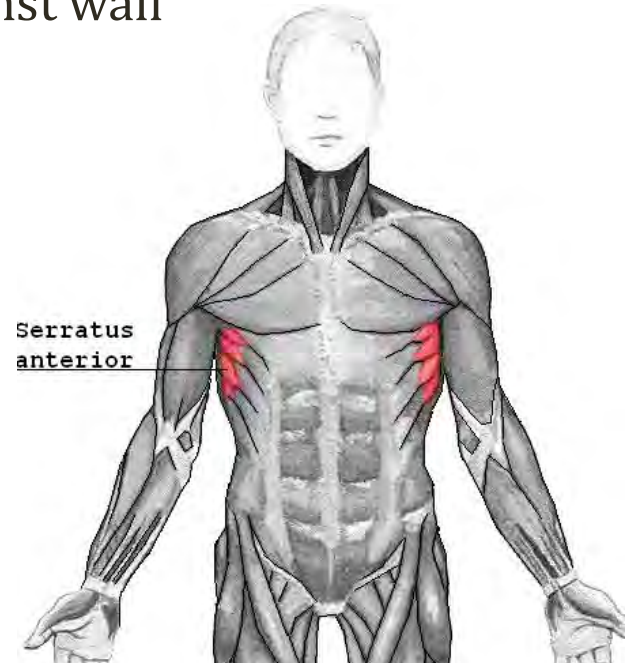
- Brachial plexus: Klumpke palsy
 - Lower plexus injury
 - Symptoms worse with elevation of arms/hands
- Venous compression: Arm swelling
- Arterial compression (rare)
 - Hand ischemia (pain, pallor, cool temperature)
 - Lower systolic blood pressure
 - Weak distal pulses

Long Thoracic Nerve

- Innervates **serratus anterior muscle**
 - Pulls scapula against rib cage
- Lesion (trauma): **winging of scapula**
 - Patient presses outstretched arm against wall
 - Scapula protrudes from back



Dwaipayanc/Wikipedia



Bildbearbetning: sv:Användare:Chrizz

Wrist

Jason Ryan, MD, MPH

Wrist Bones

- Carpus = wrist
- Eight carpal (wrist) bones
 - A: Scaphoid
 - B: Lunate
 - C: Triquetrum
 - D: Pisiform
 - E: Trapezium
 - F: Trapezoid
 - G: Capitate
 - H: Hamate



Dr. Jochen Lengerke/Wikipedia

Scaphoid

- Most commonly fractured carpal bone
- Palpable in anatomic snuff box
- Classically from **FOOSH injury**
 - Falling On an Out-Stretched Hand
- Complications of fractures
 - Avascular necrosis
 - Nonunion



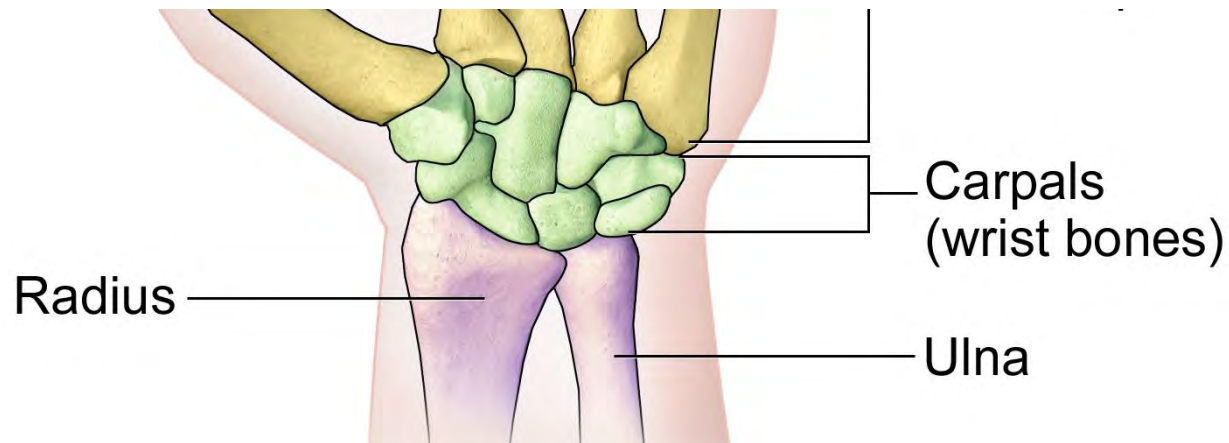
M0rphzone/Wikipedia



Public Domain

Scaphoid Blood Supply

- Blood supply: Radial artery
 - Palmar and dorsal branches
- Radial artery supplies distal bone
- Proximal portion relies on **retrograde flow**



Scaphoid Fracture

Complications

- **Avascular necrosis**
 - Loss of blood supply
 - Especially waist fractures
- **Nonunion**
 - Failure of bone to heal



Public Domain

Lunate Dislocation

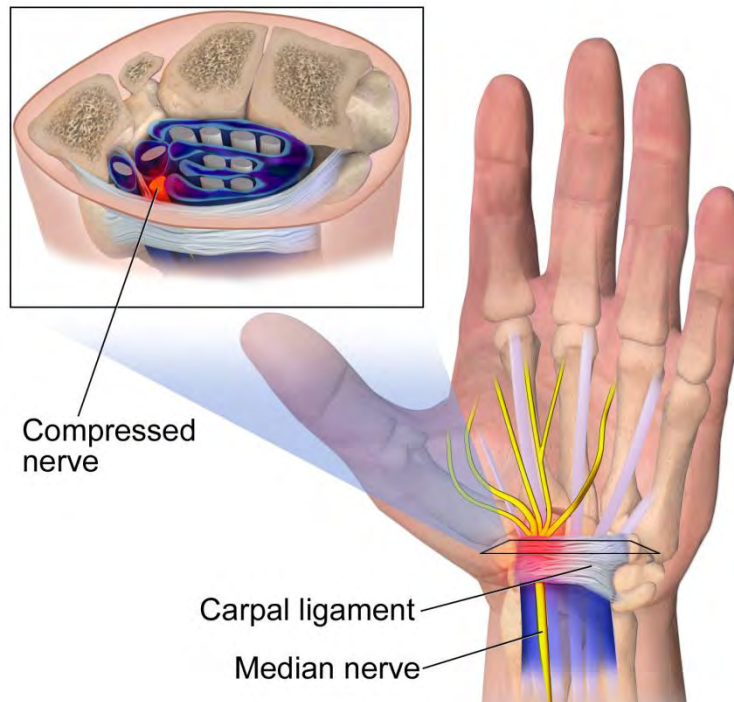
- Caused by trauma/fall
- Lunate attached to radius
- Other bones forced backwards
- Lunate displaced toward palm
- Wrist painful/swollen



Dr. Jochen Lengerke/Wikipedia

Lunate Dislocation

- Lunate may compress **carpal tunnel**
- **Median nerve** dysfunction



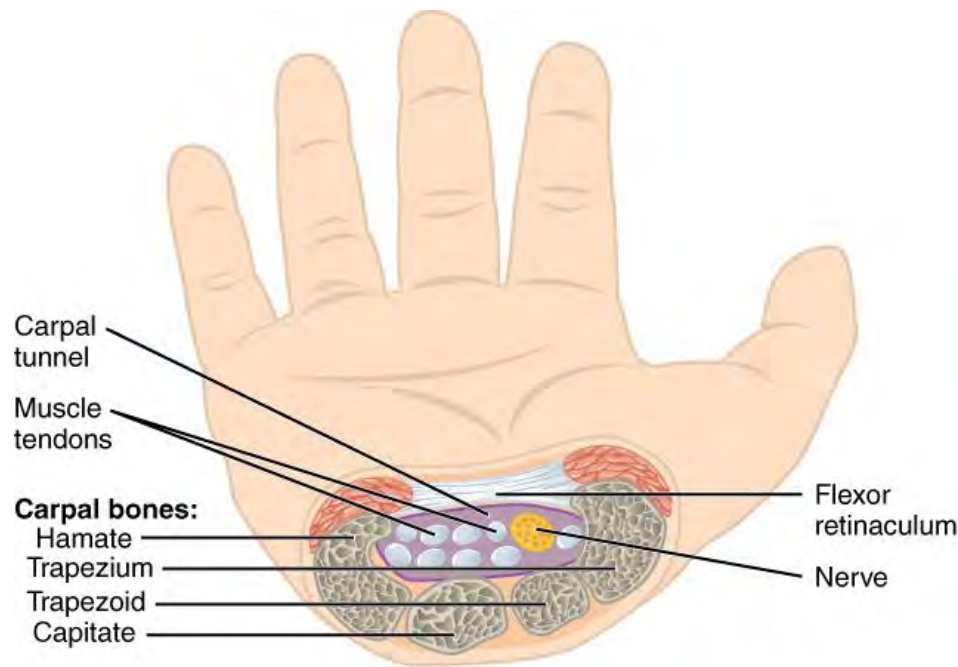
Compressed
nerve

Carpal ligament

Median nerve

Carpal Tunnel

- Transverse carpal ligament (flexor retinaculum)
- Carpal bones (inferiorly)



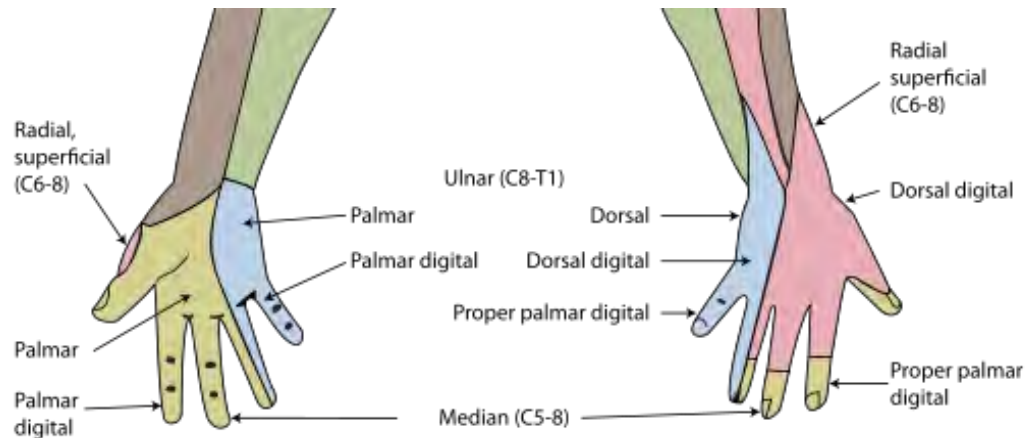
OpenStax College/Wikipedia

Carpal Tunnel Syndrome

- Entrapment of median nerve in carpal tunnel
- Symptoms of **median nerve dysfunction**

Median Nerve Lesions

- Motor loss to thumb side:
 - Thumb movement (thenar muscles)
 - Flexion/extension of lateral fingers (lumbricals)
- Sensory loss thumb side:
 - Thenar eminence, lateral 3 ½ fingers



Wikipedia/Public Domain

Carpal Tunnel Syndrome

- Begins with sensory symptoms
- Untreated can lead to motor symptoms
- Classic hallmark: **pain or paresthesia**
 - Described as numbness and tingling
 - Distribution of median nerve

Carpal Tunnel Syndrome

Risk Factors

- Repetitive use of hands/wrists (controversial)
- Obesity
- Pregnancy (edema)
- Other disorders
 - Diabetes
 - Rheumatoid arthritis
 - Hypothyroidism

Acromegaly

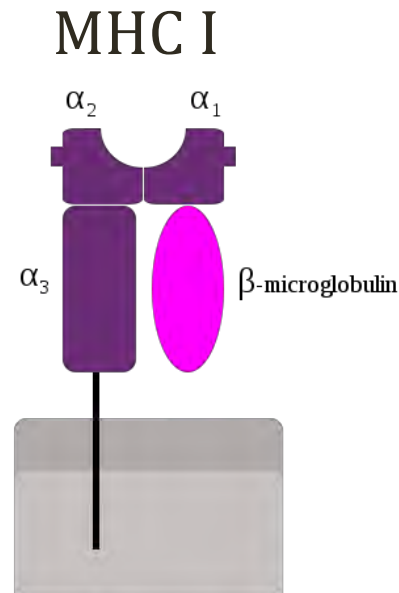
- Growth hormone excess in adults
- Often caused by pituitary adenoma
- Enlarged jaw and coarse facial features
- Enlarged **hands and feet**
 - Classic sign: Increasing glove/shoe size
 - Rings that no longer fit
 - Up to 1/3 have carpal tunnel syndrome



Philippe Chanson and Sylvie Salenave

Dialysis-related Amyloidosis

- Amyloid deposits form from **$\beta 2$ microglobulin**
- Complication of renal failure
- Dialysis does not effectively remove $\beta 2$ microglobulin
- Bones, joints, tendons
- Shoulder pain
- **Carpal tunnel syndrome**



atropos235

Carpal Tunnel Syndrome

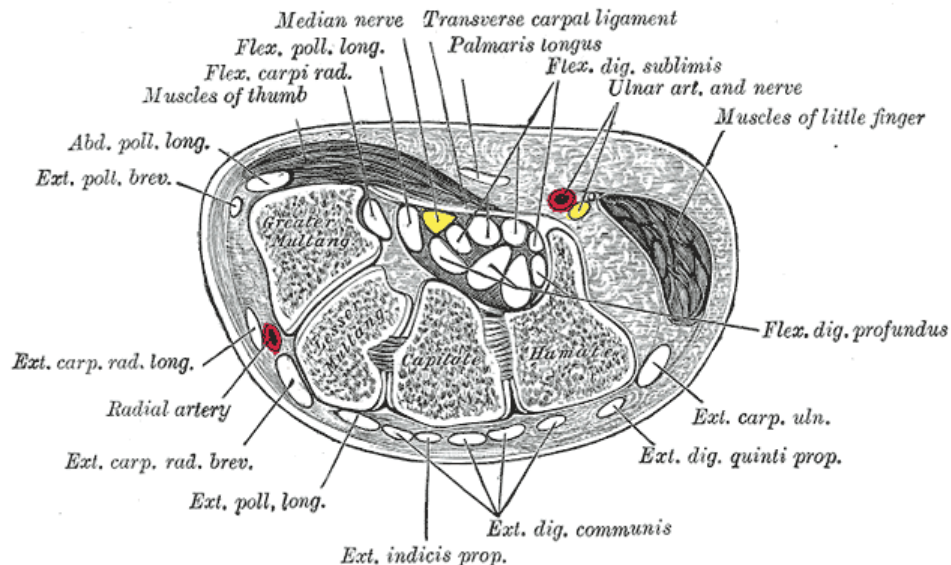
Physical Exam

- Tinel's sign
 - Patient extends wrist
 - Percussion (light tapping) over thumb side of wrist
 - Tingling in distribution of median nerve = positive
- Phalen maneuver
 - Patient asked to flex wrist and hold for 60 seconds
 - Tingling in distribution of median nerve = positive

Guyon's Canal

Ulnar Canal

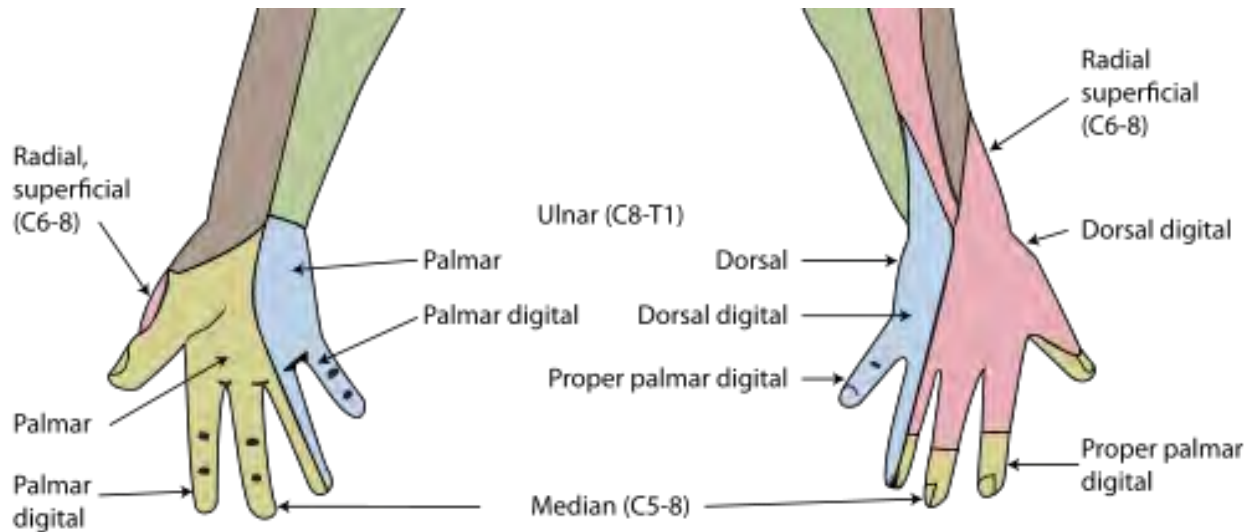
- Above transverse carpal ligament
- Roof formed by palmar fascia
- Passage of **ulnar nerve** and artery into wrist



Wikipedia/Public Domain

Ulnar Nerve Lesions

- Loss of abduction/adduction (interossei)
- Motor loss to little finger side (little/ring fingers)
 - Hypothenar muscles, medial two lumbricals
- Sensory loss little finger side



Guyon's Canal Syndrome

- Overuse of the wrist
- Many cases reported in **bicyclists**
 - Direct pressure from handlebars



Public Domain

Pediatric Fracture

- Often from trauma
- Often incomplete

Greenstick Fracture

- **Bent bone** from fracture
- Fracture **does not extend through width of bone**
- Often occur in distal radius from trauma
- **Bending force (from side)** applied to bone
- Often FOOSH injury (fall on an outstretched hand)

Greenstick Fracture

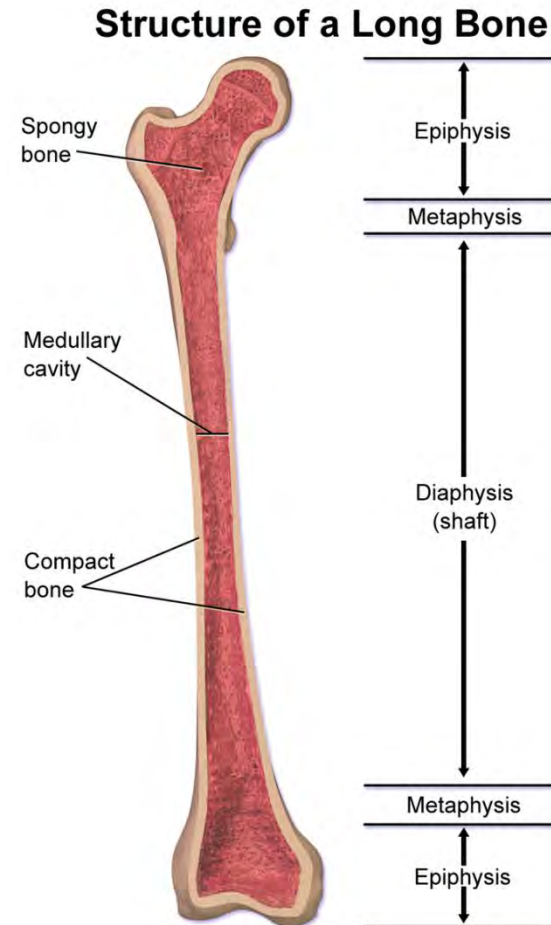


Hellerhoff/Wikipedia

Torus Fracture

Pediatric Fracture

- “Buckle fracture”
- **Axial force** trauma
 - Force into bone
- Occurs in distal metaphysis
 - Diaphysis = shaft
 - Epiphysis = rounded end
 - Metaphysis = widening
- Metaphysis: most porous bone



BruceBlaus/Wikipedia

Torus Fracture



James Heilman, MD/Wikipedia

Hand

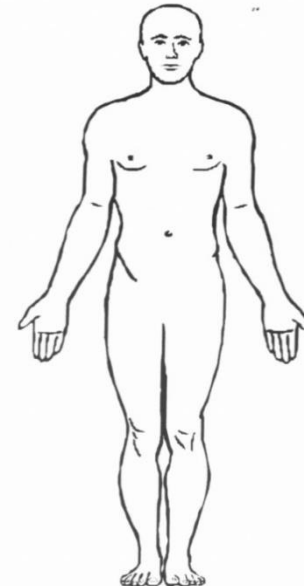
Jason Ryan, MD, MPH

Terminology

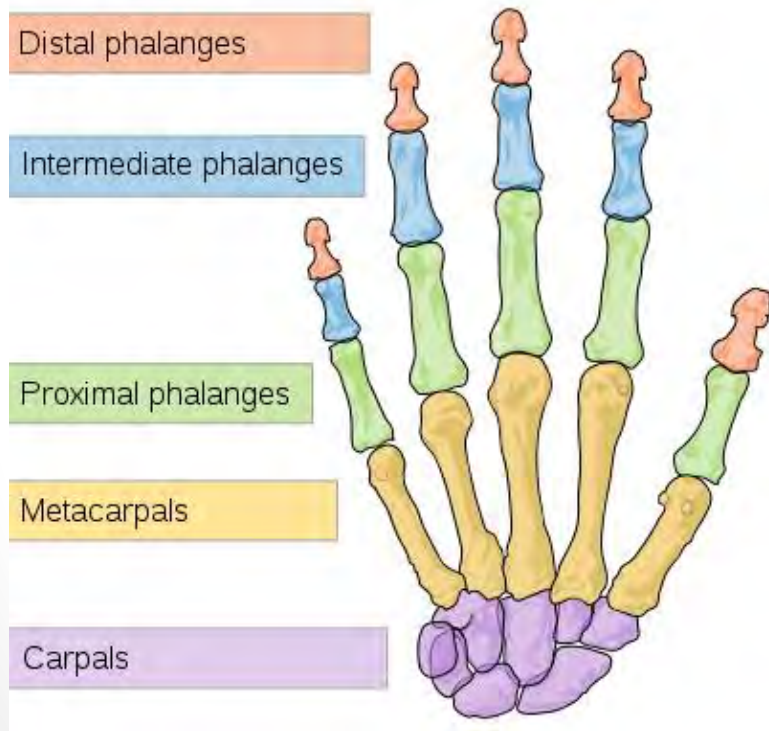
- Thumb = 1st digit
- Index = 2nd digit
- Middle (long) = 3rd digit
- Ring = 4th digit
- Pinky (small) = 5th digit
- “Volar” = palm of hand
- “Dorsal” = back of hand
- Thumb = lateral
- Little finger = medial



Pixabay/Public Domain

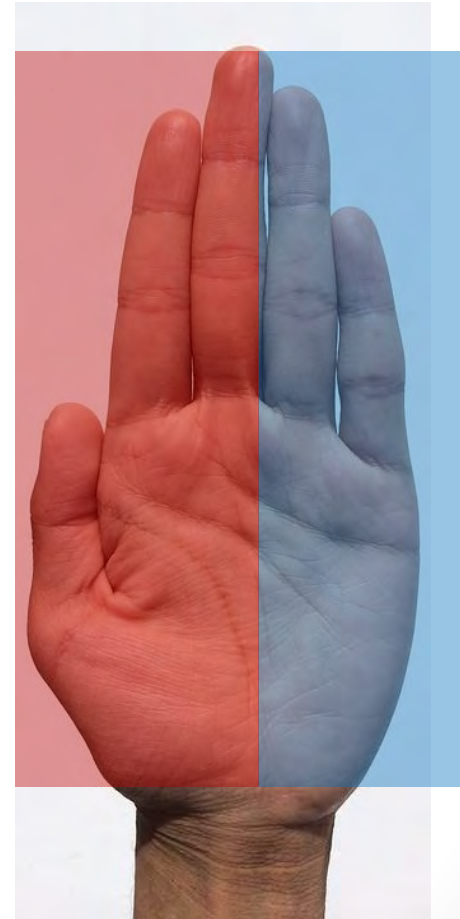


Bones and Joints



Ulnar and Median Nerves

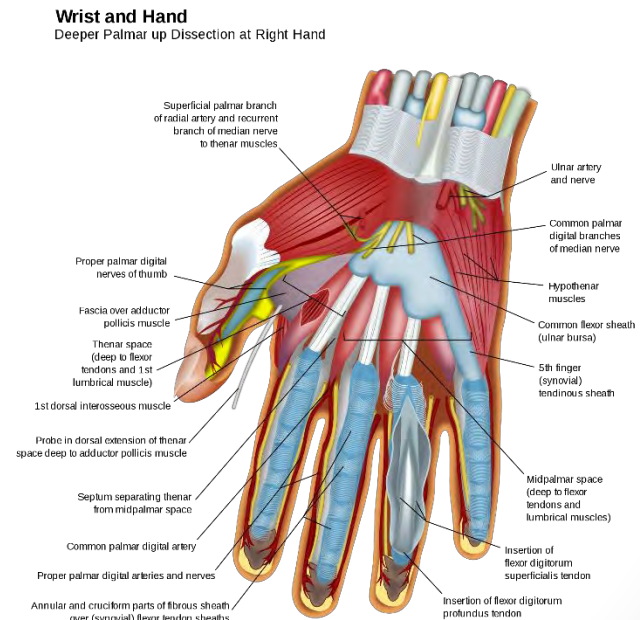
- Ulnar nerve
 - Structures toward ulnar bone (little finger)
- Median nerve
 - Structures toward radius (thumb)



Hand Muscles

- **Intrinsic**

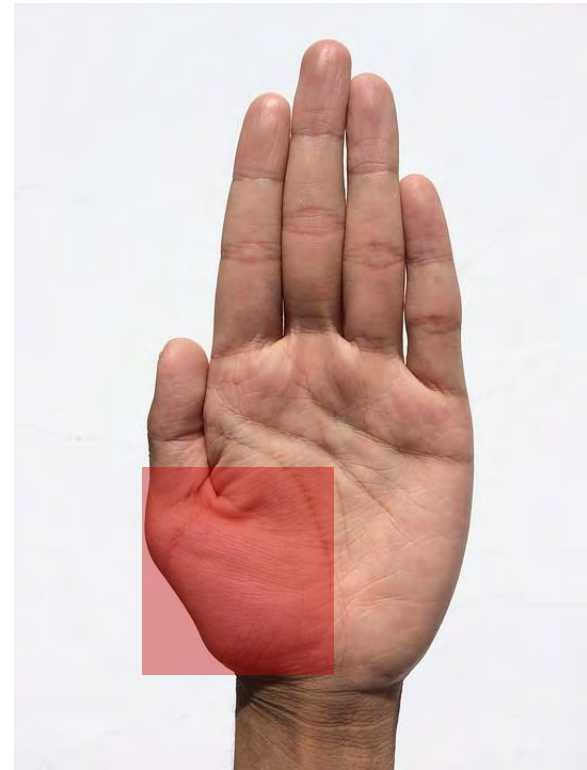
- Thenar (thumb)
- Hypothenar (little finger)
- Interosseous muscles (abduction/adduction)
- Lumbrical muscles (four fingers)



The Photographer/Wikipedia

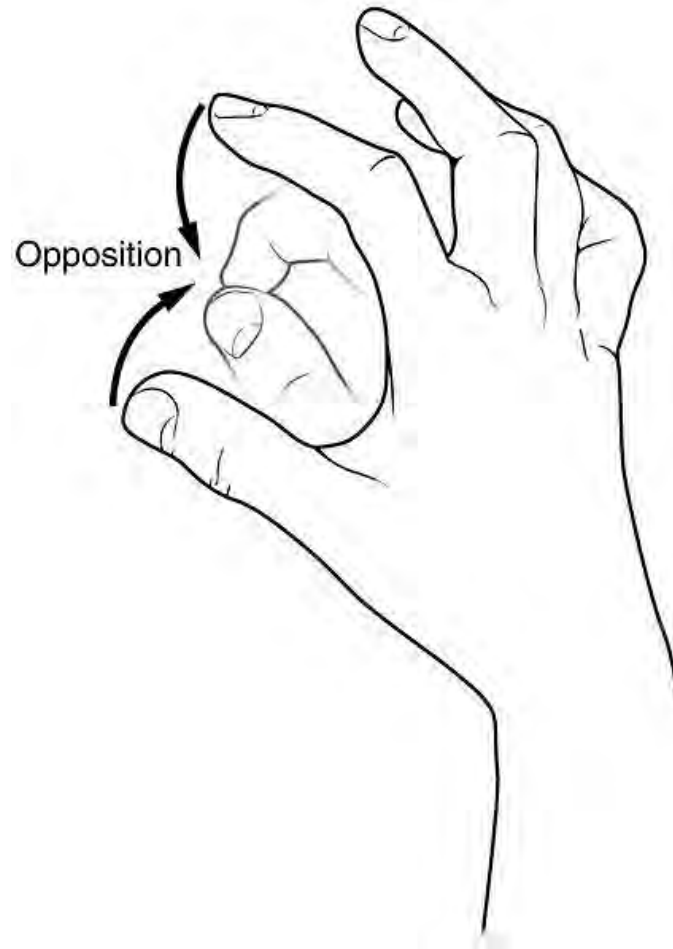
Thenar Muscles

- Three muscles
 - Abductor pollicis brevis
 - Flexor pollicis brevis
 - Opponens pollicis
- Associated with thumb
- Form **thenar eminence** of palm
- Innervated by **median nerve**
- Atrophy in median lesions



Pixabay/Public Domain

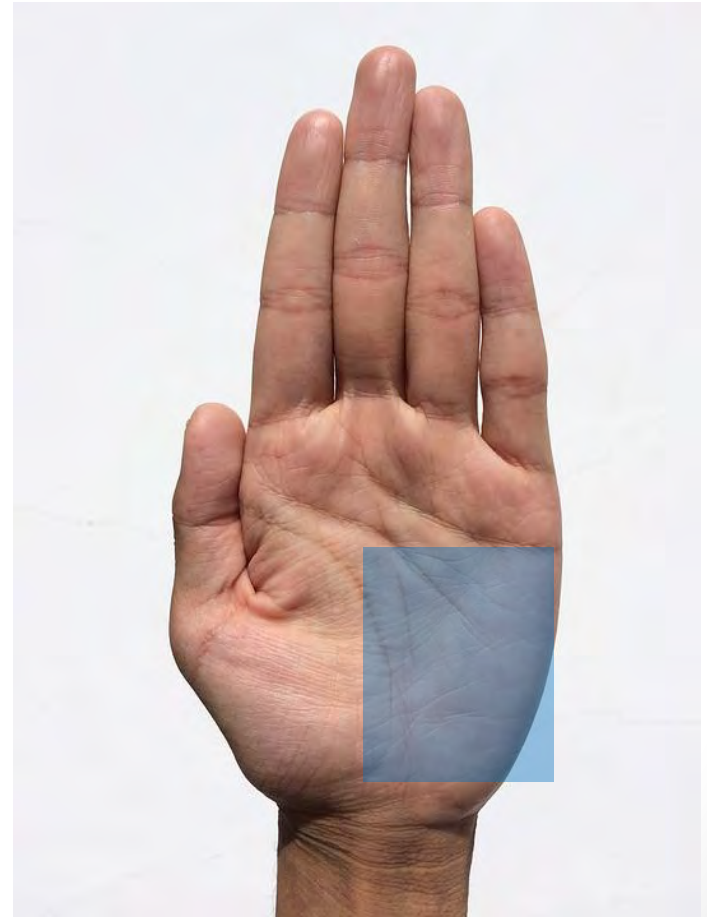
Thumb Opposition



Connexions/Wikipedia

Hypothenar Muscles

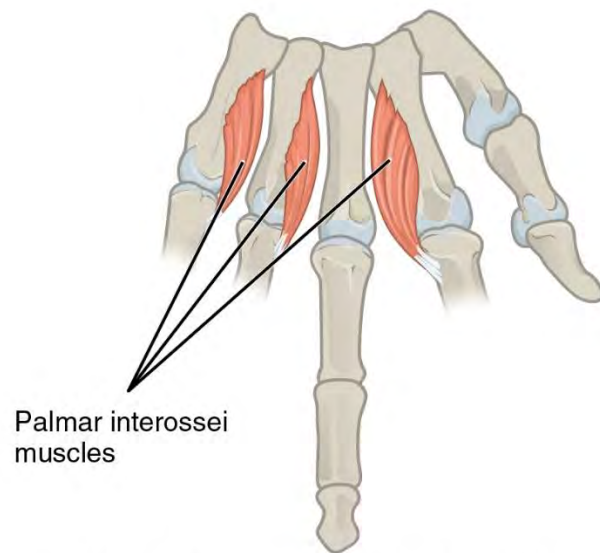
- Three muscles
 - Opponens digiti minimi
 - Flexor digiti minimi brevis
 - Abductor digiti minimi
- Associated with little finger
- Form hypothenar eminence
- Innervated by **ulnar nerve**
- Atrophy in ulnar lesions



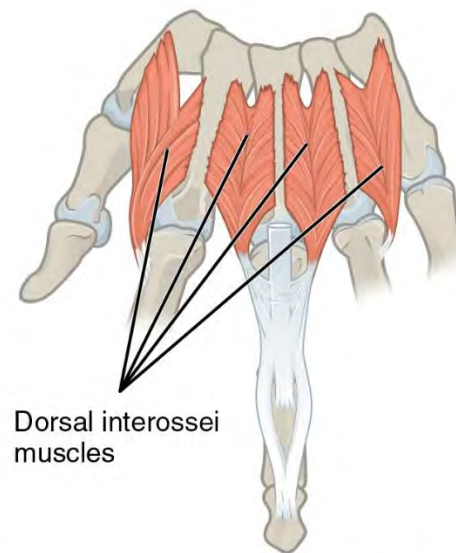
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Interosseous Muscles

- **Abduct and adduct fingers** (not thumb)
 - Dorsal = abduction
 - Palmar = adduction
- Innervated by **ulnar nerve**



Interossei muscles of left hand (palmar view)



Interossei muscles of left hand (dorsal view)

Lumbricals

- Originate: tendons of flexor digitorum profundus
 - Forearm (extrinsic) muscle that flexes fingers
- **Flex** metacarpophalangeal joints
- **Extend** interphalangeal joints
- Medial two lumbricals: **ulnar nerve**
 - Near little finger
- Lateral two lumbricals: **median nerve**
 - Near thumb

L Shape



Lumbricals

- Loss of lumbricals: claw fingers
 - Metacarpophalangeal joints extended (cannot flex)
 - Interphalangeal joints flex (cannot extend)

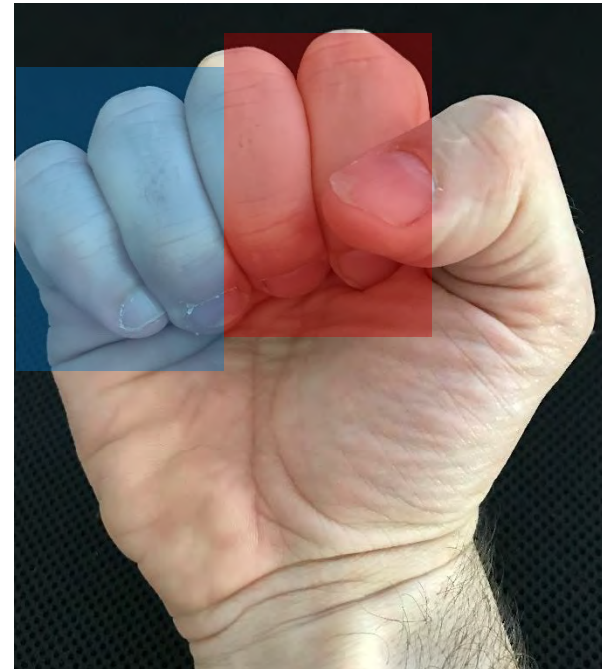


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Extrinsic Hand Muscles

Flexors

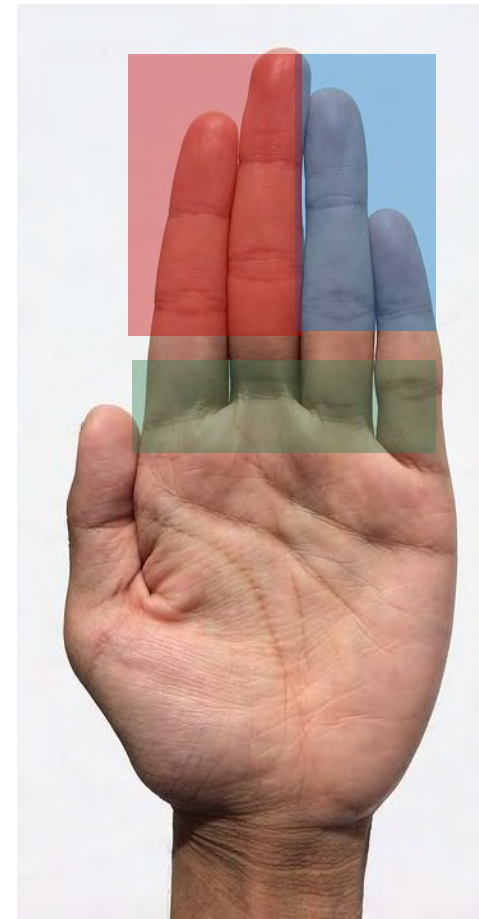
- Underside of forearm
- **Flexor digitorum profundus**
 - Median/ulnar portions
- Flex digits → make fist
- Lateral two digits (thumb)
 - **Median nerve**
- Medial two digits (little finger)
 - **Ulnar nerve**



Extrinsic Hand Muscles

Extensors

- Back of the forearm
- Straighten digits
- Extensor digitorum (**radial nerve**)
- Strongly extends MCP joints
- PIP/DIP extension: Lumbricals
 - Lateral two digits: **Median nerve**
 - Medial two digits: **Ulnar nerve**



Wrist Flexion and Extension

Major Flexors

Median and Ulnar Nerves

Flexor carpi radialis

Flexor carpi ulnaris



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Major Extensors

Radial Nerve

Extensor carpi radialis longus

Extensor carpi radialis brevis

Extensor carpi ulnaris



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Wrist Deviation

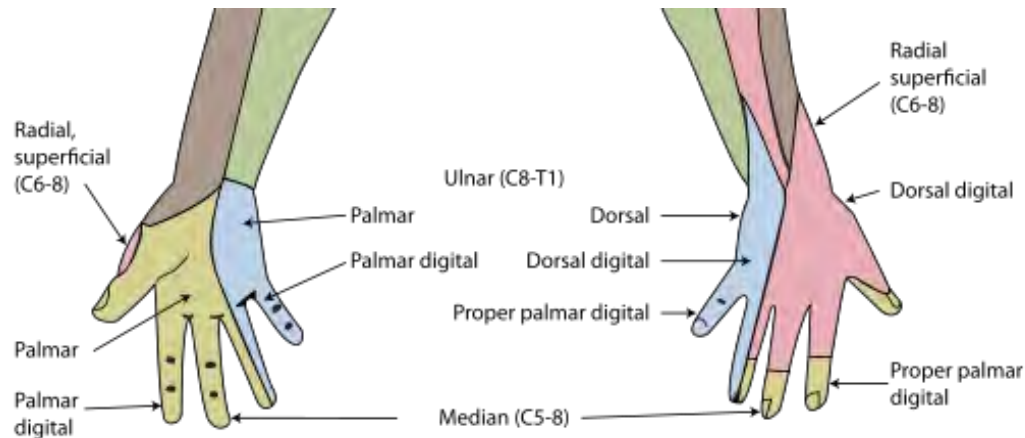
- Seen in lesions involving flexor muscles
- To ulnar (little finger) side with median lesions
- To radial (thumb) side with ulnar lesions



PublicDomainPictures.net

Median Nerve Lesions

- Motor loss to thumb side:
 - Thumb movement (thenar muscles)
 - Flexion/extension of lateral fingers (lumbricals)
- Sensory loss thumb side:
 - Thenar eminence, lateral 3 ½ fingers

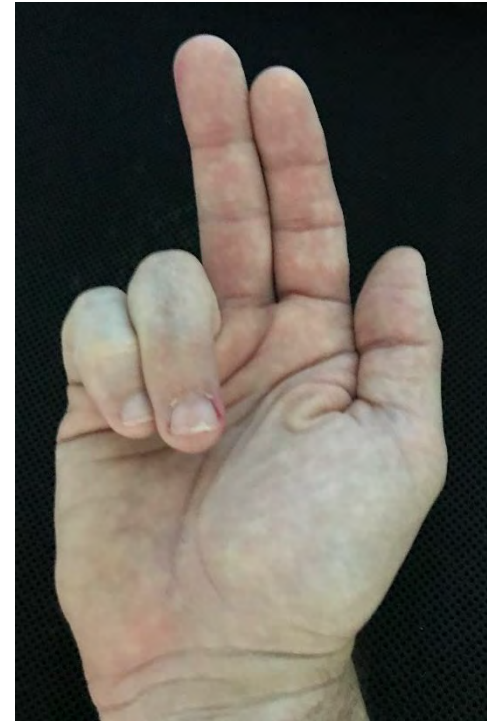


Median Nerve Lesions

- Thumb:
 - Flexion/abduction/opposition absent (thenar muscles)
- Lateral digits:
 - Loss of lumbricals
 - **“Clawed” lateral digits**

Median Nerve Lesions

- “Pope’s blessing”
 - Also called Hand of Benediction
 - **Ask patient to make fist**
 - Thumb, lateral fingers cannot flex
 - MCP extended



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Median Nerve Lesions

- “Ape hand”
 - **At rest**
 - Thumb adducted
 - Cannot oppose/abduct thumb
 - Thenar atrophy



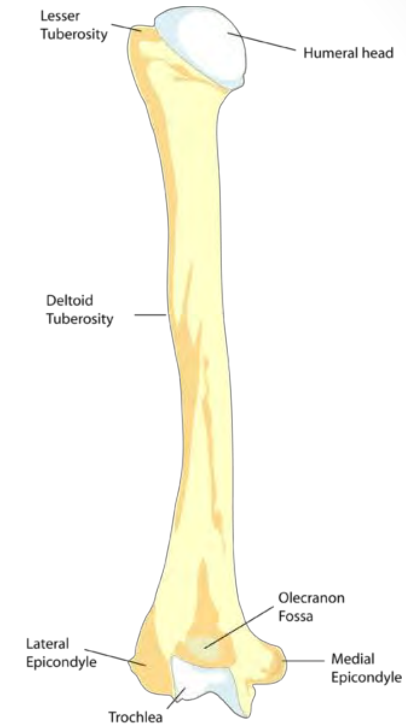
Mcstrother/Wikipedia

Median Nerve Lesions

- Wrist lesions
 - Laceration
 - Carpal tunnel syndrome
- Flexor muscles intact
- No wrist deviation

Median Nerve Lesions

- Elbow lesions
 - **Supracondylar fracture of humerus**
 - Loss of most flexors/pronators in forearm
 - Forearm supinated
 - Flexion weak
 - **Ulnar deviation**
 - Pull of the flexor carpi ulnaris

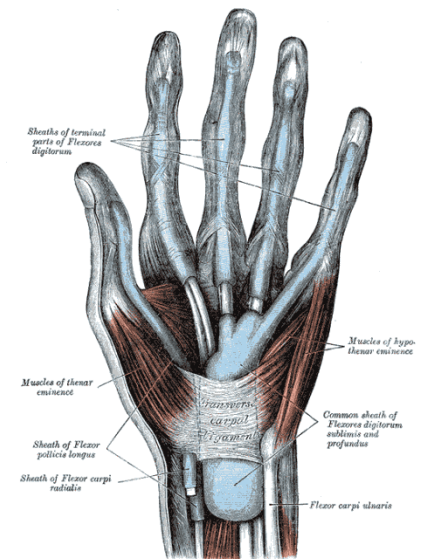


BDB/Wikipedia

Recurrent Branch

Median Nerve

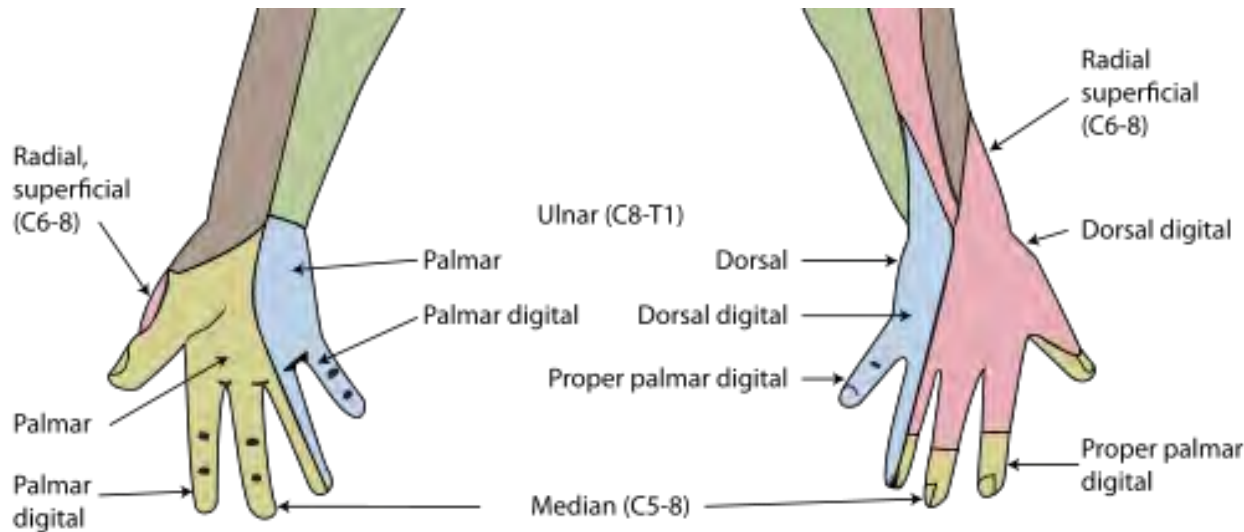
- Motor innervation to thenar muscles
- No sensory innervation
- Superficial nerve near flexor retinaculum
 - Fibrous band on palm side of hand
 - Covers carpal bones
 - Forms carpal tunnel
- Injured in **superficial laceration**
- Immobilizes thumb
- Sensation normal



Wikipedia/Public Domain

Ulnar Nerve Lesions

- Loss of abduction/adduction (interossei)
- Motor loss to little finger side (little/ring fingers)
 - Hypothenar muscles, medial two lumbricals
- Sensory loss little finger side



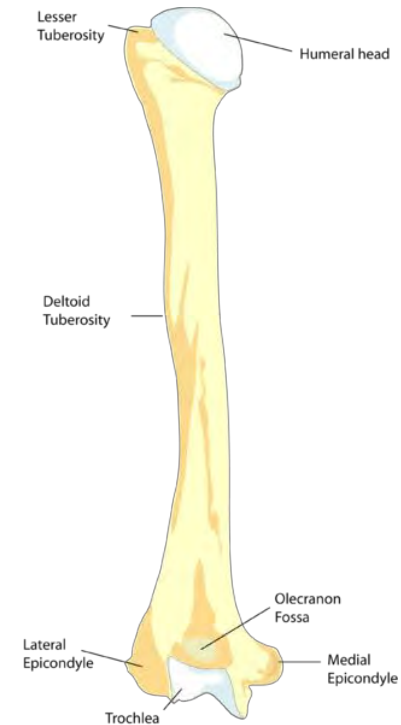
Ulnar Claw

- Hand position at rest (fingers straight/not flexed)
- Caused by paralysis of medial lumbricals
- Extension of metacarpophalangeal joints
- Flexion at interphalangeal joints



Ulnar Nerve Lesions

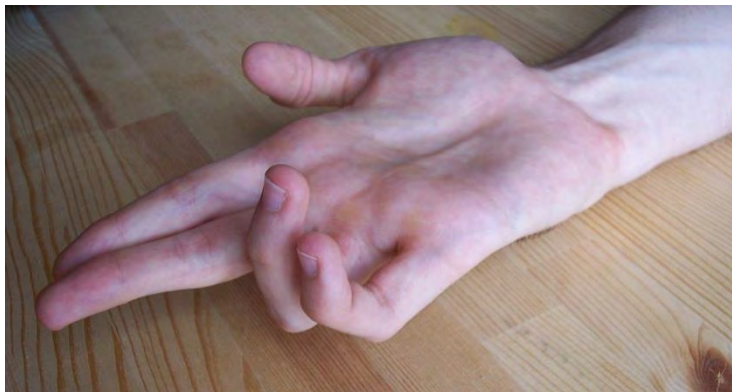
- Wrist lesions
 - Lacerations
 - Guyon Canal Syndrome
- Elbow lesions
 - **Fracture at medial epicondyle**
 - Loss of flexor carpi ulnaris
 - **Radial deviation** of wrist with flexion



BDB/Wikipedia

Ulnar Paradox

- Proximal (elbow) lesions: ulnar claw may not be seen
- Flexion at interphalangeal joints not present
- Proximal lesions: loss of flexor digitorum profundus
- Ulnar digits paralyzed without clawing
- Proximal lesions appears less severe (“paradox”)



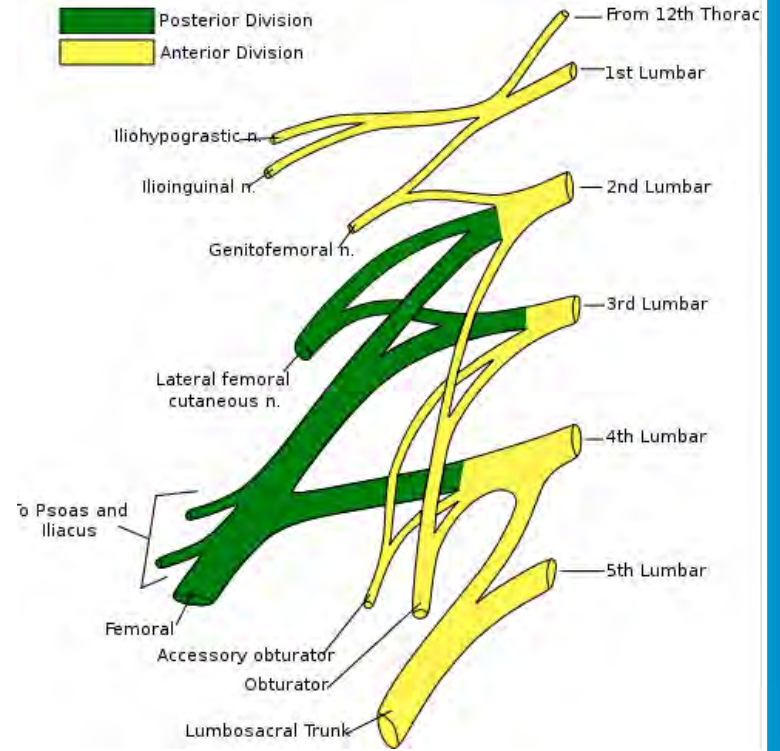
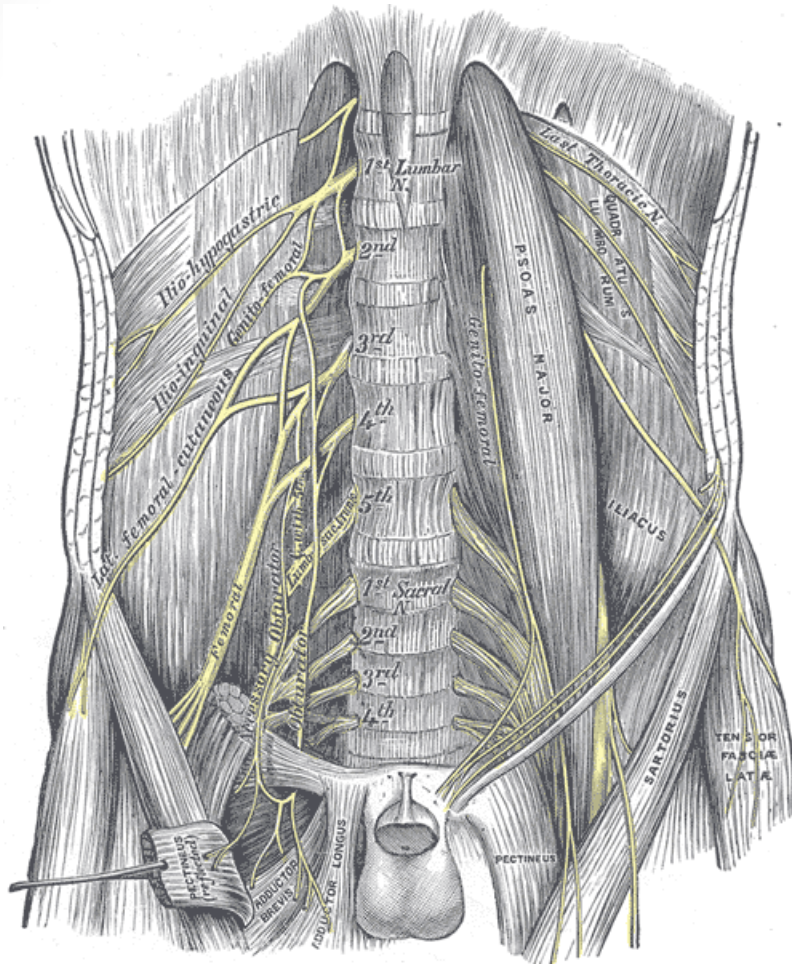
Mcstrother /Wikipedia

Lumbosacral Plexus

Jason Ryan, MD, MPH

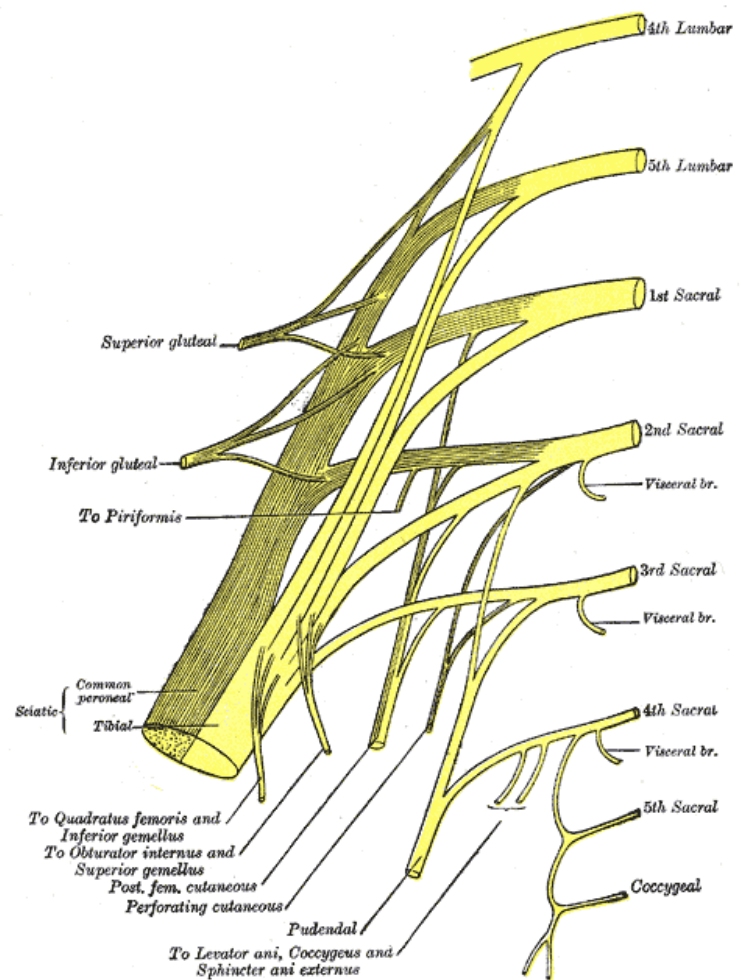
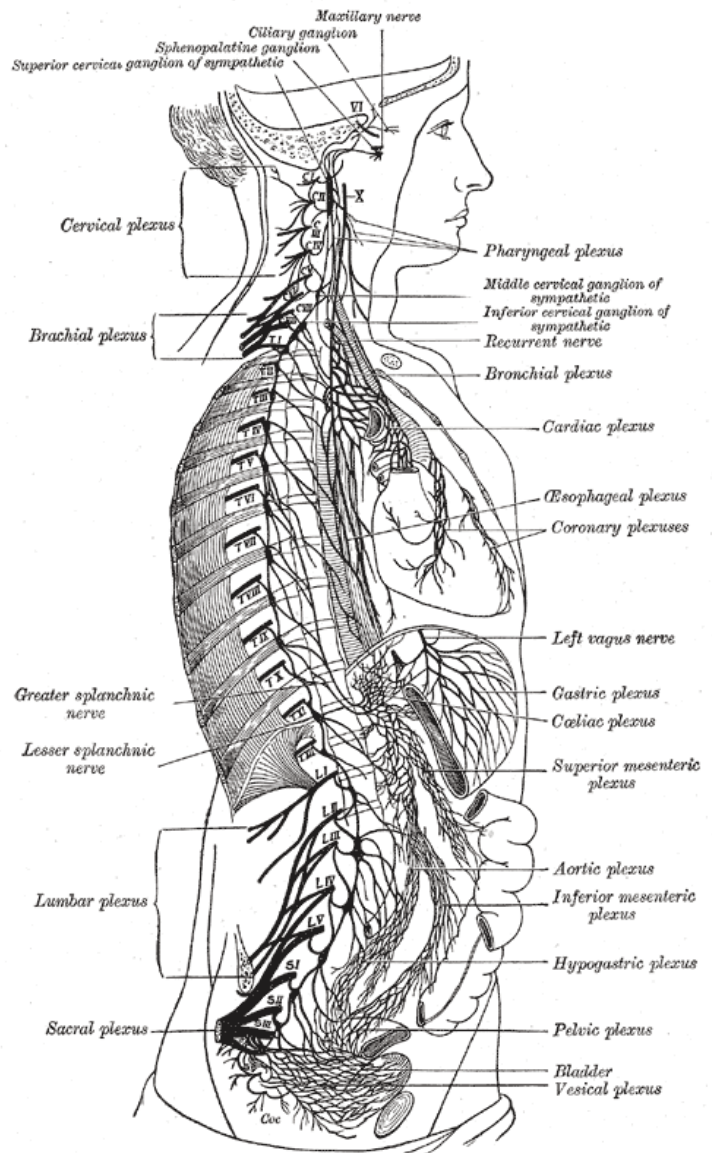
Lumbar Plexus

- Network of nerves T12 to L4
- Lumbar region of spine
- Supplies skin and muscles of lower limb



Sacral Plexus

- Network of nerves L4-S4
- Sacral region of spine
- Supplies skin/muscles of pelvis and lower limb

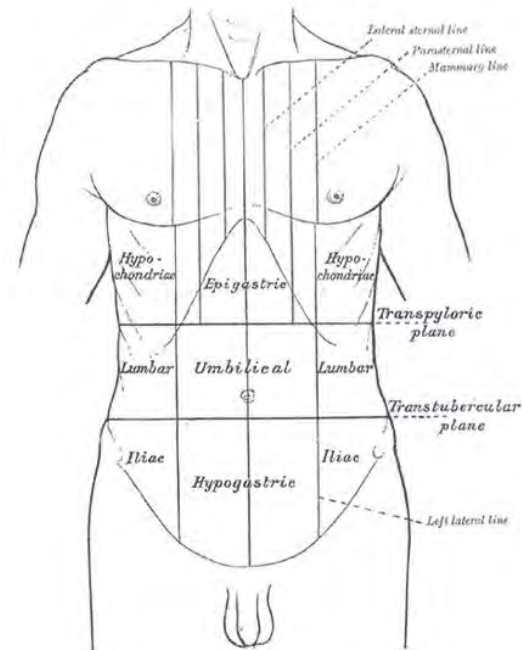
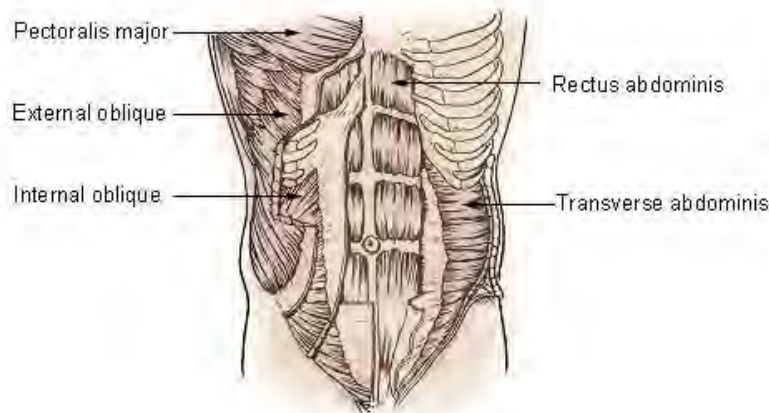


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Iliohypogastric

- T12-L1
- Motor: internal oblique and transversus abdominis
- Sensory: Suprapubic (hypogastric) region
 - Below umbilicus
 - Above pubic bone

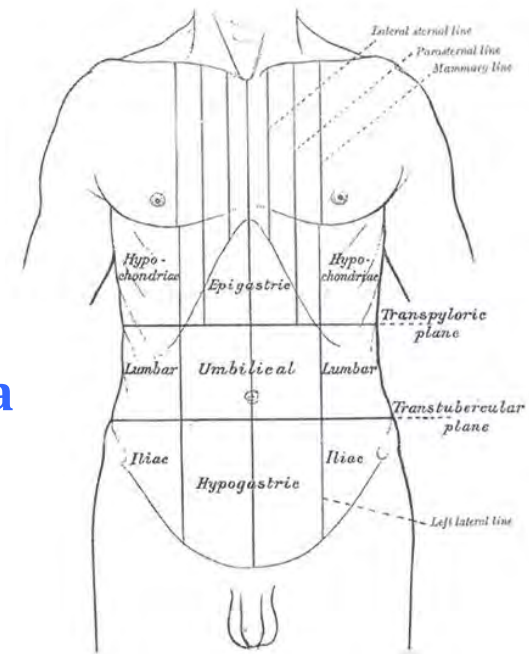
Muscles of the Trunk



Wikipedia/Public Domain

Iliohypogastric

- Commonly injured in **abdominal/pelvic surgery**
 - Laparotomy, laparoscopic surgery
 - Hernia surgery, hysterectomy
 - Transverse incisions
 - Sutures may trap nerves
 - May also involve Ilioinguinal nerve
- Symptoms occur after surgery:
 - Burning pain or paresthesia (tingling)
 - Radiates from incision to **suprapubic area**
 - Sometimes labia/scrotum, or thigh



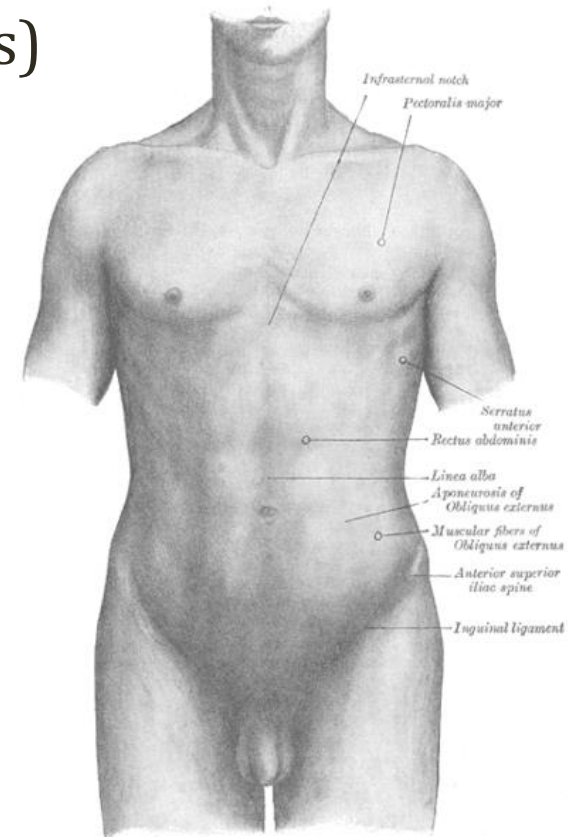
Wikipedia/Public Domain

Genitofemoral Nerve

- L1-L2
- Motor: **Cremasteric muscle**
 - Muscle covering testis and spermatic cord
- Sensory (genital branch):
 - Males: skin of anterior scrotum
 - Females: skin over mons pubis and labia majora
- Sensory (femoral branch): skin upper anterior thigh

Genitofemoral Nerve

- Injured in **abdominal surgery**
 - Often damaged by retractor blades
- **Absent cremasteric reflex** (males)
 - Stroke inner thigh
 - Scrotum rises ipsilateral side
- **↓ sensation anterior thigh**
- ↓ sensation labia/scrotum



Wikipedia/Public Domain

Lateral Femoral Cutaneous

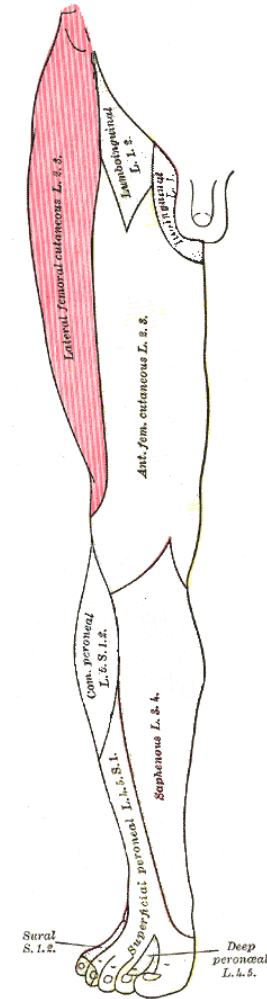
- Pure sensory nerve from L2-L3
- Courses under inguinal ligament into thigh
- Compressed by **tight clothing, obesity, pregnancy**



Tibor Végh

Lateral Femoral Cutaneous

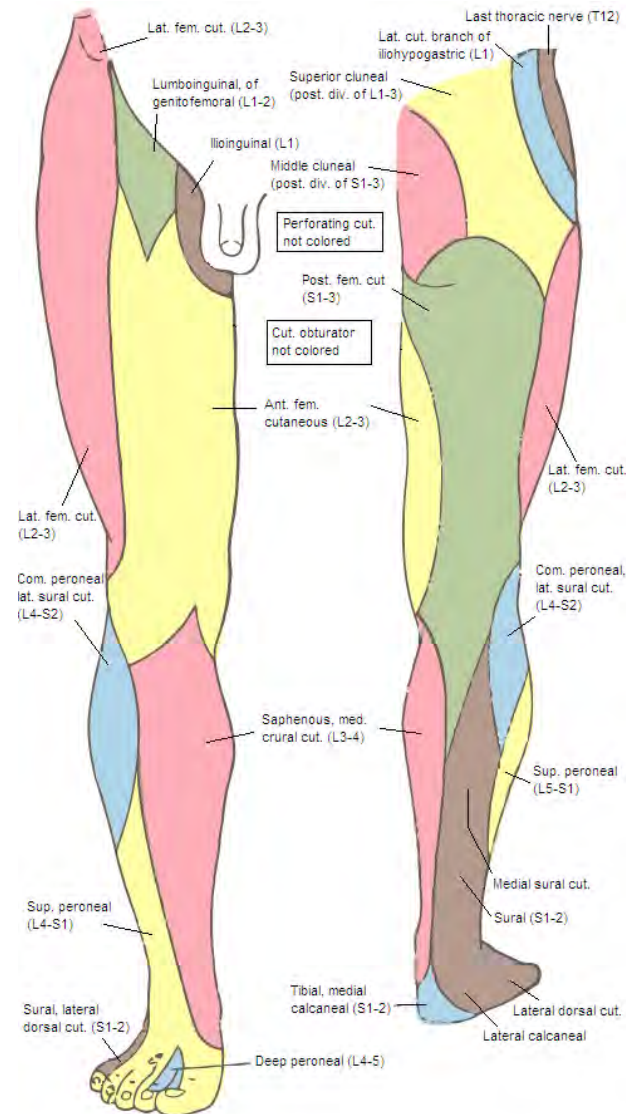
- **Meralgia paresthetica**
 - Outer thigh nerve syndrome
 - Burning pain
 - Paresthesia (numbness/tingling)
 - Hypoesthesia (diminished sensation)



Obturator Nerve

L2-L4

- Obturare = Latin “to close”
- Closes (adducts) thigh
- Motor: **Thigh adductors**
 - Adductor Longus
 - Adductor Brevis
 - Adductor Magnus
 - Gracilis
 - Obturator Externus
- Sensory: **Medial thigh**

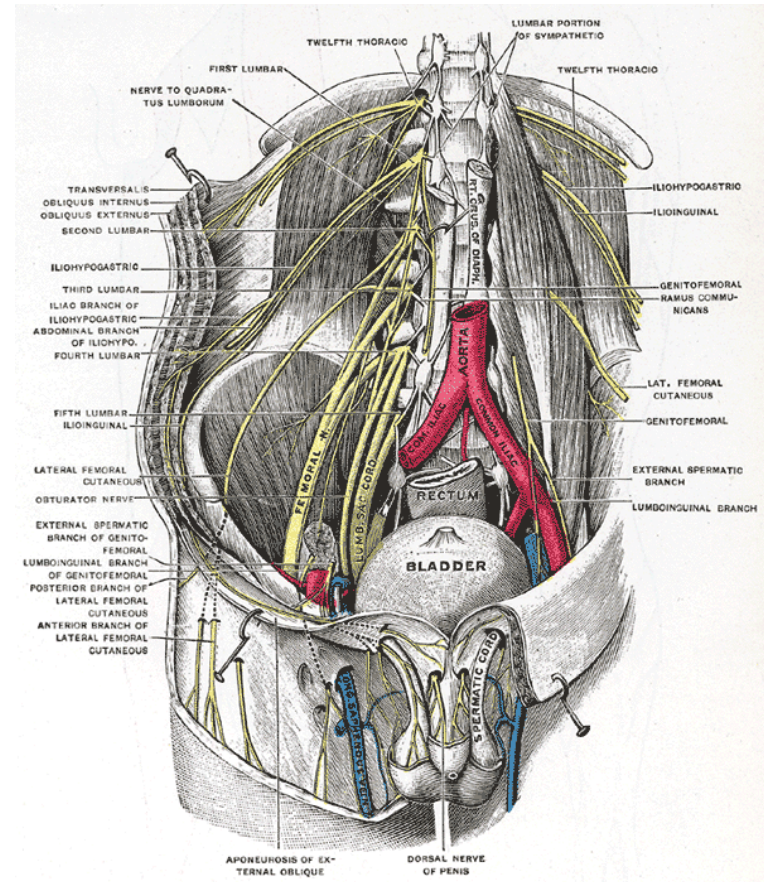


Obturator Nerve

- Courses through posterior pelvis
- Injured in **pelvic surgery**
- Trocar into pelvis
- Weak adduction
- Numbness medial thigh



Trocar



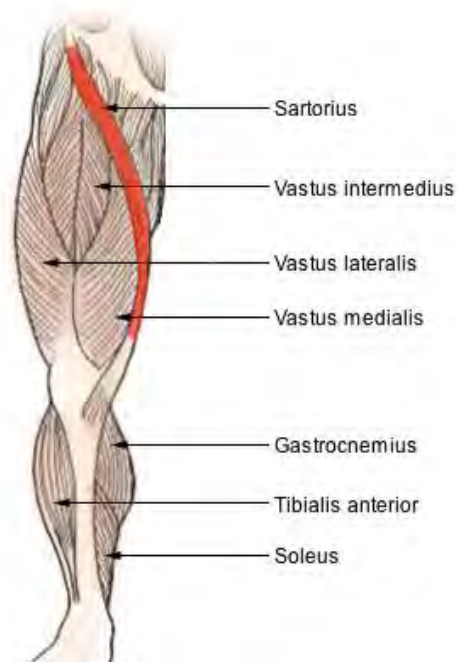
Femoral Nerve

- L2-L4
- Motor and sensory
- Motor: anterior thigh muscles
- Hip flexors and knee extensors

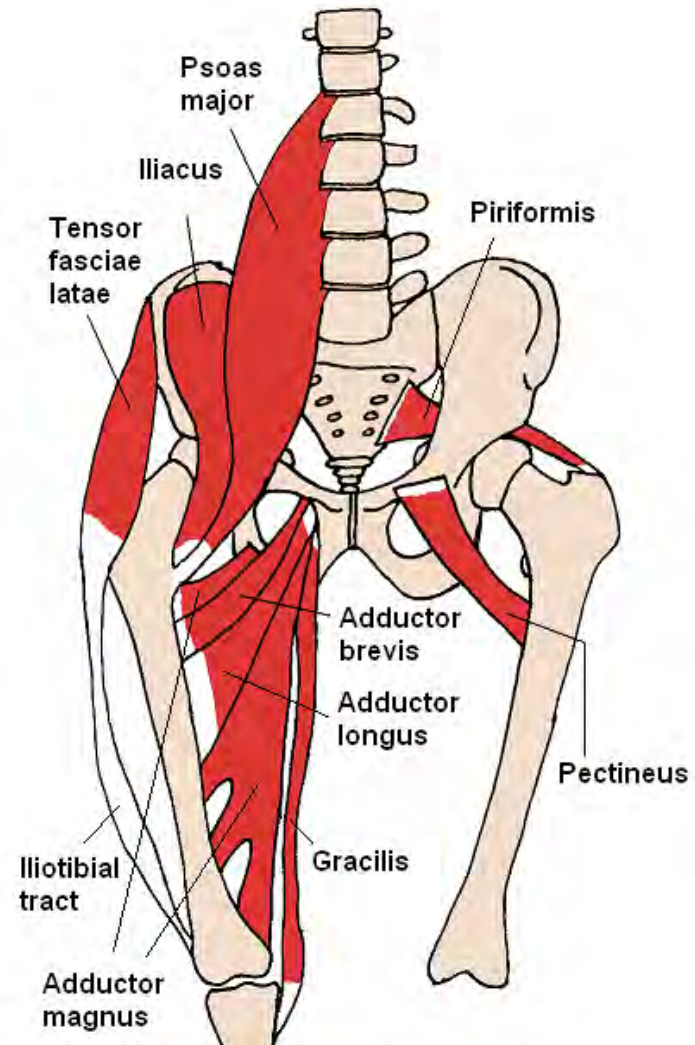
Femoral Nerve

Hip Flexors

- Pectineus
- Iliacus (part of iliopsoas)
- Sartorius



Wikipedia/Public Domain



Beth ohara/Wikipedia

Femoral Nerve

Knee Extensors

- Quadriceps femoris
 - Rectus femoris
 - Vastus lateralis
 - Vastus medialis
 - Vastus intermedius (deep to rectus)

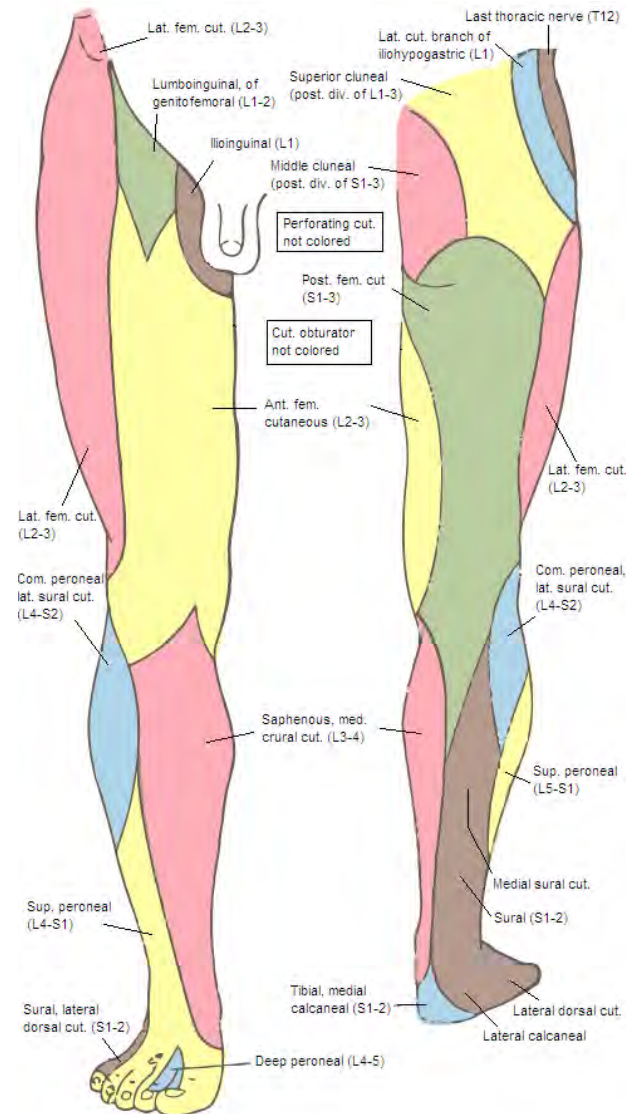


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Femoral Nerve

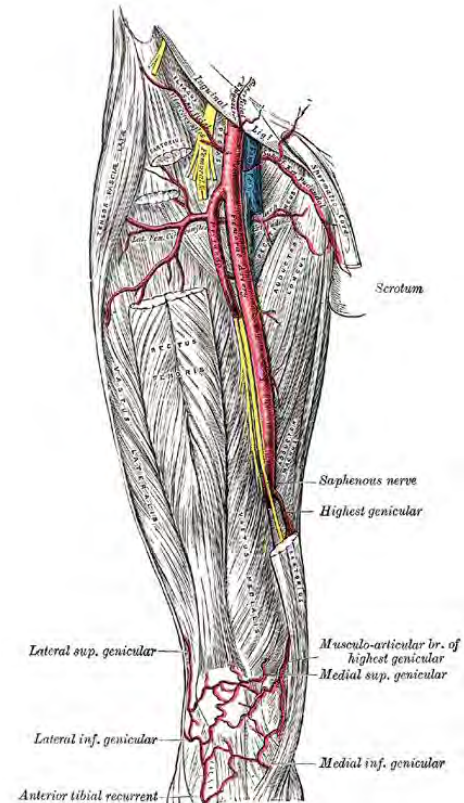
Sensory

- Anterior cutaneous branches
 - Skin of anteromedial thigh
- Saphenous nerve
 - Skin on medial leg and foot
- **Saphenous vein stripping**
 - CABG
 - May damage saphenous nerve
 - Numbness lower leg



Femoral Nerve Block

- Anesthesia to leg for surgical procedures
 - Along with obturator and femoral cutaneous block
- Femoral nerve at groin
 - Lateral to medial
 - **Nerve-artery-vein-lymph (NAVL)**



Wikipedia/Public Domain

Femoral Nerve

Injury

- Rarely injured by pelvic fracture or surgery
- Weakness: **flexion of thigh, extension at knee**
- Absent patellar reflex
- Numbness, tingling, burning pain in thigh/knee

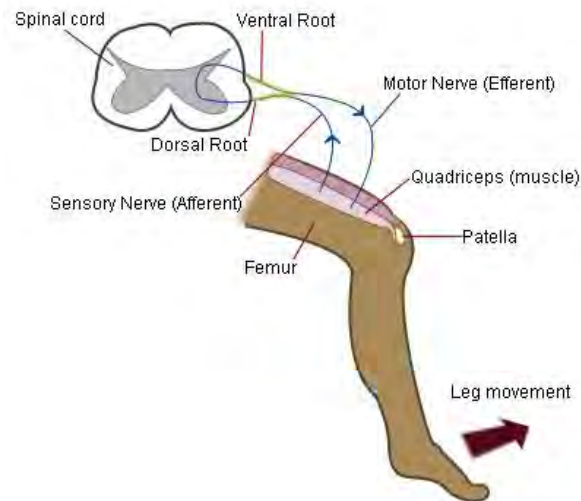
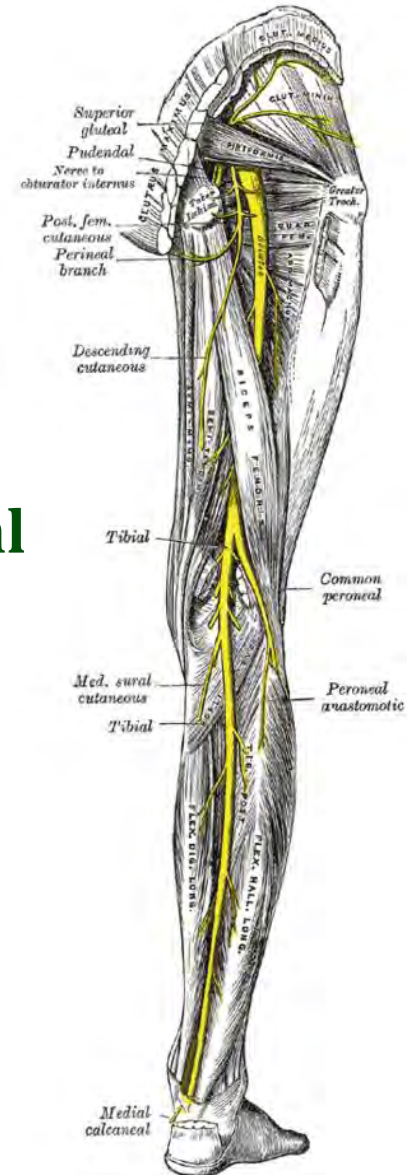


Image courtesy of ChristinaT3

Sciatic Nerve

- L4-S3
- Largest nerve in the body (2cm wide!)
- Motor/Sensory
- Branches: **common peroneal** and **tibial**

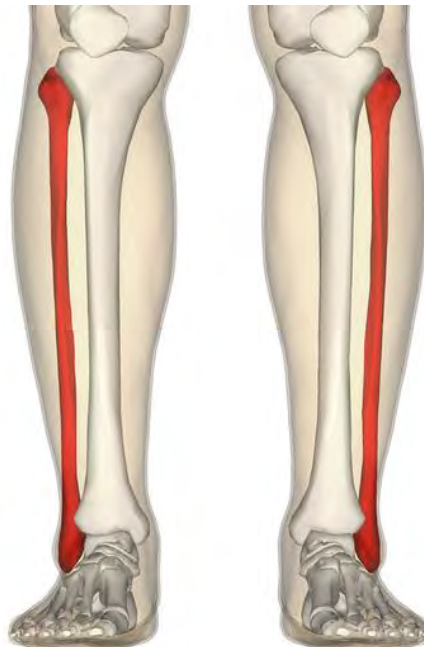


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Common Peroneal Nerve

Common Fibular Nerve

- Motor/sensory to lower leg
- Fibula: Latin word for clasp
- Peroneus: Greek work for clasp



Anatomography/Wikipedia

Common Peroneal Nerve

Motor Functions

- Short head of biceps femoris
 - Hamstring muscle (flexes knee)
- Branch: Superficial fibular nerve
 - Muscles of lateral lower leg
 - Fibularis longus and brevis
 - Evert the foot
- Branch: Deep fibular nerve
 - Muscles of anterior lower leg
 - Tibialis ant, extensor digitorum longus, extensor hallucis longus
 - **Dorsiflexion of foot**, extension of toes
 - Also some intrinsic muscles of foot

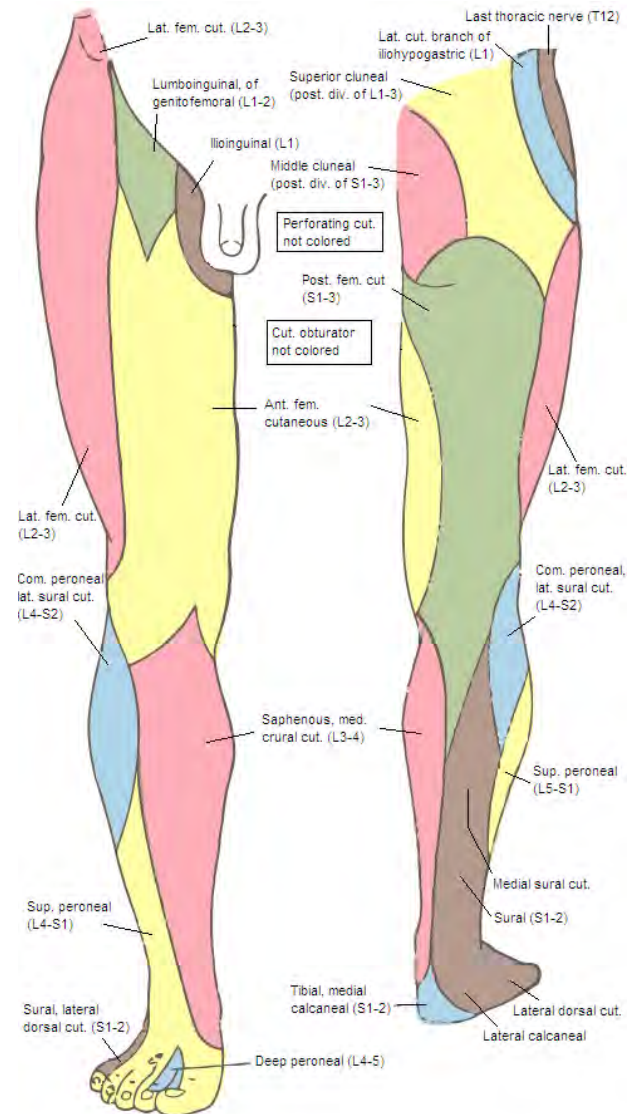


Connexions/Wikipedia

Common Peroneal Nerve

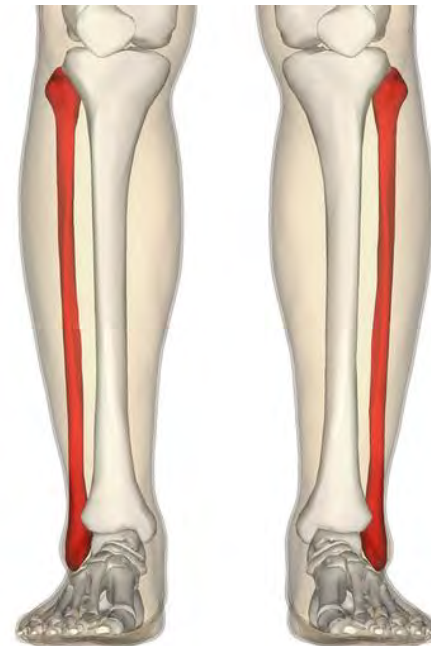
Sensory Functions

- Lower leg
- **Dorsum of foot**



Common Peroneal Nerve

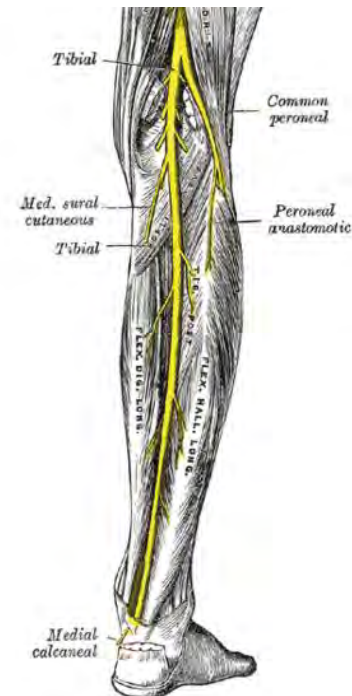
- Wraps around fibula below knee
- Injured by:
 - Prolonged lying (bed rest, surgery)
 - Leg casts
 - Fibular neck fracture
- Symptoms:
 - **Foot drop (weak dorsiflexion)**
 - Foot feels limp (patient may trip)
 - Sensory loss dorsum foot, lateral shin



Anatomography/Wikipedia

Tibial Nerve

- Course: down the leg, posterior to tibia
- Motor to posterior leg muscles
- At foot travels under medial malleolus
 - Through tarsal tunnel
- **Sensory to heel/sole**



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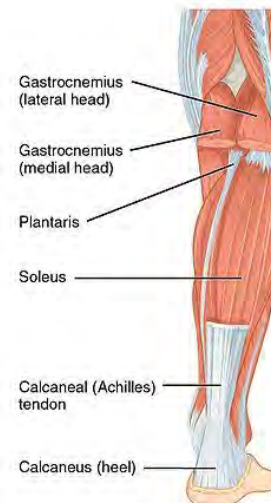
Tibial Nerve

Posterior Leg Muscles

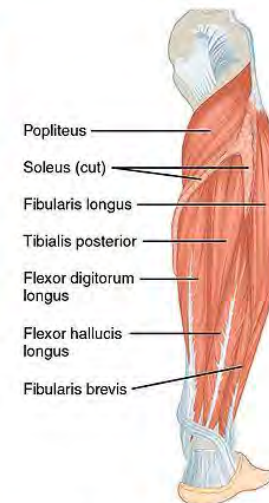
- Many deep and superficial muscles
 - Popliteus
 - Flexor hallucis Longus
 - Flexor digitorum Longus
 - Tibialis posterior
 - Plantaris
 - Soleus
 - Gastrocnemius



Superficial muscles of the right lower leg (anterior view)



Superficial muscles of the right lower leg (posterior view)

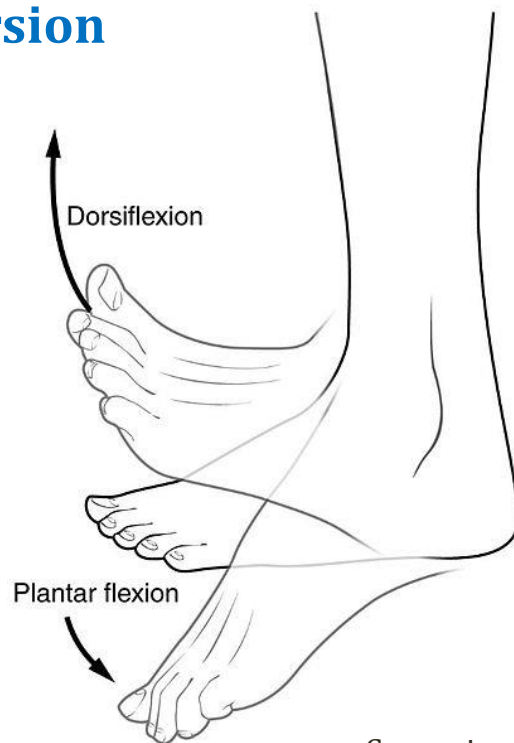


Deep muscles of the right lower leg (posterior view)

Tibial Nerve

Posterior Leg Muscles

- Many actions:
 - **Plantar flexion**
 - Toe flexion
 - **Inversion**



Connexions/Wikipedia

Tibial Nerve Damage

- At heel from **tarsal tunnel narrowing**
 - Often following fracture/dislocation
 - Symptoms mostly sensory
 - Pain, burning, numbness on sole of foot
- At knee from **large Baker's cyst or trauma** (rare)
 - Loss of plantar flexion (can't stand on toes)
 - Loss of toe flexion
 - Loss of inversion

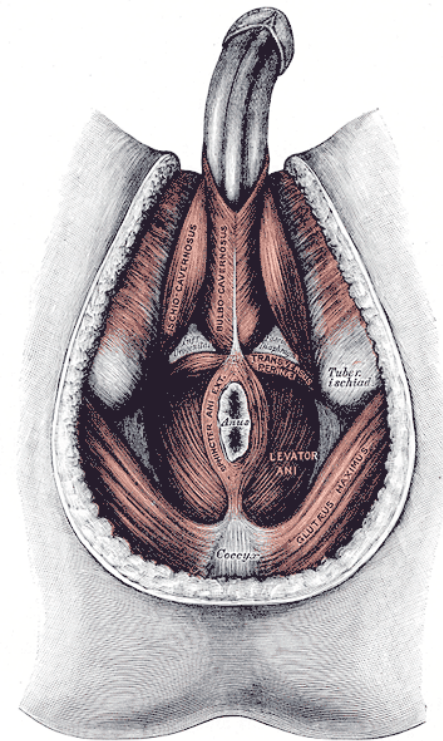
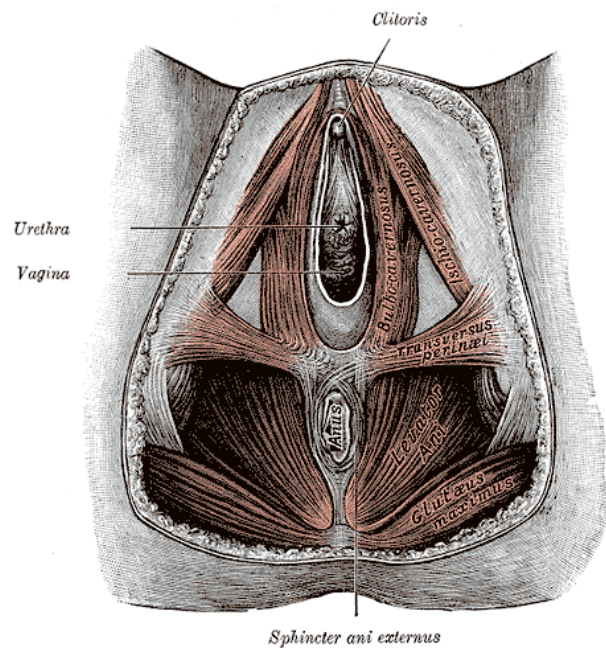
Pudendal Nerve

S2-S4

- Pudendal = Latin “to be ashamed”
- Nerve supply to **genital area**
- Motor:
 - Muscles of perineum
 - External urethral sphincter
 - External anal sphincter
 - Levator ani
- Sensory: penis/clitoris and skin of perineum

Perineum

- Floor of pelvis between legs



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Pudendal Nerve

- Often injured from stretching in **vaginal childbirth**
- Perineal pain worse with sitting
- Vulvar/scrotal pain
- Fecal/urinary incontinence



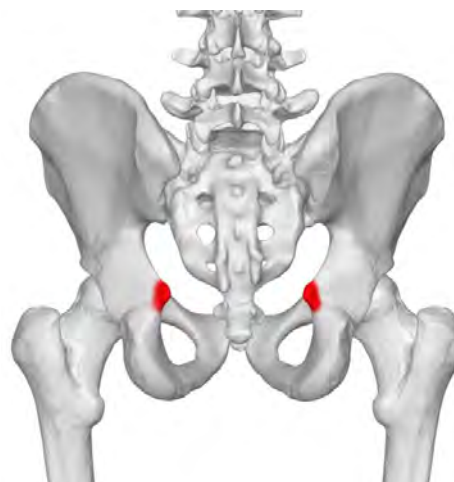
Tom Adriaenssen/Wikipedia

Pudendal Nerve Block

- Used in vaginal childbirth to reduce pain
 - Largely replaced by epidural anesthesia
- Anesthesia to **ischial spine of pelvis**
 - Point of entry for nerve to pelvis
 - Lithotomy position: spine palpable through vagina



Saltanat ebli/Wikipedia



BodyParts3D/Wikipedia

Lumbar Radiculopathy

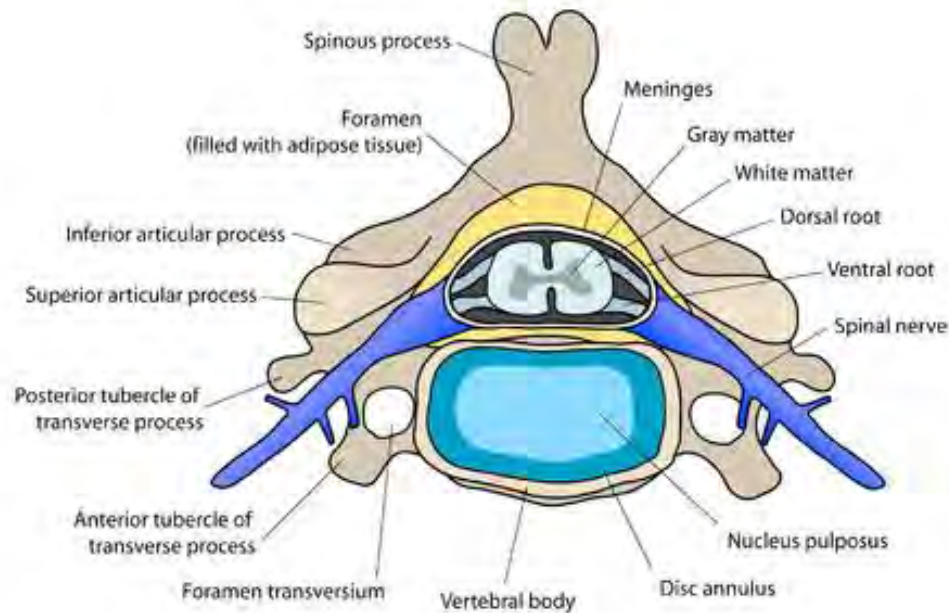
Jason Ryan, MD, MPH

Radiculopathy

- Compression of nerve root at spine
- Lumbar radiculopathy = radiculopathy lumbar spine
- Many causes:
 - Herniated disc
 - Spondylolisthesis
 - Spinal stenosis

Intervertebral Discs

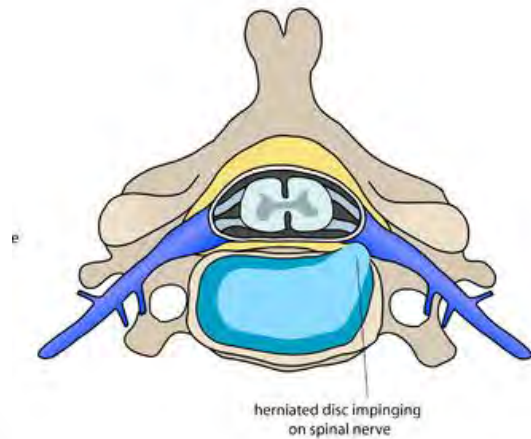
- Cushion between vertebrae
- Outer fibrous ring: annulus fibrosus
- Soft center: nucleus pulposus



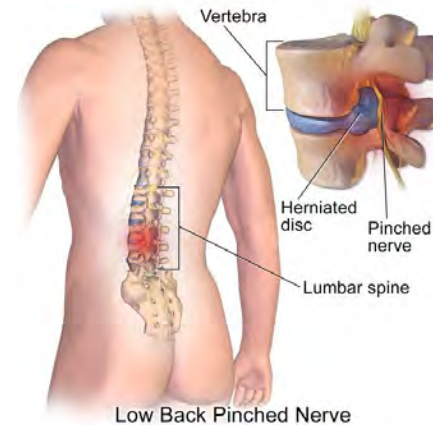
debivort/Wikipedia

Herniated Disc

- Most common cause of radiculopathy
- Degeneration of annulus fibrosis
- Bulging/extrusion of nucleus pulposus
- Unilateral nerve compression



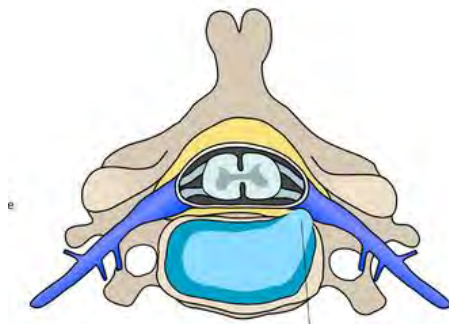
debivort/Wikipedia



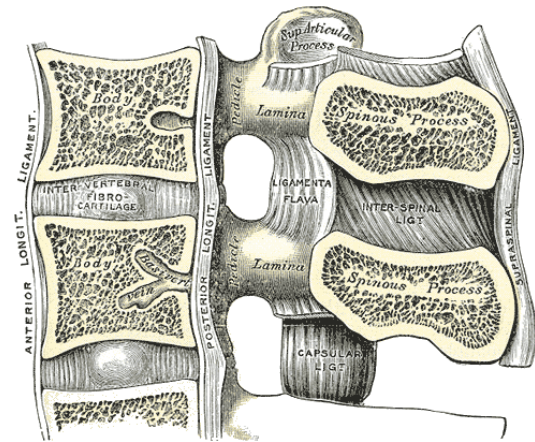
BruceBlas/Wikipedia

Herniated Disc

- Often occurs posteriorly
- Two ligaments contain disc in spine
 - Anterior and posterior longitudinal ligaments
- **Posterior longitudinal ligament**
 - Sits within spinal canal
 - Covers posterior surface of vertebrae
 - Weaker containment than anterior ligament



debivort/Wikipedia



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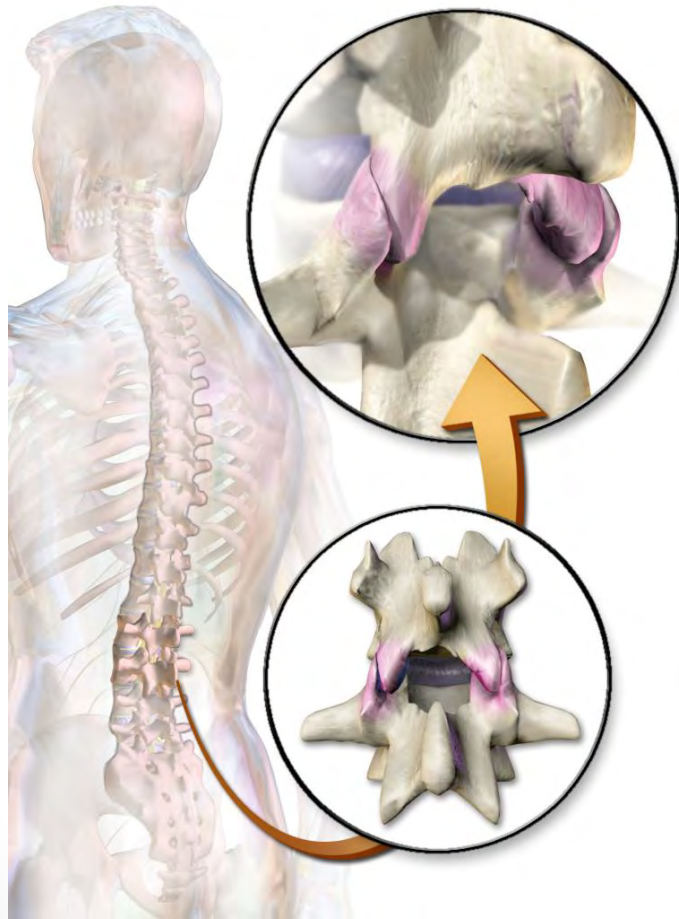
Spondylolisthesis

- Forward displacement of one vertebra over another
 - Spondylo = vertebrae/spine
 - Listhesis = movement
 - Spondylosis = degeneration of the spinal column
- May cause radiculopathy

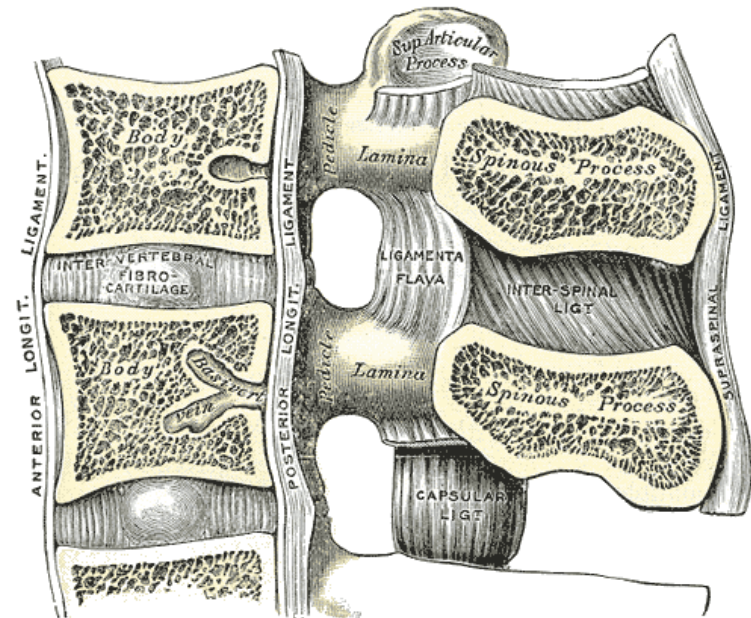
Spinal Stenosis

- Narrowing of spinal canal
- Usually age-related
- Intervertebral discs shrink → narrows foramen
- **Facet joint arthritis → bone spurs**
- **Ligamentum flavum hypertrophies**
- Leads to nerve root compression
- Standing (straight spine) narrows lumbar canal

Spinal Stenosis



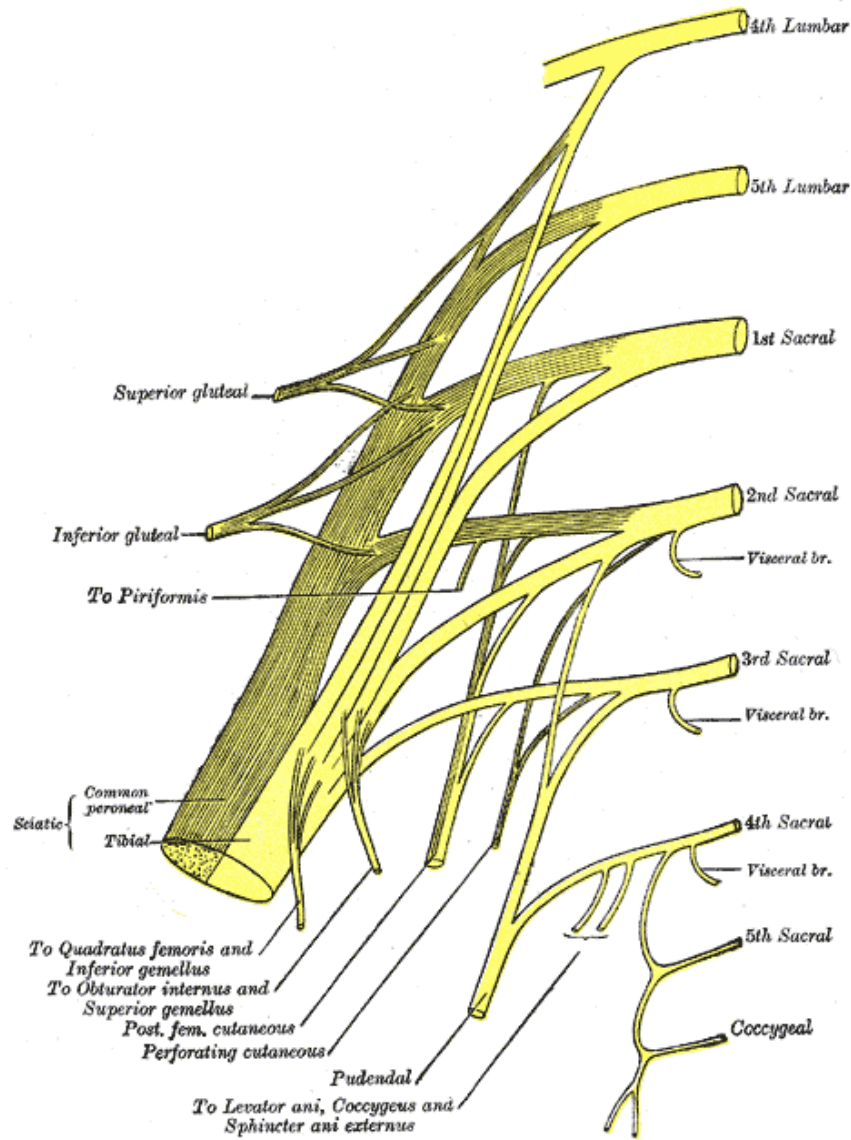
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Neurogenic Claudication

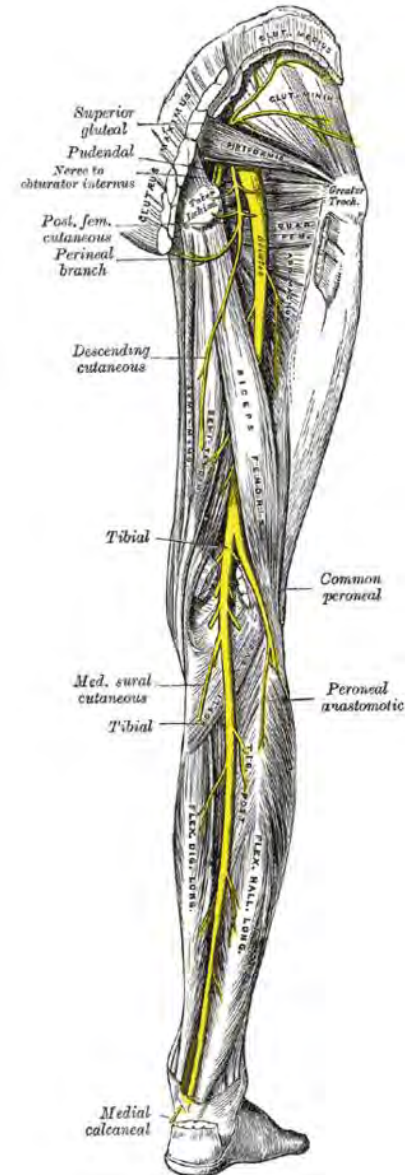
- Leg pain with walking in spinal stenosis
- Can mimic vascular claudication
- Features of neurogenic claudication
 - Often persists with rest when standing
 - **Improves with stooped/flexed posture**



Wikipedia/Public Domain

Sciatic Nerve

- Largest nerve in the body (2cm wide!)
- Branches into common peroneal/tibial
- **Motor:**
 - Muscles of posterior thigh
 - Hamstring portion of adductor magnus
 - Branches: muscles of leg/foot
- **Sensory:**
 - No direct sensory functions
 - Branches: skin of lateral leg, heel, and foot

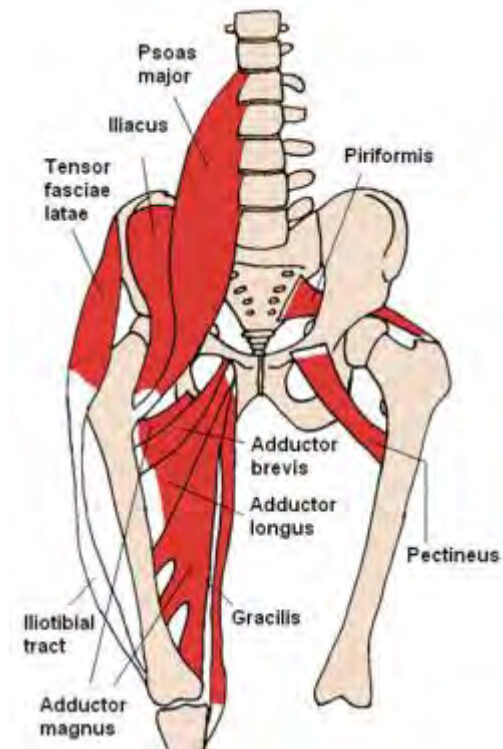


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Sciatic Nerve

Motor

- Hamstrings
 - Three posterior thigh muscles
 - Semimembranosus (medial)
 - Semitendinosus
 - Biceps Femoris (lateral)
- Adductor magnus
 - Medial thigh muscle
 - Two portions
 - Hamstring portion similar to hamstrings
- **Knee flexion, hip extension, hip rotation**



Beth ohara/Wikipedia

Sciatica

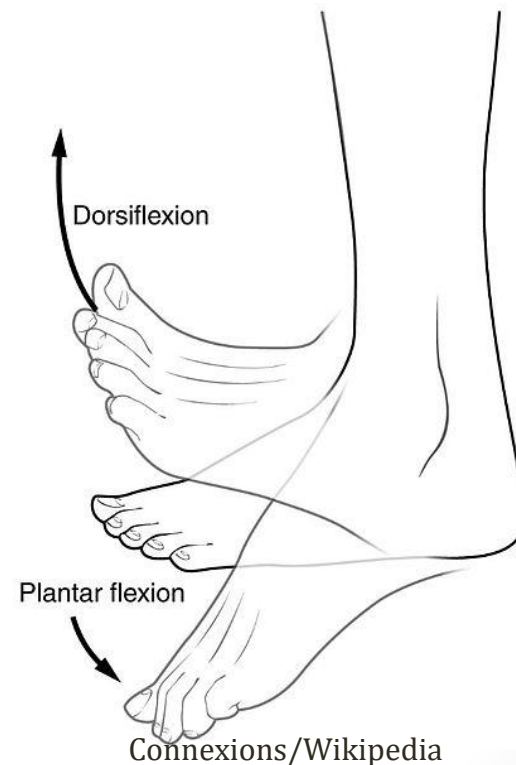
- Clinical syndrome with many causes
- Often used to describe **pain** of lumbar radiculopathy
- Low back pain radiating along path of sciatic nerve
 - Low back → buttocks → back of thigh
- Commonly caused by **herniated disk**
 - Compresses nerve at root (radiculopathy)
 - Inflammation, pain and numbness in affected leg

Sciatic Neuropathy

- **Hip fracture or dislocation**
 - Sciatic nerve behind hip joint
 - Posterior dislocations: most common type
- Hip replacement surgery
- **Prolonged compression** (coma/bed rest)
- If severe may cause:
 - Hamstring muscle weakness
 - Loss of dorsiflexion /foot drop (common peroneal nerve)
 - Sensory loss in lower leg/foot

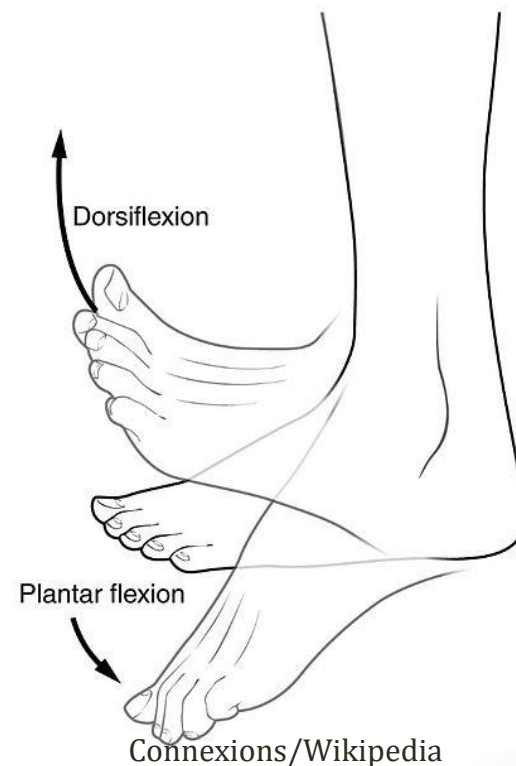
Radiculopathy Syndromes

- **Nerve root L5:** most common
 - Herniated disc at L4/L5 vertebrae
 - Back pain down lateral leg
 - Weak **foot dorsiflexion**, toe extension
 - Difficult walking on heels
 - Common Peroneal Nerve



Radiculopathy Syndromes

- S1 nerve root: 2nd most common
 - L5/S1 disc
 - Pain down back of leg
 - Weakness **plantar flexion**
 - Difficulty standing on toes
 - **Ankle reflex lost**
 - Tibial nerve

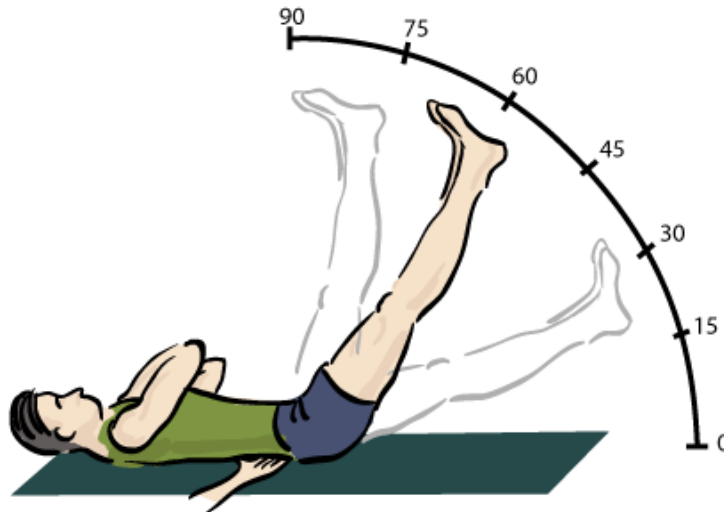


Radiculopathy Syndromes

- L2/L3/L4 nerve roots
 - Higher nerve roots → **thigh/knee symptoms**
 - Supply **femoral nerve**
 - Pain to anterior thigh and knee
 - Weakness: hip flexion, knee extension
 - **Reduced knee (patellar) reflex**

Straight Leg Raise Test

- Bedside maneuver for lumbar radiculopathy
- Examiner raises extended leg on symptomatic side
- Stretches sciatic nerve and nerve roots
- Lasègue's sign: worsening pain



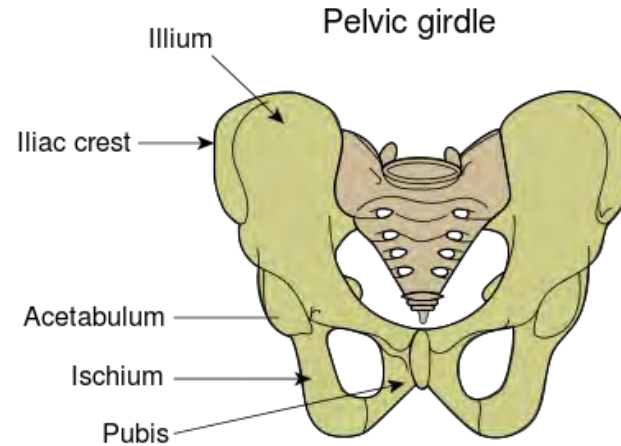
Davidjr74/Wikipedia

Hip

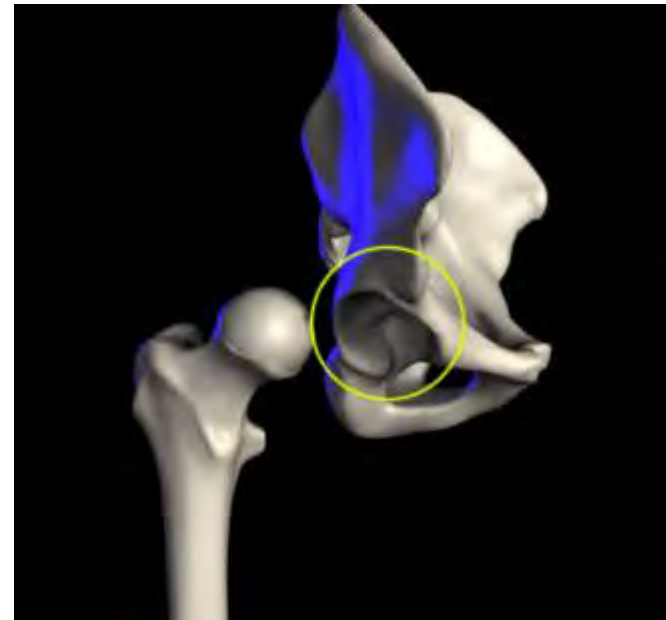
Jason Ryan, MD, MPH

Hip Joint

- Head of femur
- Acetabulum of pelvis
- Movements
 - Abduction
 - Adduction
 - Flexion
 - Extension
 - Internal/external rotation



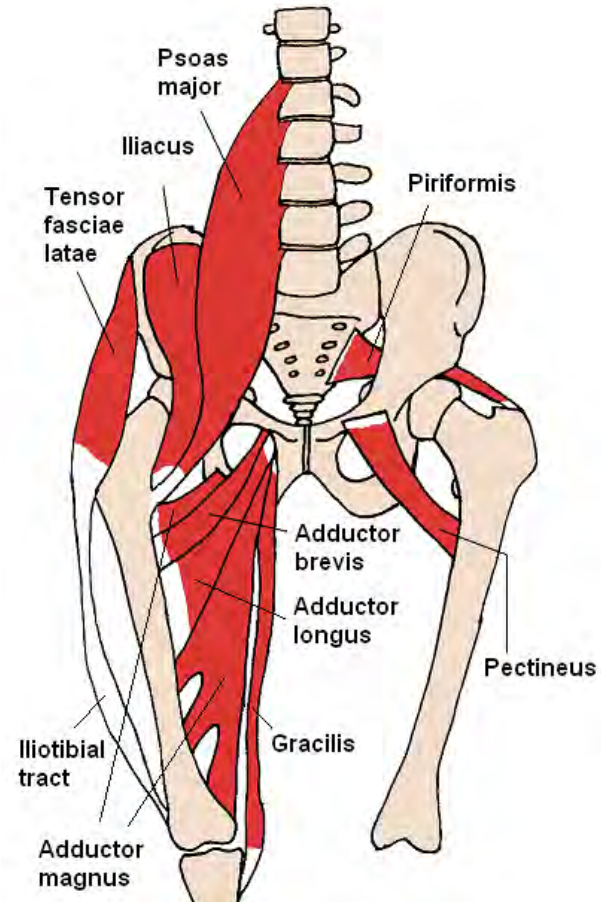
U.S. National Cancer Institute



Protohiro

Major Flexors

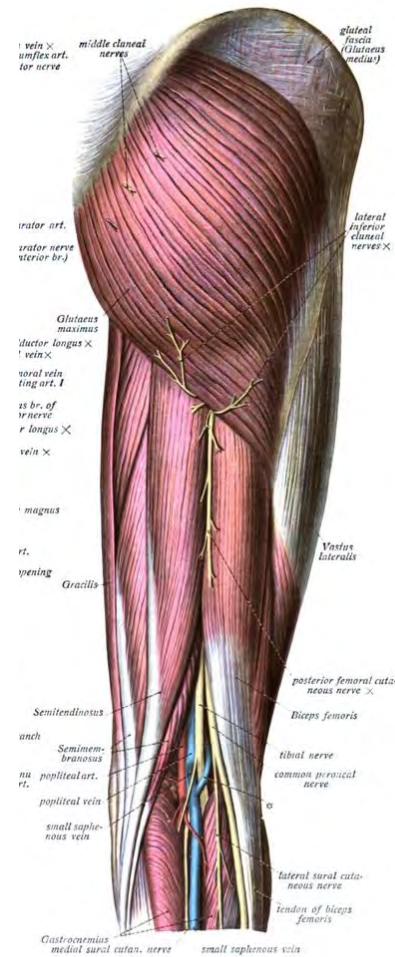
- **Iliopsoas**
 - Psoas major and iliacus
 - Combine at inferior ends
- Tensor fasciae latae
- Sartorius
- Pectinius



Beth ohara/Wikipedia

Major Extensors

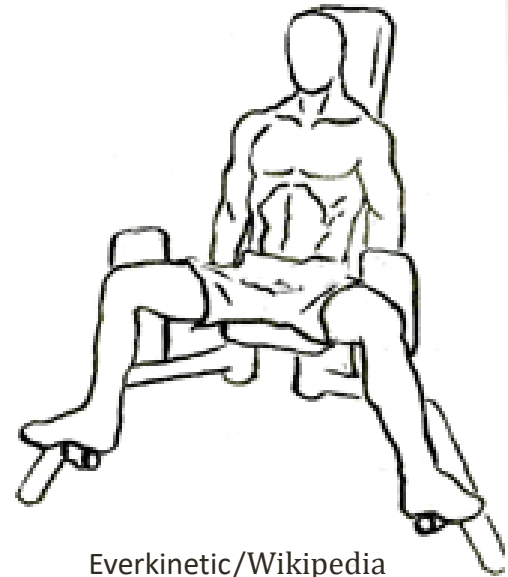
- **Gluteus maximus**
- **Hamstrings**
 - Hip extensors/knee flexors
 - Semimembranosus
 - Semitendinosus
 - Biceps femoris



Wikipedia/Public Domain

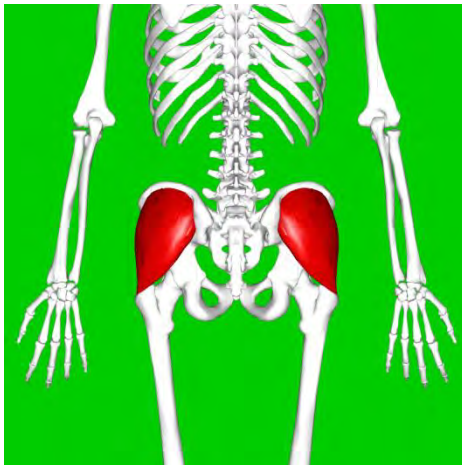
Major Abductors

- Gluteus medius
- Gluteus minimus

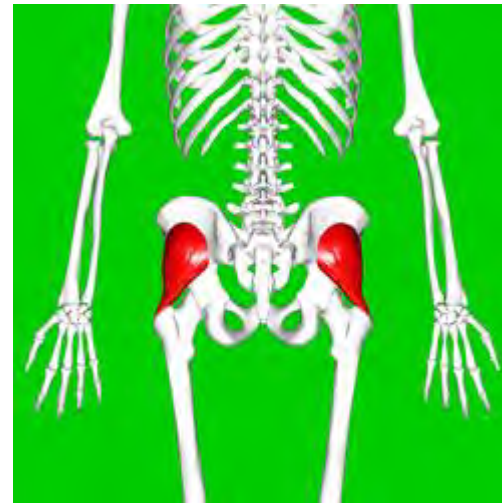


Everkinetic/Wikipedia

Gluteus Medius

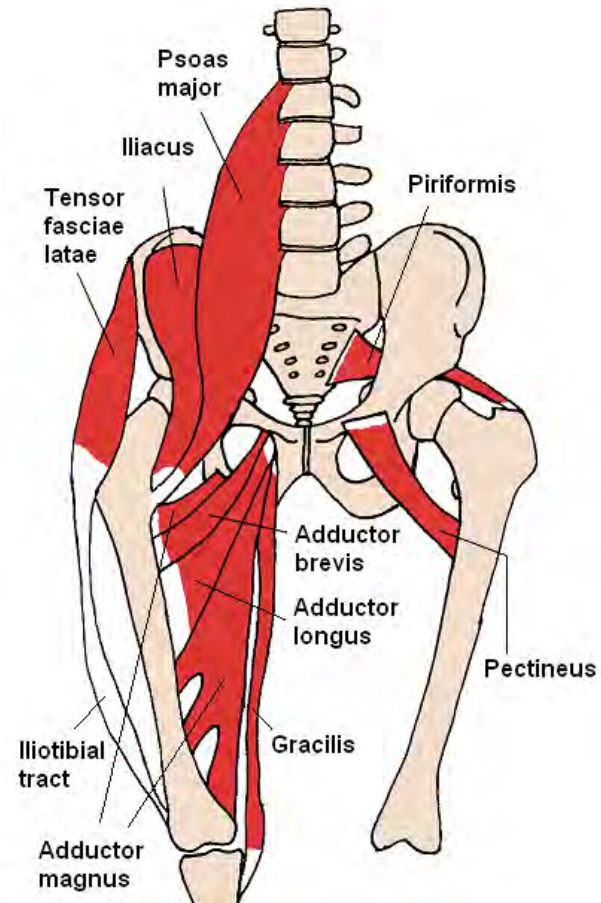


Gluteus Minimus



Major Adductors

- **Adductor** magnus
- **Adductor** longus
- **Adductor** brevis
- Others (pectineus, gracilis)

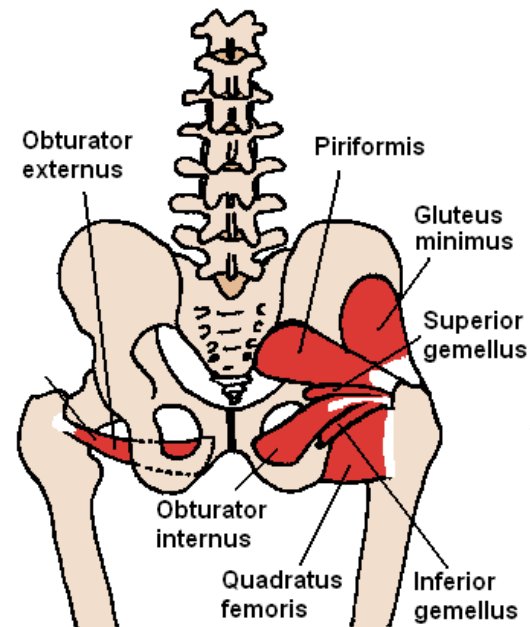


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External Rotation

Knee away midline/Foot toward midline

- Gluteus maximus
- Several “external rotators”
 - Obturator internus
 - Gemellus superior/inferior
 - Quadratus femoris



Beth ohara/Wikipedia

Internal Rotation

Knee toward midline/Foot away midline

- No primary/major internal rotator muscles
- Many muscles contribute
 - Gluteus medius/minimus
 - Tensor fasciae latae
 - Adductor longus/brevis
 - Posterior head of adductor magnus
 - Pectineus

Superior Gluteal Nerve

- From sacral plexus (L4-S1)
- Pure motor nerve
- **Gluteus minimus/medius (abductors)**
- Tensor fasciae latae (flexor)

Superior Gluteal Nerve

- Injured by intramuscular injection to buttocks
 - Upper/outer quadrant used to avoid injury
- Weakness on hip abduction → difficulty walking
- Classic finding: **Trendelenburg sign**
 - Pelvis tilts with walking
 - **Weight bearing leg** cannot maintain balance

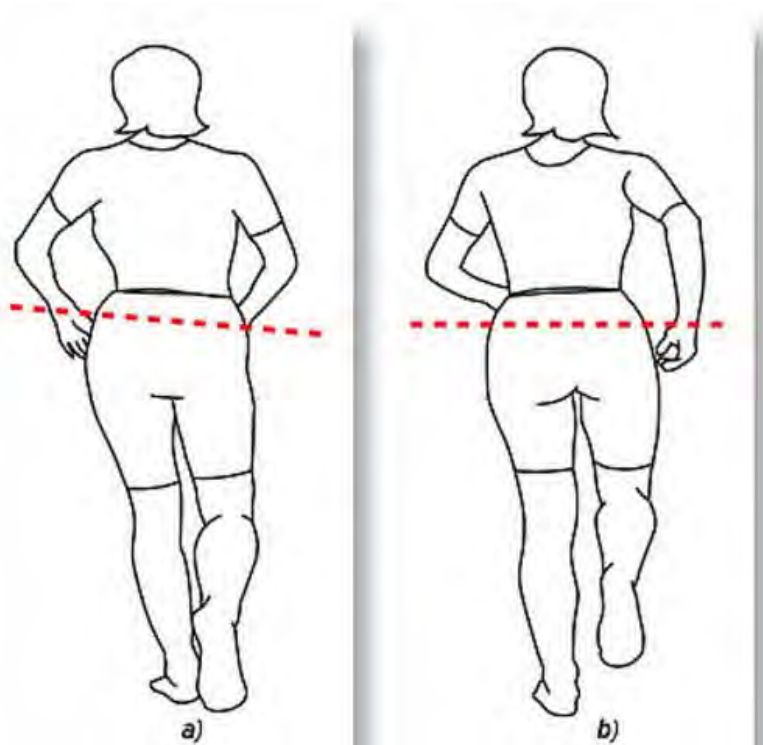


Upper, outer
quadrant

Bebop7/Wikipedia

Trendelenburg Sign/Gait

- Classically seen with weak hip abduction
- Also seen in some other hip disorders



sportEX journals/Flickr

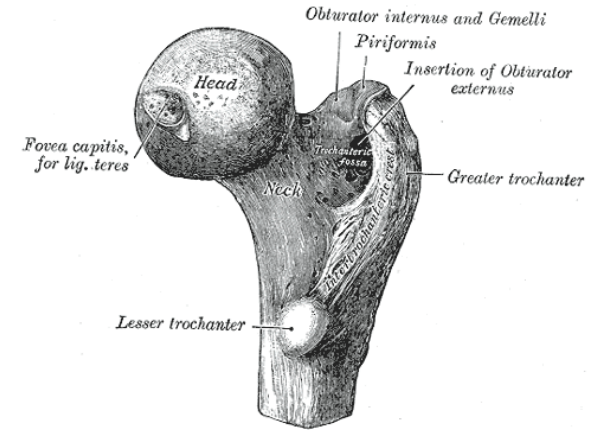
Inferior Gluteal Nerve

- Motor to **gluteus maximus**
- Rarely injured by pelvic masses
- Weakness of hip extension
 - Standing from sitting position

Avascular Necrosis

Osteonecrosis

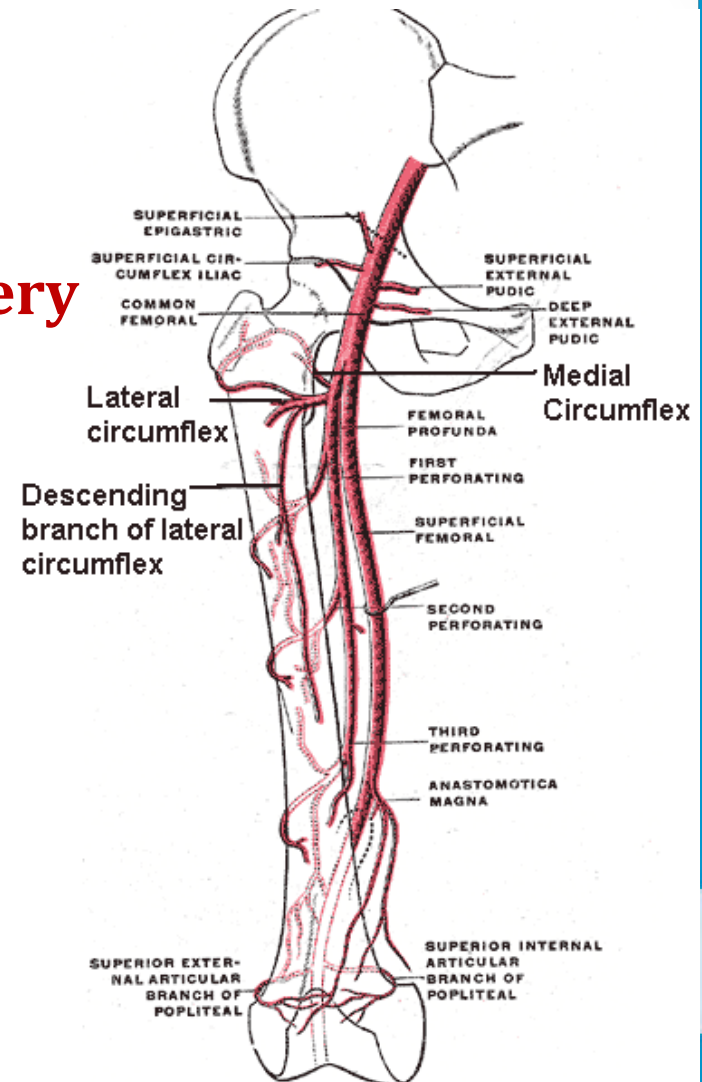
- Compromise of bone blood vessels
- Necrosis of bone tissue
- Common at **femoral head**
- Groin pain: most common complaint
- Also thigh, buttock pain
- Difficulty with weight bearing or hip movement



Avascular Necrosis

Osteonecrosis

- Often caused by trauma
 - Femoral neck fracture
- **Medial circumflex femoral artery**
 - From profunda femoris artery
 - Blood supply to neck of femur
- Damage: avascular necrosis



Avascular Necrosis

Osteonecrosis

- Many non-traumatic causes
 - **Steroid therapy**
 - Systemic lupus erythematosus
 - Heavy alcohol consumption
 - Sickle cell anemia
 - Gaucher disease (lysosomal storage disease)

SCFE

Slipped Capital Femoral Epiphysis

- Fracture through growth plate
- Slippage of overlying end of femur
- Most common hip disorder in adolescence (12-14yrs)
- Causes groin pain on affected side
- Can lead to avascular necrosis



Dr. Jochen Lengerke

Legg-Calvé-Perthes Disease

- Idiopathic avascular necrosis
- Hip disorder in **children** (4-8 years)
- **Abnormal blood flow** to femoral head
- Presents as hip pain and limping



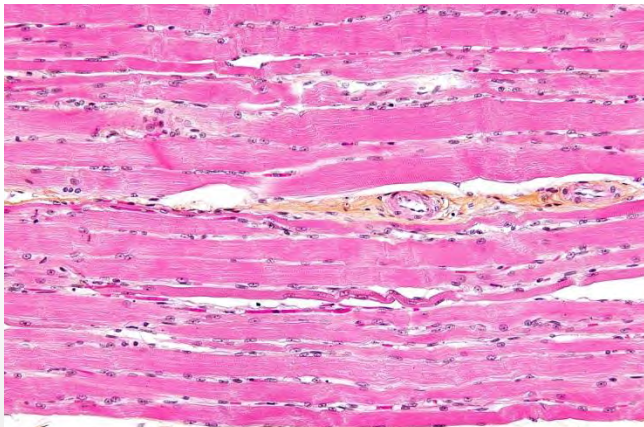
[James Heilman, MD/Wikipedia](#)

Skeletal Muscle

Jason Ryan, MD, MPH

Types of Muscle

- Cardiac and **Skeletal**
 - “Striated” muscle
 - Striations seen under microscope
- Smooth



Skeletal Muscle

- Bundles of **muscle fibers** (cells)
 - Narrow and long
 - Contain **myofibrils** (contractile structures)
- Attaches to skeletal bones
- Attachment closest to spine: origin
- Attachment furthest from spine: insertion

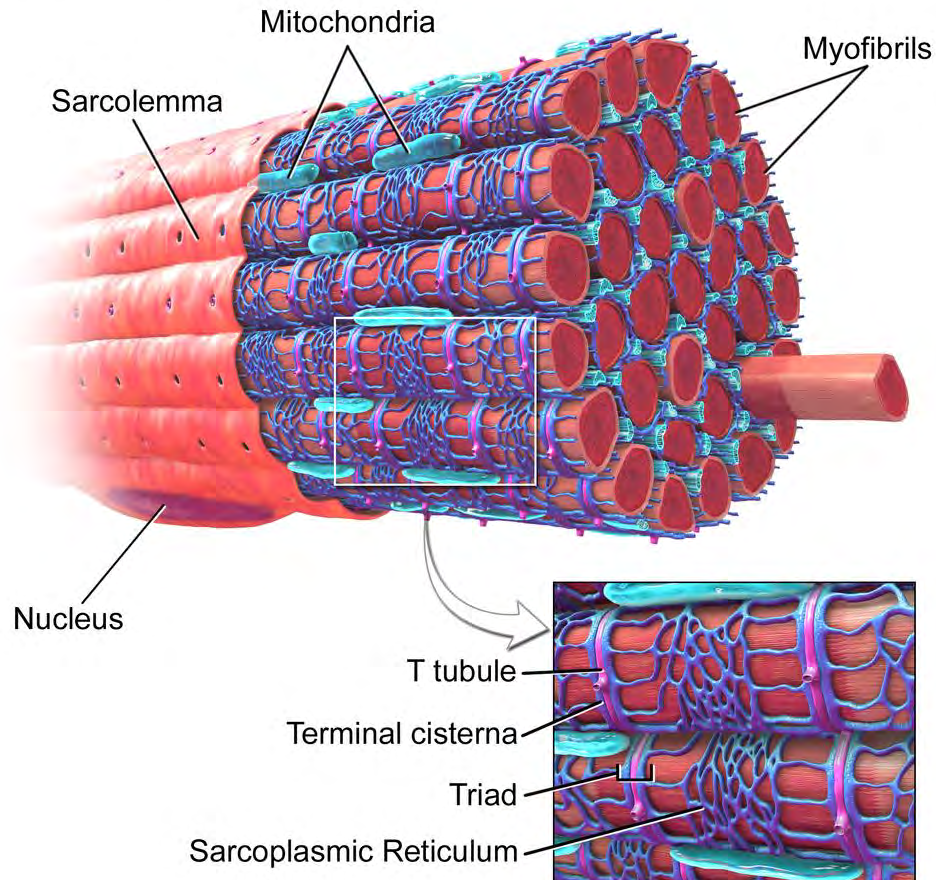
Skeletal Muscle

Vocabulary

- Fiber = muscle cell
- Sarcolemma = plasma membrane
- Myofibrils = contractile structures within cells
- T-tubule = invaginations of plasma membrane
- Sarcoplasmic reticulum
 - Intracellular structure
 - Similar to endoplasmic reticulum
 - Important for **calcium storage**
- Terminal cisternae = SR near T-tubule
- Triad = T-tubule with cisternae on either side

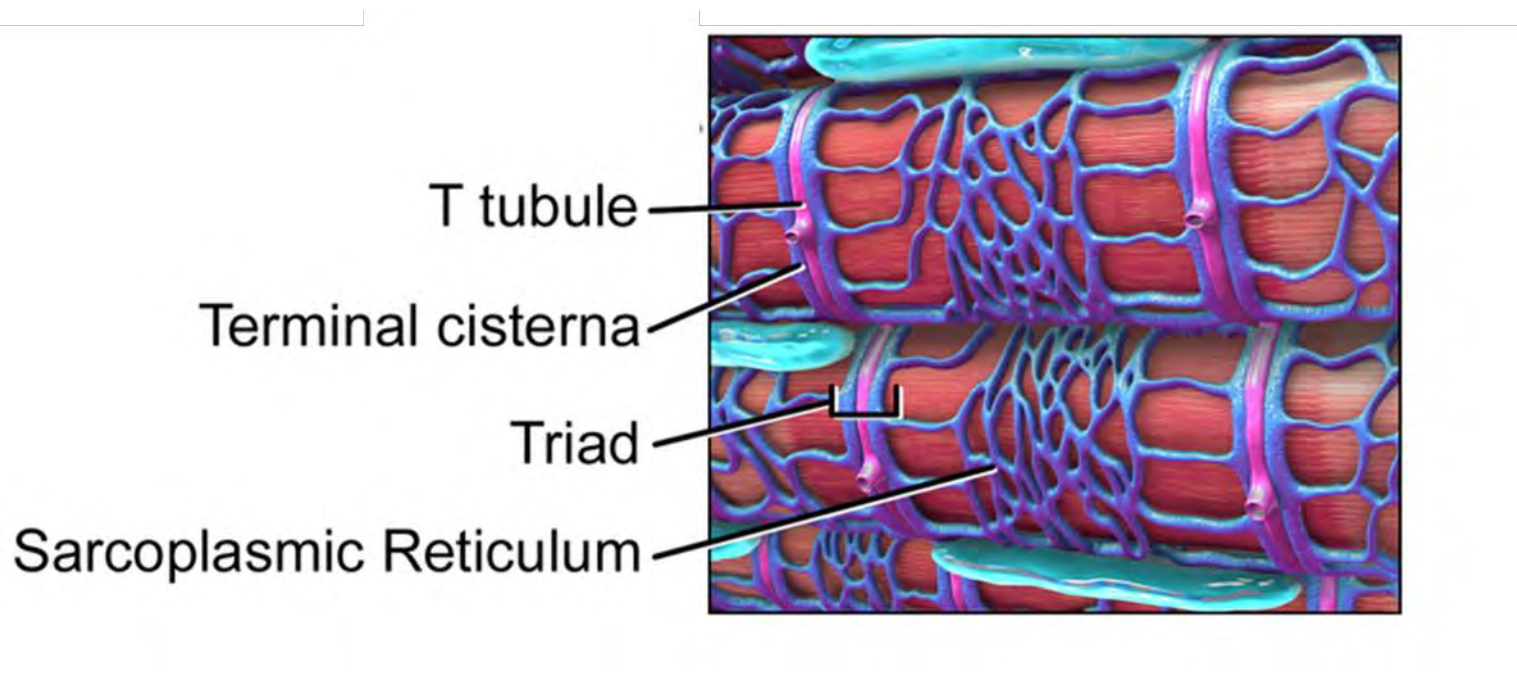
Muscle Fiber

Skeletal Muscle Fiber



BruceBlaus/Wikipedia

Muscle Fiber



BruceBlaus/Wikipedia

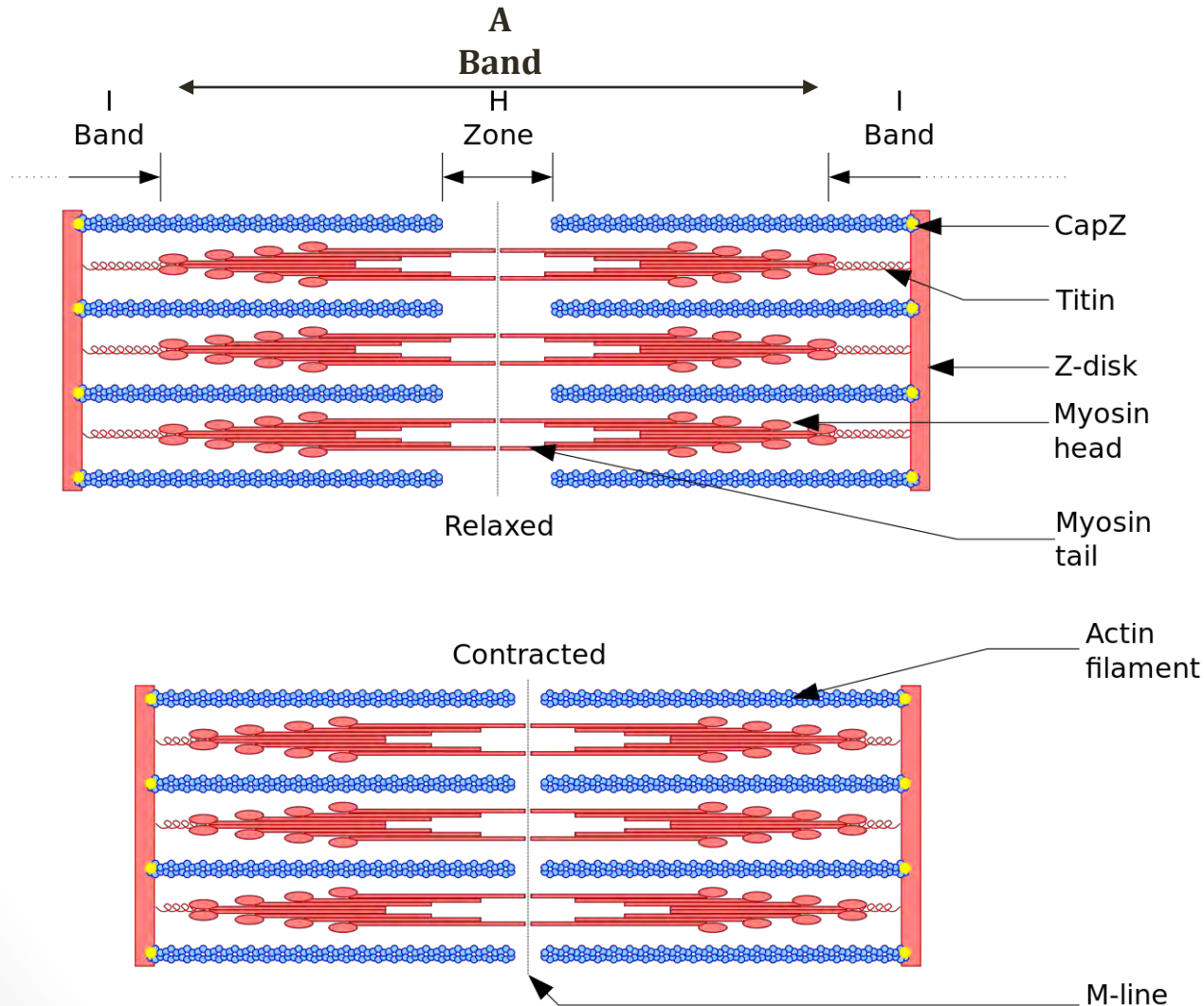
Sarcomeres

- Contractile structures **within myofibrils**
- Contain **actin and myosin filaments**
- Actin
 - Forms thin filaments
 - **Polymers** of protein actin
- Myosin
 - Forms thick filaments
 - Composed of protein myosin
 - Head and tail domains

Sarcomeres

- Z disks
 - Ends of sarcomeres
 - Mechanical stability
 - Contain filaments **vimentin and desmin**
- Titin
 - Cytoskeletal protein
 - Tethers myosin to Z disks

Sarcomere

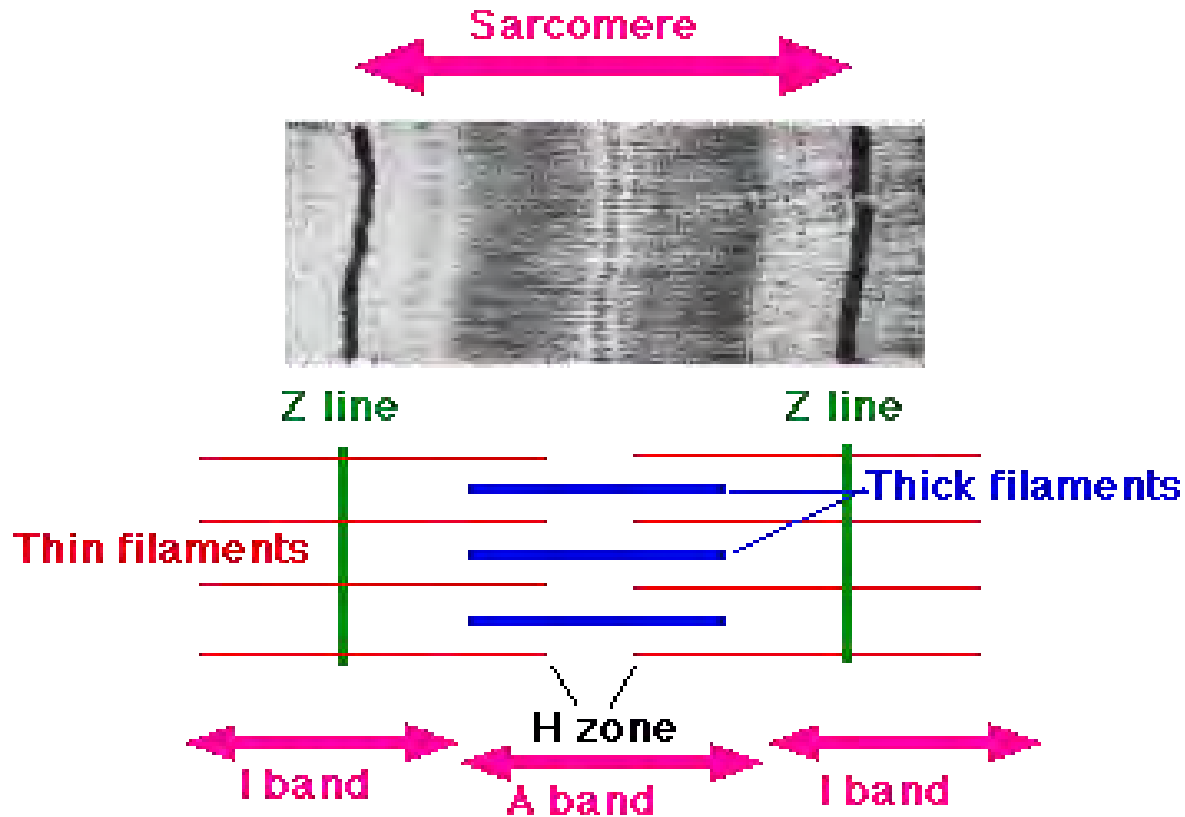


David Richfield/Wikipedia

Sarcomere

- I Band: Light band near Z disks
 - Mostly actin
- A Band: Between I bands
 - Actin and myosin overlap
 - **No change with contraction**
- H Band: Center of sarcomere
 - Myosin only (no actin)
 - Shrinks in size with contraction
- M line: Central proteins for alignment/stability

Sarcomere

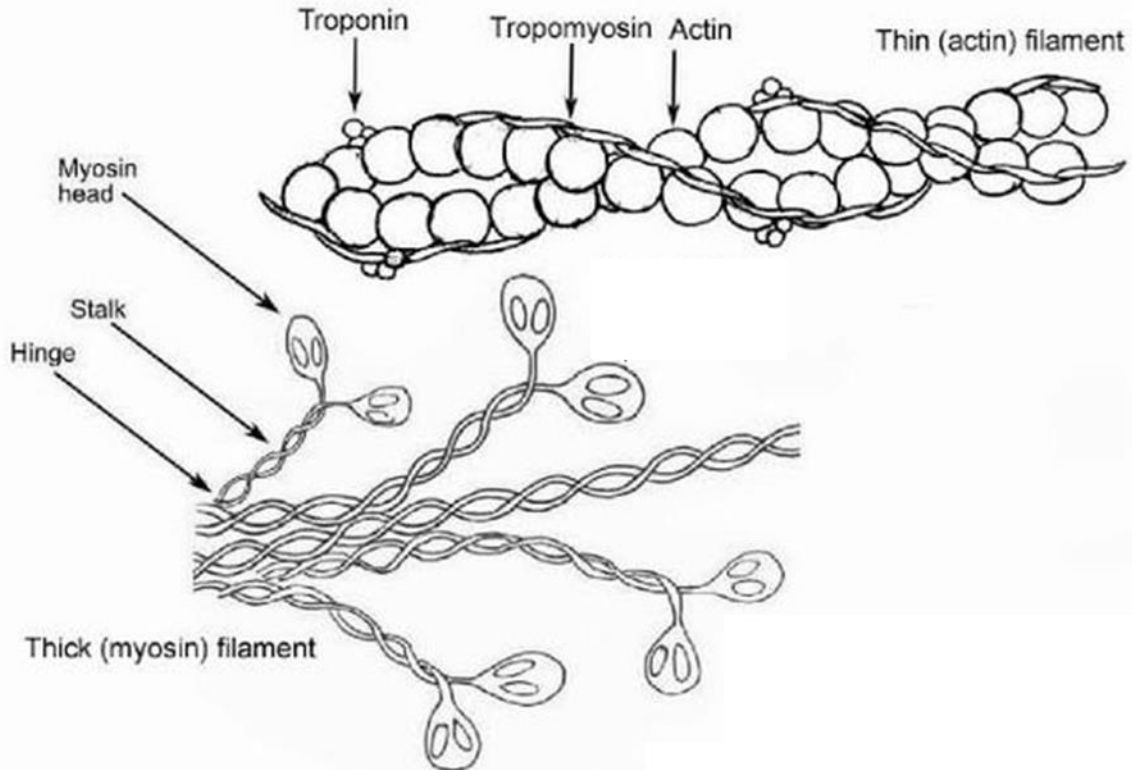


Sameerb/Wikipedia

Sarcomere

- Thin filaments
 - Mostly actin
 - Troponin
 - Tropomyosin
- Thick filaments
 - Myosin
 - Myosin head binds actin → contraction

Skeletal Muscle



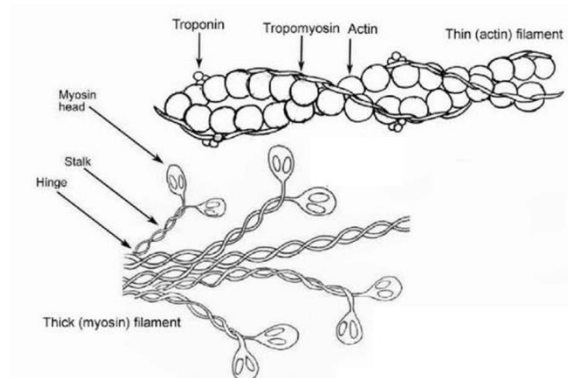
Raul654/Wikipedia

Troponin

- Complex of three subunits
- Troponin C: binds calcium
- Troponin T: binds tropomyosin
- Troponin I: inhibits myosin binding to actin
- Cardiac troponin used to diagnose MI

Muscle Contraction

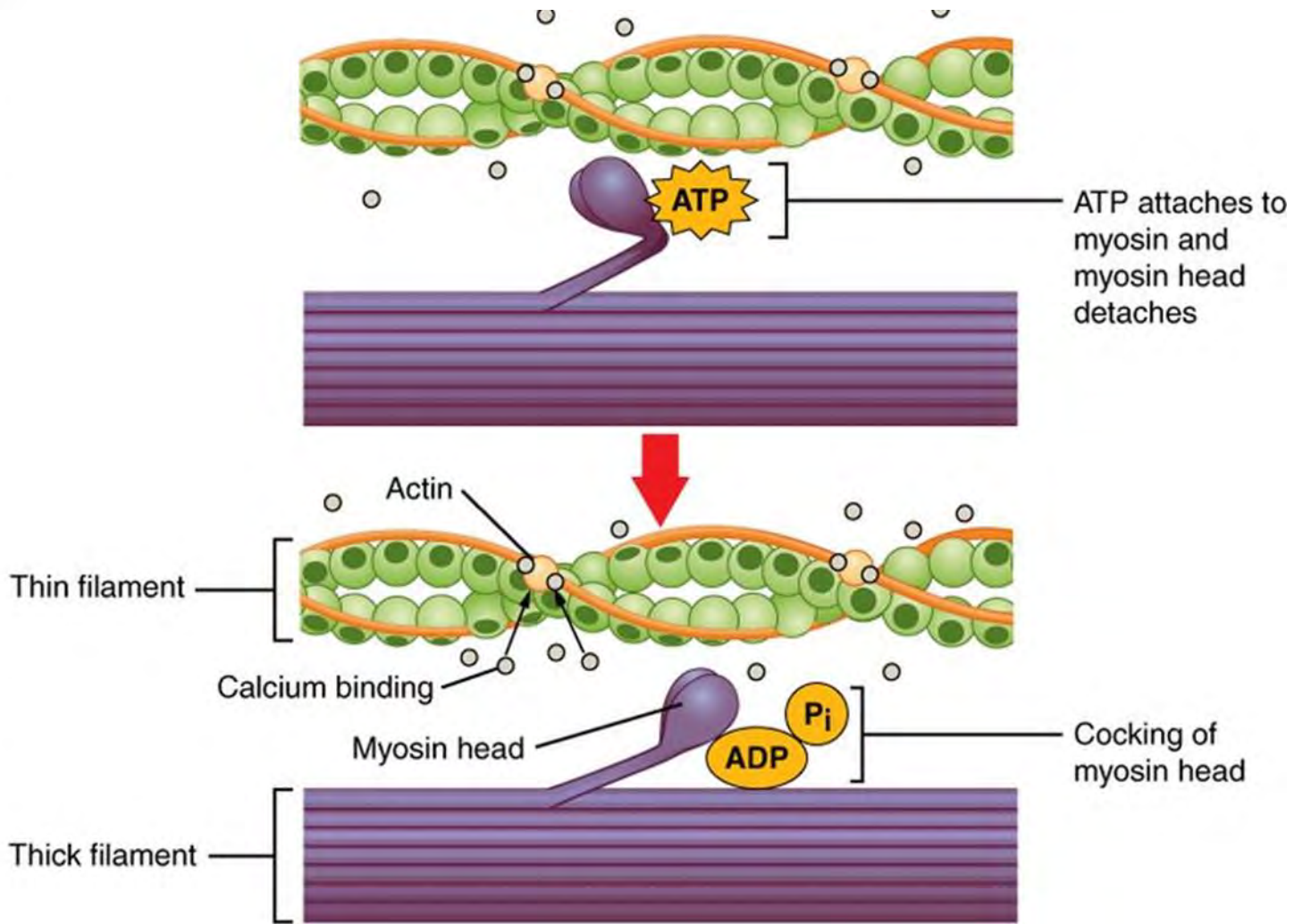
- Initiated with **calcium**
- Tropomyosin blocks “binding groove” for myosin
- Calcium binds troponin
- Ca-Troponin → removal of tropomyosin block
 - Conformational change in tropomyosin
 - Skeletal muscle contraction: “Thin filament regulated”

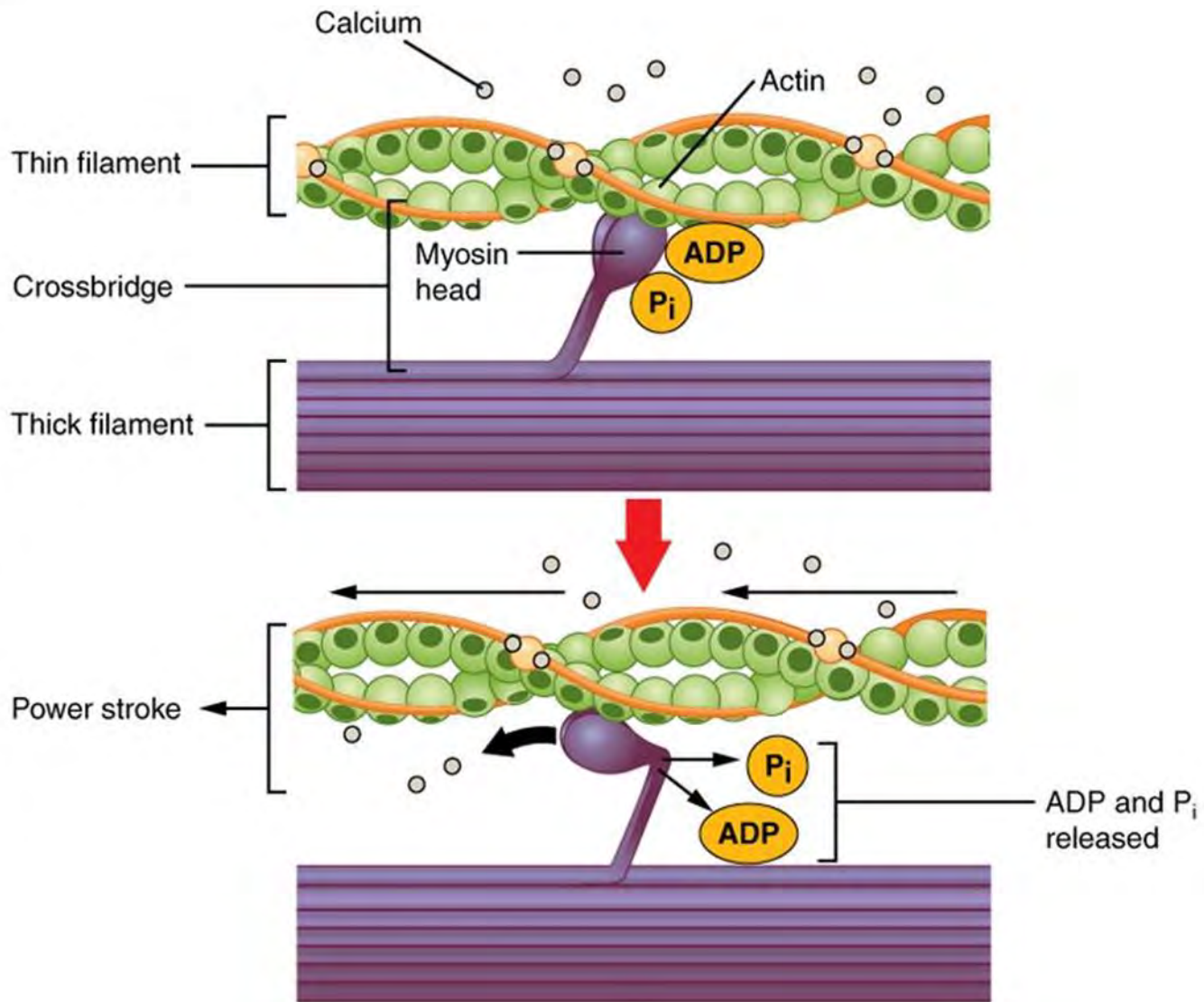


Raul654/Wikipedia

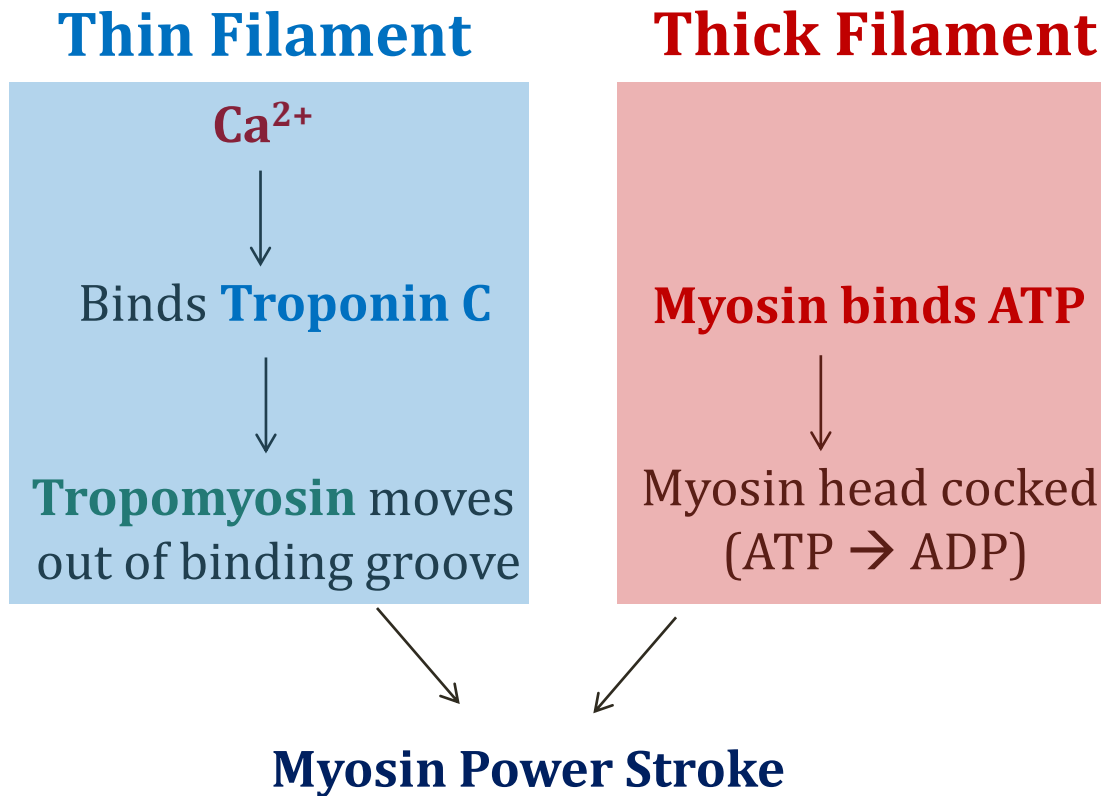
Muscle Contraction

- Myosin binds ATP at rest
- Hydrolyzes to ADP and Pi
- Assumes “cocked” position (ready for contraction)
- Tropomyosin block removed → myosin binding
 - Myosin binds to actin
 - Moves along actin filament
 - “Power stroke”
- Myosin binds new ATP

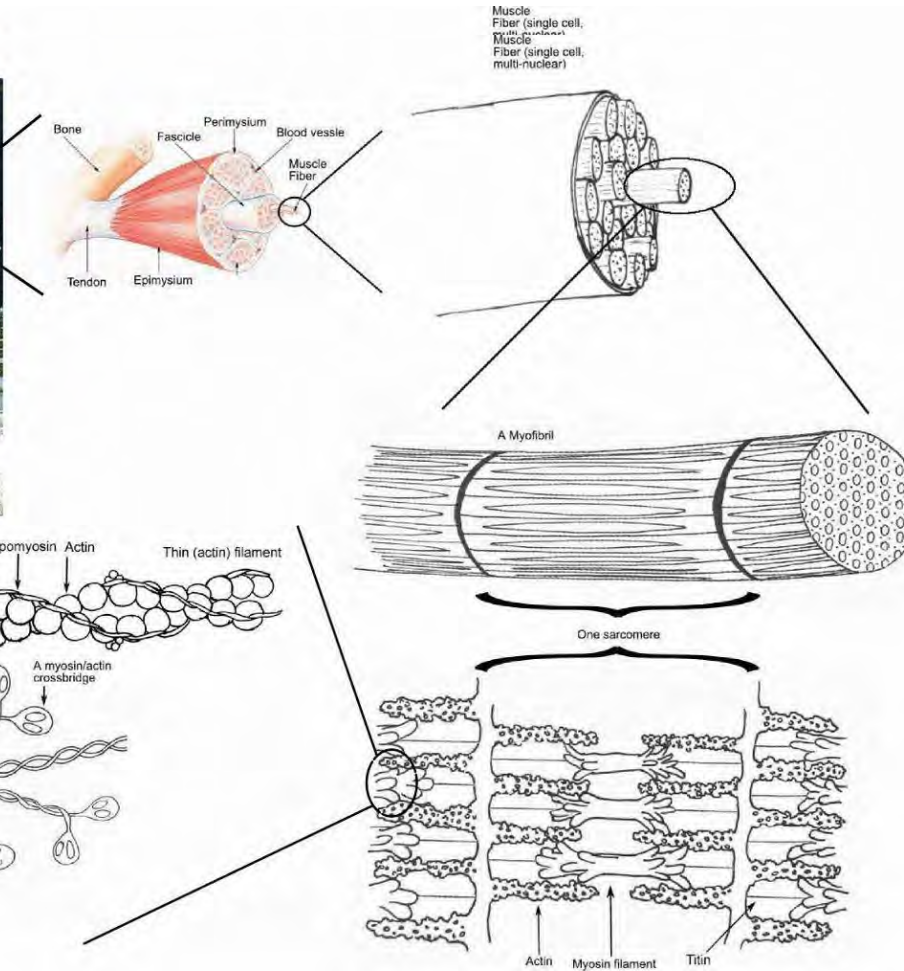
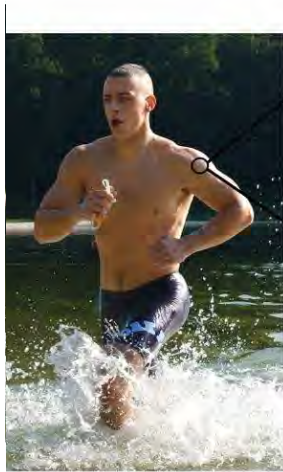




Contraction



Skeletal Muscle

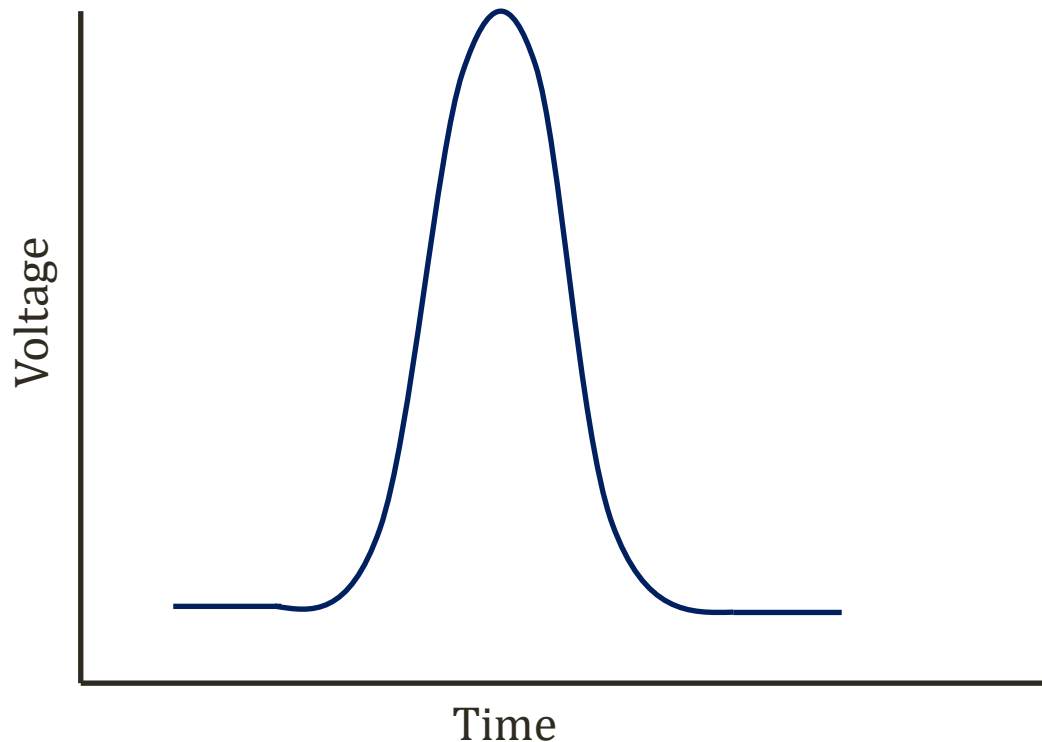


Raul654/Wikipedia

Action Potential

Skeletal Muscle

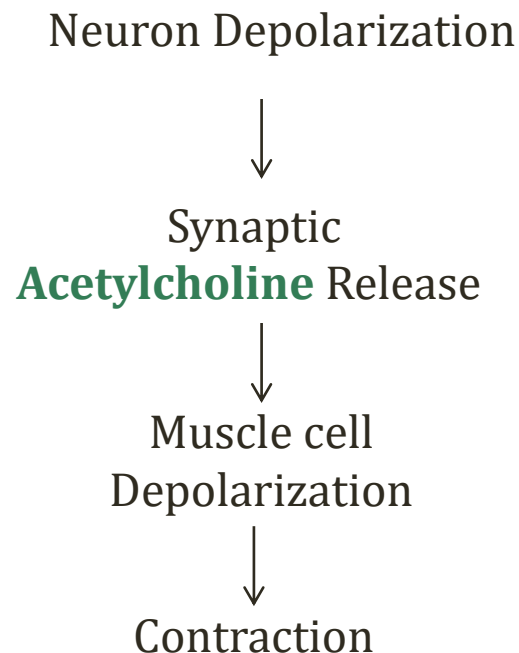
- Action potential = change in membrane voltage
- Required for skeletal muscle contraction



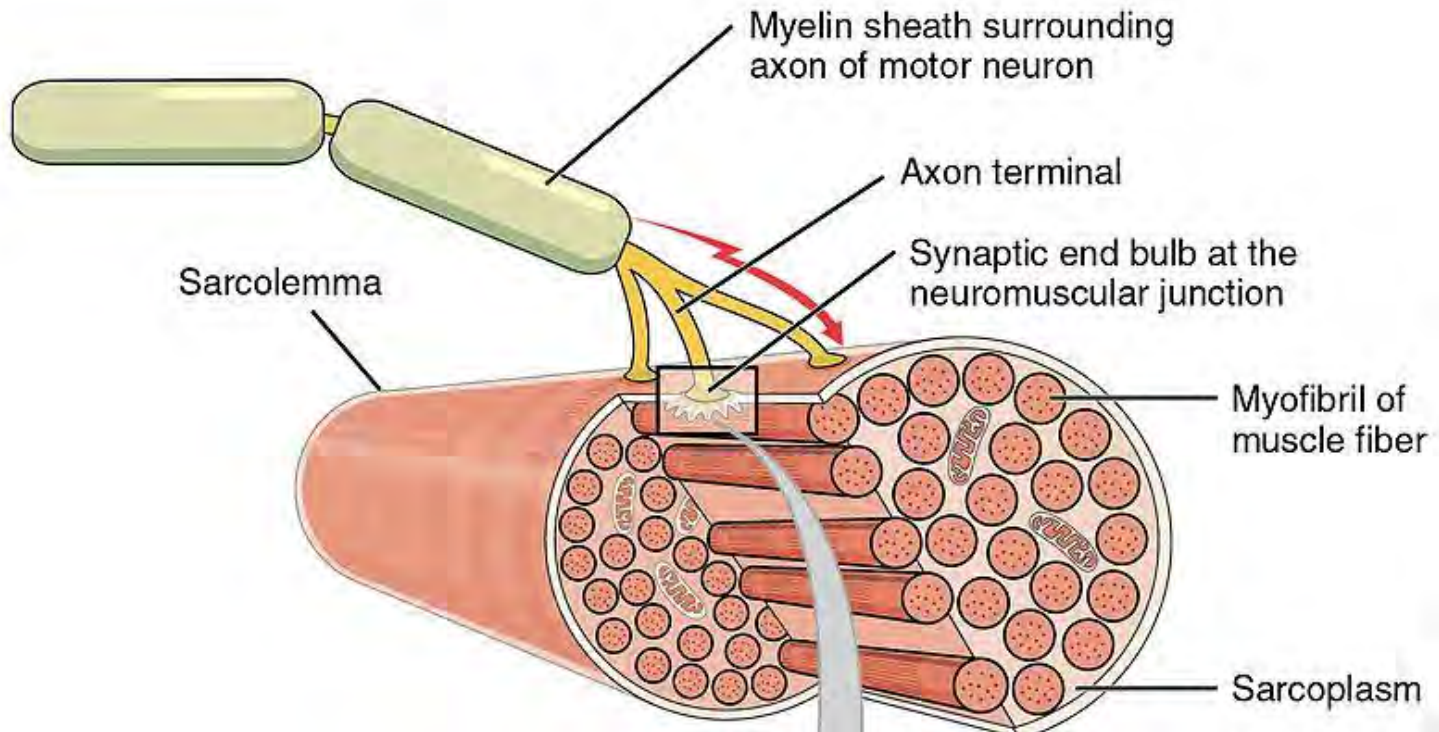
EC Coupling

Excitation-Contraction Coupling

- Contraction (via Ca^{2+}) linked to action potential
- Contraction occurs when cell depolarizes

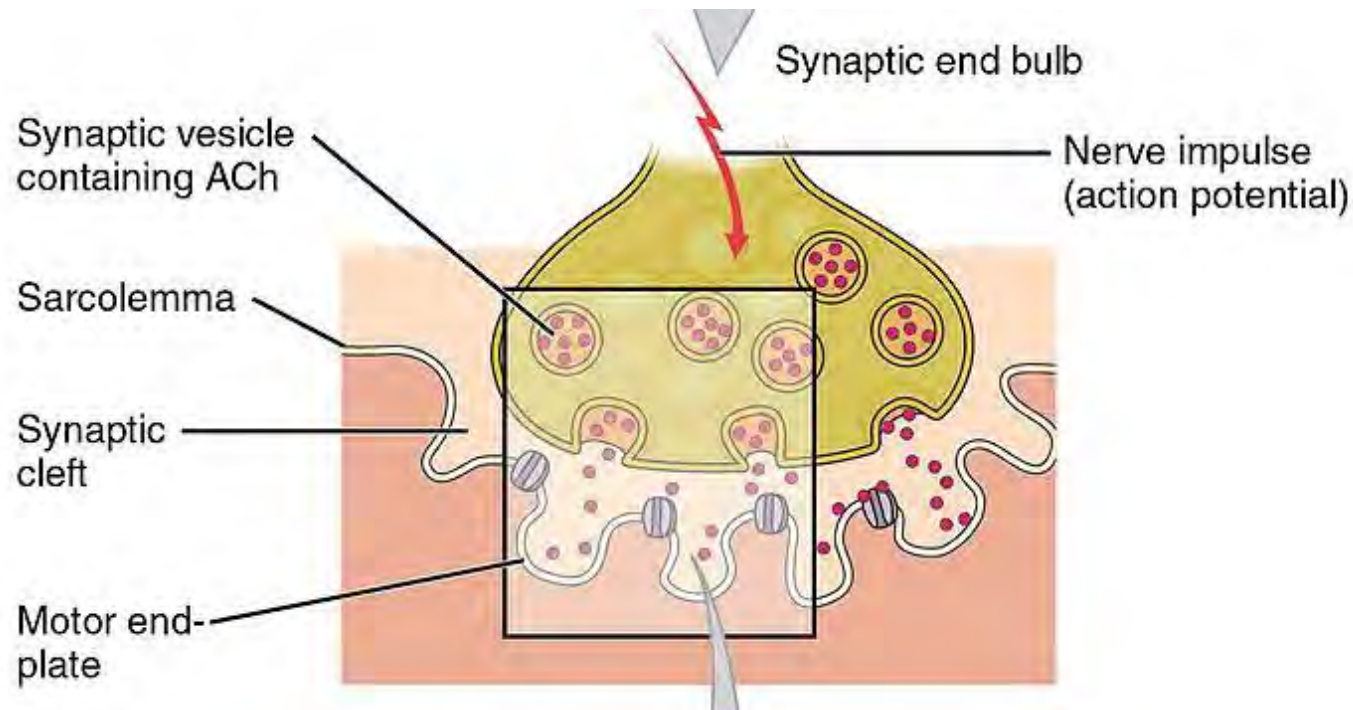


Skeletal Muscle

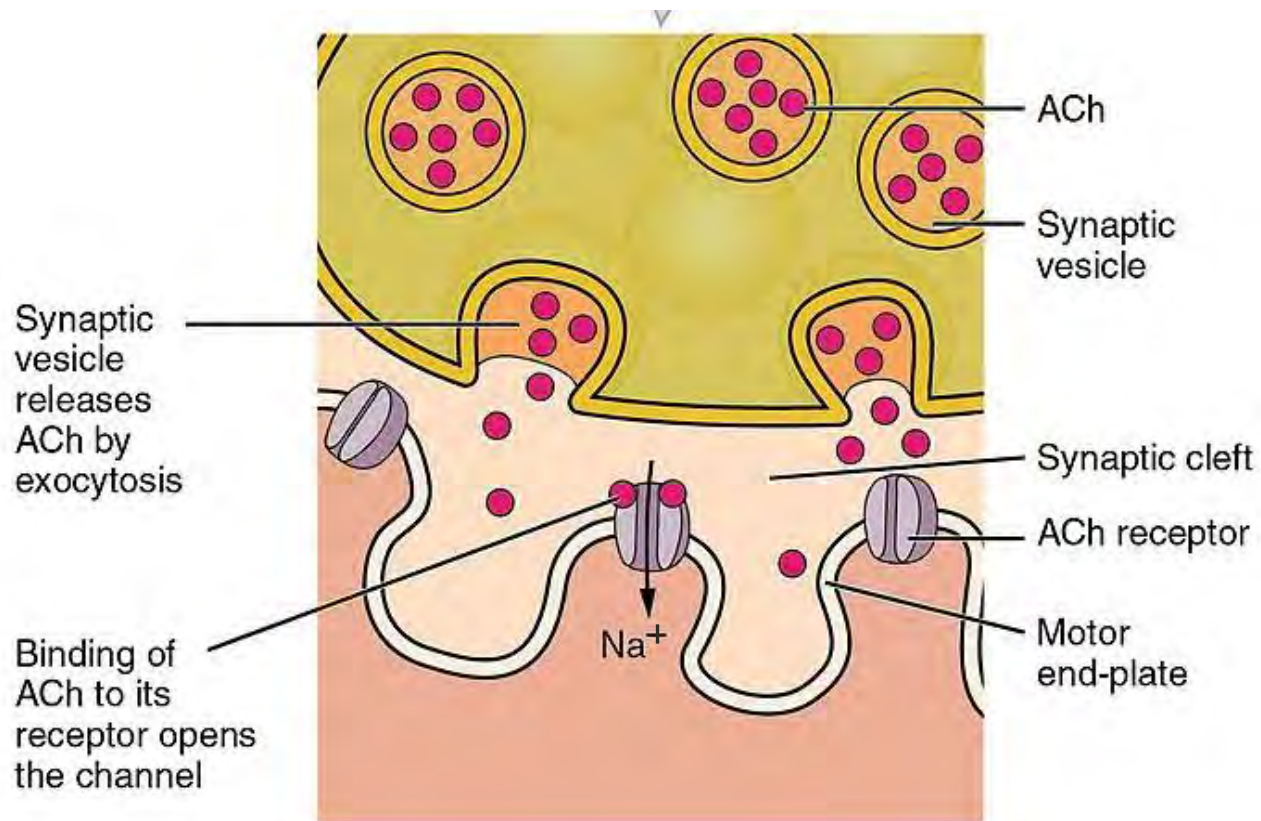


Skeletal Muscle

Neuron depolarization → presynaptic **calcium entry** into neuron
Muscle: **Nicotinic Acetylcholine Receptors**

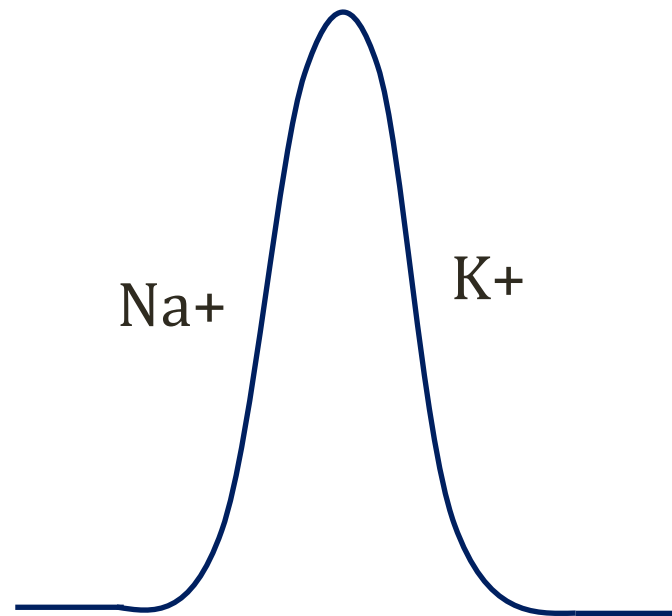


Skeletal Muscle



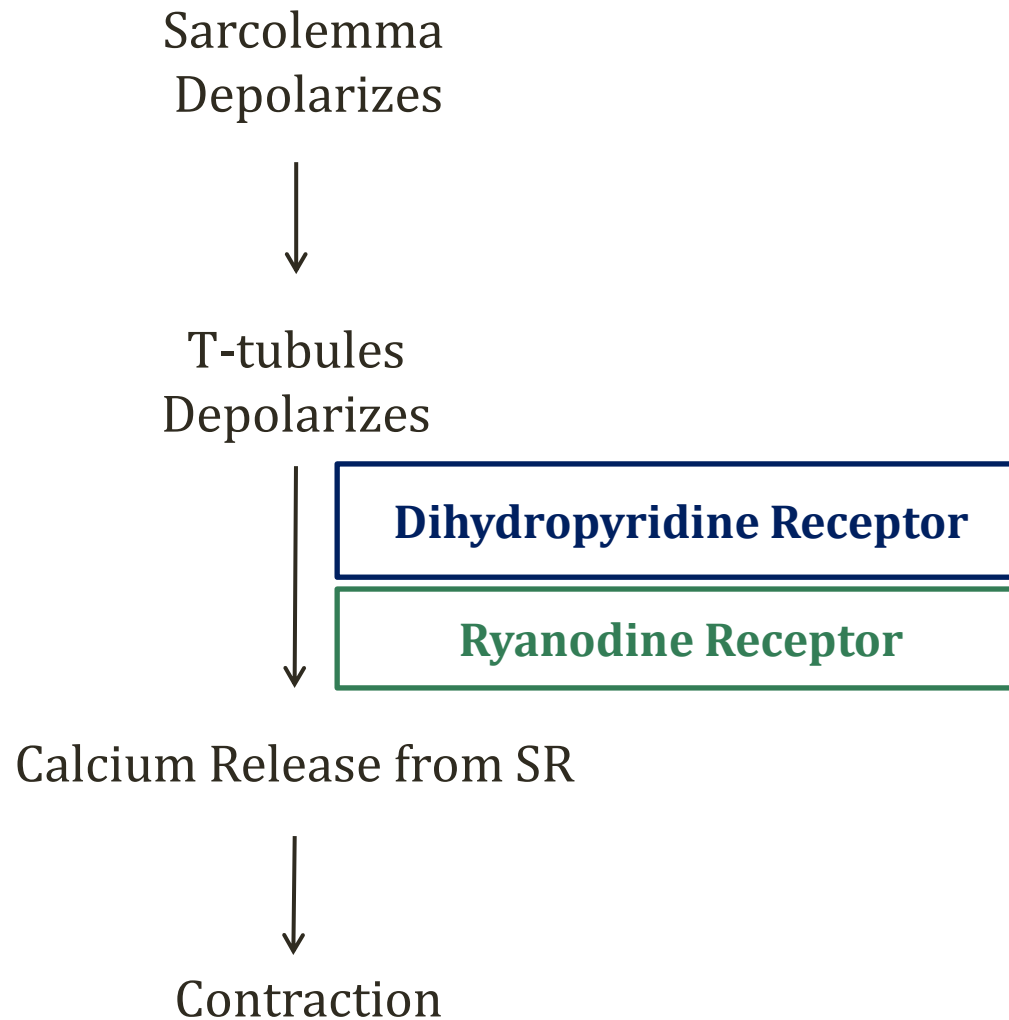
Action Potential

Skeletal Muscle



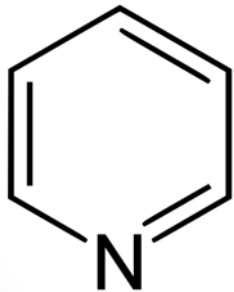
EC Coupling

Excitation-Contraction Coupling

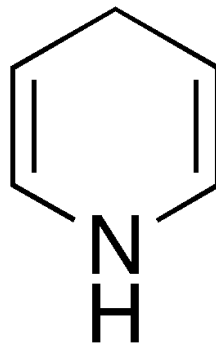


Dihydropyridine Receptors

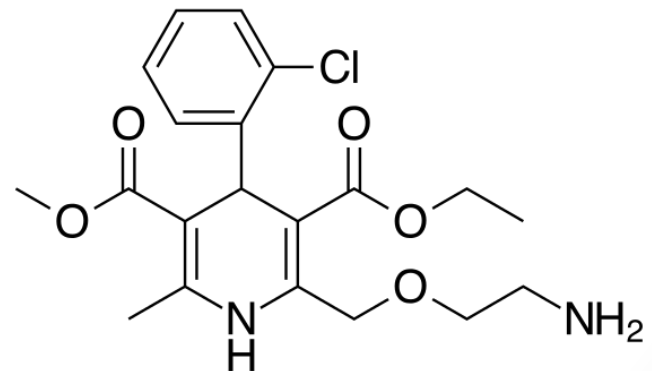
- Proteins that span gap between T-tubule and SR
- 5 subunits - one subunit binds dihydropyridine drugs
- L-type Ca^{2+} channels (capable of conducting Ca^{2+})
- **Conformational change with depolarization**
- Opens **ryanodine receptor** on terminal cisternae



Pyridine
Boards & Beyond
STUDY SMARTER



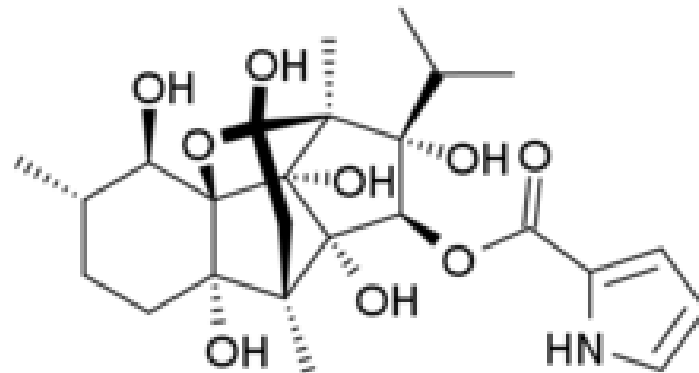
Dihydropyridine



Amlodipine

Ryanodine Receptors

- Bind ryanodine (poison found in plants)
 - No role in physiologic function of receptor
- Large protein embedded in SR
- **Releases calcium → initiates contraction**
- Opened by DHPRs

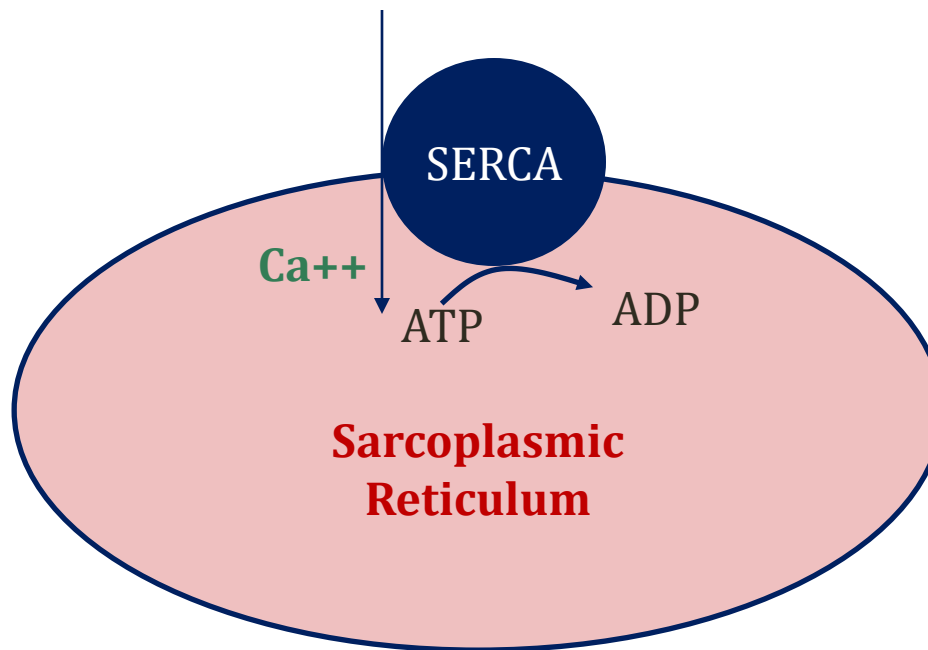


Ryanodine

SERCA

Sarco/endoplasmic reticulum Ca^{2+} -ATPase

- Transfers Ca^{2+} from cytosol back into SR
- ATPase uses ATP hydrolysis



Malignant Hyperthermia

- Rare, dangerous reaction to anesthetics
 - Halothane, succinylcholine
- **Muscle damage:** ↑CK, K⁺
- Fever, muscle rigidity after surgery
- Cause: **abnormal ryanodine receptors**
 - Excessive calcium release
 - Consumption of ATP for SR reuptake of calcium
 - ATP consumption → heat → tissue damage
- Treat with **dantrolene**

Dantrolene

- Muscle relaxant
- **Antagonist to ryanodine receptors**
- Blocks release of calcium from SR
- Reduces calcium in cytoplasm for contraction



Pixabay/Public Domain

Slow and Fast Twitch



Pixabay/Public Domain

- **Slow-twitch fibers**
 - Time to peak tension = slow
 - Also called red fibers (deep red color)
 - Color from amount of myoglobin (binds O₂)
 - Extra myoglobin resists fatigue
 - More mitochondria = more oxidative phosphorylation
 - More fatty acid metabolism
 - Moderate glycolysis activity
- Postural muscles (spine) = more slow twitch
 - Sustained tone

Slow and Fast Twitch

- **Fast-twitch fibers**
 - Time to peak tension = fast
 - Also called white (pale color)
 - Primarily metabolize **glucose and glycogen**
 - More glycogen storage
 - Increased activity of glycolysis enzymes
 - Few mitochondria = less oxidative phosphorylation
- Eyes muscles = many fast twitch fibers
- Most muscles a mixture of fast/slow fibers

Cardiac Muscle

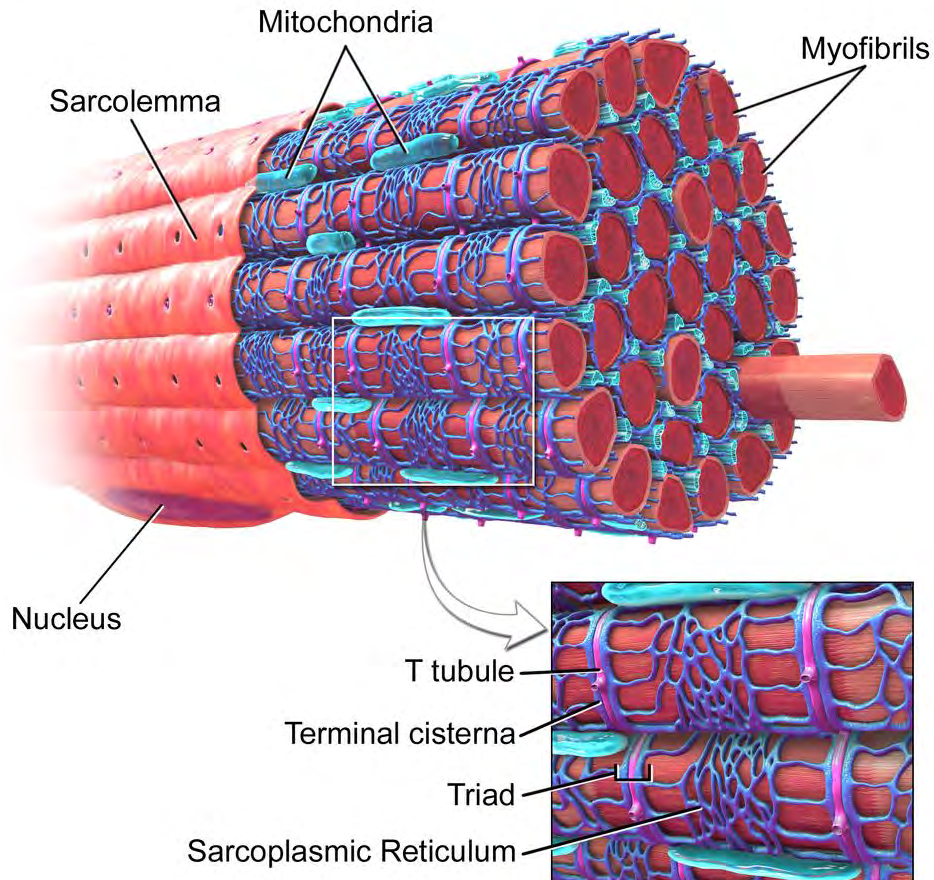
Jason Ryan, MD, MPH

Cardiac Muscle

- Many similarities with skeletal muscle
 - Striated
 - Sarcomeres for contraction
 - Actin and myosin
 - Troponin and tropomyosin
 - T-tubules abut sarcoplasmic reticulum

Dyads

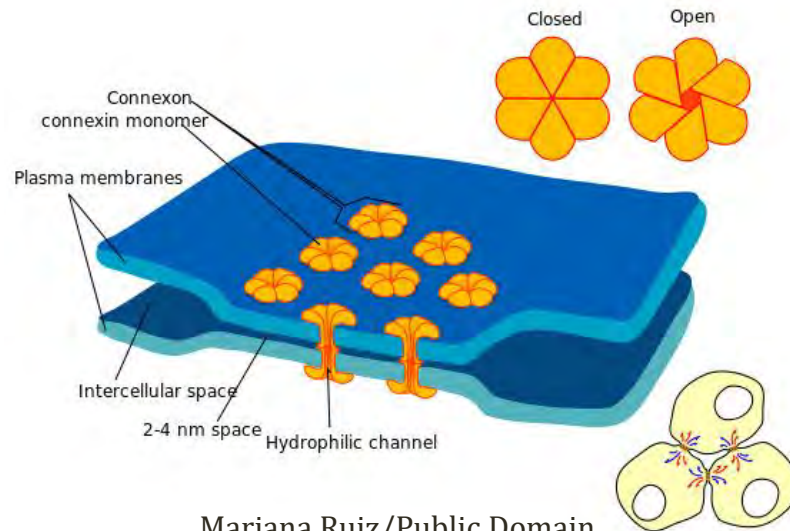
Skeletal Muscle Fiber



BruceBlaus/Wikipedia

Cardiac Muscle

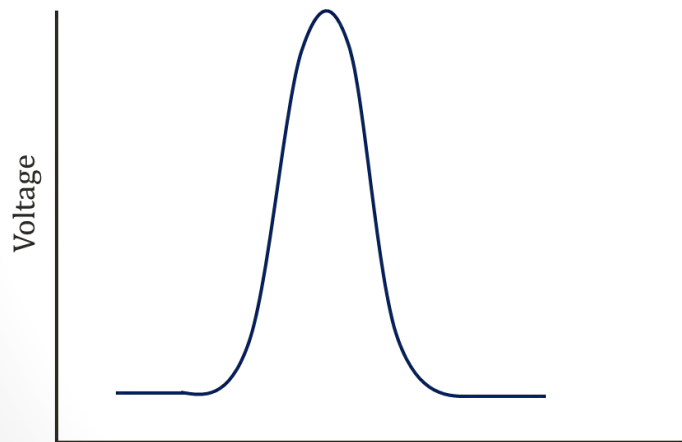
- Involuntary
- Depolarized by pacemaker cells (SA node)
- **Gap junctions**
 - Depolarization spreads from cell to cell



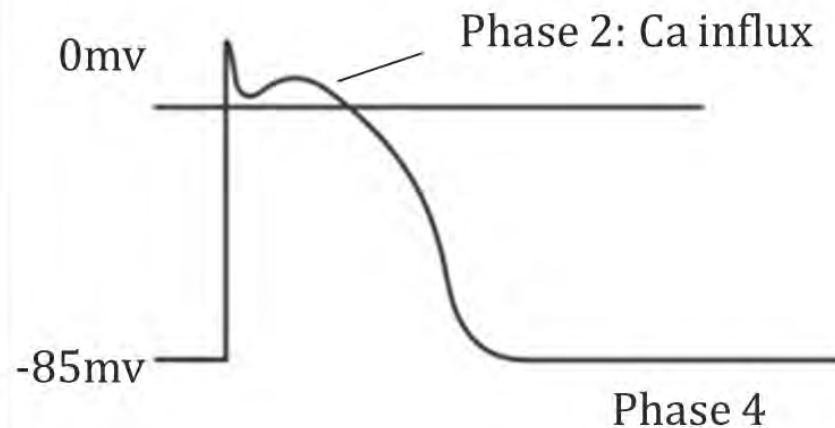
Cardiac Muscle

- Different action potential
- Phase 2: Calcium influx via **L-type calcium channels**

Skeletal Muscle

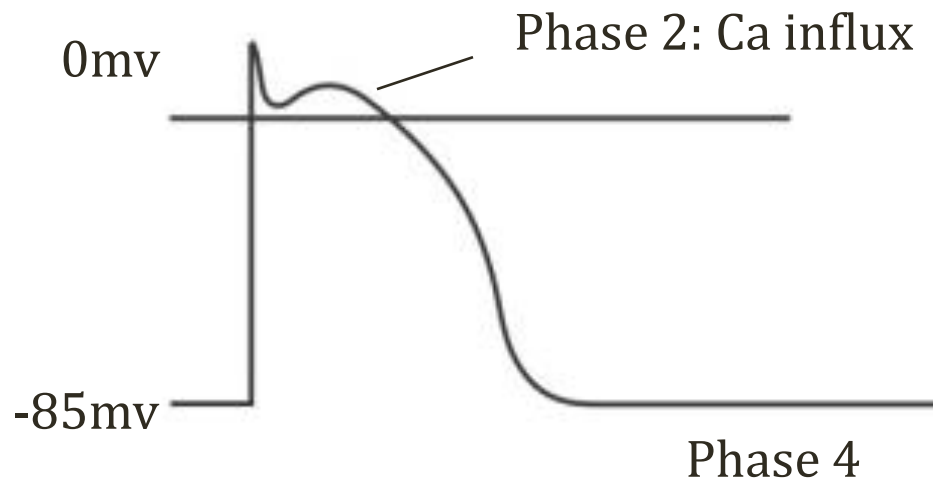


Cardiac Muscle



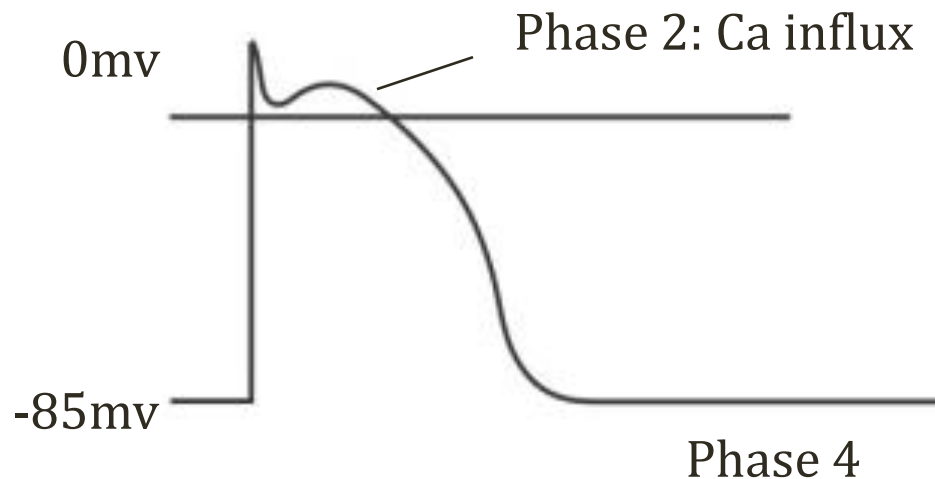
Cardiac L-type Ca⁺ Channels

- Also dihydropyridine receptors
- Low affinity for dihydropyridine Ca⁺ blockers
 - Amlodipine, nifedipine
- Higher affinity for non-dihydropyridine Ca⁺ blockers
 - Diltiazem, verapamil



Cardiac L-type Ca^{2+} Channels

- Ca influx important (unlike skeletal muscle)
- Triggers SR calcium release via ryanodine receptor
- **“Calcium-triggered calcium release”**



Contractility

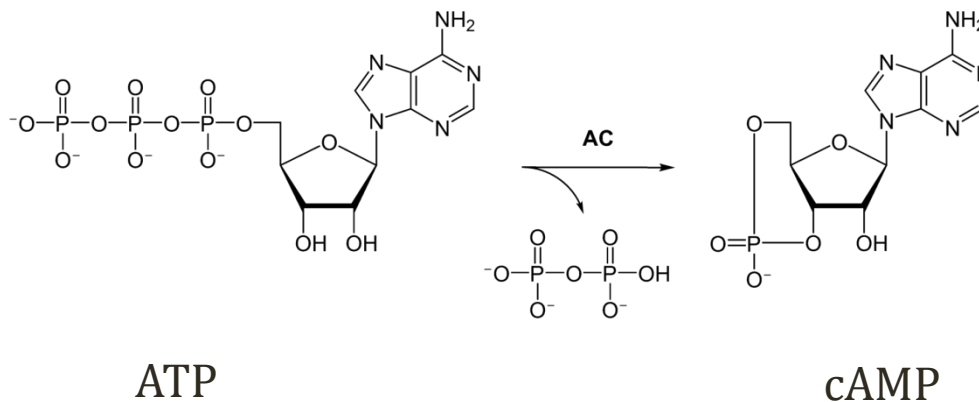
- All cardiac muscle cells contract
- Cannot recruit extra fibers to ↑ contractility
- **More calcium into cell → more contraction**
 - More Ca⁺ entry via L-type Ca channels
 - More Ca-triggered calcium release from SR
 - “Increased calcium transient”

Contractility

- Non-dihydropyridine calcium channel blockers
 - Diltiazem, verapamil
 - Block L-type calcium channels in cardiac myocytes
 - Decrease contractility (negative inotropes)
 - Also slow conduction and lower heart rate

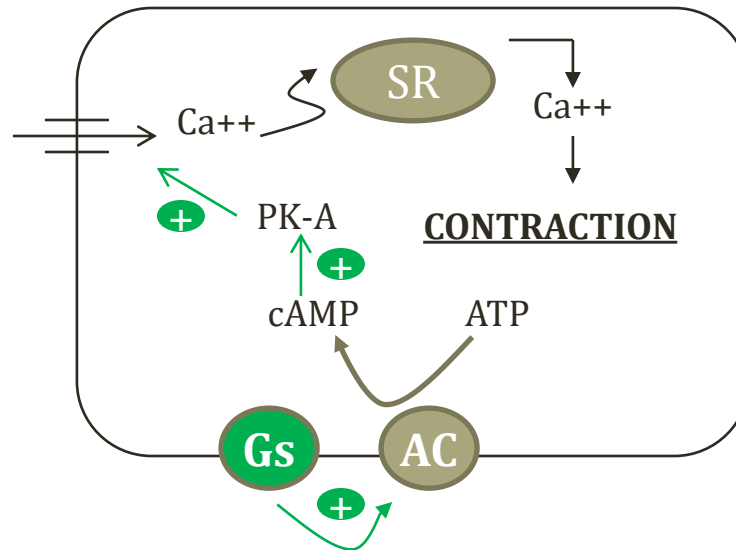
Sympathetic Nervous System

- Increases contractility
- Works through G proteins on cardiac myocytes
- Alter intracellular cAMP levels via **adenyl cyclase**
- cAMP increase protein kinase A (PKA)
- PKA phosphorylates Ca channels → more Ca into cell



Cardiac Muscle Cells

Cardiac Muscle



β_1 Receptors

Linked Gs proteins

↑cAMP

↑Calcium

↑Contractility

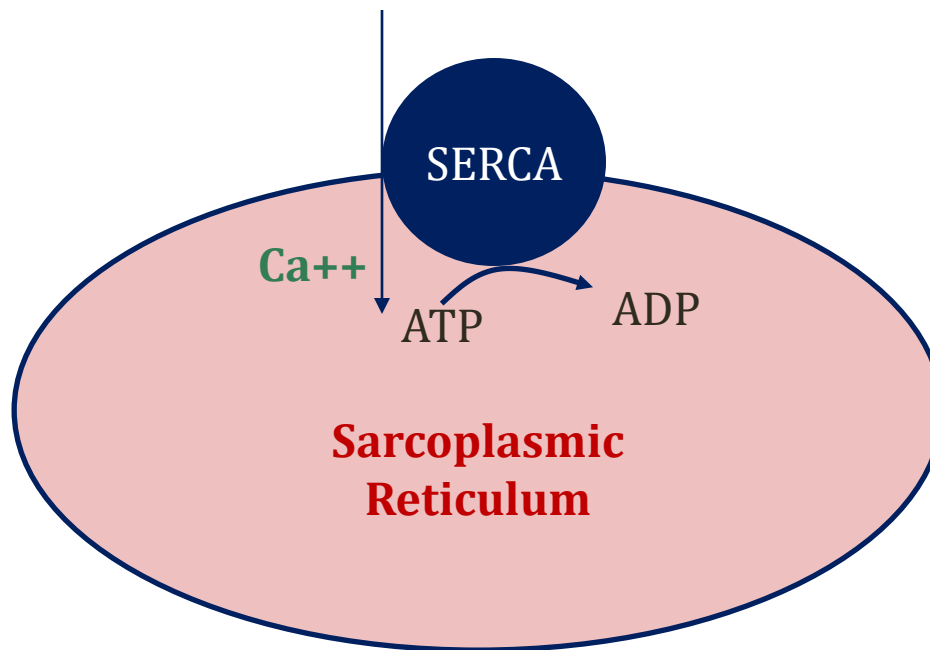
Lusitropy

- Lusitropy = **myocardial relaxation**
- Opposite of contractility
- Accompanies increases in contractility
- Faster contraction → faster relaxation

SERCA

Sarco/endoplasmic reticulum Ca^{2+} -ATPase

- Mediates lusitropy
- Transfers Ca^{2+} from cytosol back into SR
- ATPase uses ATP hydrolysis



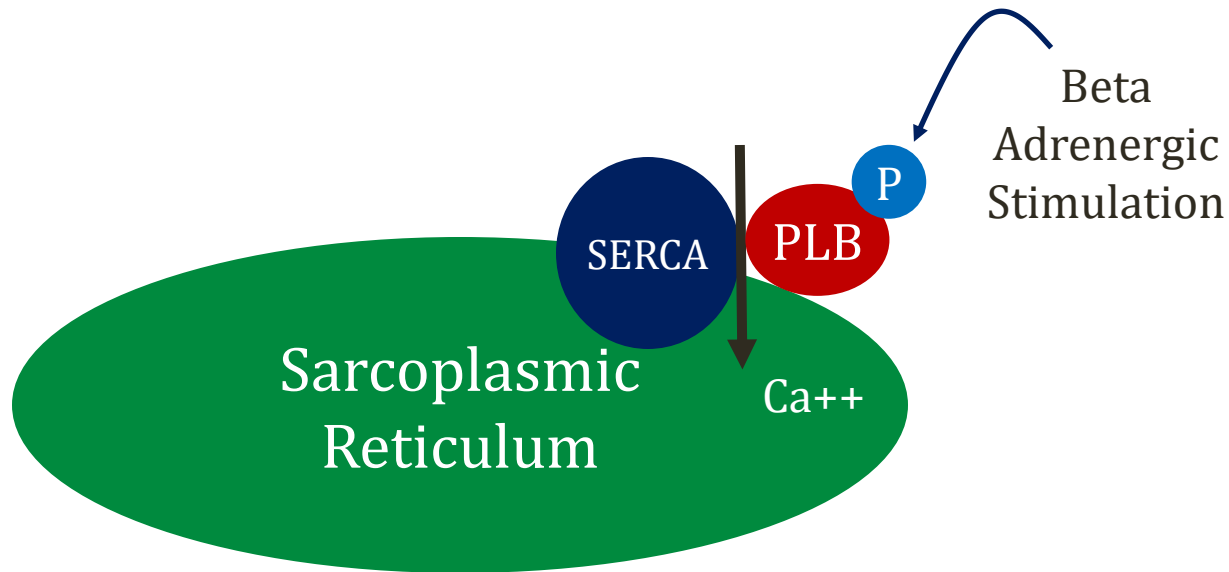
Lusitropy

- Key regulatory protein: **Phospholamban**
 - **Inhibitor:** sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA)
 - Phosphorylated via beta adrenergic stimulation (PKA)
 - Stops inhibiting SERCA
 - Result: SERCA takes up calcium → relaxation

SERCA

Sarco/endoplasmic reticulum Ca^{2+} -ATPase

- Sympathetic stimulation \rightarrow phosphorylates PLB
- Inactivates PLB (relieves inhibitory effect)
- Allows SERCA to uptake more calcium

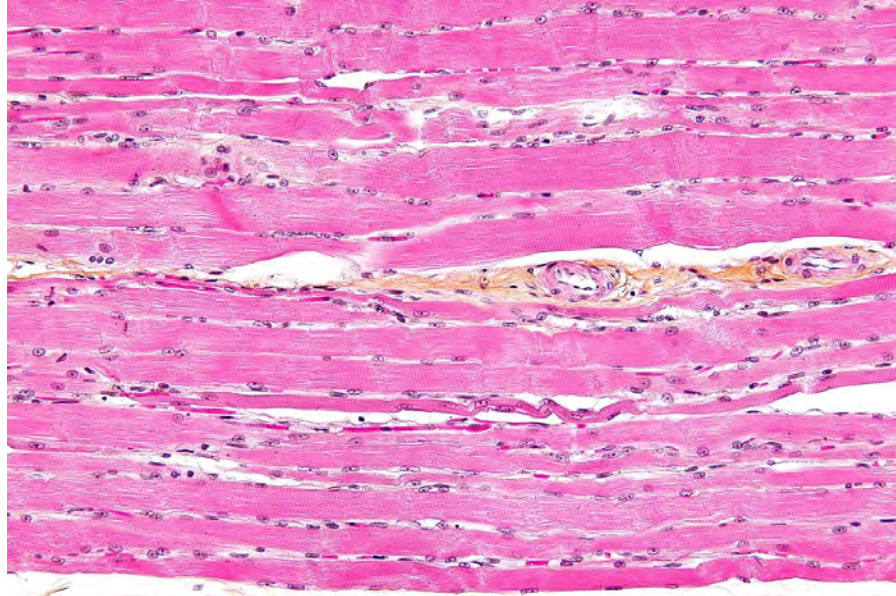


Smooth Muscle

Jason Ryan, MD, MPH

Types of Muscle

- Cardiac and Skeletal
 - “Striated” muscle
 - Striations seen under microscope
- Smooth



Nephron/Wikipedia

Smooth Muscle Cells

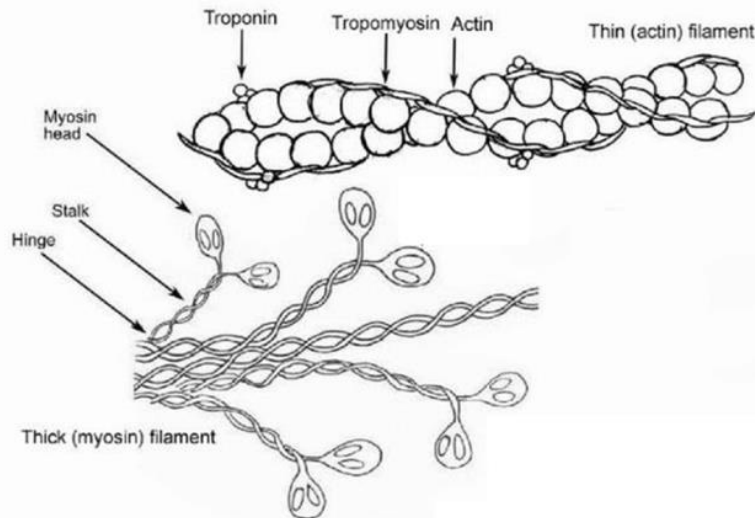
- Components of organs
 - Intestines, airways, blood vessels
- Propels organ contents (intestines)
- **Changes resistance to flow (blood vessels)**
- Contains actin and myosin
- Function differently than in striated muscle

Smooth Muscle Cells

- Do not depend on action potentials
- Do not require membrane depolarization to contract
- **Slow, sustained contraction**
 - Contrast with cardiac cells: rapid, quick contraction
- **Calcium** → contraction (as in striated muscle)

Myosin Light Chain

- Actin = thin filaments
- **Myosin = thick filaments**
- Myosin = heavy and light chains
- **Myosin light chains** = modified to control contraction
- Smooth muscle: “Thick filament regulated”



MLC Phosphorylation

- Regulates contraction/tone
- **Only phosphorylated MLC interacts with actin**
- Myosin light chain kinase
 - Phosphorylates myosin
- Myosin light chain phosphatase
 - De-phosphorylates myosin

CONTRACTED



Myosin
Light Chain
Phosphatase



Myosin
Light Chain
Kinase

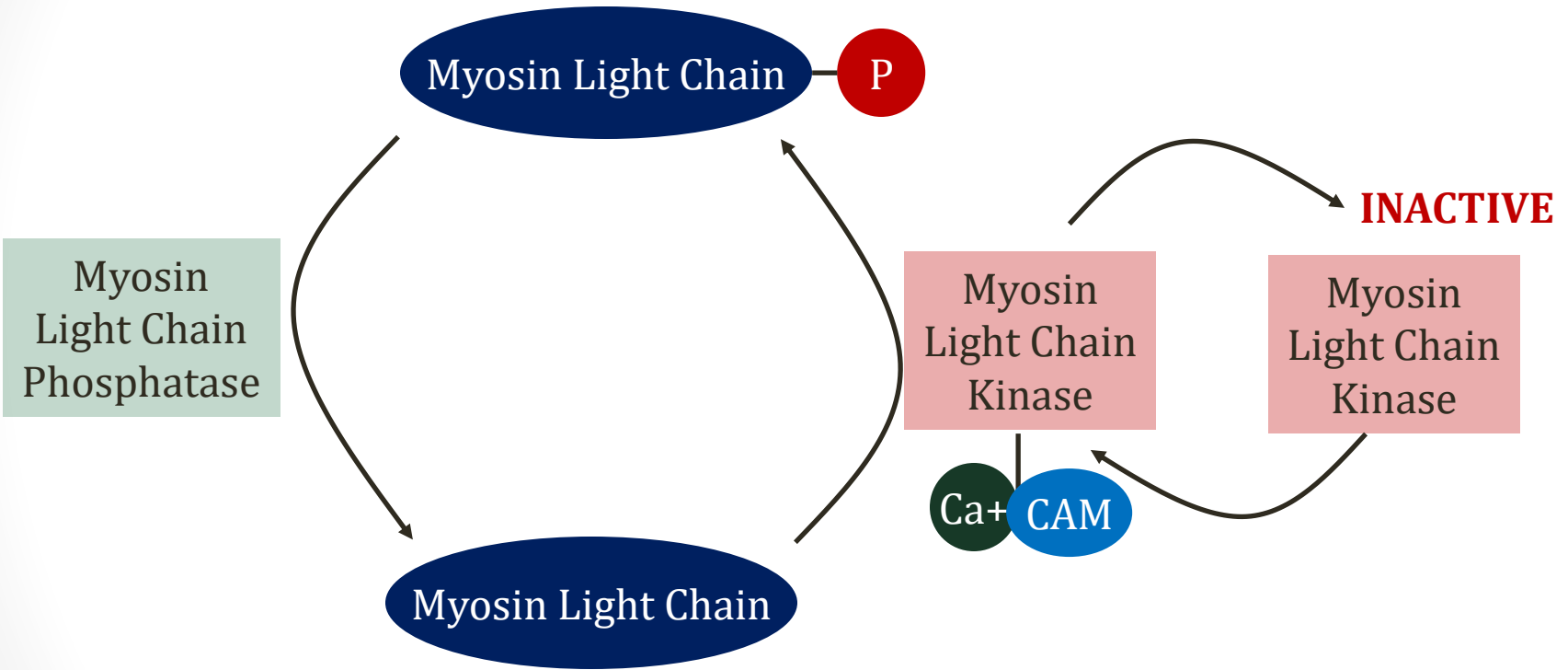


Relaxed

Calcium-Calmodulin

- **Calmodulin (CAM)**
 - Smooth muscle cell protein
 - Ubiquitous (lots inside cells)
- Binds calcium
- Calcium-CAM activates MLCK
- **Calcium → contraction**

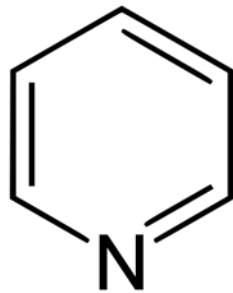
CONTRACTED



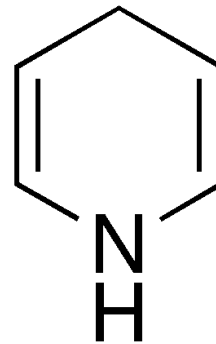
Relaxed

L-type Calcium Channels

- Allow calcium into smooth muscle cells
- Bind **dihydropyridines**
- “Dihydropyridine receptors”



Pyridine

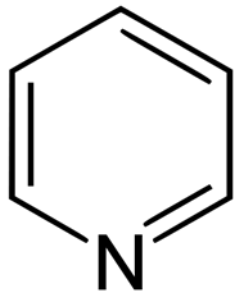


Dihydropyridine

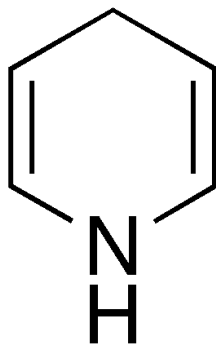
Dihydropyridine Drugs

Amlodipine, Felodipine, Nicardipine

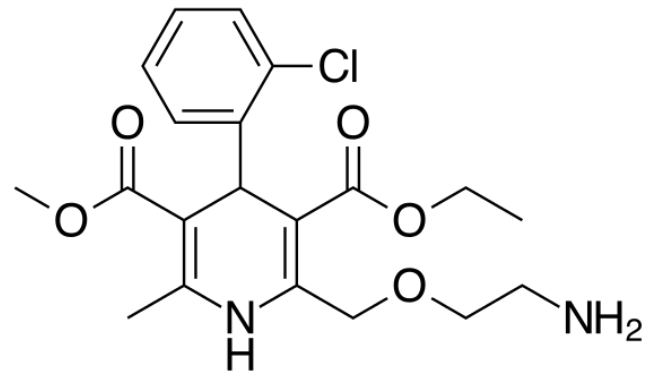
- **L-type calcium channel blockers**
- Vascular smooth muscle **relaxation**
 - Less Ca → relaxation
- Used to lower blood pressure in hypertension



Pyridine



Dihydropyridine



Amlodipine
(Dihydropyridine Calcium
Channel Blocker)

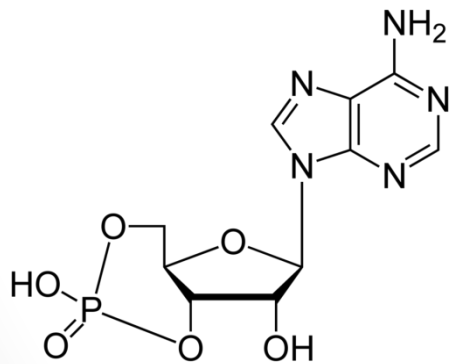
Smooth Muscle Tone

Regulation

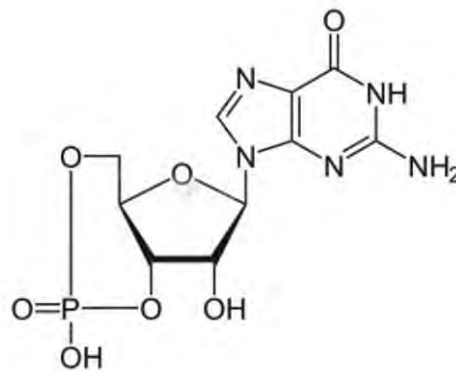
- Two major regulators of contraction/tone:
 - **Calcium in cell**
 - **Myosin light chain phosphorylation**
- Both modified to alter tone
 - Autonomic nervous system
 - Local factor (i.e. vasodilator)
- Work through 2nd messengers and G proteins

Second Messengers

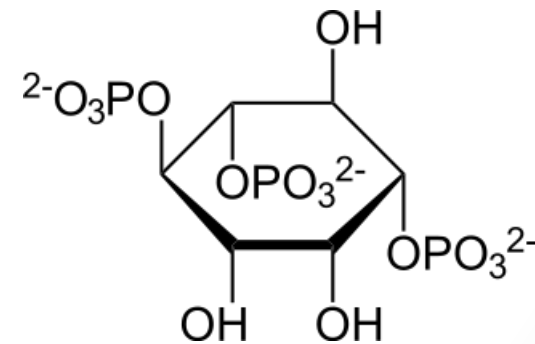
- Three major 2nd messengers: **cAMP, cGMP, IP3**
 - Cyclic AMP
 - Cyclic GMP
 - Inositol trisphosphate



cAMP



cGMP

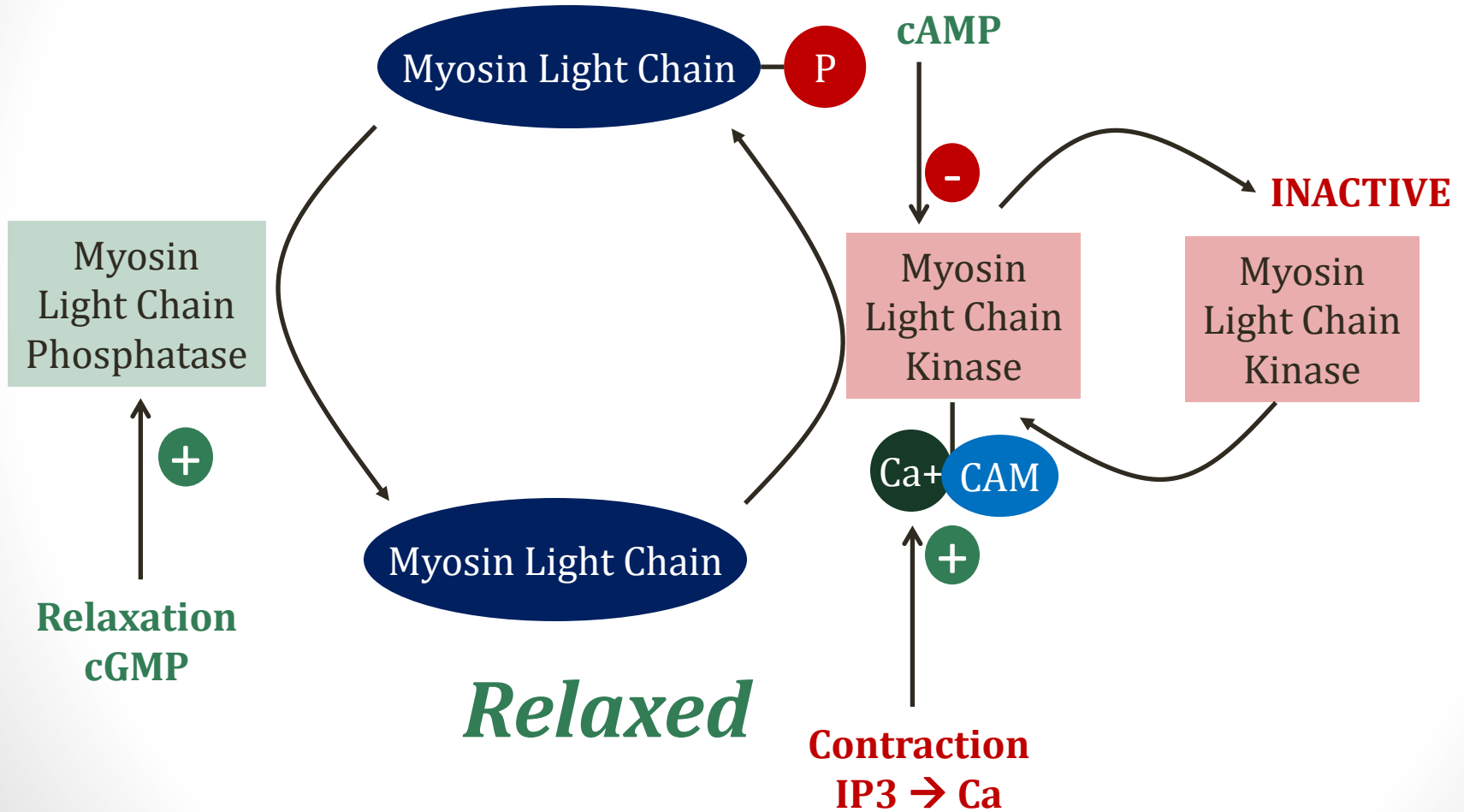


IP3

Second Messengers

- **Calcium**
 - IP₃ → Calcium release from SR → *contraction*
- **Myosin light chain phosphorylation**
 - cAMP → MLC kinase inhibition → *relaxation*
 - cGMP → MLC phosphatase activation → *relaxation*

CONTRACTED



2nd Messengers

- Norepinephrine/epinephrine
 - IP3, cAMP
- Vasopressin
 - IP3
- Adenosine
 - cAMP
- Prostaglandins
 - cAMP

Smooth Muscle Tone

Regulation

Local Signal/Neurotransmitter



Nitric Oxide
G-Proteins

2nd Messenger



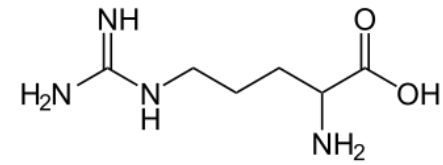
Calcium

MLC Phosphorylation



Tone

Nitric Oxide

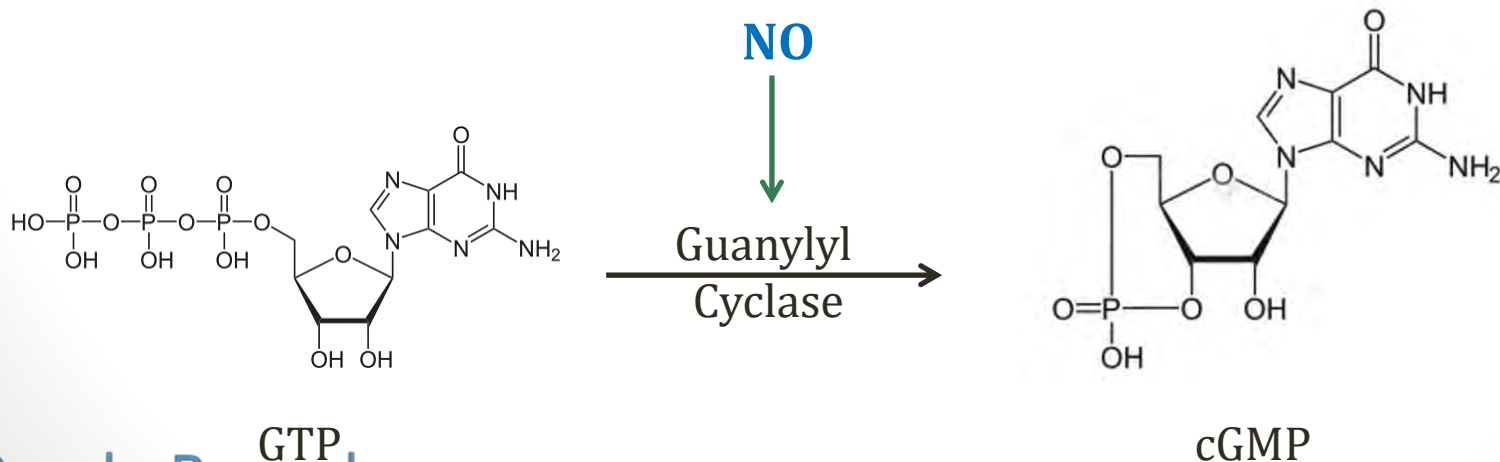


Arginine

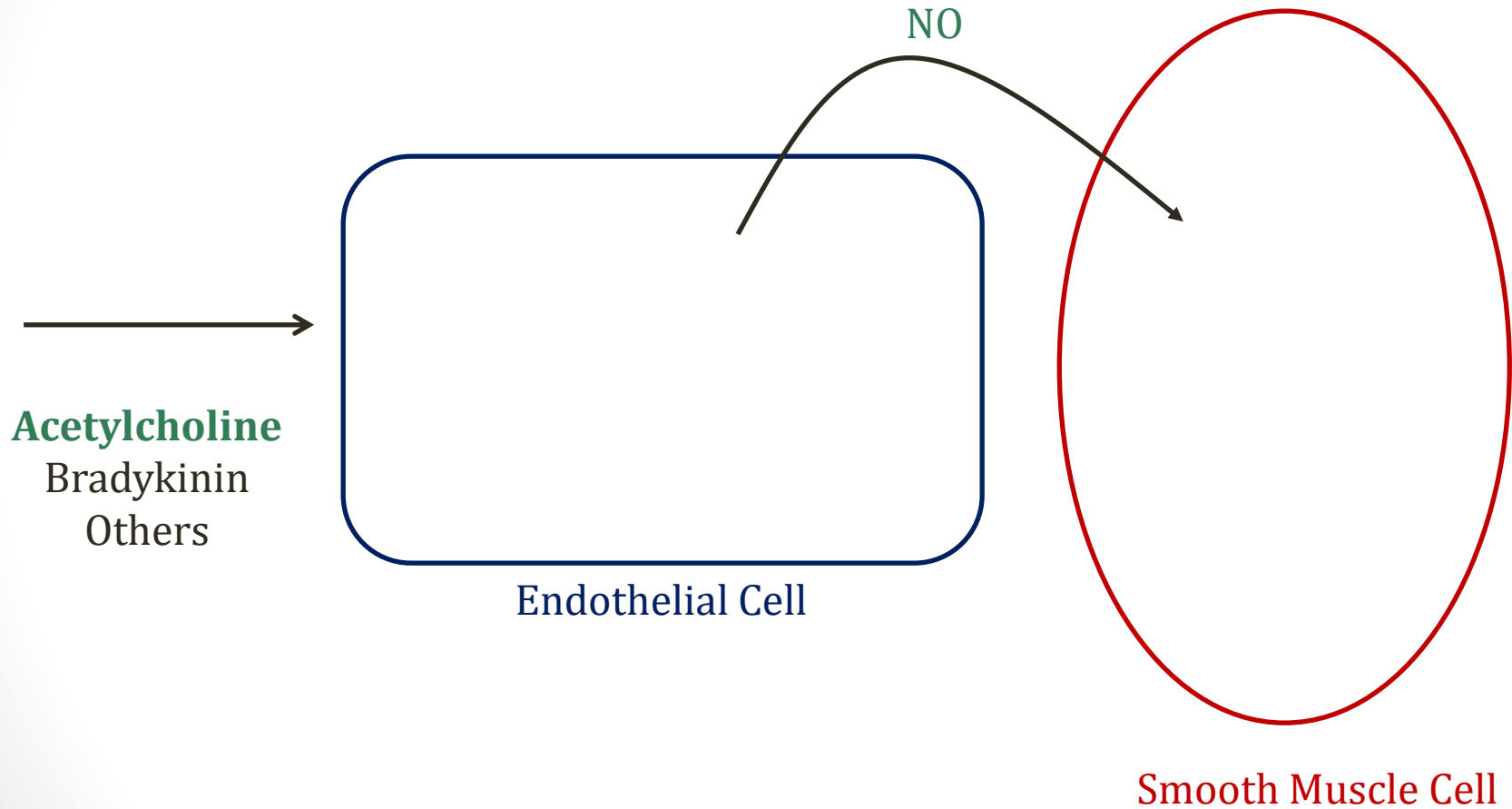
- Also called EDRF
 - Endothelial derived relaxing factor
- Synthesized by **endothelial cells** from **L-arginine**
- Basal production
- Many stimuli for increased production
 - Blood flow/shear stress
 - Acetylcholine
 - Bradykinin
 - Substance-P

Nitric Oxide

- NO diffuses into smooth muscle cells
- Activates guanylyl cyclase
- GTP \rightarrow cGMP
- cGMP \rightarrow + MLC Phosphatase \rightarrow **relaxation**

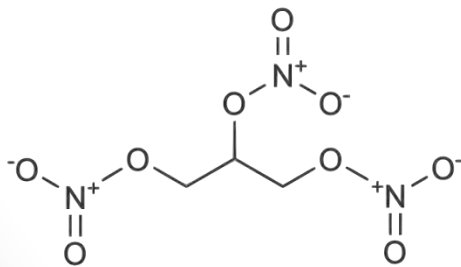


Nitric Oxide

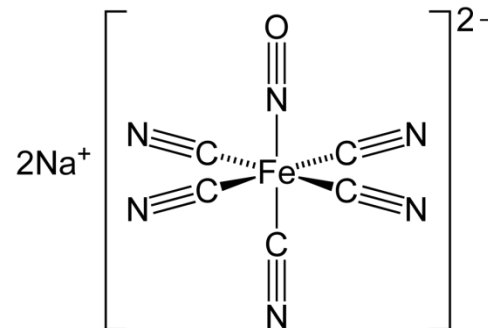


Nitric Oxide Drugs

- Nitroglycerine
 - Vasodilator
 - Angina, heart failure
 - Converted to NO in smooth muscle cells
- Nitroprusside
 - Vasodilator for hypertensive emergency
 - Nitric oxide donor



Nitroglycerine



Nitroprusside

G Proteins

- Activated by neurotransmitters (i.e. epinephrine)
- Transmit signals to smooth muscle cells
- Work through smooth muscle 2nd messengers

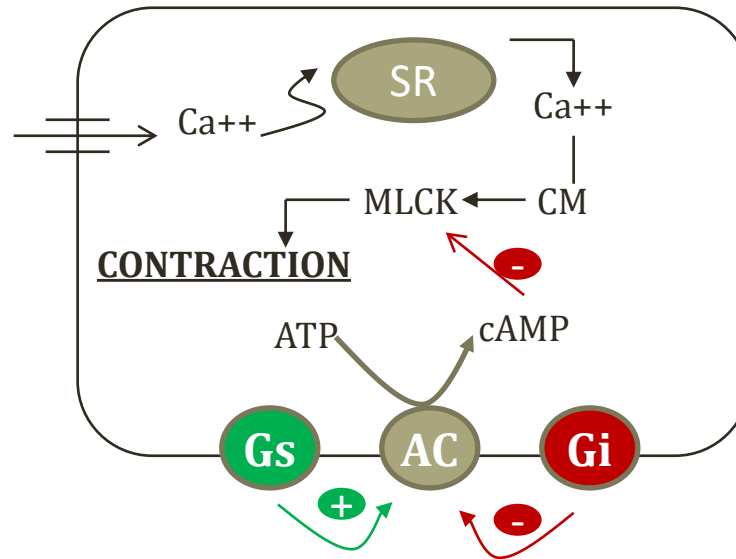
G Proteins

Smooth Muscle Effects

- Gs proteins → relaxation
 - Increase **cAMP**
 - Inhibit MLCK
- Gi proteins → contraction
 - Decrease **cAMP**
- Gq proteins → contraction
 - Increase **IP3**

Gs and Gi Systems

Vascular Smooth Muscle

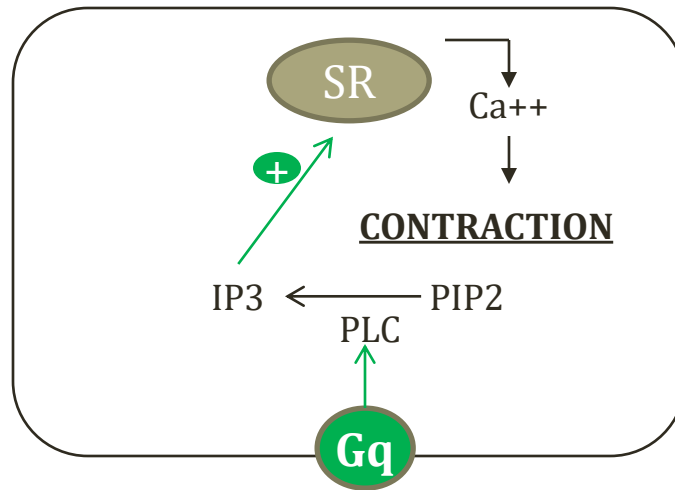


Stimulation (Gs) → Relaxation

Inhibition (Gi) → Contraction

Gq Systems

Vascular Smooth Muscle



Gq → Contraction

G-Protein Systems

Receptor	G protein Class
$\alpha 1$	q
$\alpha 2$	i
$\beta 1$	s
$\beta 2$	s
M1	q
M2	i
M3	q

Bone

Jason Ryan, MD, MPH

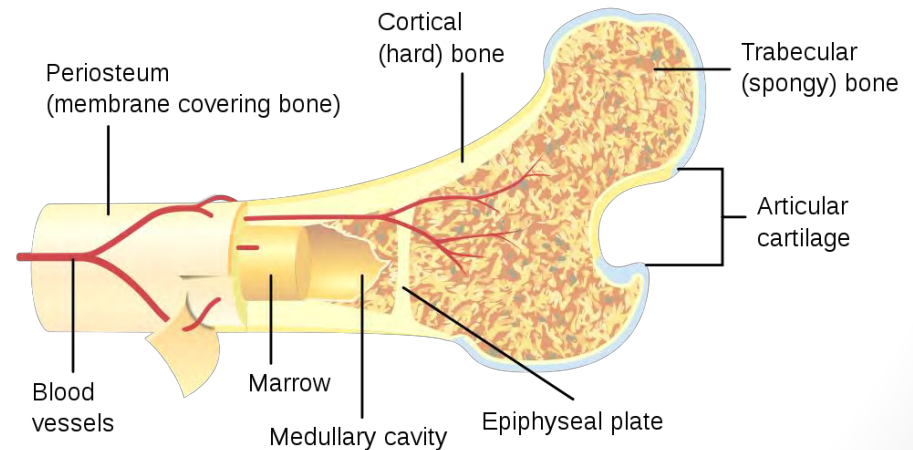
Types of Bones

- Long bones
 - Support weight, allow movement
 - Legs, arms
- Flat bones
 - Protect organs (skull)
- Short bones (wrists, ankle)
- Irregular bones (vertebrae)
- Sesamoid bones
 - Embedded in tendons
 - Patella

Bone

Macroscopic Structure

- Periosteum
 - Membrane
 - Covers outer surface of bones
 - Blood vessels
 - Sensory nerves
- Cortical bone
 - “Compact bone”
 - Hard, exterior bone

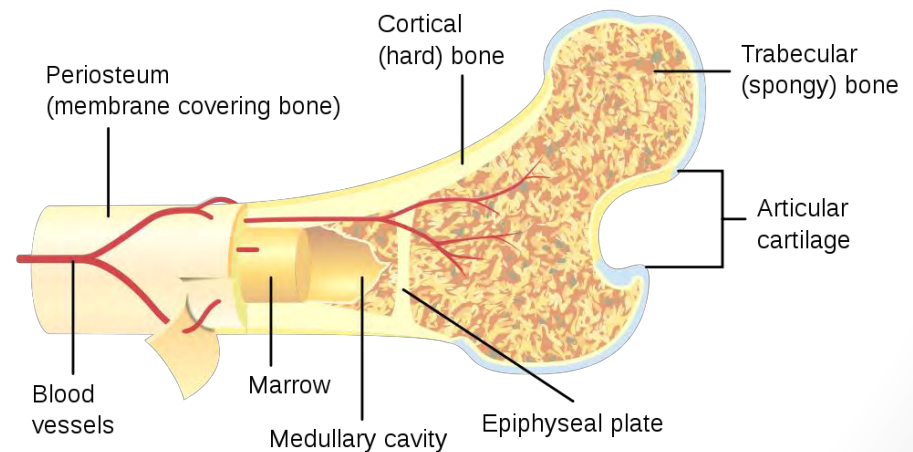


Pbroks13 /Wikipedia

Bone

Macroscopic Structure

- Trabecular bone
 - “Cancellous bone”
 - “Spongy bone”
 - Soft, flexible
 - Found at ends of long bones
 - Trabeculated
 - Lots of surface area
- Medullary cavity
 - Contains marrow

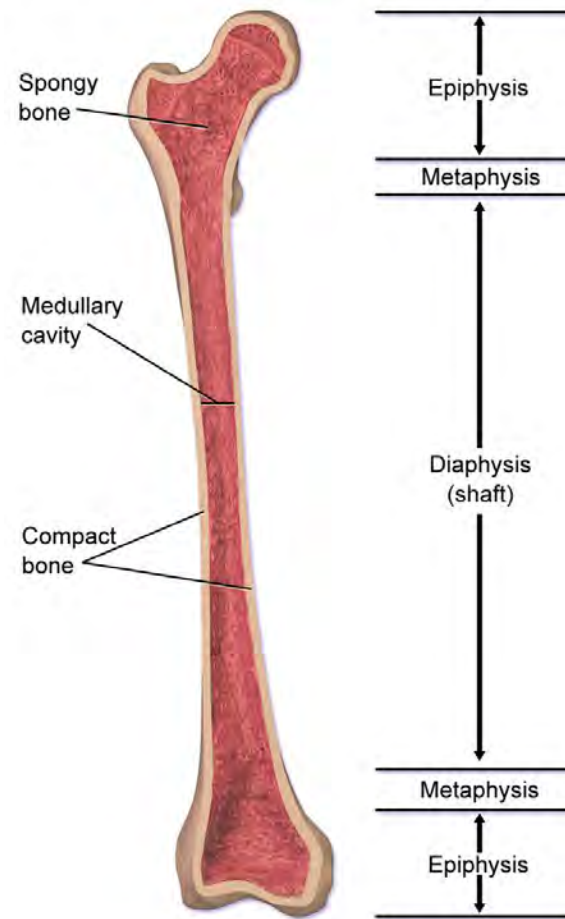


Pbroks13 /Wikipedia



Long Bones

- Epiphysis
 - Covered by cartilage
- Metaphysis
 - Widening
- Diaphysis
 - Shaft



BruceBlaus /Wikipedia

Bone Cells

- Osteoblasts
 - Synthesize bone matrix
- Osteoclasts
 - Specialized macrophages
 - Derived from circulating monocytes
 - Secrete **acid (H+) and proteases**
 - Dissolve bone matrix
- Osteocyte
 - Osteoblasts buried in bone matrix become osteocytes
 - Control local calcium and phosphate levels

Bone Matrix

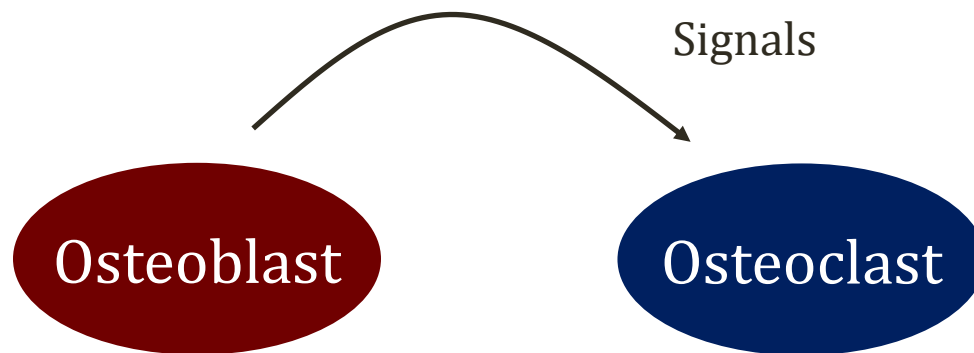
- Extracellular component of bone
- Synthesized by osteoblasts
- **Type I collagen**
- Hydroxyapatite: $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$
- Bone: 99% of body calcium; 85% phosphorus

Bone Matrix

- First synthesized as **osteoid**
 - Non-mineralized bone matrix
 - Mostly proteins
 - Laid down by osteoblasts
- Followed by mineralization with calcium/phosphate

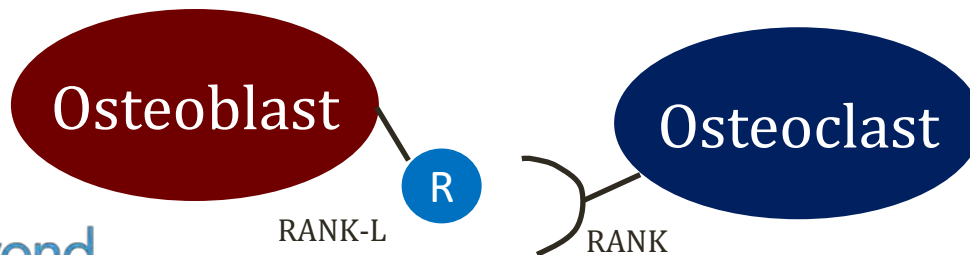
Bone Turnover

- Balance between formation/breakdown
- Modulated by **signals from osteoblasts**
- Some stimulate osteoclasts
- Some limit osteoclasts
- Combination determines formation/breakdown



Bone Turnover

- RANK
 - Receptor activating nuclear factor $\kappa\beta$
 - **Receptor** expressed on surface of **osteoclasts**
 - Ligand binds to receptor \rightarrow synthesis of NF- κ B
 - Osteoclast stimulation
- RANK-L
 - Receptor activating nuclear factor $\kappa\beta$ **ligand**
 - Binds RANK
 - Expressed by osteoblasts

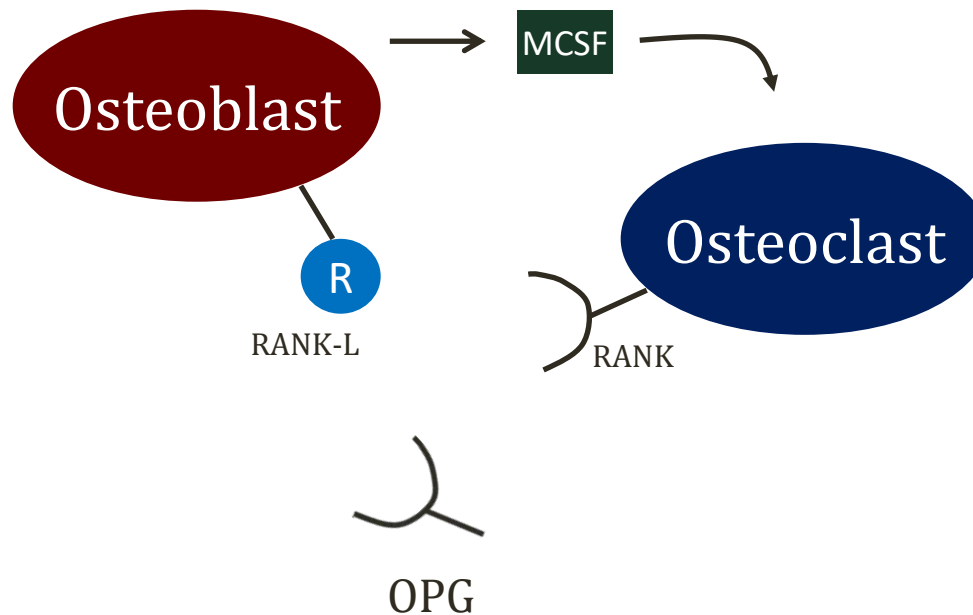


Bone Turnover

- **Osteoprotegerin (OPG)**
 - Decoy receptor for RANK-L
 - Binds RANK-L
 - Prevents RANK-L from binding RANK
 - Made by osteoblasts
- **M-CSF**
 - Macrophage colony stimulating factor
 - Secreted by osteoblasts
 - Stimulates osteoclasts

Bone Formation

More RANK-L/MCSF → More osteoclast activity
More OPG → Less osteoclast activity



Bone Formation

- Endochondral ossification
- Membranous ossification

Endochondral Ossification

- Occurs during embryogenesis
- **Long bones** develop from hyaline cartilage
- Secreted by chondroblasts and chondrocytes
- Cartilage “mold” of bone forms (**anlagen**)
- Growth → chondrocytes die
- Osteoblasts delivered from blood

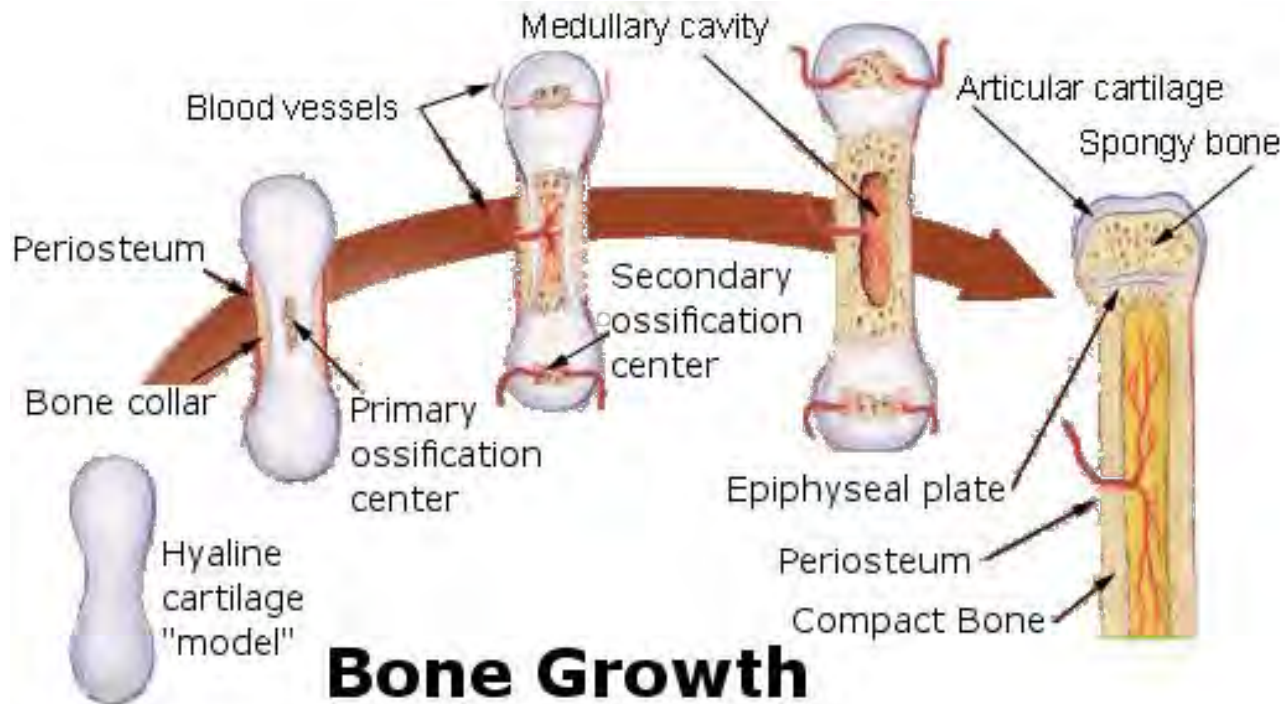


Chaldor/Wikipedia

Endochondral Ossification

- At center (diaphysis)
 - Osteoblasts lay down matrix (“ossification”)
 - “Primary center of ossification”
- At ends (epiphysis)
 - Osteoblasts also lay down matrix
 - “Secondary center of ossification”
- Eventually anlagen (cartilage) trapped
- Forms epiphyseal (growth) plate

Endochondral Ossification



Chaldor/Wikipedia

Growth Plate

Epiphyseal Plate

- Found at ends of long bones
 - Between metaphysis and epiphysis
 - Physis = growth plate
- Contains hyaline cartilage
- Chondrocytes grow toward epiphysis
- Osteoblasts lay down matrix
- Growth toward diaphysis
- Growth plate “closes” at puberty
- Forms epiphyseal line



Gilo1969/Wikipedia

Woven and Lamellar

- First type of bone formed: woven bone
 - Also called primary or immature
 - Disorganized collagen fibers
 - Weaker
- Woven bone later remodeled to lamellar bone
 - Layered bone
 - Organized
 - Stronger
- Woven bone seen in adults **after injury**

Membranous Ossification

- Matrix formed directly
- Not from cartilage
- Osteoblasts lay down woven bone
- Later remodeled to lamellar bone
- Formation of most **flat bones**
 - Calvaria (skull)
 - Facial bones

Achondroplasia

- Most common cause of dwarfism
- Genetic disorder
 - Fibroblast growth factor receptor-3 (FGFR3) gene mutation
 - Most (80%) cases due to **spontaneous mutation**
 - Autosomal dominant
 - Survivors = heterozygous
 - Homozygous = stillborn

Achondroplasia

- Defective **endochondral ossification**
 - Gain-of-function mutation
 - Growth factor activated (turned on)
 - Inhibits chondrocyte proliferation
- Arms, legs short
- Torso, head largely normal



Wikipedia/Public Domain

Mucopolysaccharidoses

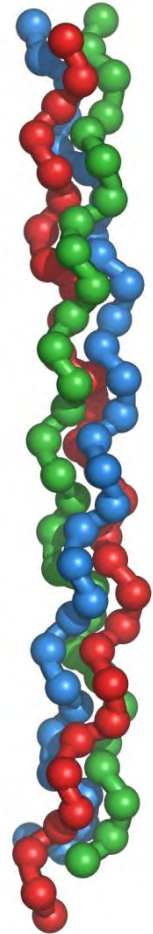
Lysosomal storage diseases

- **Hunter's and Hurler's syndromes**
- Inability to metabolize heparan and dermatan sulfate
- Chondrocytes degrade mucopolysaccharides
- Accumulation → chondrocyte death
- Short stature, malformed bones common

Osteoblasts

Activity Markers

- **Alkaline phosphatase**
- Osteocalcin
 - Major non-collagen protein in bone matrix
- Type I procollagen
 - Three pro-alpha chains
 - Secreted from osteoblasts
 - Forms tropocollagen and collagen



Vossman

Alkaline Phosphatase

- Enzyme found in bone and liver (different forms)
- Also a placental form
 - Placental alkaline phosphatase (PALP)
 - Seen in some germ cell tumors
- Major protein present in bone tissue
- Bound to osteoblasts and free
- Creates **alkaline environment** for calcium deposition

Acidosis

- Stimulates osteoclasts
- May cause hypercalcemia from bone breakdown
- May reduce bone mineral density
- Complication of some RTAs



Parathyroid Hormone

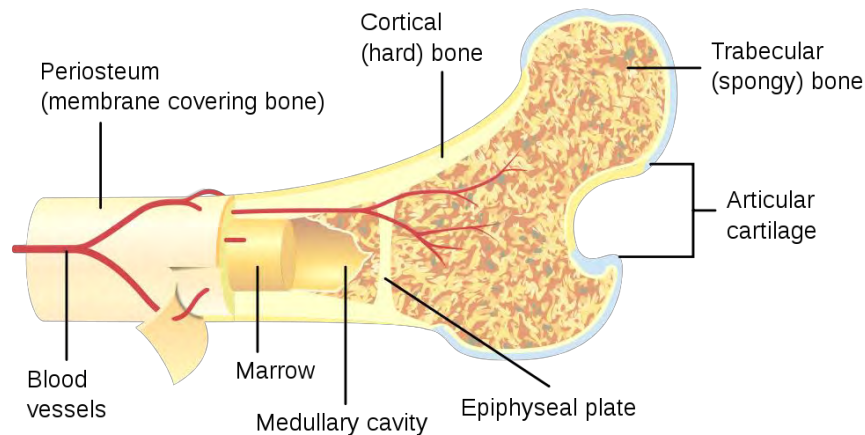
- Multiple effects on bone
- Stimulates bone **resorption and formation**
- Dominant effect varies with dosage/timing

Parathyroid Hormone

- Continuous administration of PTH
 - Bone resorption → ↑ serum calcium
 - Important physiologically
- Low dose once daily bolus administration
 - Increased bone mass (bone formation)
 - **Teriparatide** used to treat osteoporosis

Parathyroid Hormone

- Cortical bone
 - ↓ in response to continuous PTH
- Trabecular bone
 - ↑ in response to intermittent, low dose PTH
 - Teriparatide strengthens spine (lots of trabecular bone)



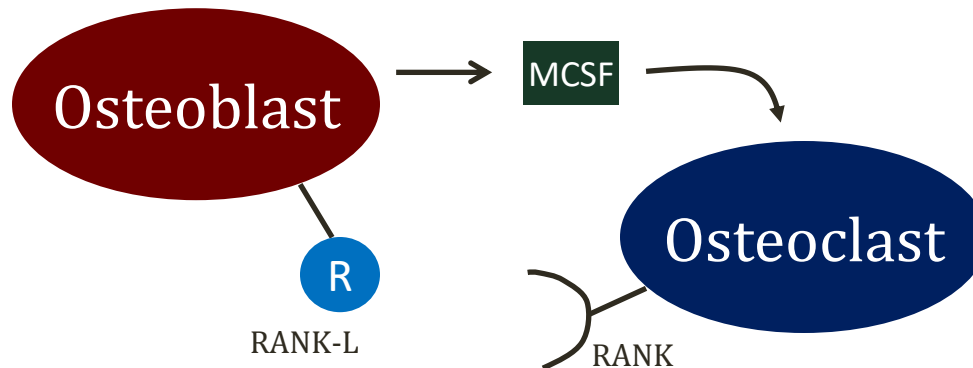
Pbroks13/Wikipedia

Parathyroid Hormone

- **Osteoblasts**
 - Contain PTH receptors
 - Can ↑ bone mass in response to PTH
- **Osteoclasts**
 - No PTH receptors
 - Activated indirectly by osteoblasts

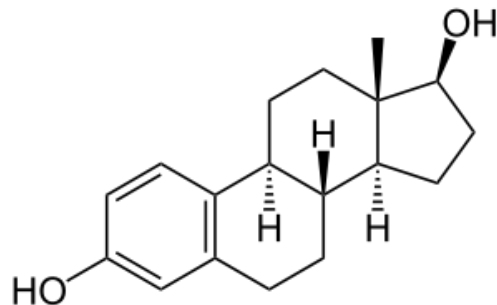
Parathyroid Hormone

- **M-CSF**
 - Secreted by osteoblasts
- **RANK-L**
 - Expressed on surface of osteoblasts
- Both produced by osteoblasts → activate osteoclasts



Estrogens

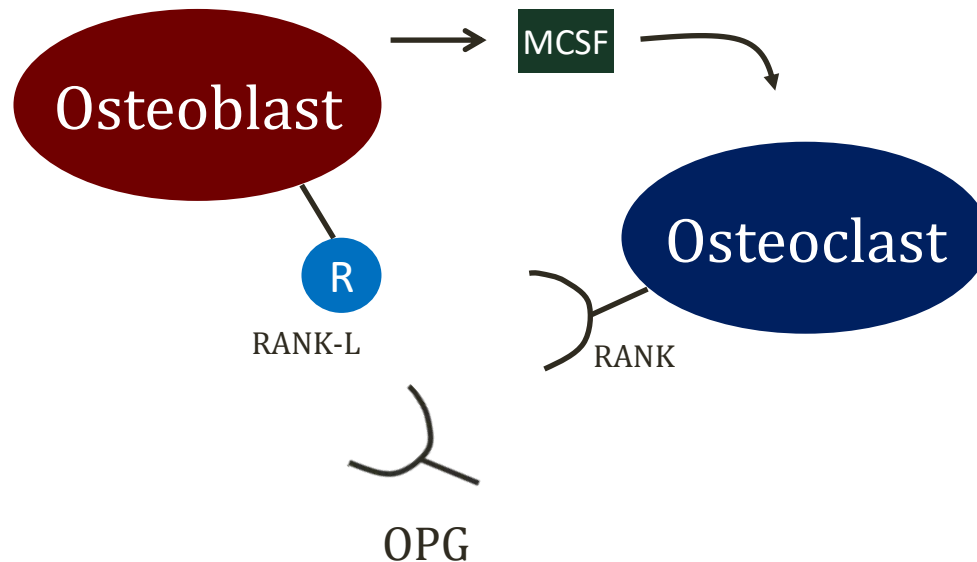
- Numerous effects on bone
- **Close growth plate at puberty**
- **Increase bone density**
- Loss of estrogen at menopause → osteoporosis



Estradiol
(17β-estradiol)

Estrogens

- Induce apoptosis of osteoclasts
- Stimulate OPG synthesis by osteoblasts
 - More OPG → Less osteoclast activity
- Decrease M-CSF and RANK production



Bone Disorders

Jason Ryan, MD, MPH

Bone Disorders

- Osteoporosis (thin bones)
- Osteopetrosis (thick bones)
- Rickets/Osteomalacia (nutritional bone disorders)
- Paget's disease (↑ bone turnover)

Osteopetrosis

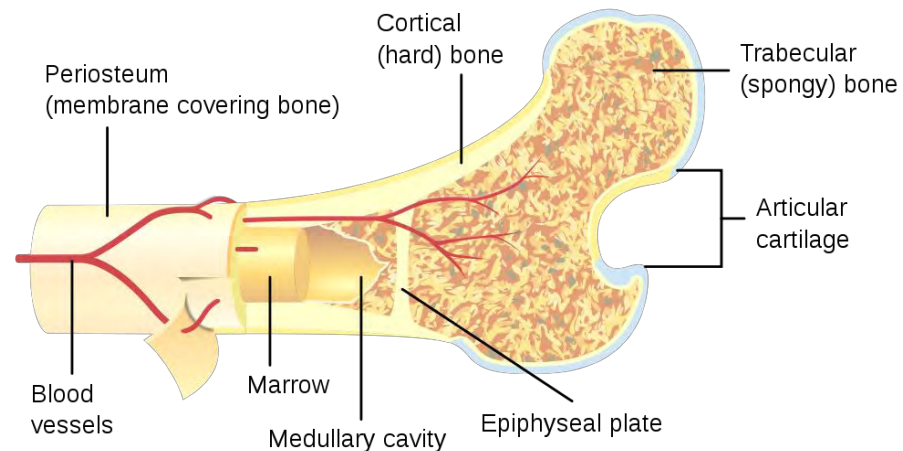
- Defective **osteoclast activity**
- Osteoblastic activity \gg osteoclastic activity
- **Increased** bone density

Osteopetrosis

- Autosomal recessive (infantile) form
 - Most severe form
 - Presents in infancy
 - Mutations in **carbonic anhydrase type II gene**
 - Also may have renal tubular acidosis
 - Children may have seizures, intellectual disability
- Autosomal dominant form
 - Albers-Schönberg disease
 - Presents in adolescence
 - Milder form of disease
 - May be asymptomatic – identified by x-ray

Osteopetrosis

- **Bones prone to fracture**
- Excess bone → loss of bone marrow
 - **Pancytopenia**
 - Enlarged liver and spleen (extramedullary hematopoiesis)
- Excess bone in skull → **cranial nerve compression**
 - Vision loss
 - Deafness
 - Facial paralysis
- Hydrocephalus



Pbroks13 /Wikipedia

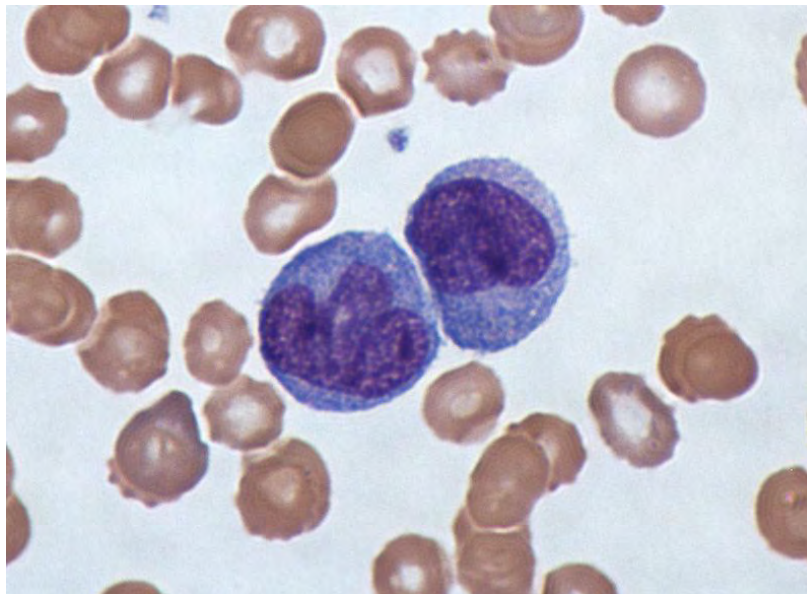
Osteopetrosis



Konstantinos et al. Rare causes of scoliosis and spine deformity, 10.1186/1748-7161-2-15

Osteopetrosis

- Potentially curable with **bone marrow transplant**
- Used for infantile form
- Osteoclasts derived from monocytes/macrophages



Dr Graham Beards/Wikipedia

Rickets and Osteomalacia

- Nutritional bone disorders
- **Low calcium or vitamin D intake**



Feedmystarvingchildren/Flickr

Rickets and Osteomalacia

- Poor mineralization of **osteoid**
 - Non-mineralized bone matrix
 - Mostly proteins
 - Laid down by osteoblasts
 - Later mineralized with calcium and phosphate
- Sites of osteoid and new bone growth:
 - Children: Growth plates
 - Children and adults: Bone turnover

Growth Plates

- Found at ends of long bones in children
- Contains hyaline cartilage
- Chondrocytes grow toward epiphysis
- Osteoblasts lay down matrix toward diaphysis



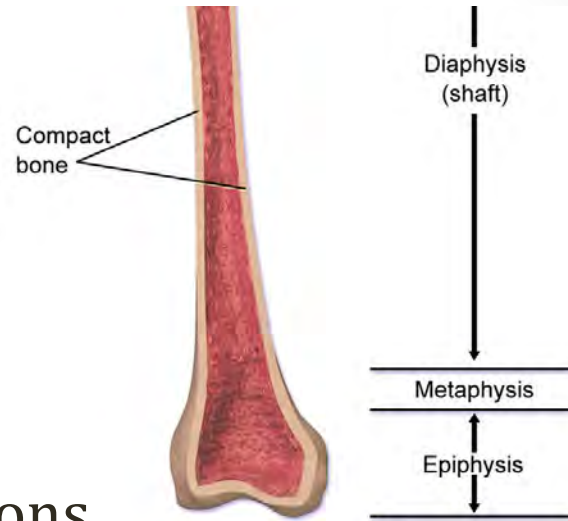
Gilo1969/Wikipedia

Rickets

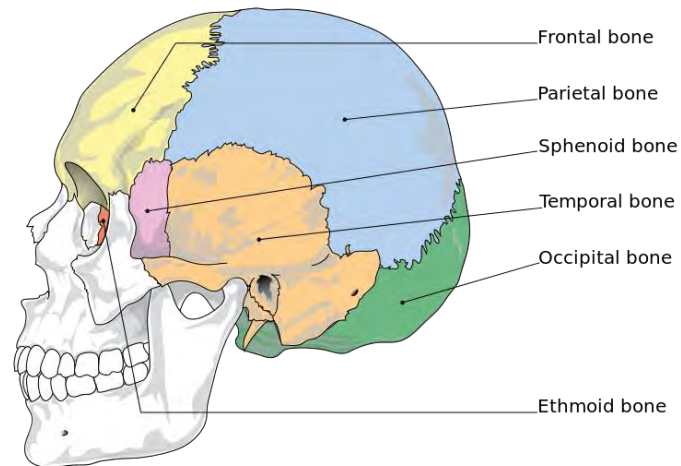
- **Growth plate thickens**
 - Chondrocytes expand (disorganized growth)
 - Osteoblasts lay down **osteoid only**
- Bone thickening from **osteoid accumulation**
- Distorted bone growth

Rickets

- Epiphyseal widening
- Bowed legs (genu varum)
- Swelling at costochondral junctions
 - Rachitic rosary
- Craniotabes (soft skull)
 - Occipital/parietal bones
 - Collapse with pressure



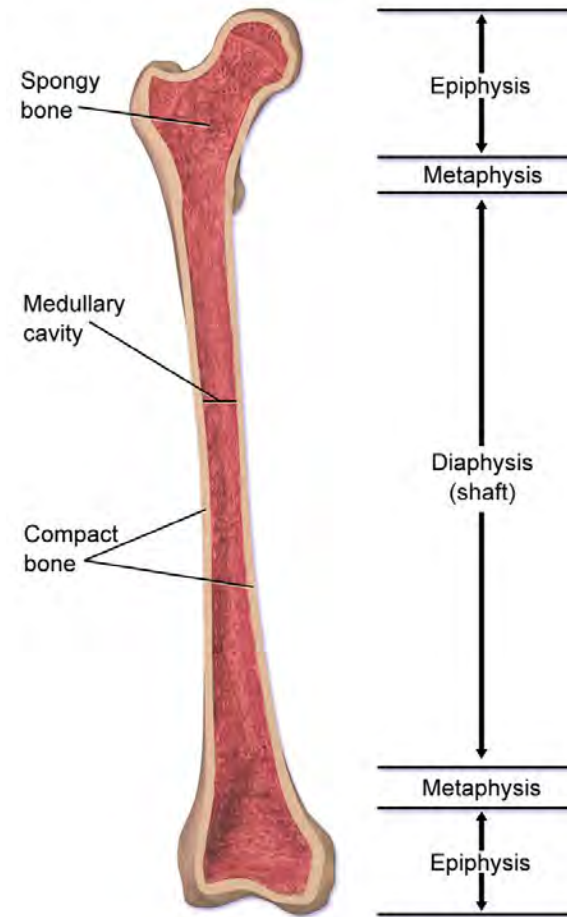
BruceBlaus /Wikipedia



Epiphyseal Widening

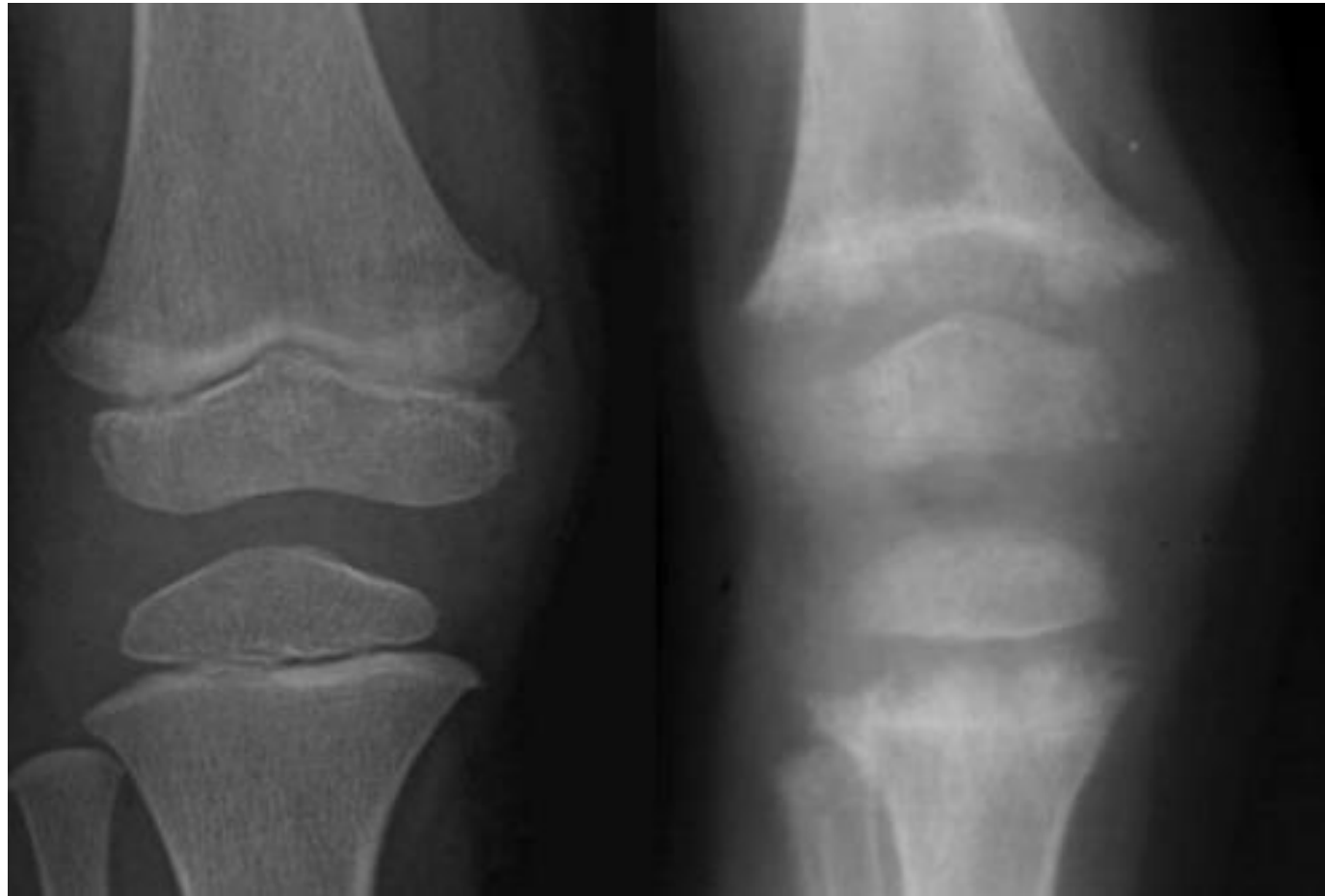


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BruceBlaus /Wikipedia

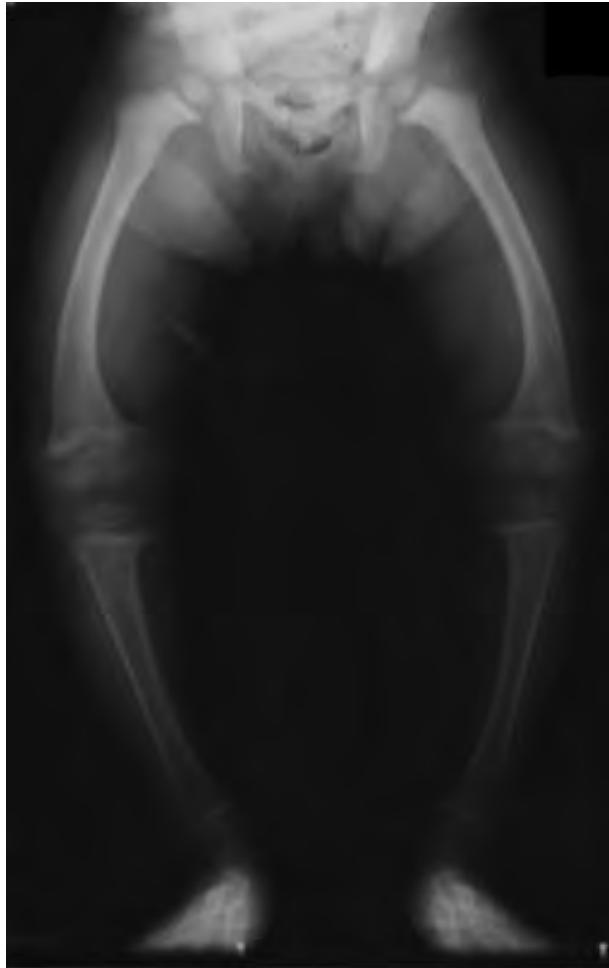
Growth Plate Fraying



Normal

Rickets

Genu Varum



Michael L. Richardson, M.D./Wikipedia

Rachitic Rosary



Ma Wady/Public Domain



Frank Gaillard/Wikipedia

Osteomalacia

- Children and adults
- Occurs in areas of bone turnover
- **Bone pain**/tenderness
- Most often spine, pelvis, and legs
- Fractures

Osteomalacia

- Two classic x-ray findings:
 - Pseudofractures
 - Looser Zones
- Caused by:
 - Repaired stress fractures, inadequately mineralized
 - Erosion of bone by arterial pulsations

Pseudofracture



CalgaryCentre/Slideshare

Looser Zone



Pintrest/Public Domain

Rickets and Osteomalacia

Causes

- Vitamin D deficiency
 - Maternal deficiency during pregnancy
 - Reduced sun exposure
 - Fat malabsorption
 - Cystic fibrosis, pancreatitis, Celiac disease, IBD
 - Liver and renal failure (both activate vitamin D)
- Calcium deficiency (rare)
 - Only seen with severe dietary deficiency
- Treatment: **Vitamin D and Ca supplementation**

Rickets and Osteomalacia

Lab Findings

- ↓ Calcium
- ↓ Vitamin D

Vitamin D

- Liver: 25-OH Vitamin D (calcidiol)
- Kidney: 1,25-OH₂ Vitamin D (calcitriol; active form)
- 25-OH Vitamin D = storage form
 - Constantly produced by liver
 - Available for activation by kidney as needed
- Serum **25-OH VitD** best indicator vitamin D status
 - Long half-life
 - Liver production not regulated by PTH

Rickets and Osteomalacia

Lab Findings

- ↑ Parathyroid hormone (PTH)
 - Normal response of parathyroid gland
- ↓ Phosphate
 - Excretion promoted by PTH
- ↑ Bone alkaline phosphatase
 - ↑ osteoblast activity

Paget's Disease

Osteitis Deformans

- **Focal** disorder
- Common in **older patients**
 - Average age at diagnosis: 70

Paget's Disease

Osteitis Deformans

- Excessive bone remodeling
- Overgrowth of bone at focal sites of bone
- New bone: abnormally large, deformed
- Exact cause unknown
- Believe to be due to abnormal **osteoclasts**

Paget's Disease

Osteitis Deformans

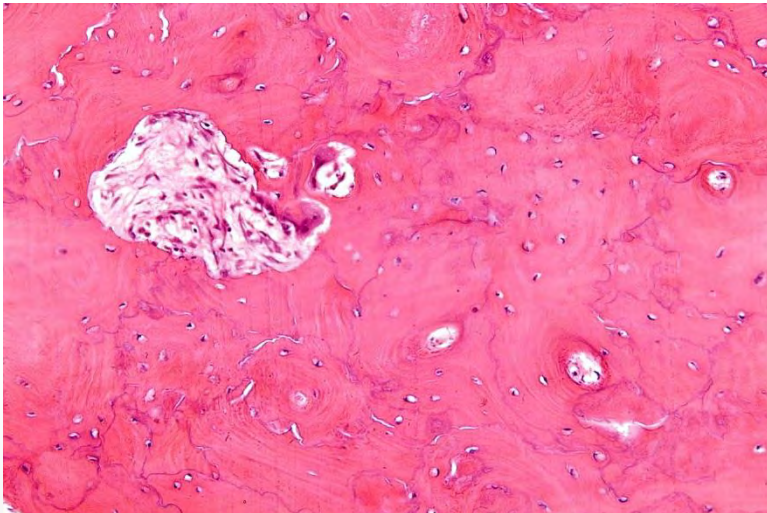
- Evolves through phases/stages
- Initial phase: **osteolytic**
 - Osteoclasts breakdown bone
 - Bizarre shape, numerous
 - Multi-nucleated
- Mixed phase: osteolytic-osteoblastic
- Final phase: Osteosclerotic
 - Bone formation dominates
 - **Hypervascularity** of bone occurs

Paget's Disease

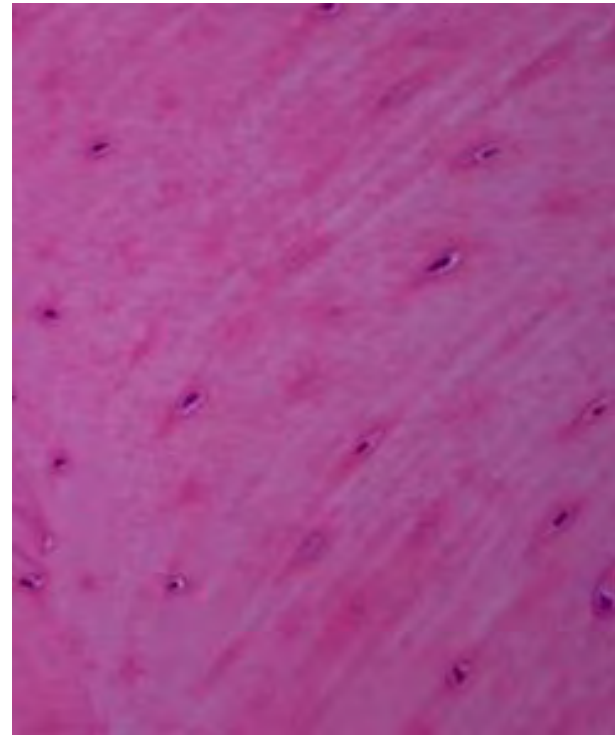
Bone Morphology

- Hallmark: mosaic pattern of lamellar bone
- Cement lines

Paget's



Normal



Nephron/Wikipedia

Paget's Disease

Clinical Features

- May be asymptomatic
- Often affects long bones, skull, spine
- Pathologic fractures (most common complication)
 - “Chalkstick” fracture
- Bone pain (microfractures)
- Bowing of legs

Chalkstick Fracture



Hellerhoff/Wikipedia

Paget's Disease

Clinical Features

- Enlarged skull (increased hat size)
- Cranial nerve compression (deafness)
- Radiculopathy at spine
- Erythema may occur over affected bone area
 - Due to hypervascularity

Paget's Disease

Clinical Features

- **High output heart failure**
 - AV fistula in new bone
- Osteosarcoma
 - Increased risk in Paget's disease

Paget's Disease

Clinical Features

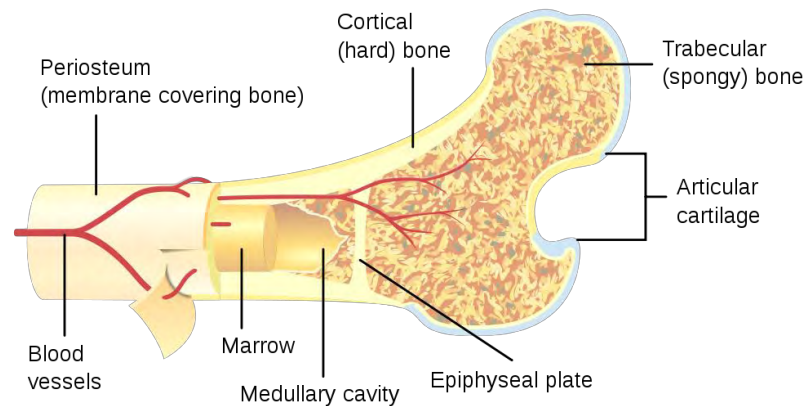
- Increase **bone alkaline phosphatase**
- Treatment: bisphosphonates and calcitonin

Osteitis Fibrosa Cystica

- Classic bone disease of **hyperparathyroidism**
- Clinical features: Bone pain and fractures
- Parathyroid adenoma
 - ↑ PTH
 - **Hypercalcemia**
 - ↓ Phosphate

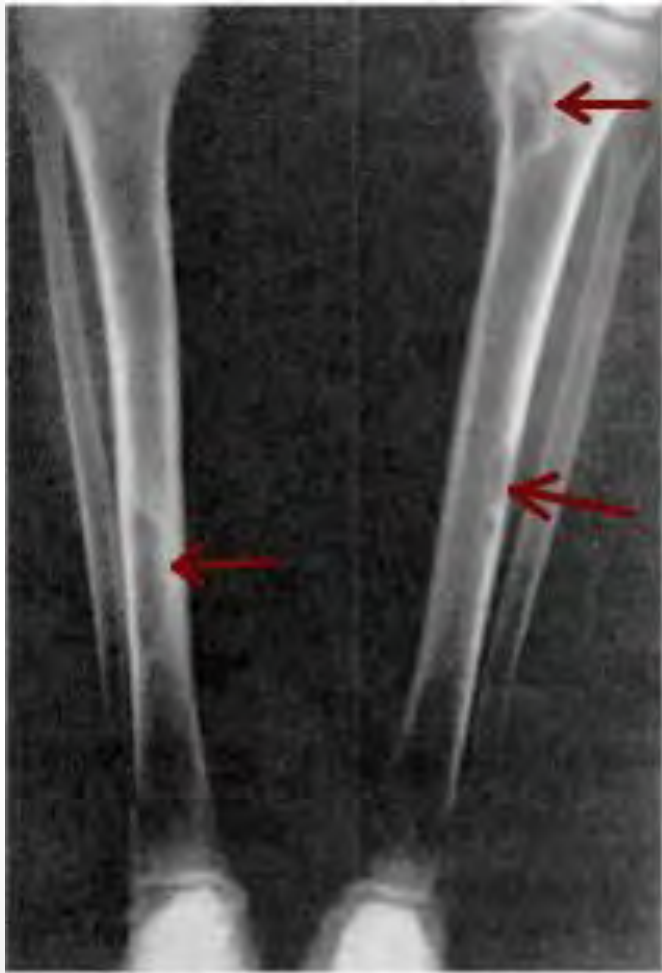
Osteitis Fibrosa Cystica

- **Subperiosteal** bone resorption
 - Commonly seen in bones of fingers
 - Irregular or indented edges to bones
- **Brown tumors** (osteoclastoma)
 - Collections of giant osteoclasts in bone
 - Mixed with stromal cells and matrix proteins
 - Appear as black spaces in bone on x ray



Pbroks13 /Wikipedia

Osteitis Fibrosa Cystica

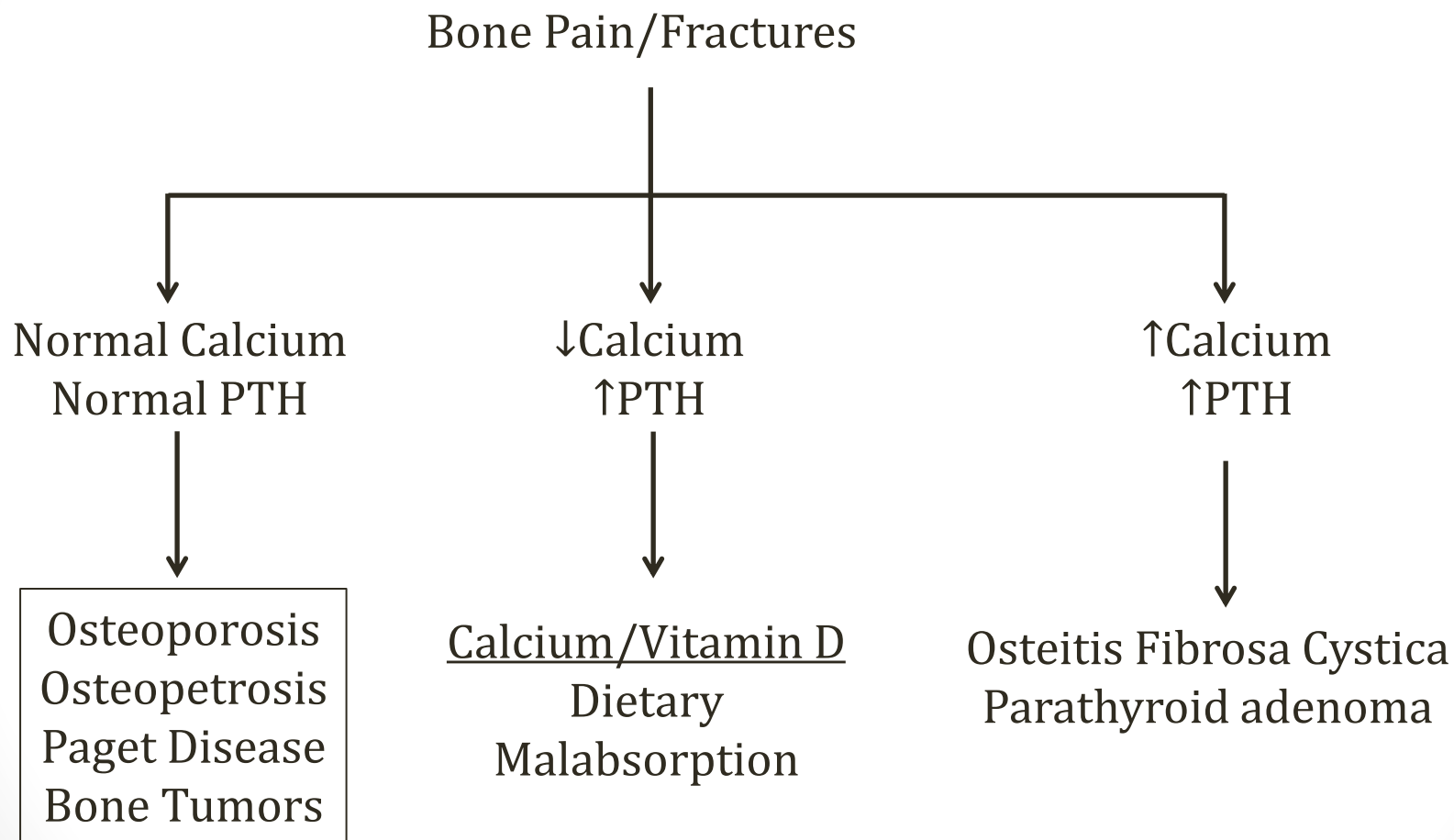


Frank Gaillard/Wikipedia

Renal Osteodystrophy

- Bone abnormalities seen in renal failure
- Hypocalcemia
- Hyperparathyroidism
- Osteitis Fibrosa Cystica
- Rickets/osteomalacia
- Osteopenia/osteoporosis
- Growth retardation
- Bone pain
- Fractures

Bone Pain/Fractures



Osteoporosis

Jason Ryan, MD, MPH

Osteoporosis

- Porous bone
- **Weak bones** prone to fracture
- No clinical symptoms until fracture



Normal bone



Osteoporosis

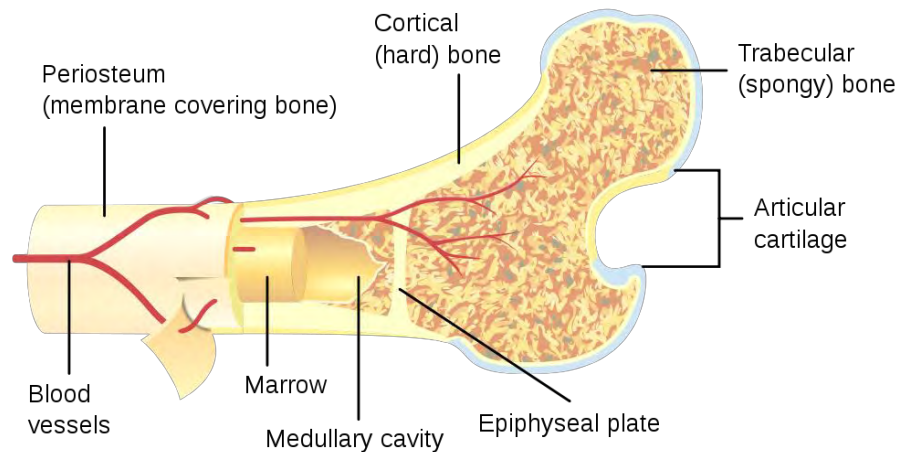
BruceBlaus/Wikipedia

Terminology

- Osteopenia: ↓ bone mass
- Osteoporosis: markedly ↓ bone mass
- Osteoporosis associated with ↑ fracture risk

Osteoporosis

- Trabecular bone > cortical bone
 - Trabecular bone: high surface area
 - Osteoblasts/osteoclasts found on surface
- High trabecular bone content:
 - Spine
 - Head of femur (hip)
 - Wrist (distal radius)



Osteoporosis

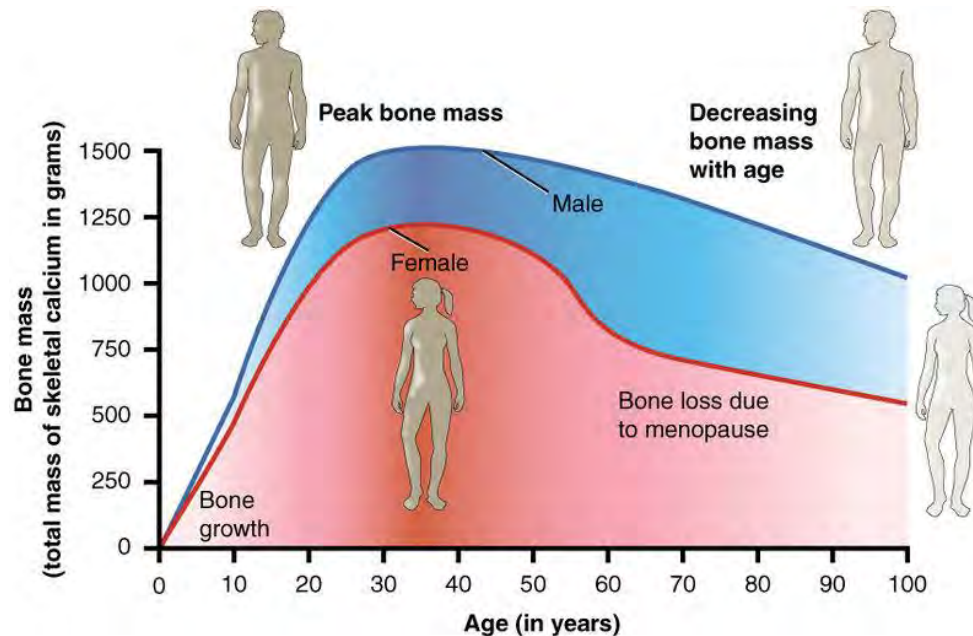
- Common in elderly, white women



Dr. Ryan's Grandmother

Bone Mass

- Peak bone mass occurs in young adulthood
 - Many influences: gender, genetics, diet
- Decreases slowly thereafter
 - Each resorption/formation cycle → some bone loss



Bone Loss

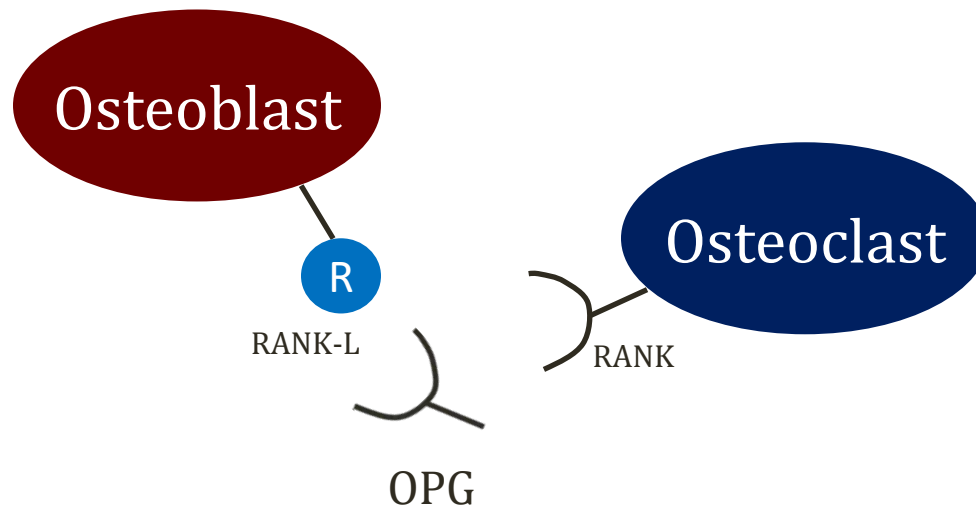
- Males achieve higher peak bone mass
- Bone loss less likely to lead to osteoporosis
- Whites > African Americans
- **Weight-bearing activity** → ↑ bone mass



Everkinetic/Wikipedia

Menopause

- Accelerates bone loss in women
- Caused by **estrogen deficiency**
 - **Increased osteoclast activity**
 - Increased levels of RANK-L
 - Decreased osteoprotegerin (OPG)



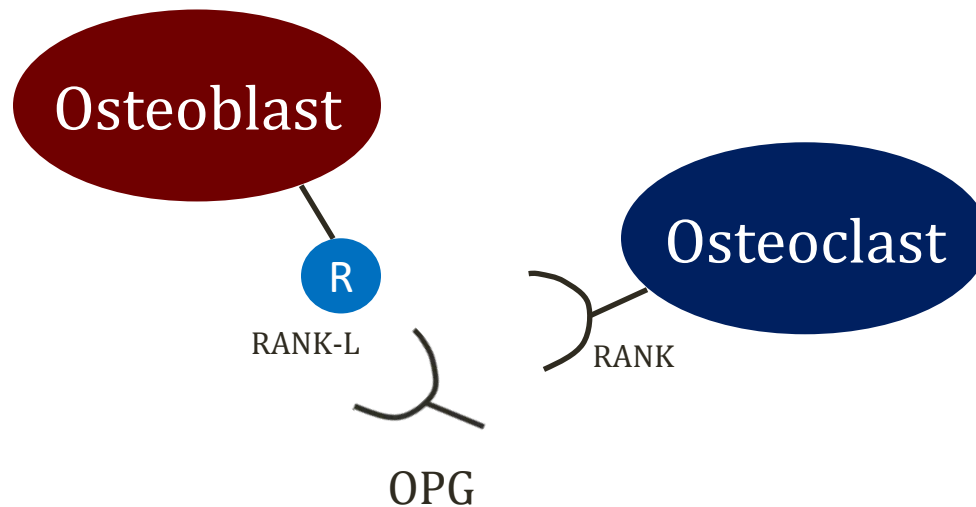
Osteoporosis

- Most osteoporosis: senile/postmenopausal
- **Calcium, PTH, Alkaline phosphatase all normal**
- Less commonly: **secondary** osteoporosis

Osteoporosis

Secondary Causes

- **Glucocorticoids**
 - Increase bone resorption
 - Reduce bone formation
 - Suppress synthesis of OPG
 - Increase RANK production



Osteoporosis

Secondary Causes

- Alcohol
 - Heavy use associated with osteoporosis
 - Often leads to falls/hip fracture
 - Moderate use effects not clear
- Smoking
 - Accelerates bone loss



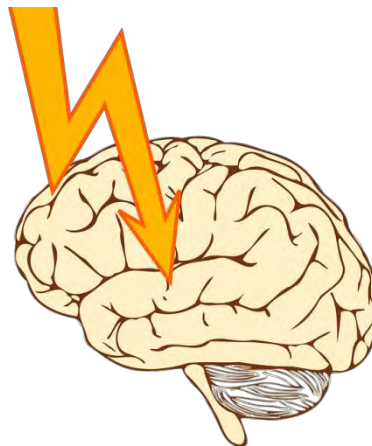
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Anticonvulsants

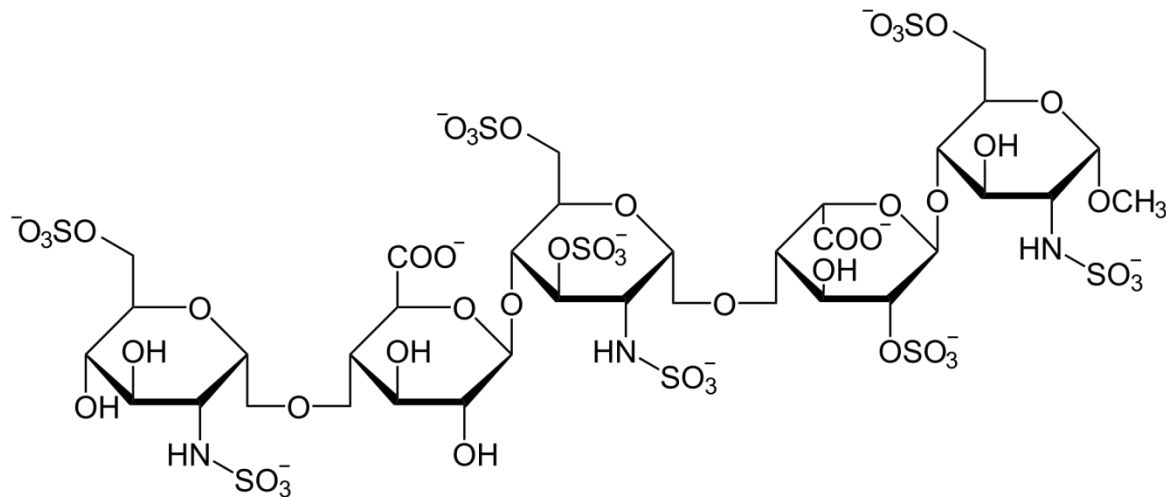
- **Phenobarbital, Phenytoin, Carbamazepine**
- Used to treat seizures/epilepsy
- Risk of osteoporosis with long term therapy
- Increase activity of **P450 enzymes**
- Increases breakdown of vitamin D
- Less calcium → increased PTH → bone loss



Pixabay/Public Domain

Anticoagulants

- **Unfractionated Heparin**
 - Decreases bone formation
 - Increases resorption
- Only with long term use
- Low molecular weight heparin: unclear bone effects



Unfractionated Heparin

Thyroid Replacement

- **Hyper**thyroidism → osteoporosis/fractures
- Levothyroxine (T4) used in **hypo**thyroidism
- Too high dose → **iatrogenic hyperthyroidism**
 - If mild may produce no symptoms
- Key test: TSH
- If TSH is low (“suppressed”) need to lower dose
- Many elderly, post-menopausal women take T4

Osteoporosis

Secondary Causes

- Hyperparathyroidism
- Hyperthyroidism
- Multiple myeloma
 - Myeloma cells → Increase osteoclast activity
 - Results in “lytic” bone lesions of MM
- Malabsorption syndromes
 - Celiac disease, Crohn’s, Ulcerative Colitis
 - Poor absorption calcium and vitamin D

Osteoporosis

Diagnosis

- **Fragility fracture**
 - Fall from standing height or less
 - Not from major trauma (i.e. MVA)
 - Spine, hip, wrist, humerus, rib, or pelvis
 - Also a spontaneous vertebral “compression” fracture
- **T score of -2.5 or lower**

DXA

Dual-energy X-ray absorptiometry

- Two X-rays of different energy levels aimed at bones
- **T score**: patient BMD vs. healthy 30-year-old BMD
- Normal: -1.0 or higher (least fractures)
- Osteopenia: -1.0 to -2.5
- Osteoporosis: -2.5 or lower (most fractures)
- Recommended for **screening in women >65**



Nick Smith photography/Wikipedia

Fractures

- Hip
 - Weight-bearing joint
 - Easily injured from fall
- Spine
 - Lower thoracic/lumbar spine
 - “Compression” fractures
 - Often occur slowly over time
 - Minor trauma of daily activities
 - **Loss of height**
 - Kyphosis (forward curved spine)
 - Back pain



James Heilman/Wikipedia

Osteoporosis Drugs

Jason Ryan, MD, MPH

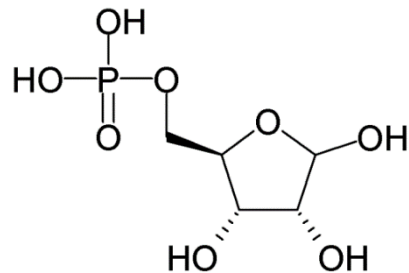
Osteoporosis Therapy

- All patients: lifestyle modification
- Weight-bearing exercise
- Avoidance of heavy alcohol use
- Smoking cessation
- Calcium and vitamin D supplementation

Bisphosphonates

Alendronate, Pamidronate, Ibandronate, Zoledronate

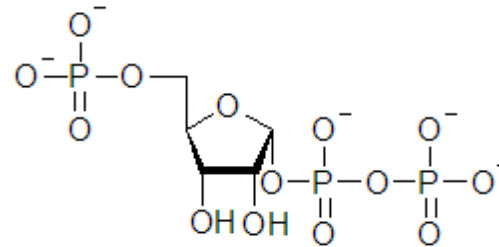
- First line therapy
- Analogs of **pyrophosphate**
- Used to make nucleotides
 - Pyrimidines/purines
 - Purines: ATP, GTP
 - Pyrimidines: Uridine, Cytidine, Thymidine



Ribose 5-phosphate



Purine Synthesis

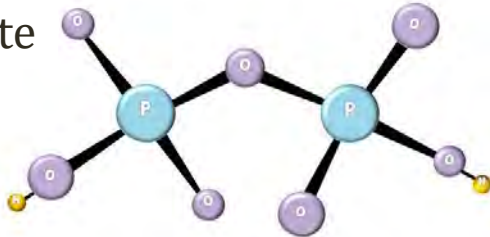


5-Phosphoribosyl-1-pyrophosphate
(PRPP)

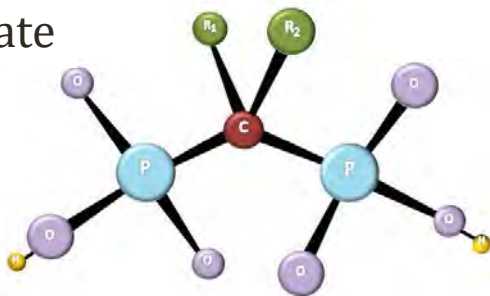
Bisphosphonates

- Two phosphonate (PO_3) groups attached to carbon
- Vary by side chains (R_1 and R_2)
- Oral and IV drugs

Pyrophosphate



Bisphosphonate



Wikipedia/Public Domain

Agent	R_1 side chain	R_2 side chain
Etidronate	-OH	$-\text{CH}_3$
Clodronate	-Cl	-Cl
Tiludronate	-H	$-\text{S}-\text{C}_6\text{H}_4-\text{Cl}$
Pamidronate	-OH	$-\text{CH}_2-\text{CH}_2-\text{NH}_2$
Neridronate	-OH	$-(\text{CH}_2)_5-\text{NH}_2$
Olpadronate	-OH	$-(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$
Alendronate	-OH	$-(\text{CH}_2)_3-\text{NH}_2$
Ibandronate	-OH	$-\text{CH}_2-\text{CH}_2-\text{N} \begin{cases} \text{CH}_3 \\ (\text{CH}_2)_4-\text{CH}_3 \end{cases}$
Risedronate	-OH	
Zoledronate	-OH	

Bisphosphonates

- Phosphonate groups bind calcium
- Accumulate in bone
- Taken up by osteoclasts
- **Inhibit osteoclasts**
- Various mechanisms depending on drug/side chain

Bisphosphonates

Adverse Effects

- Oral drugs (Alendronate, Risedronate)
 - Upper GI upset
 - Reflux, esophagitis, esophageal ulcers
 - Local effects of bisphosphonates on mucosa
 - Often taken weekly
 - **Take with water on empty stomach**
 - **Remain upright for 30 minutes**

Bisphosphonates

Adverse Effects

- IV drugs (Pamidronate, Ibandronate, Zoledronate)
 - **Flu-like symptoms**
 - 24 to 72 hours after infusion
 - Low-grade fever, myalgias
 - Treated with ibuprofen and acetaminophen
 - Long dosing intervals: 3-months to annually

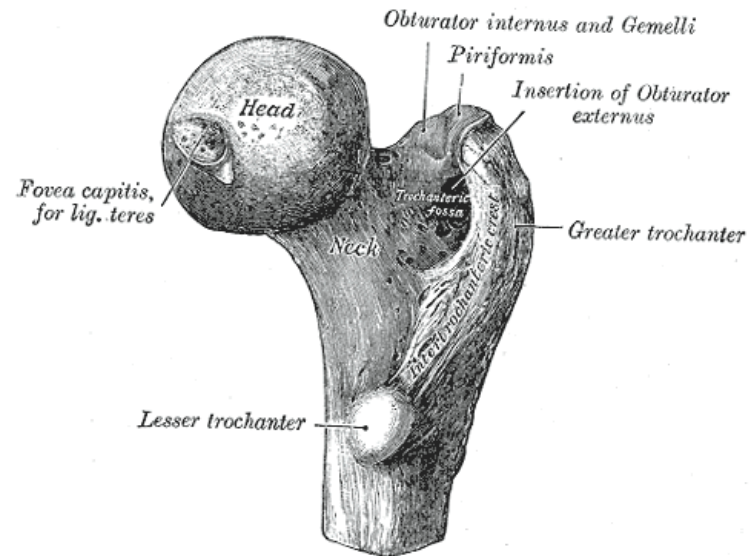
Bisphosphonates

Adverse Effects

- Atypical femur fractures
- Osteonecrosis of the jaw
- Rare, serious complications
- Associated with IV and oral drugs

Atypical Femur Fractures

- Most hip fractures:
 - Intracapsular (femoral neck or head)
 - Trochanteric
 - Associated with trauma
- Atypical fractures
 - Below lesser trochanter
 - Diaphyseal (femoral diaphysis)
 - No or minimal trauma



Wikipedia/Public Domain

Jaw Osteonecrosis

- Avascular necrosis of jaw
- Pain, swelling of mandible
- May lead to exposed bone, local infection
- May cause pathologic fracture of jaw
- Often occurs in setting of dental disease



Dake/Wikipedia

Teriparatide

- Recombinant human parathyroid hormone (PTH)
- Continuous administration of PTH
 - Bone resorption → ↑ serum calcium
 - Important physiologically
- Low dose once daily bolus administration
 - Increased bone mass
 - **Increased osteoblast bone formation**
 - Contrast with most therapies: inhibit osteoclasts
- Teriparatide: Subcutaneous daily injection

Teriparatide

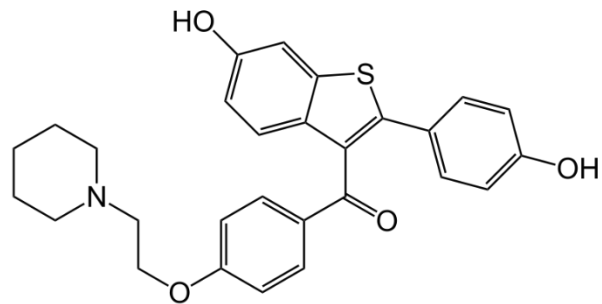
Adverse Events

- Brief rise in serum calcium
 - Drug has quick on/off effect over hours
 - Rarely leads to very high levels or symptoms
- Theoretical risk of **osteosarcoma**
 - Very few cases reported
 - High doses for long duration → cancer in rats

Raloxifene

SERM (Selective Estrogen Receptor Modulator)

- Estrogen actions on bone
- Anti-estrogen in breast/uterus
- Also used for prevention of breast cancer
- May cause hot flashes
- Associated with DVT/PE
- Minimal effects on uterus
 - Not associated with bleeding, hyperplasia/cancer



Calcitonin

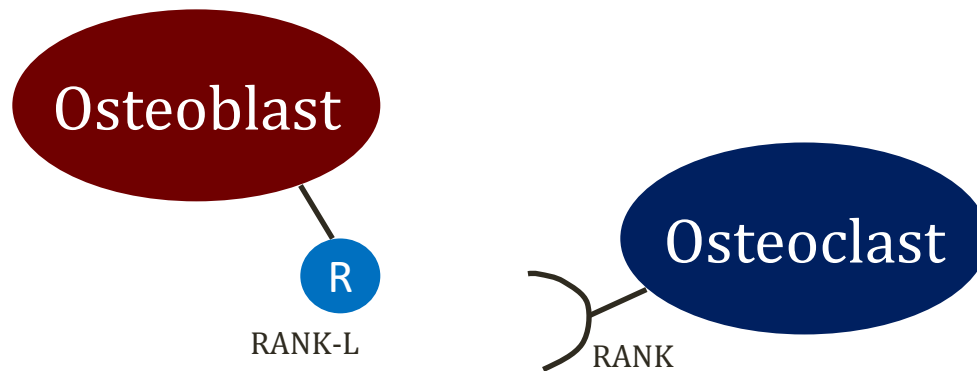
- Hormone produced by thyroid
- Synthesized by parafollicular cells (C-cells)
- Binds to osteoclasts
- Inhibits bone resorption
- **Salmon calcitonin** used in humans



Wikipedia/Public Domain

Denosumab

- Monoclonal RANK-L antibody
- Blocks osteoblast activation of osteoclasts

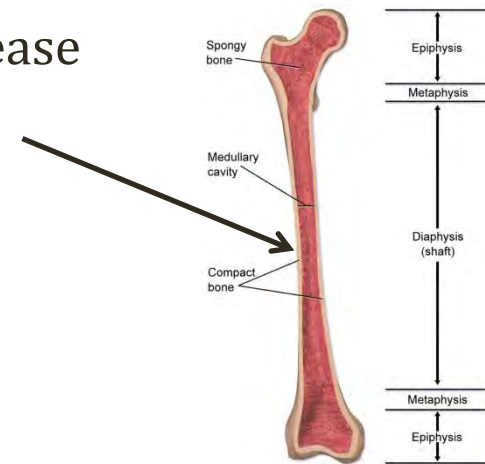


Bone Tumors

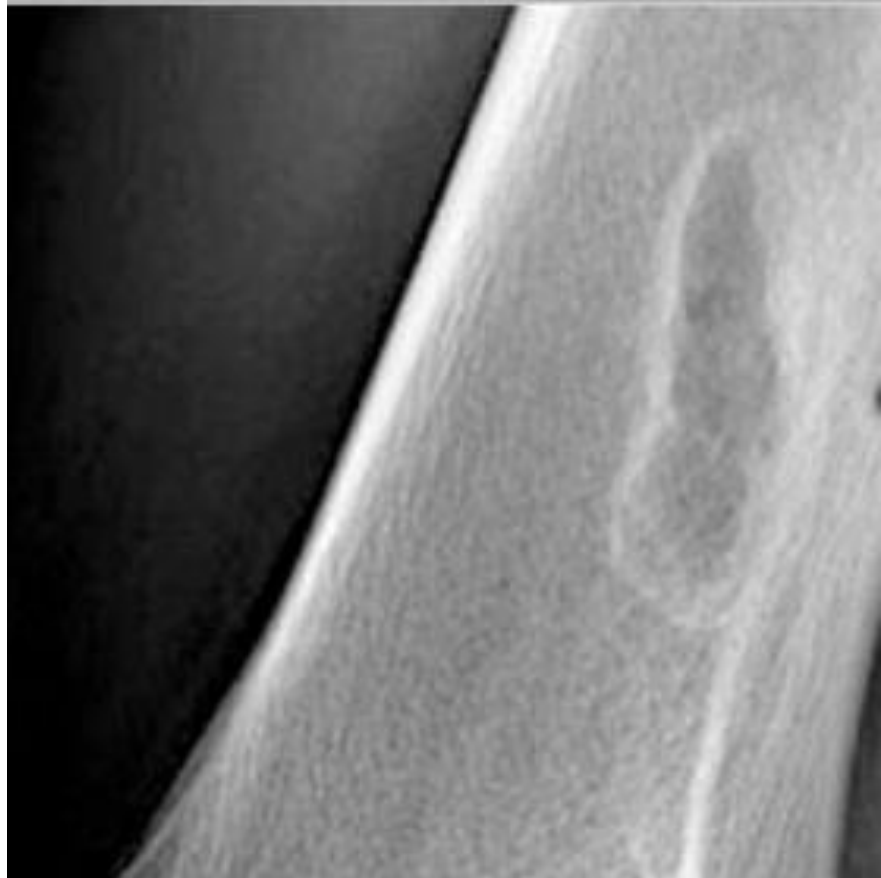
Jason Ryan, MD, MPH

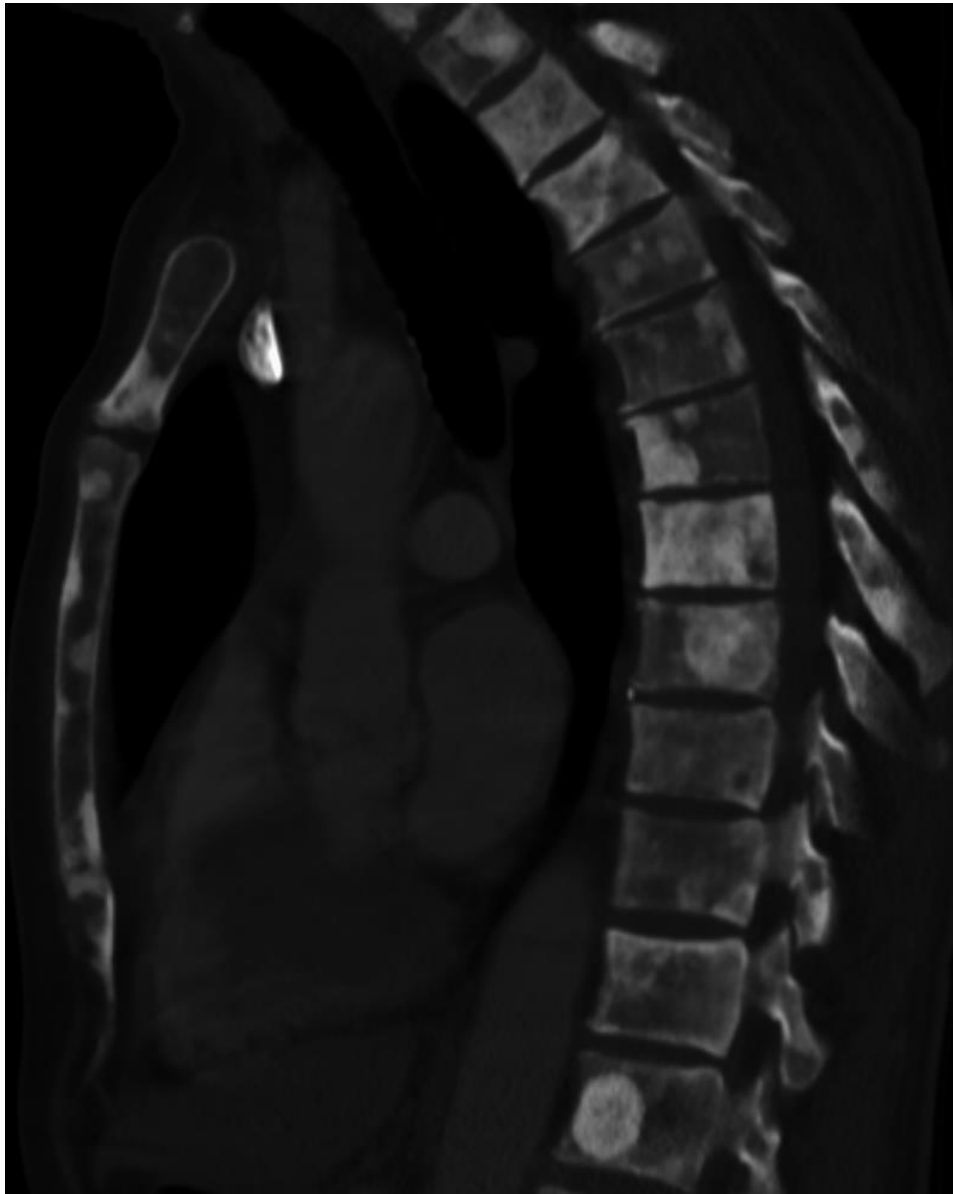
Bone Metastasis

- Bone metastasis >> primary bone tumors (rare)
- Common in diaphysis
- **Osteoclastic** lesions
 - Bone breakdown by metastasis
 - Multiple Myeloma: classic osteolytic disease
- **Osteoblastic** lesions
 - Deposition of new bone
 - Prostate CA: classic osteoblastic lesion



BruceBlaus /Wikipedia





James Heilman, MD /Wikipedia

Primary Bone Tumors

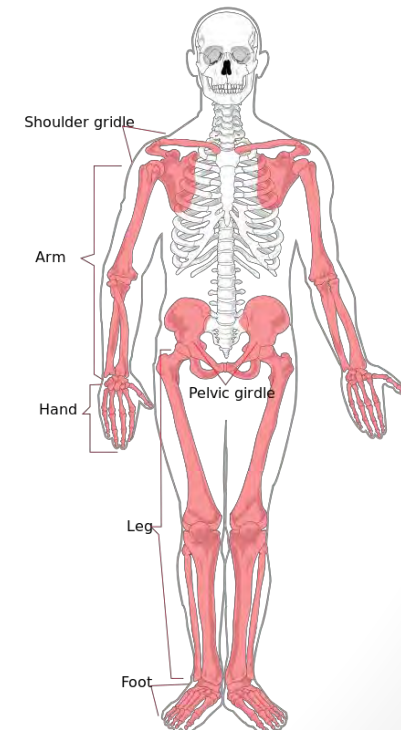
- Often occur in children/young adults
- Often involve long bones especially at knees
- Most are more common in males

Primary Bone Tumors

- Can be an incidental finding
- May cause bone pain
- May cause **pathologic fractures**
 - Fracture in bone weakened by underlying abnormality
 - Often from minor trauma
 - Proximal femur and humerus: Most frequent sites

Osteoid Osteoma

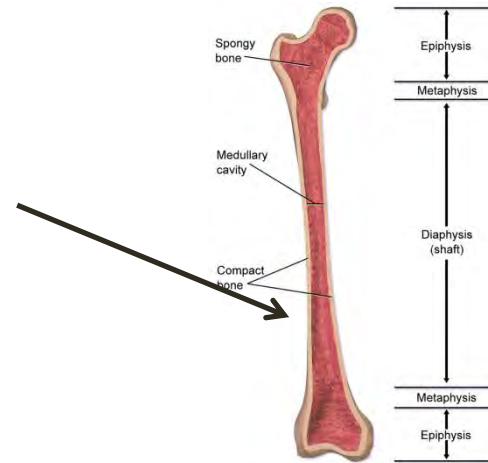
- Benign tumor of bone
- Small tumors (<2cm) of young men (teens/20s)
- Occur in “appendicular skeleton”
 - Not in “axial” skeleton
- Most cases at knee
 - Tibia/fibula
- Presents as **bone pain** at night
- **Responsive to aspirin**



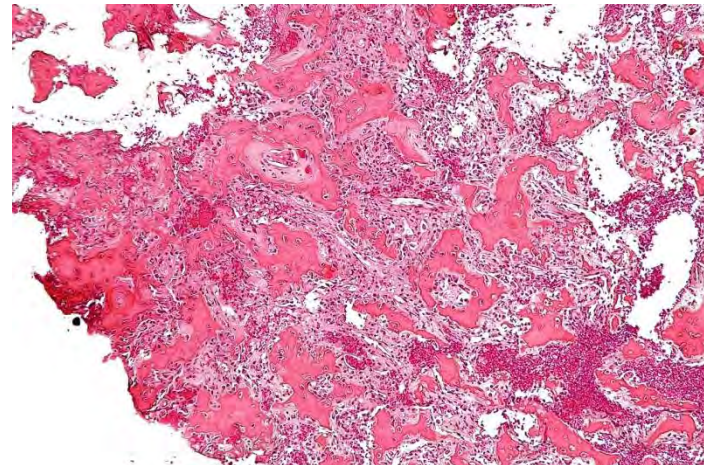
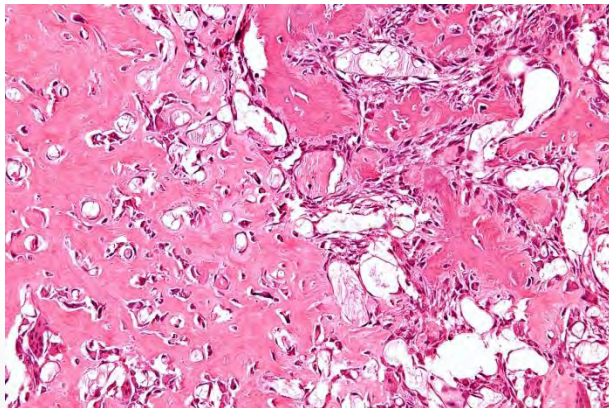
Wikipedia/Public Domain

Osteoid Osteoma

- **Surface of cortex/diaphysis**
- Tumor of osteoblasts
- **Osteoid core**
 - Non-mineralized bone matrix
 - Mostly proteins
- Rim of woven bone



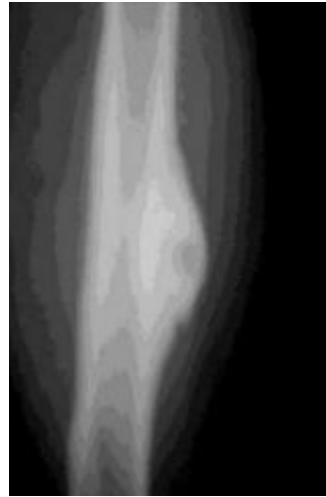
BruceBlaus /Wikipedia



Nephron/Wikipedia

Osteoid Osteoma

- Central osteoid core = radiolucent (clear)
- Surrounded by “reactive” bone



Vinod Naneria/Slideshare

Osteoblastoma

- Larger (>2cm) tumor
- Often involves **spine**
- **Pain not responsive to aspirin**

Gardner's Syndrome

- Variant of FAP
 - Familial Adenomatous Polyposis
 - APC gene mutation
- Colonic polyp disorder
- Multiple extra-colonic manifestations
- **Osteomas** (benign bone growths)
 - Often occur in patients with Gardner's
 - Usually in **skull or mandible**
 - Often painless, palpable
- May precede development of colon symptoms



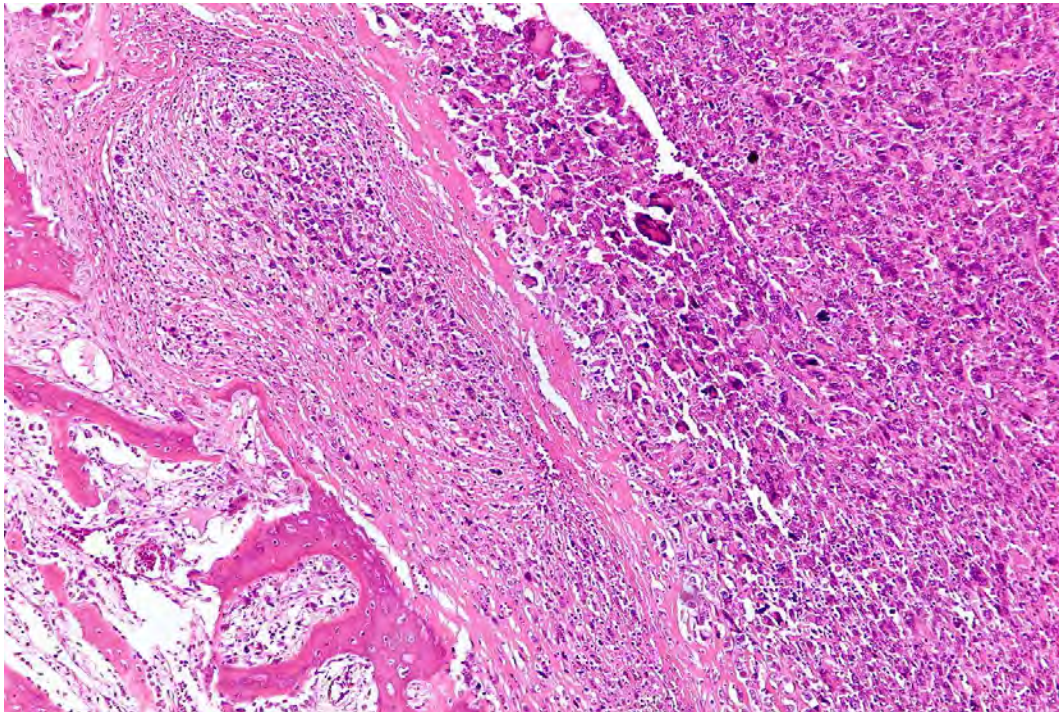
Osteoma of Ear Canal
(Didier Descouens)

Osteosarcoma

- **Malignant bone tumor of osteoblasts**
- Most common primary bone tumor
- More common in males
- **Bimodal age distribution**
 - 75% young adults (<20years)
 - 25% older adults with bone disease (i.e. Paget's)

Osteosarcoma

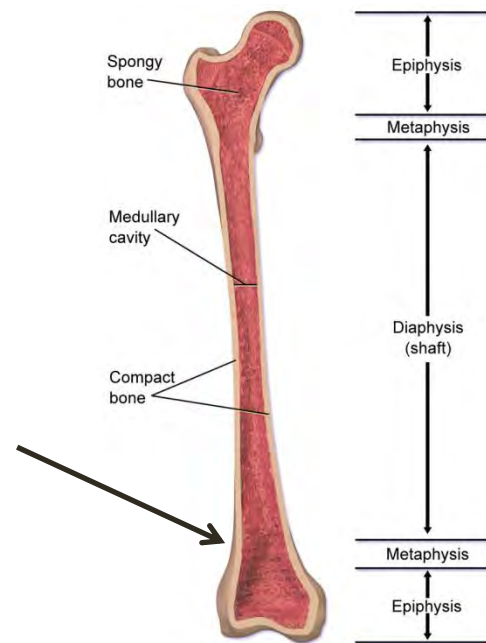
- Malignant cells of varying shape (pleomorphic cells)
- Irregular osteoid formation (pink)



Nephron/Wikipedia

Osteosarcoma

- Painful, enlarging mass on bone
- May present as pathologic fracture
- Usually occurs in **metaphysis of long bones**
- 50% cases occur at knee
 - Distal femur
 - Proximal tibia



BruceBlaus /Wikipedia

Classic X-ray Findings

- **Codman triangle**
 - Tumor breaks through cortex
 - Lifts periosteum
- **Sunburst/Sunray sign**
 - Tiny bone fibers in periosteum

Classic X-ray Findings



Ajimsha619/Wikipedia



Ernesto Dury/Slideplayer

Osteosarcoma

Associated Conditions

- **Prior radiation**
 - Often years after radiation therapy for childhood cancer
- Paget's disease
- Inherited genetic conditions
 - Familial cancer syndromes
 - Germline mutations
 - Familial retinoblastoma (Rb gene mutation)
 - Li Fraumeni syndrome (p53 tumor suppressor gene)

Osteosarcoma

Treatment

- Treated with surgical resection or amputation
 - **“En bloc” resection**
 - Removal of entire tumor in one piece
 - Together with a layer of healthy tissue
 - Limb salvage when possible
- **Always treated with chemotherapy**
 - Presumed all patients have metastasis
 - Prior treatment with surgery alone → poor survival
 - Chemo may be given before surgery to shrink tumor
 - “Neoadjuvant” therapy

Ewing Sarcoma

- Malignant bone tumor
- Undifferentiated primitive **neuroectoderm** cells
- Youngest age of presentation of all bone tumors
 - 80% cases < 20 years old
- Boys > Girls
- Whites >> African Americans

Ewing Sarcoma

- Occurs in **diaphysis** of long bones
 - Most commonly femur
 - Also tibia, fibula, humerus
 - Seen in bones of pelvis
- Aggressive with early metastasis
- Treatment: surgery/chemo/radiation
 - 5-year survival: 70% in localized disease
 - 33% metastases at diagnosis



Michael Richardson, M.D.

Ewing Sarcoma

- Painful, growing mass over bone
- Often warm, swollen
- May see fever, leukocytosis
- May be confused with osteomyelitis
- **Blood cultures and tumor aspiration: sterile**



Image courtesy Wikipedia/Public Domain

Onion Skin

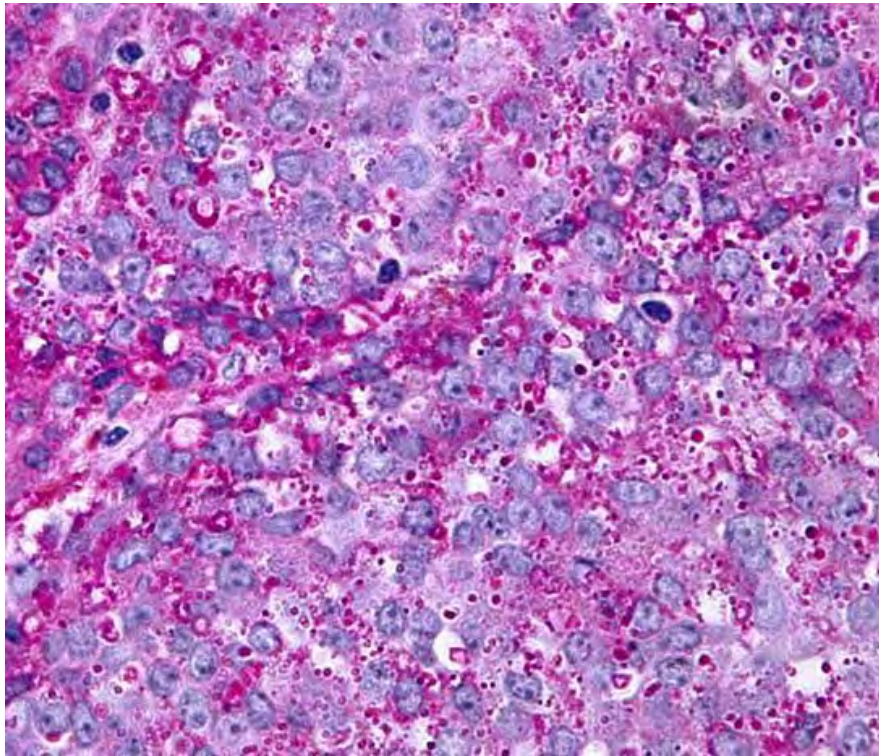
- Classic X-ray finding
- Layering near periosteum
- Splitting/thickening of cortex



Michael Richardson, M.D.

Ewing Sarcoma

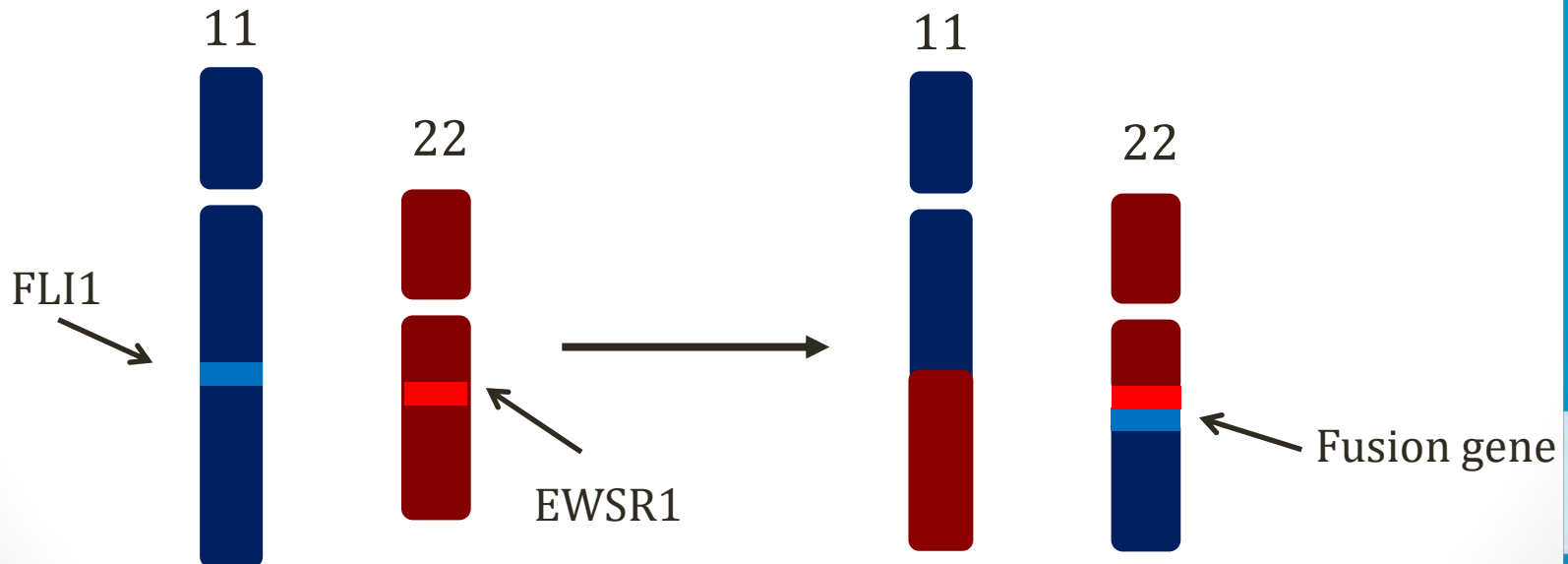
- Sheets of small, round cells



Nephron/Wikipedia

Ewing Sarcoma

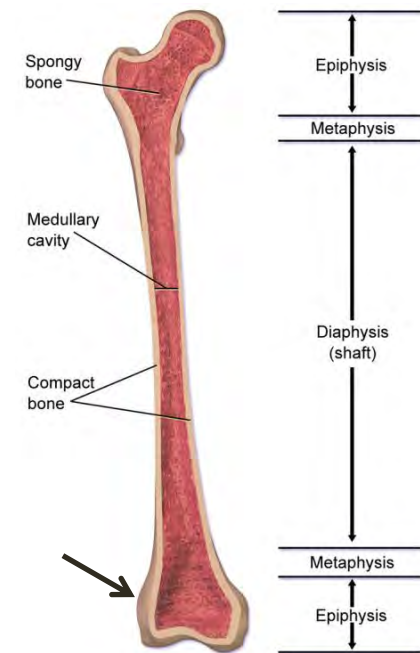
- 85% of cases associated with **genetic translocation**
- Chromosomes 11 and 22
- Fusion of EWSR1 gene (22) to FLI1 gene (11)
- Detected with FISH



Giant Cell Tumor

Osteoclastoma

- Multi-nucleated giant osteoclasts
- Bone resorption by tumor
- Usually benign but **locally aggressive**
- Occurs in **epiphysis**
- Most commonly in femur/tibia (at knee)

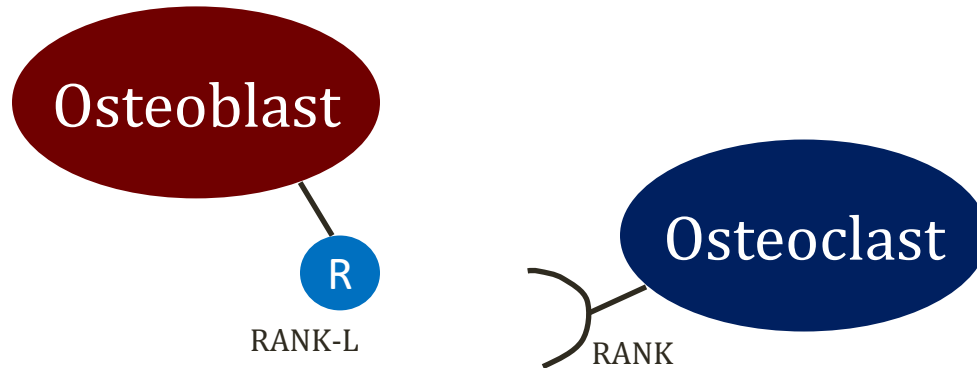


BruceBlaus /Wikipedia

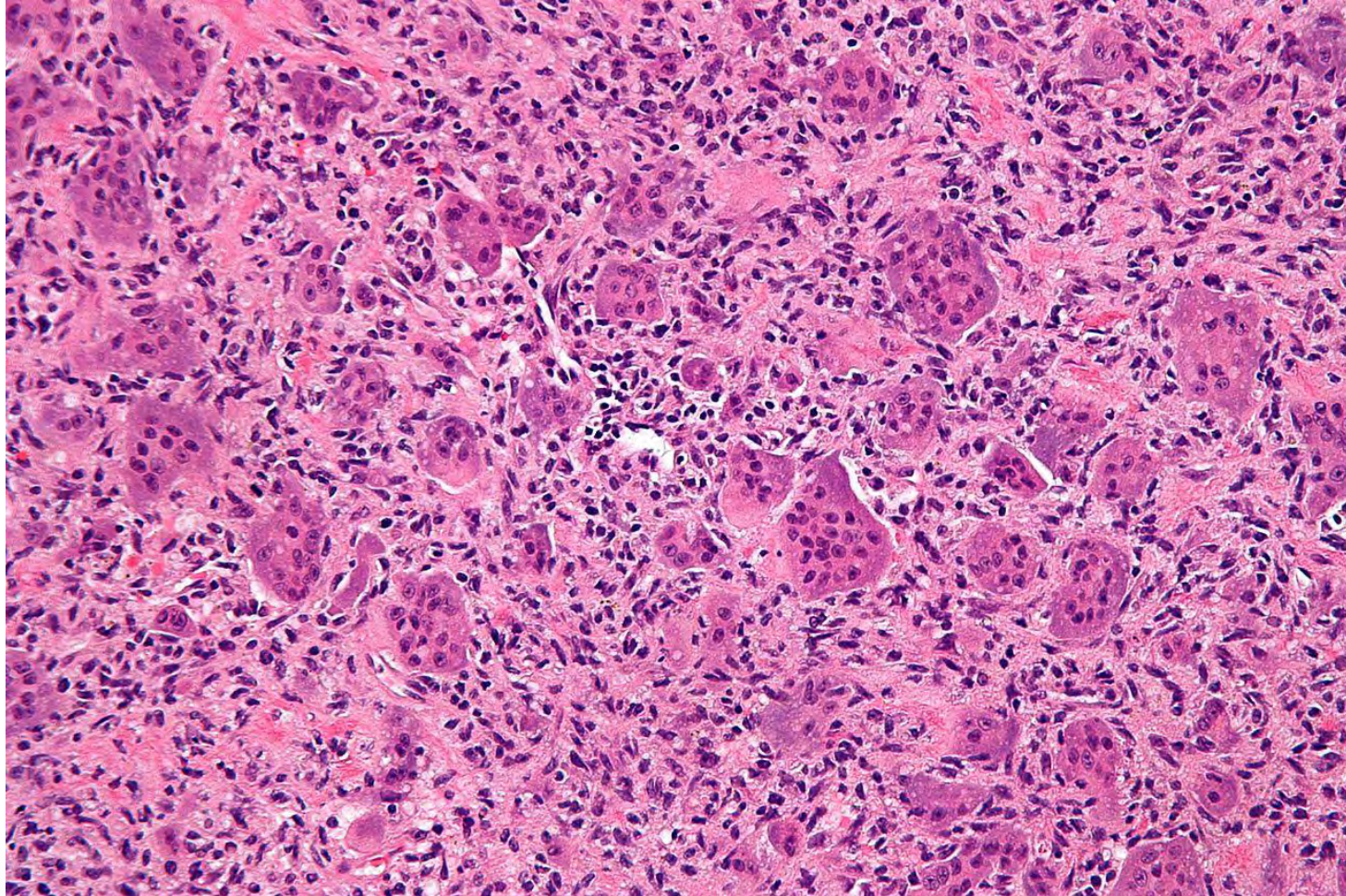
Giant Cell Tumor

Osteoclastoma

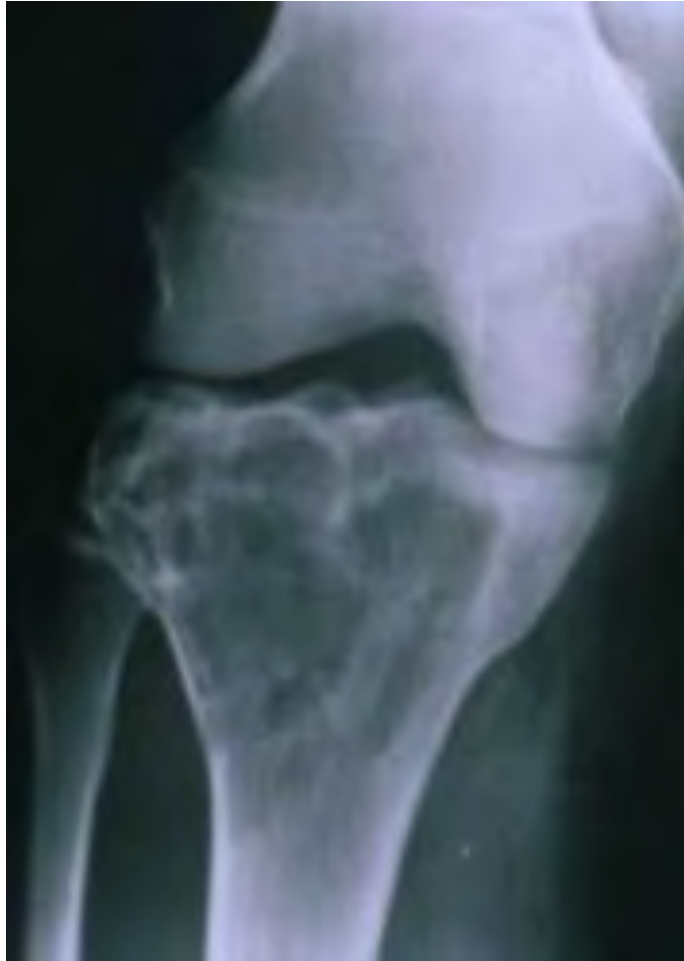
- Stromal tumor cells express **high levels RANK-L**
- Drives osteoclasts activity in tumor
- Leads to giant osteoclastic cells



Giant Cell Tumor



Giant Cell Tumor



Sudheer Kumar/Slideshare

Osteochondroma

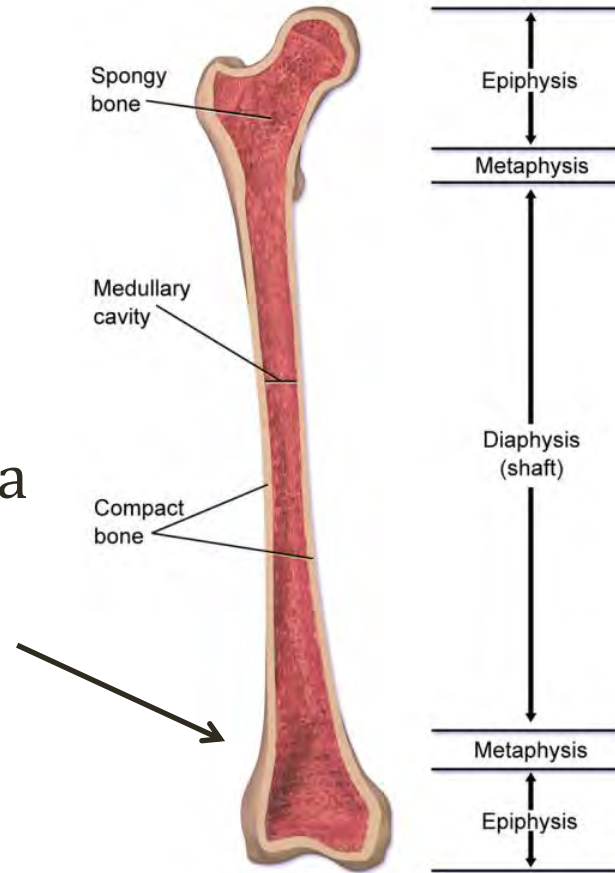
- Benign **cartilage-forming** tumor
- Occur in late adolescence/early adulthood
- More common in males
- Slow growing mass attached to stalk
 - **Cartilage-capped** bone spur
 - “Exostosis:” new bone on surface of bone
- Can cause pain
- Often detected incidentally



Michael R Carmont, Sian Davies,
Daniel Gey van Pittius and Robin Rees

Osteochondroma

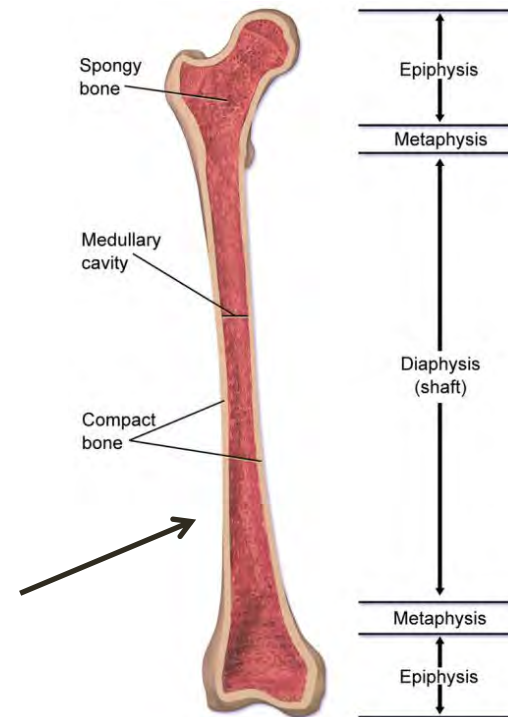
- Arise from **growth plate**
- Lateral projection
- Found at metaphysis
- Stop growing with GP closure
- Treated with simple excision
- Rarely lead to chondrosarcoma
- Cartilage cap → malignant



BruceBlaus /Wikipedia

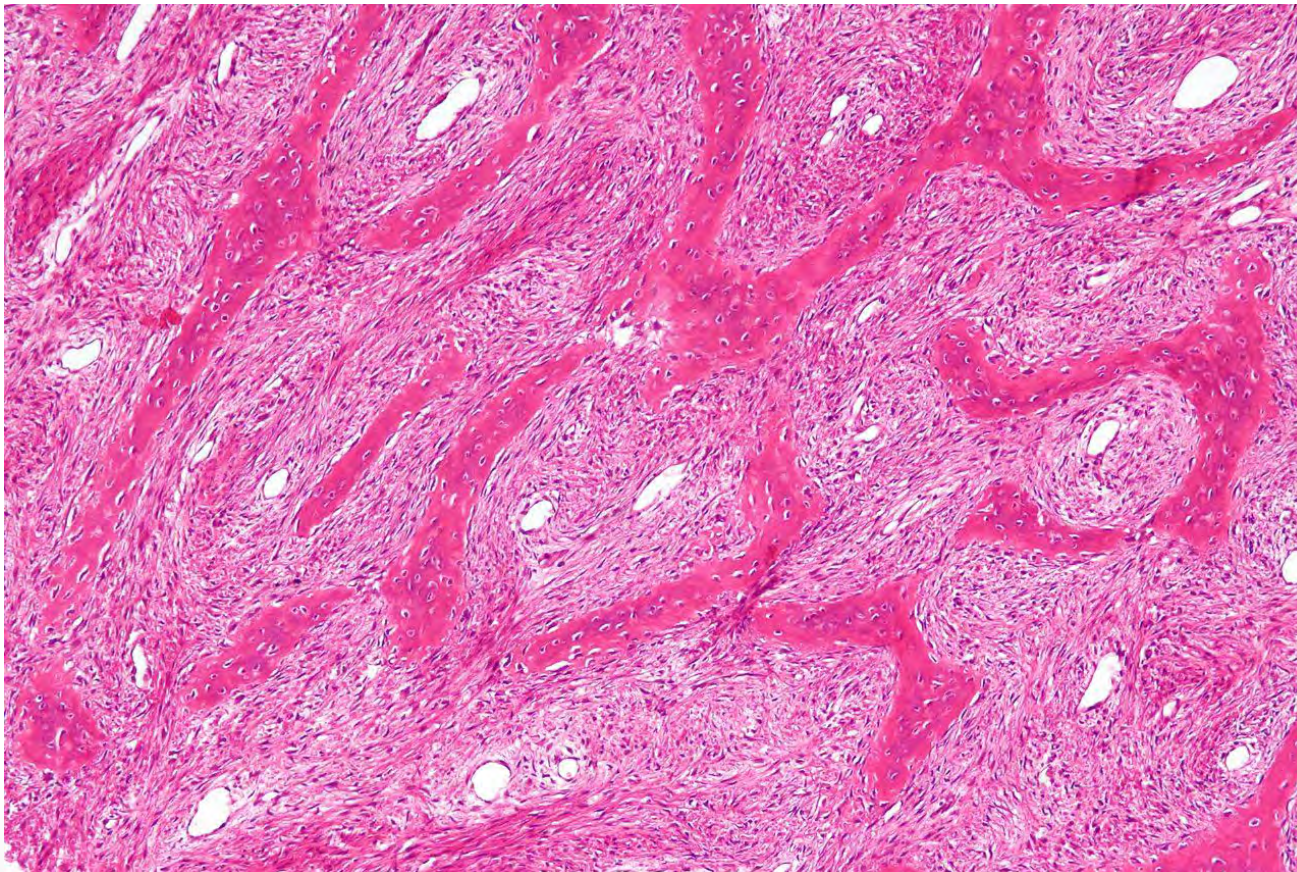
Fibrous Dysplasia

- Benign tumor
- Woven bone surrounded by fibroblasts
- Occurs in early adolescence
- Grows until growth plate closes
- Often asymptomatic
- May cause pain, fractures
- Occurs in **medulla/diaphysis**



Fibrous Dysplasia

- “Chinese character” trabeculae of woven bone



Nephron/Wikipedia

Fibrous Dysplasia

- X-ray: Lytic lesion in diaphysis



Alison Leggitt/Slideplayer

Simple Bone Cyst

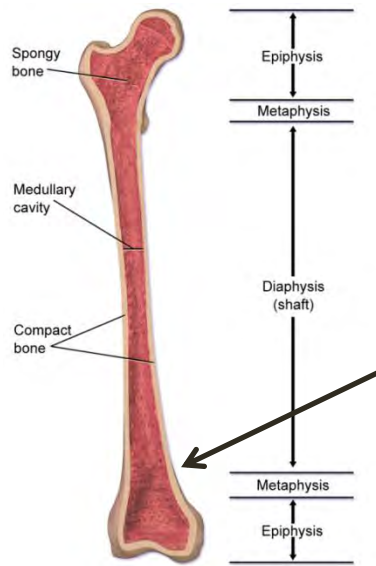
Unicameral Bone Cyst

- Fluid-filled spaces with fibrous lining
- Usually occur < 20 years old
- Most common locations: proximal humerus and femur
- Commonly an incidental finding
- May lead to pathologic fracture
- Treatment: Observation with serial X-rays
- Rarely require surgery
- Often spontaneously improve

Simple Bone Cyst

Unicameral Bone Cyst

- Found in metaphysis
- Abutting growth plate



BruceBlaus /Wikipedia



Arif S/Slideshare

Chondroma

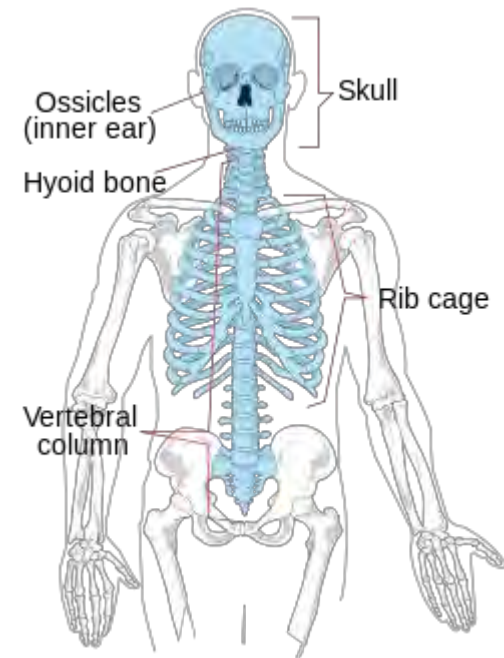
- Benign cartilage tumor
 - In medullary cavity: endochondromas
 - Surface of bone: juxtacortical chondromas
- Occur in small bones of hands and feet



[Bratgoul/Wikipedia](#)

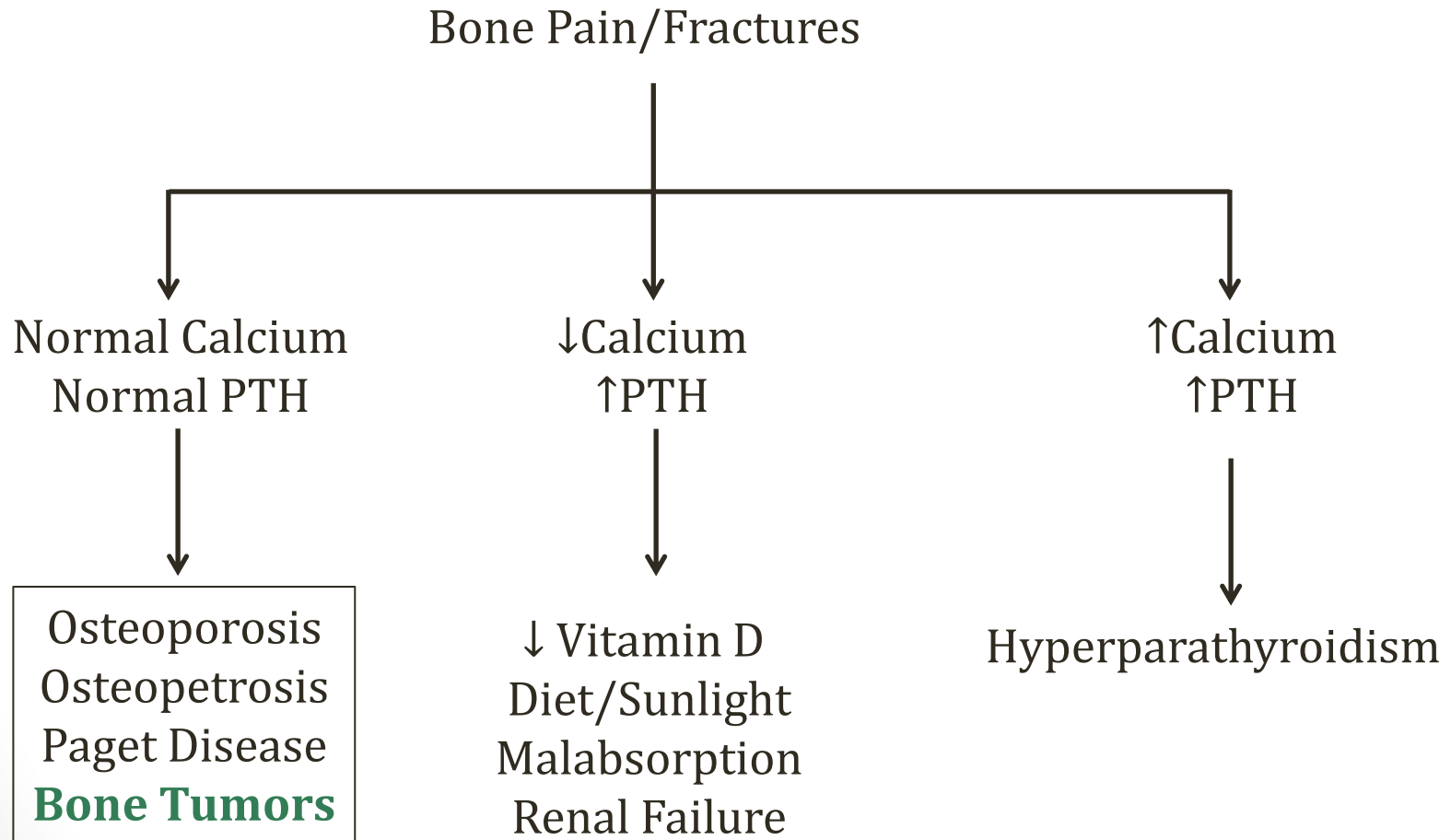
Chondrosarcoma

- Malignant cartilage tumor
- Also occurs in medulla
- Occur centrally
- Pelvis, shoulder, ribs
- Distal extremities rarely involved

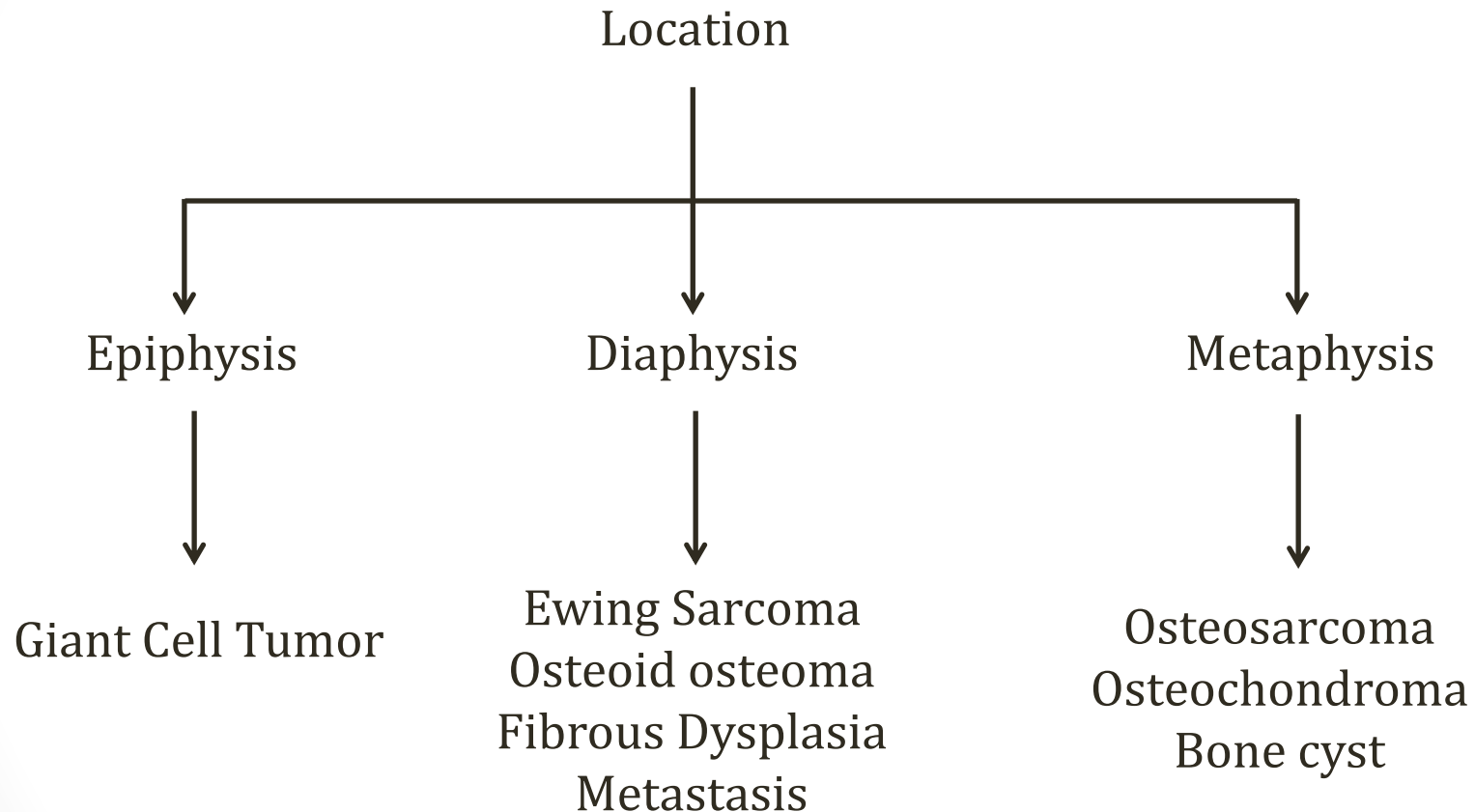


Wikipedia/Public Domain

Bone Pain/Fractures



Long Bone Tumors



Langerhans Cell Histiocytosis

- Bone variant: **Eosinophilic granuloma**
- Occurs as bone mass in children
- Most commonly involved bone: **skull**
- Biopsy: Langerhans cells/eosinophils
 - Langerhans cells: Dendritic cells
 - Myeloid origin
 - Similar to histiocytes (tissue macrophages)
 - Express CD1a, S100, CD207

Osteoarthritis

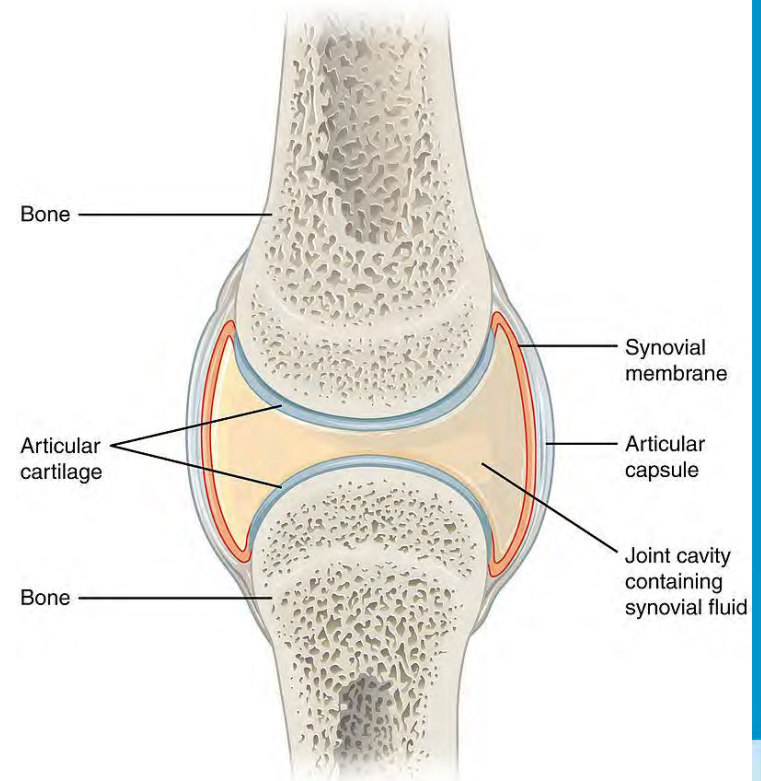
Jason Ryan, MD, MPH

Arthritis

- Joint inflammation
- Joint pain, warmth, stiffness
- Many types
 - Osteoarthritis
 - Rheumatoid arthritis
 - Septic arthritis
 - Gouty arthritis
 - Psoriatic arthritis
 - Reactive arthritis

Synovial Joints

- Fingers, hips, knees
- Articular cartilage
 - **Type II collagen**
- Synovium
 - Secretes synovial fluid
 - Hyaluronic acid

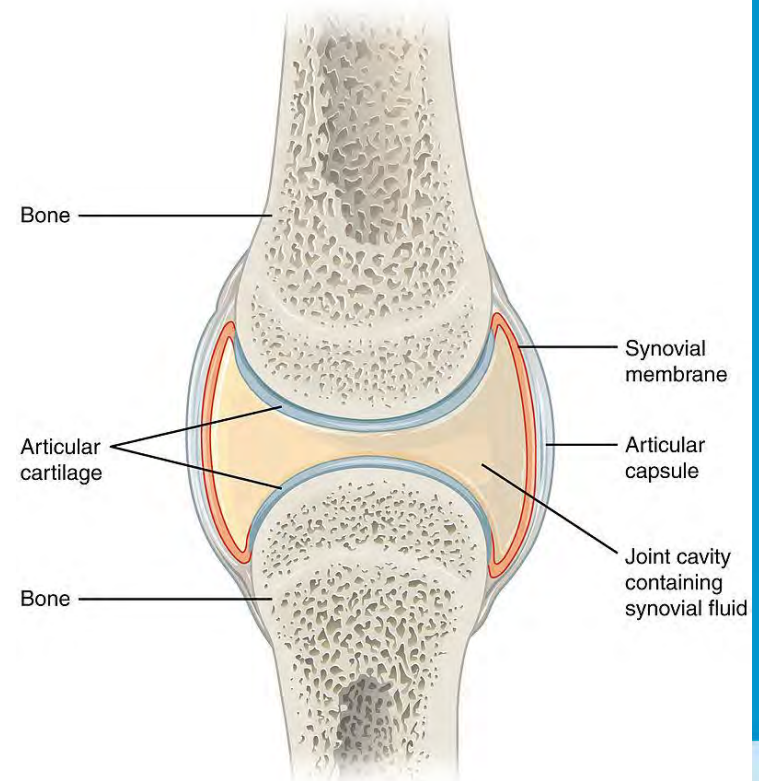


OpenStax College/Wikipedia

Osteoarthritis

Pathophysiology

- **Hyaline cartilage** breakdown
- **Abnormal chondrocytes**
 - Only cell type in cartilage
 - Normally quiescent
 - Proliferate in OA
 - Inadequate repair
 - Secrete proteases
 - Secrete cytokines
 - Eventually die → exposed bone



OpenStax College/Wikipedia

Osteoarthritis

- **Low WBC in synovial fluid**
- “Non inflammatory arthritis”

Disease	White Blood Count (cells/mm ³)
Normal	<200
Osteoarthritis	200-2000
Rheumatoid Arthritis	2k-50k
Gout	2k-50k
Septic Arthritis	>50k

Osteoarthritis

Classic X-ray Findings

- Joint space narrowing
- Subchondral sclerosis
- Osteophytes (bone spurs)
- Subchondral cyst

Joint Space Narrowing



James Heilman, MD/Wikipedia

Subchondral Sclerosis

- Thickening of the subchondral bone
- ↑ collagen with abnormal mineralization

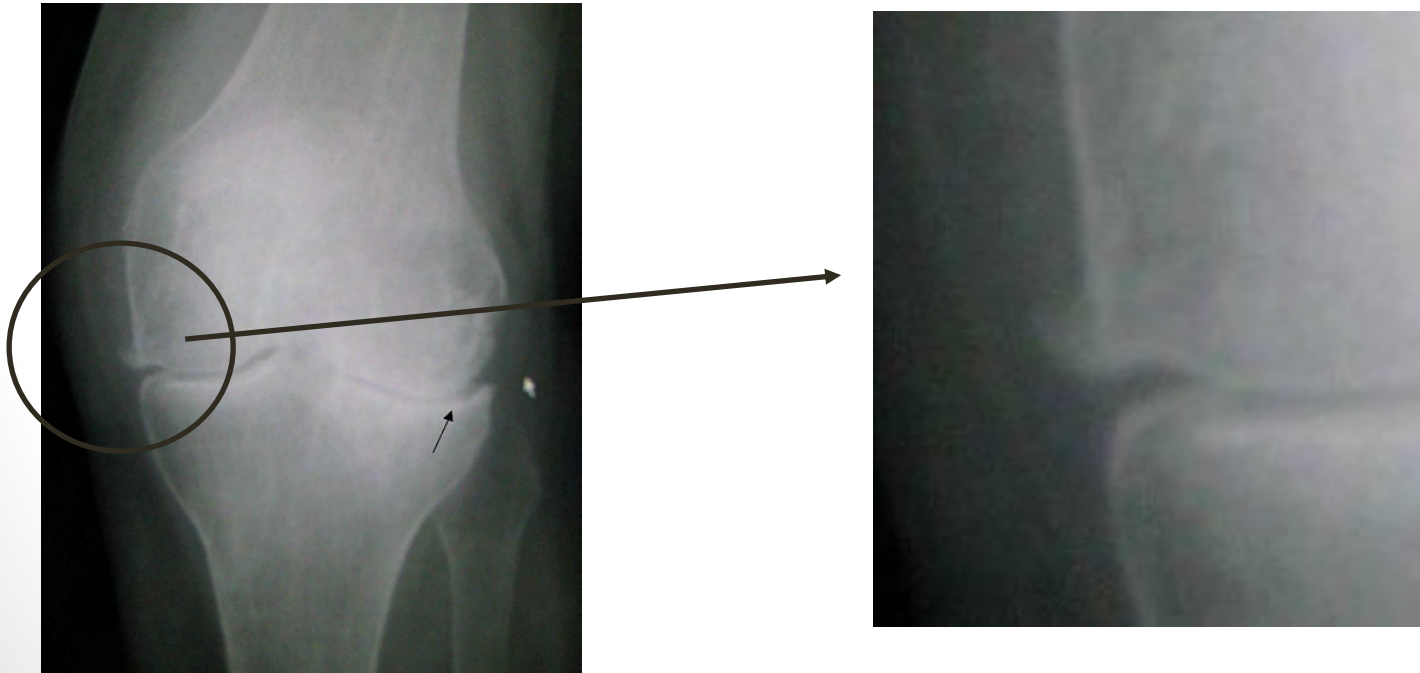


James Heilman, MD/Wikipedia

Osteophytes

Bone Spurs

- Thickening of the subchondral bone at joint margins
- Often insertion points of tendons or ligaments



James Heilman, MD/Wikipedia

Subchondral Cysts

- Fluid filled sack
- Bone cracks → synovial fluid accumulation



Anas Bahnassi/Slideshare

Osteoarthritis

Knee Involvement

- Often involves both knees
- More weight bearing medial knee
 - Imaging may show asymmetric narrowing on medial side

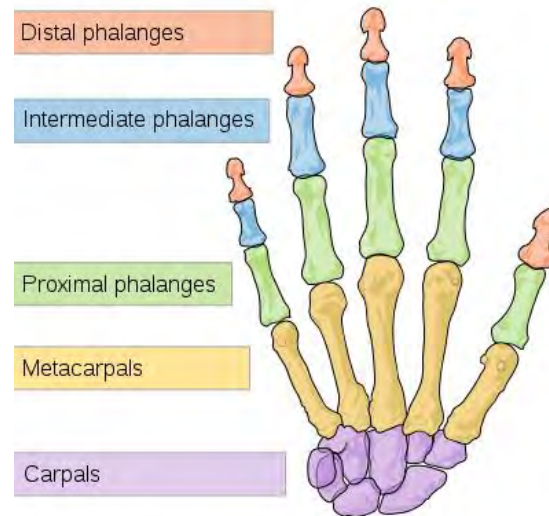


Public Domain

Osteoarthritis

Hand Involvement

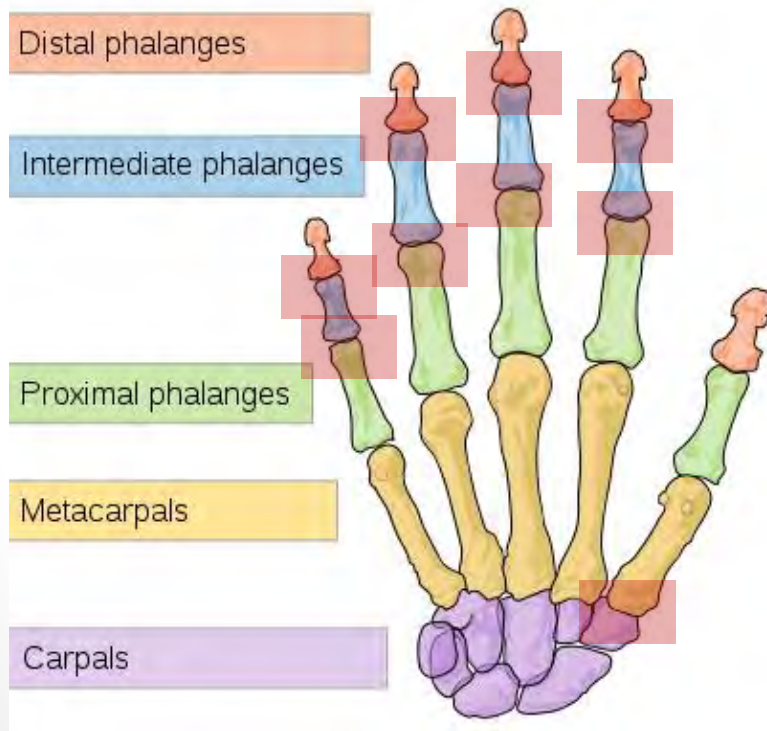
- Distal interphalangeal (DIP) joints
- Proximal interphalangeal (PIP) joints
- Not MCP
- 1st Carpometacarpal (CMC) joint



Wikipedia/Public Domain

Osteoarthritis

Hand Involvement



Osteoarthritis

Hand Involvement



Pixabay/Public Domain

Nodal osteoarthritis

- **Heberden's** (DIP) and **Bouchard's** (PIP) nodes
- Occur in patients with interphalangeal (hand) OA
- Over years, joints become less painful
- Inflammatory signs subside
- Swellings (nodes) remain
- Common at index and middle fingers
- Believed to be caused by osteophytes

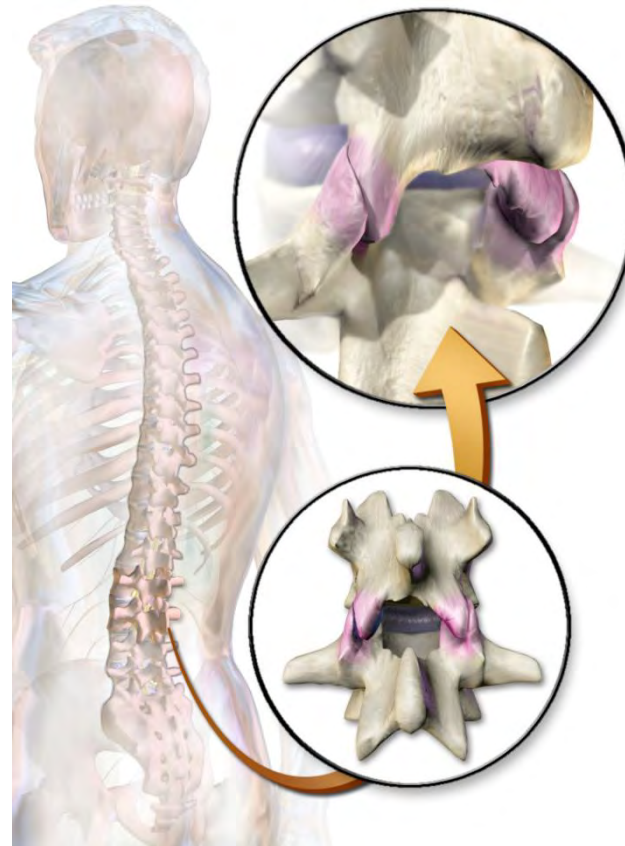
Nodal osteoarthritis



Osteoarthritis

Spine Involvement

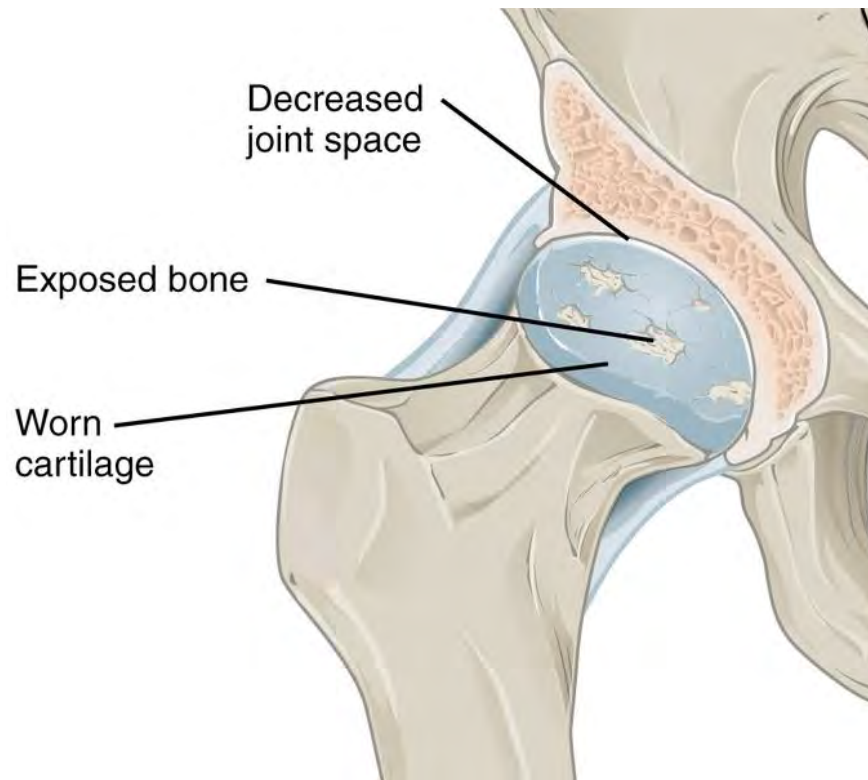
- Facet joints
- Lower cervical spine
- Lower lumbar spine



BruceBlaus/Wikipedia

Osteoarthritis

Hip Involvement



BruceBlas/Wikipedia

Osteoarthritis

Symptoms

- Joint pain
 - Especially after use of joint
 - At end of day for weight-bearing joint
 - Improves with rest
- Stiffness
- Restricted motion

Osteoarthritis

Risk Factors

- Advanced age
 - 80% patients over 55 years old
- Female gender
- Obesity
 - **Modifiable risk factor**
 - Especially the knee
 - Hands
 - Hip
- Joint injuries
 - Knee, hip



Dr. Ryan's Grandmother

Osteoarthritis

Treatment

- Exercise
- Weight loss
- Pain control
 - Acetaminophen
 - NSAIDs
- Intraarticular glucocorticoid injection
 - Short term pain relief
- Surgery
 - Total knee and hip replacement

Rheumatoid Arthritis

- Autoimmune condition
- **Women aged 40-50**
- High synovial WBC
- **Morning stiffness**
- **Pain improves with use**
- Many systemic complications
 - Uveitis
 - Serositis
 - Baker's cyst



Pixabay/Public Domain

Septic Arthritis

- **Acute onset**
- Swelling and pain usually of **single joint**
- Acute monoarthritis = medical emergency
- Must exclude septic arthritis and gout

Septic Arthritis

- **Fevers, chills, sweats**
- Synovial fluid purulent with 50k to 150k WBC
- Positive gram stain and culture
- *S. aureus* or *S. pneumoniae*
 - Often from hematogenous seeding of joint
- *Neisseria gonorrhoeae*
 - Sexually transmitted infection

Hemochromatosis

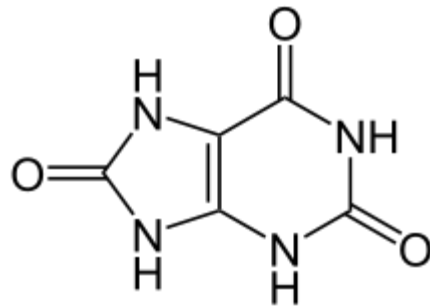
- Iron overload disorder
- Arthritis: common in hemochromatosis
- **May present as arthritis**
- Most commonly involves MCP joints
- Often presents with pain, minimal swelling
- Younger patient
- **High serum ferritin**

Gout

Jason Ryan, MD, MPH

Gout

- Monosodium **uric acid deposition** in joints
- Crystals phagocytosed by macrophages/neutrophils
- Trigger inflammatory response
- Recurrent attacks of acute arthritis
- Severe joint pain
- Redness, swelling, warmth



Uric Acid/Urate

Gout

- Hyperuricemia + **cool temperatures** + genes
- Most common: base of great toe (podagra)
 - 1st metatarsophalangeal joint
- Also often occurs in knee



James Heilman, MD/Wikipedia

Chronic Tophaceous Gout

- **Tophi:** uric acid collections in connective tissue
- Ears, tendons, bursa
- Usually not painful or tender
- Usually follows gouty arthritis
- Seen with longstanding hyperuricemia

Tophi



Herbert L. Fred, MD/Hendrik A. van Dijk



NickGorton/Wikipedia

Urate Nephropathy

- Uric acid crystals in urine
- Uric acid kidney stones
- Chronic renal failure

Gout

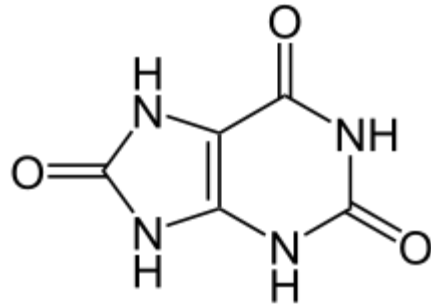
- Primary gout
 - Not due to other disease or medication
 - Cause unknown
 - Most cases associated with **under excretion of uric acid**
- Secondary gout
 - Due to other disease or medication
 - Many causes

Perez-Ruiz. **Renal underexcretion of uric acid is present in patients with apparent high urinary uric acid output.** Arthritis Rheum 2002 Dec 15 47(6):610-3

Uric Acid Excretion

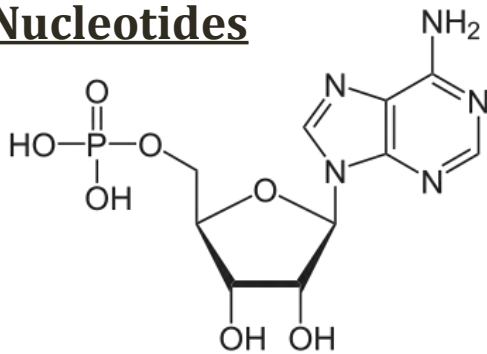
- Mostly via **kidneys/urine**
- Any reduction in GFR → ↓ uric acid excretion
 - **Renal failure**
 - **Volume depletion**
 - **Diuretics** (also ↓ uric acid secretion in urine)
- Commonly cause gout attacks

Uric Acid Production

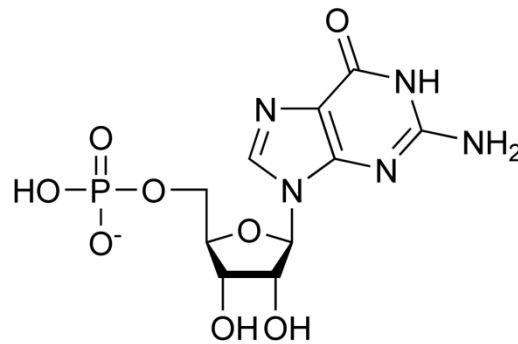


Uric Acid/Urate

Purine Nucleotides

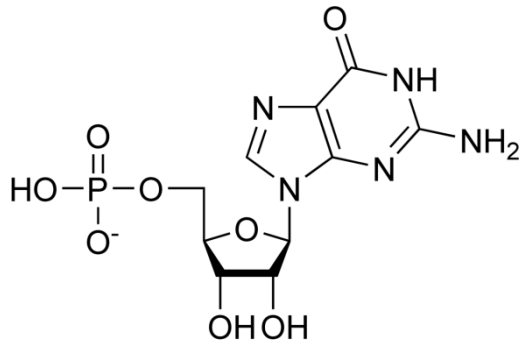


Adenosine



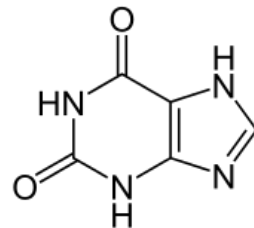
Guanosine

Uric Acid Production

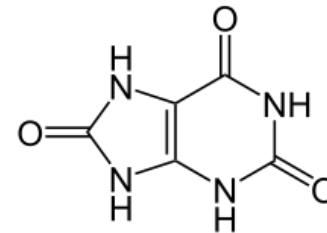


Guanosine

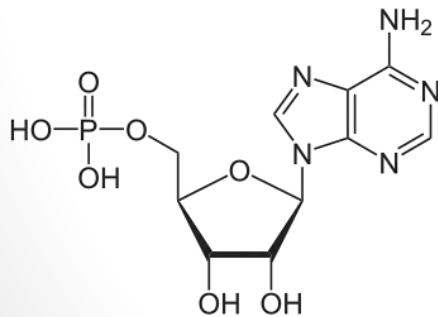
Purines



Hypoxanthine



Uric Acid



Adenosine

Purine Sources

- Red meat
- Seafood
- Trauma/surgery (tissue breakdown)
- All classic causes of gout attack



Pixabay/Public Domain

Myeloproliferative Disorders

- Chronic myeloid leukemia
- Essential thrombocytosis
- Polycythemia vera
- Associated with high cell turnover
- Hyperuricemia → gout

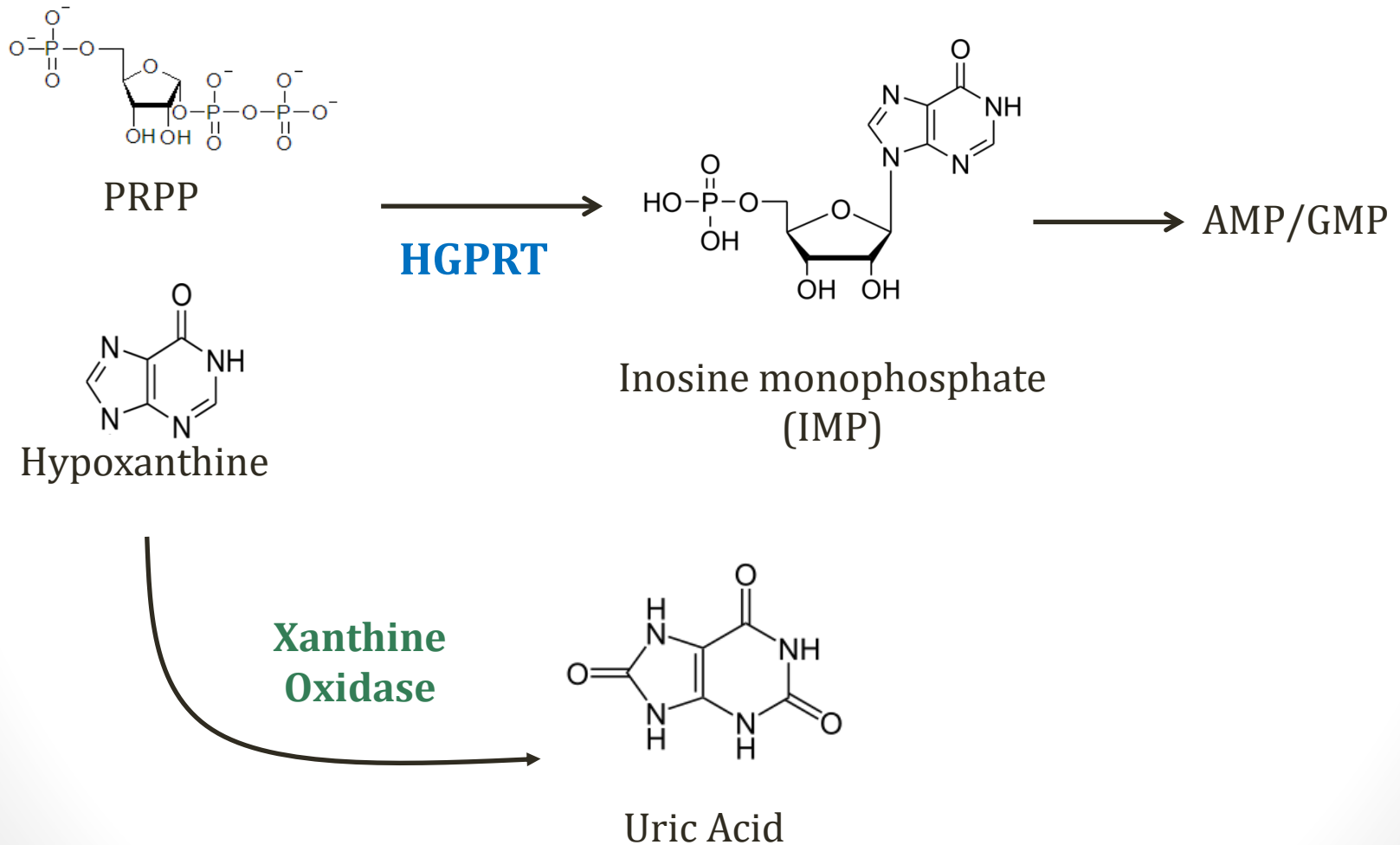


Database Center for Life Science (DBCLS)

Lesch-Nyhan Syndrome

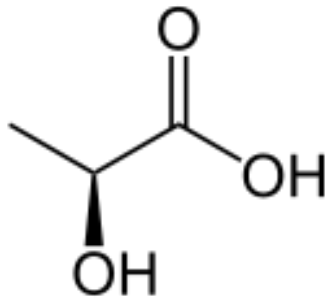
- Enzyme defect in purine salvage pathway
- **X-linked absence of HGPRT**
 - Hypoxanthine-Guanine phosphoribosyltransferase
- **Excess uric acid** production (“juvenile gout”)
- Neurologic impairment (mechanism unclear)
- Hypotonia, chorea
- Self mutilating behavior
- Classic presentation
 - Male child with motor symptoms, self-mutilation, gout

Purine Salvage Pathway



Alcohol

- Classic trigger for gout
- Metabolism consumes ATP → uric acid
- **Urate transporter-1 (URAT1)**
 - Renal uric acid transporter
 - Facilitates uric acid excretion in urine
 - **Lactic acid** produced in alcohol metabolism
 - Increased reabsorption of uric acid



Lactic Acid



Wikipedia/Public Domain

Gout Attacks

- More common in **males**
- More common among obese patients
- Classic case:
 - Obese male
 - Steak dinner with heavy alcohol consumption



Pixabay/Public Domain

Von Gierke's Disease

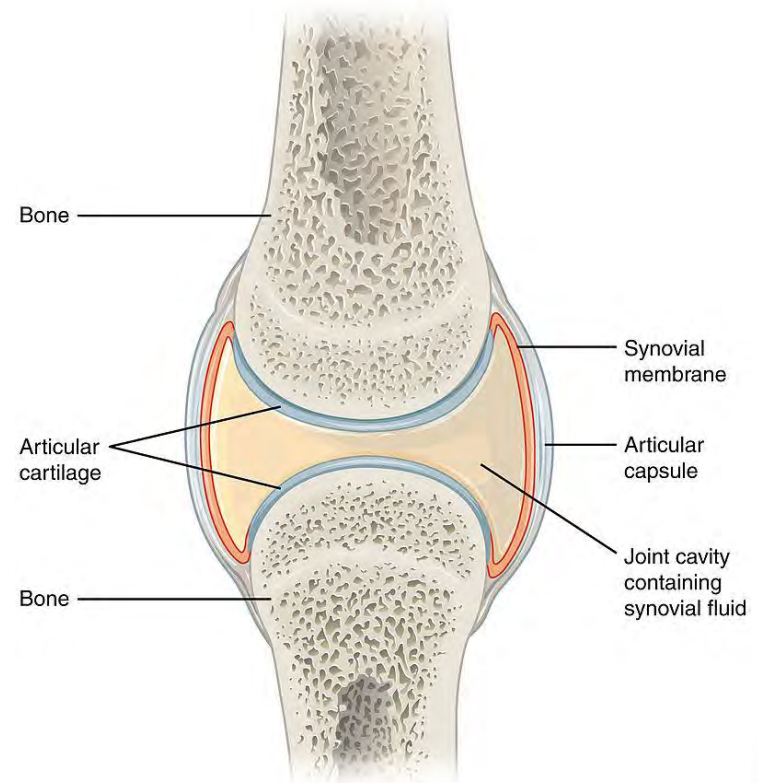
Glycogen Storage Disease Type I

- Glucose-6-phosphatase deficiency
- Presents in infancy: 2-6 months of age
- Severe hypoglycemia between meals
 - Seizures
 - **Lactic acidosis** (Cori cycle)
- Urate transporter-1 (URAT1)

Gout

Diagnosis

- **Arthrocentesis**
- Sampling of synovial fluid
- WBC 20k to 50k
- Polarized light microscopy



OpenStax College/Wikipedia

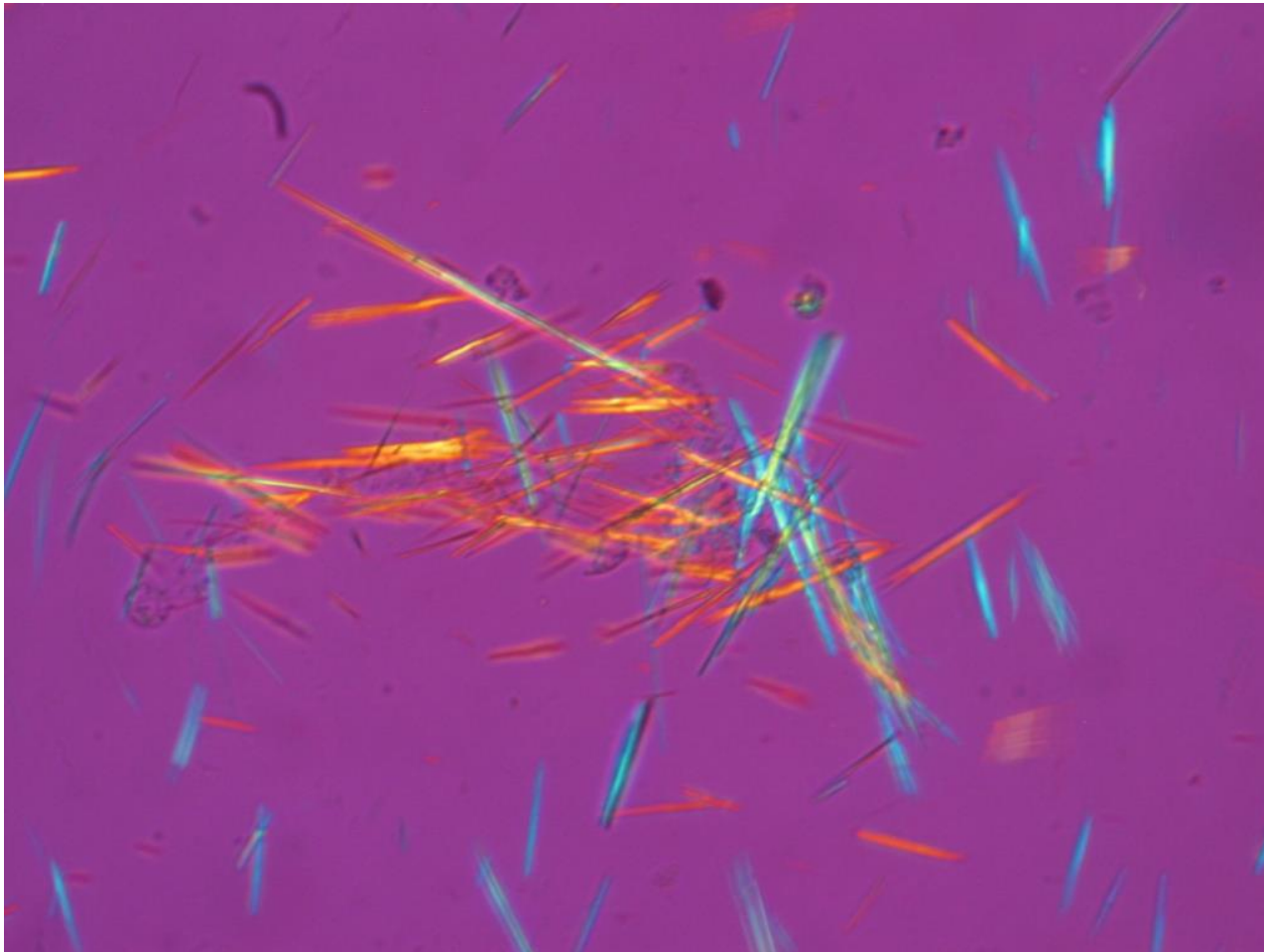
Polarized Light Microscopy

- White light
 - Unpolarized
 - Waves vibrate in random directions
- Polarized light
 - Waves vibrate only in one direction
- Isotropic
 - Reflects the same in all orientations
- Birefringent
 - Reflects polarized light in two ways
 - Reflection based on orientation

Gout Crystals

- “Negatively birefringent”
 - Two reflections of polarized
 - Change in index of refraction is negative
- **Yellow when parallel** to axis of the polarization
- **Blue when perpendicular** to polarization axis

Gout Crystals



Bobjgalindo/Wikipedia

Gout Drugs

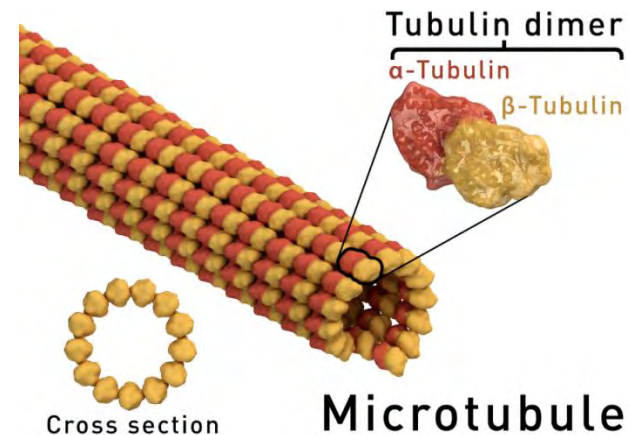
Jason Ryan, MD, MPH

Gout Treatment

- Acute attacks
 - NSAIDs
 - Glucocorticoids
 - Colchicine
- Preventative
 - Xanthine oxidase inhibitors (allopurinol, febuxostat)
 - Pegloticase
 - Probenecid

Colchicine

- **Microtubule inhibitor**
- Binding to intracellular protein tubulin
 - Microtubules: polymers of alpha and beta tubulin
- Prevents polymerization into microtubules
- Inhibits WBC migration and phagocytosis



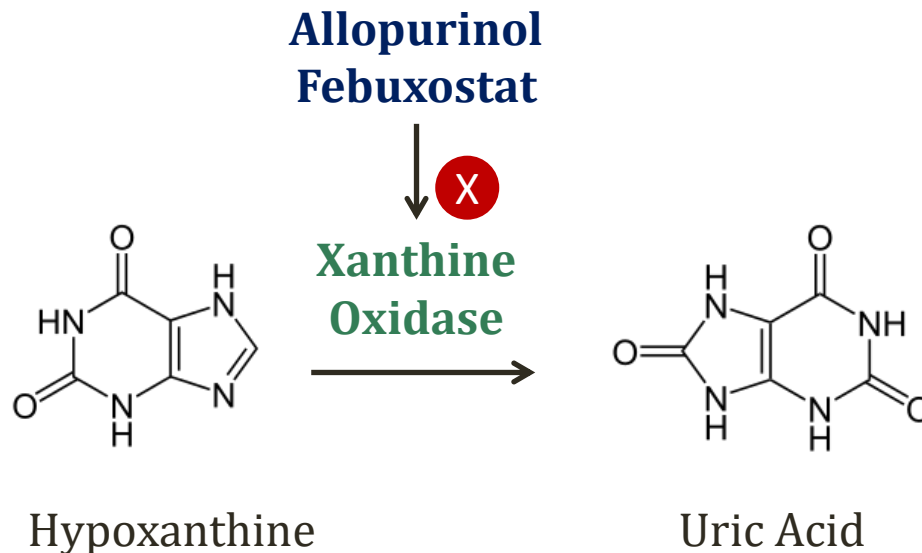
Colchicine

- Adverse effects: GI
 - Diarrhea
 - Nausea, vomiting
 - Abdominal pain
- Three main niche uses:
 - Gout
 - Pericarditis
 - Familial Mediterranean Fever

Xanthine Oxidase Inhibitors

Allopurinol, Febuxostat

- Inhibitors of xanthine oxidase
 - Allopurinol: competitive inhibitor
 - Febuxostat: non-competitive inhibitor
- Also used to prevent tumor lysis syndrome



Xanthine Oxidase Inhibitors

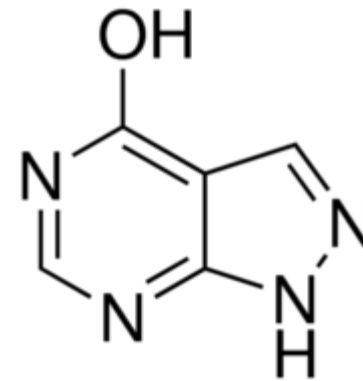
Allopurinol, Febuxostat

- Both abruptly **change serum uric acid levels**
 - May precipitate a gout attack
 - Initiated together with NSAIDs/Colchicine

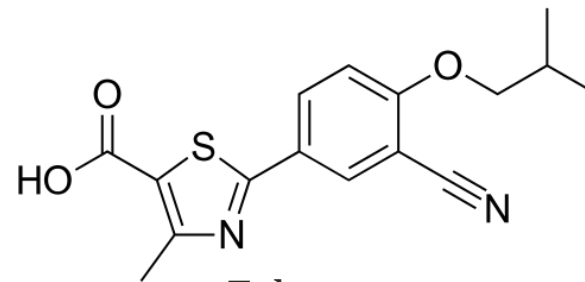
Xanthine Oxidase Inhibitors

Allopurinol, Febuxostat

- Allopurinol
 - GI upset: nausea, vomiting, diarrhea
 - Hepatic toxicity
 - Skin rash (hypersensitivity)
 - Rarely bone marrow suppression
- Febuxostat
 - 2nd line agent
 - Patients intolerant of allopurinol



Allopurinol

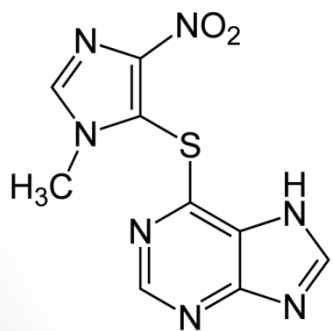


Febuxostat

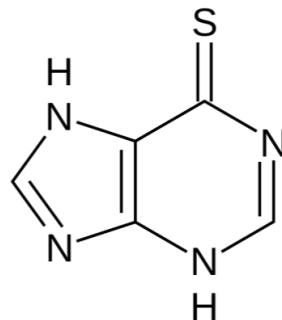
Xanthine Oxidase Inhibitors

Allopurinol, Febuxostat

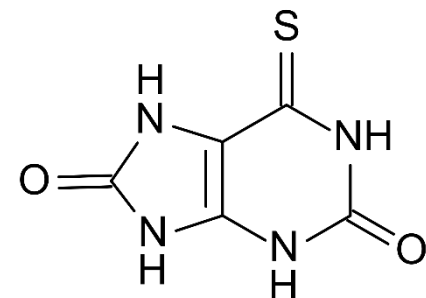
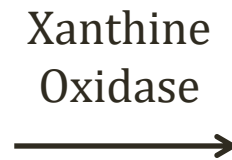
- Interact with azathioprine and 6-MP
- Both metabolized by **xanthine oxidase**
- Caution with XO inhibitors
- May boost effects
- May increase toxicity



Azathioprine



6-MP



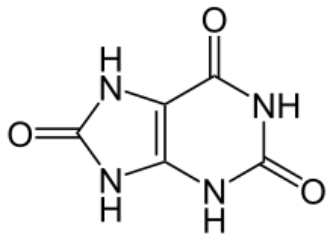
Thiouric acid
(inactive)

Pegloticase

- Intravenous drug
 - Given at infusion center every two weeks
 - Used for severe, refractory gout
- Recombinant porcine uricase (uric acid oxidase)
 - Enzyme that degrades uric acid
- Attached to polyethylene glycol (PEG)
 - Prolongs half-life
 - Limits immune reaction to drug

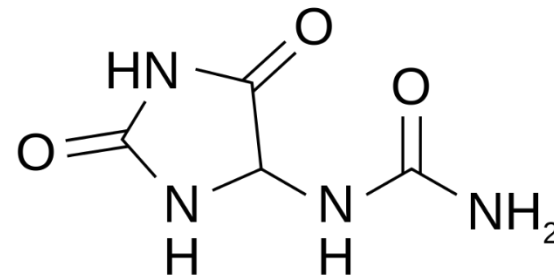
Pegloticase

- Converts uric acid to allantoin
- More water soluble
- Excreted by kidneys



Uric Acid

Pegloticase
→



Allantoin

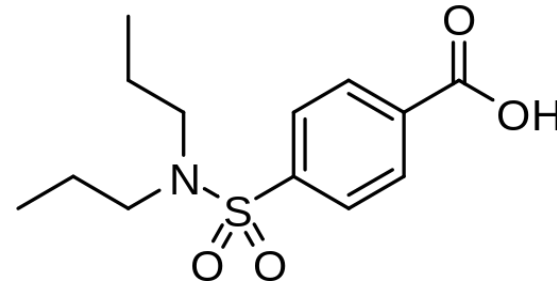
Rasburicase

- Also a recombinant uricase
- Also converts uric acid to allantoin
- Not attached to polyethylene glycol
 - Rapid on/off action
 - More immunogenic
- Used only in **tumor lysis syndrome**

Tumor Lysis Syndrome

- Occurs in treatment of some malignancies
- Rapid cell lysis → ↑ serum levels of cell contents
 - Potassium, phosphate
 - **Hyperkalemia** → arrhythmias
 - Hyperphosphatemia → **hypocalcemia**
- **Hyperuricemia** from breakdown of purines
- Uric acid nephropathy → acute renal failure

Probenecid



- “Uricosuric drug”
- Promotes uric acid excretion in urine
- **Blocks proximal tubule reabsorption of uric acid**
- Also blocks secretion of **penicillin** in urine
 - Boosts PCN levels
 - Originally develops to enhance PCN effects
- Sulfa drug
- May cause uric acid kidney stones

Aspirin

- High dosages (>2.6grams/day)
 - Inhibit secretion and reabsorption
 - Net effect: same as probenecid (uricosuric)
 - Promote uric acid excretion
 - Lower serum uric acid levels
- Low dosages
 - Inhibit secretion only
 - Less uric acid excretion
 - **Aspirin not used for pain control in gout**

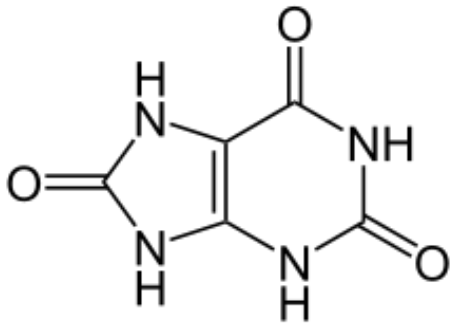
CPPD

Jason Ryan, MD, MPH

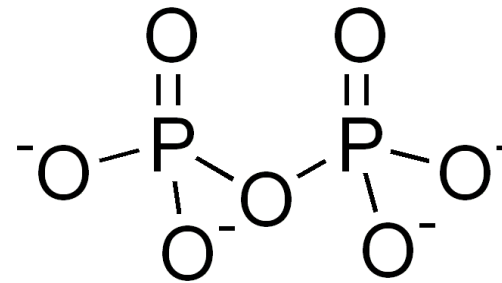
CPPD

Calcium Pyrophosphate Deposition Disease

- **Calcium pyrophosphate** deposition
- Affects joints and connective tissue
- Cause unknown



Uric Acid



Pyrophosphate

CPPD

Calcium Pyrophosphate Deposition Disease

- Occurs in older patients
 - Average age: 72-years-old
- Men = women
- Clinical features
 - Asymptomatic (discovered on imaging)
 - Acute arthritis (similar to gout)
 - Chronic joint disease (similar to OA)

Asymptomatic CPPD

- Most joints with CPPD have no symptoms
- Crystal deposits discovered on imaging
- **Chondrocalcinosis**: calcification of hyaline cartilage



Public Domain

Pseudogout

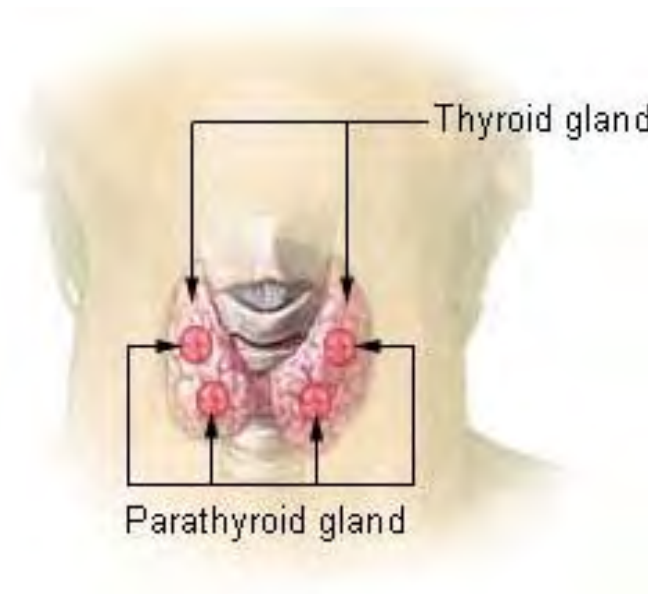
- Acute attacks of **arthritis**
- Resemble attacks of gout: pseudogout
- **Knee involved in 50% of cases**
 - Pain, redness, warmth, swelling



James Heilman, MD/Wikipedia

Pseudogout

- Provoked by trauma, surgery, medical illness
- Many flares reported after **parathyroidectomy**

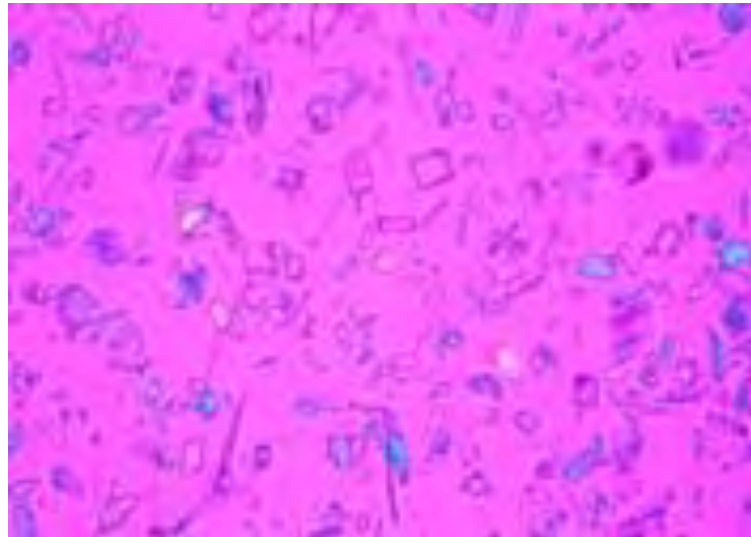


Wikipedia/Public Domain

Pseudogout

Polarized Light Microscopy

- Rhomboid crystals
- Positively birefringent
- **Blue when parallel** to light (yellow for gout)



Harriet Ribbons/Caroline Hoernig

Chronic Joint Disease

- Pseudo-osteoarthritis
- Progressive joint degeneration
- Occurs in ~50% of patients with CPPD joints
- Progressive cartilage deterioration
- Bony enlargement, tenderness similar to OA

CPPD

Treatment

- Acute pseudogout attack
 - Intraarticular glucocorticoid injection
 - NSAIDs
 - Colchicine
- Prophylaxis for pseudogout: Colchicine
- Chronic joint disease: same treatment as OA

CPPD

Associated Conditions

- Joint trauma
- Hyperparathyroidism
- Hemochromatosis

Hemochromatosis

- Hereditary iron overload disorder
- Arthritis: common in hemochromatosis
 - Iron deposition in synovial tissue
- **Calcium pyrophosphate may also deposit**
- Seen in 2/3 of patients

Seronegative Spondyloarthritis

Jason Ryan, MD, MPH

Seronegative Spondyloarthritis

- **Spondylo = spine**
- Arthritis = joint inflammation
- Seronegative = negative rheumatoid factor
- Family of disorders with common features
 - Ankylosing spondylitis
 - Psoriatic arthritis
 - Inflammatory bowel diseases
 - Reactive arthritis



Wikipedia/Public Domain

Seronegative Spondyloarthritis

- **Autoimmune disorders**
- Mediated by **T-cells**
- Unknown trigger



NicolasGrandjean/Wikipedia

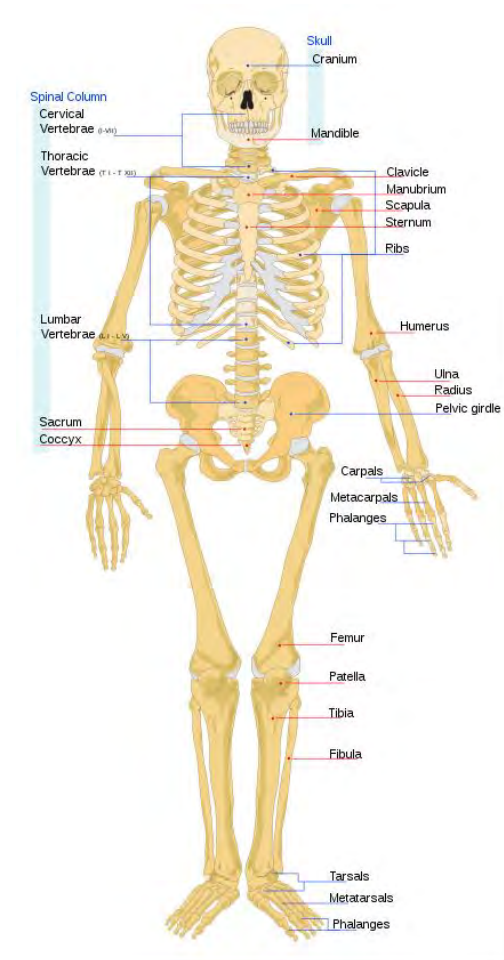
Terminology

- Monoarthritis = 1 joint
- Oligoarthritis = 2-4 joints
- Polyarthritis = >5 joints

Seronegative Spondyloarthritis

Common Features

- **Asymmetric oligoarthritis**
 - Acute attacks of joint pain and swelling
 - Often lower extremities
- Contrast with RA
 - Symmetric
 - Polyarthritis
 - Often hands



Wikipedia/Public Domain

Seronegative Spondyloarthritis

Common Features

- Axial spine inflammation
 - Commonly sacroiliac (SI) joints
- Dactylitis (sausage digits)
- Enthesitis
 - Inflammation of ligament/tendon attachment to bone

HLA B27

- Human Leukocyte Antigens
- Antigens that make up MHC class I and II molecules
- Genes on chromosome 6 determine “HLA type”
- MHC Class I Genes: HLA-A, HLA-B, HLA-C
- HLA B27: Common in spondyloarthritis disorders
 - **90% of ankylosing spondylitis cases**
 - **50% of psoriatic arthritis cases**
 - Most people with B27 never develop AS

Ankylosing Spondylitis

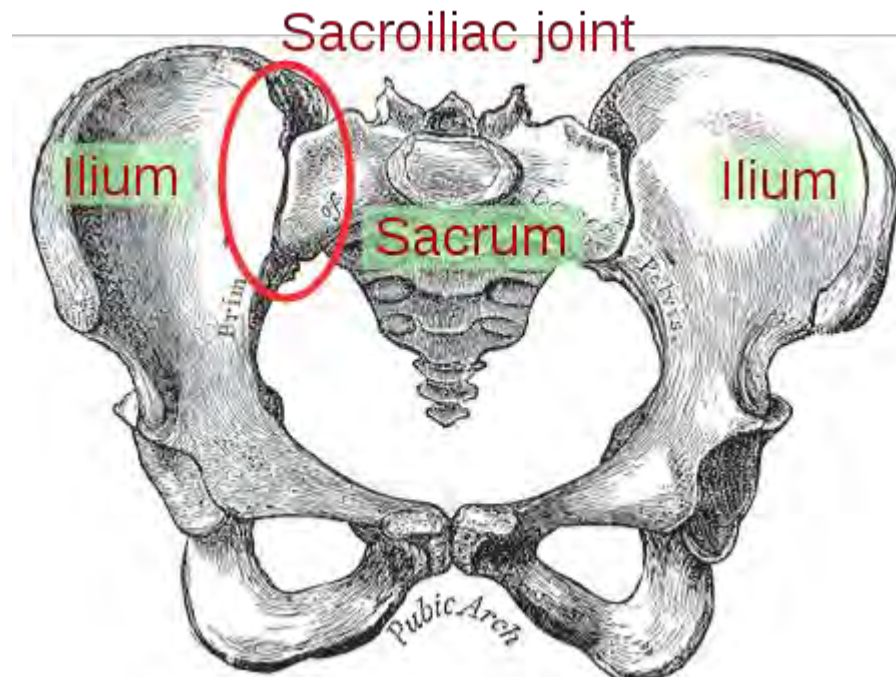
- Classic form of seronegative spondyloarthritis
- Ankylosis = new bone formation in spine → stiffness
- More common in **males**
- Usually **20-30 years old**

Ankylosing Spondylitis

- **“Inflammatory” back pain** (~75% of patients)
 - Younger age (<40 years)
 - Slow, insidious onset
 - Improves with exercise
 - Does NOT improve with rest
 - Pain at night (better with awakening/movement)

Ankylosing Spondylitis

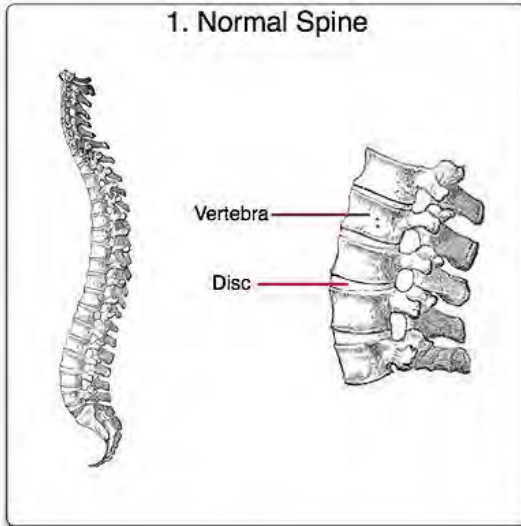
- Classically involves the sacroiliac (SI) joint
- Sacroiliitis



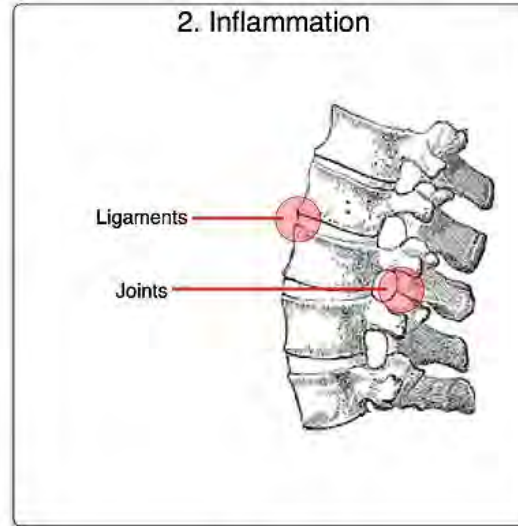
Mikael Häggström/Wikipedia

Bamboo Spine

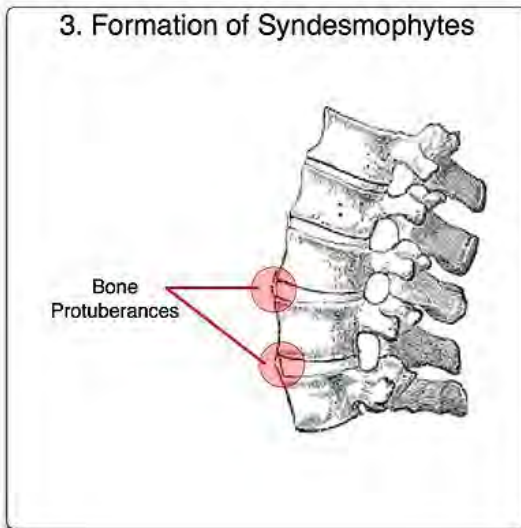
1. Normal Spine



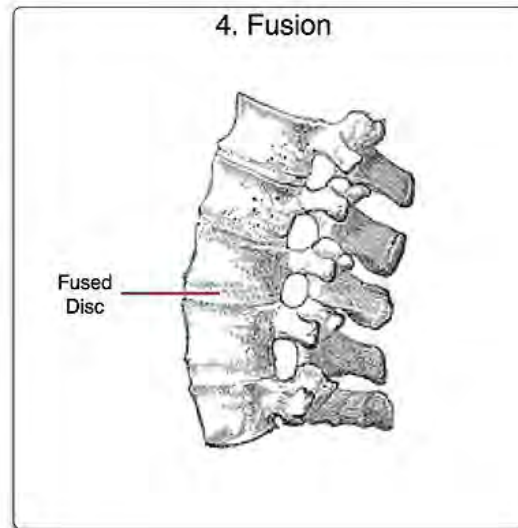
2. Inflammation



3. Formation of Syndesmophytes



4. Fusion



Bamboo Spine



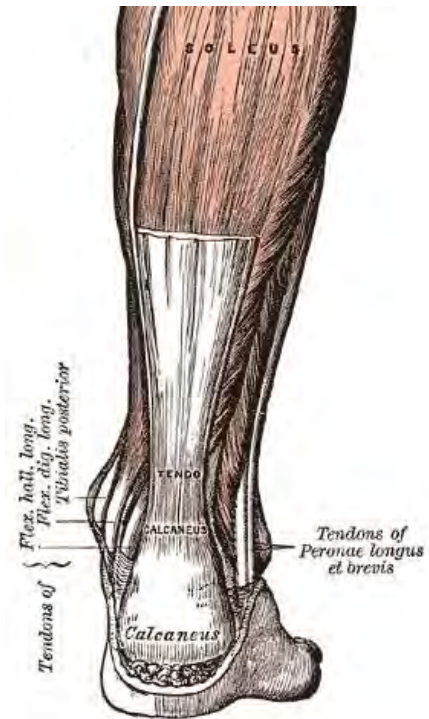
James Heilman, MD/Wikipedia

Enthesitis

- Inflammation of tendon insertions to bone
- Classically insertion of Achilles tendon to calcaneus
- Or plantar fascia to calcaneus
- Causes **heel pain**
- Common presenting feature



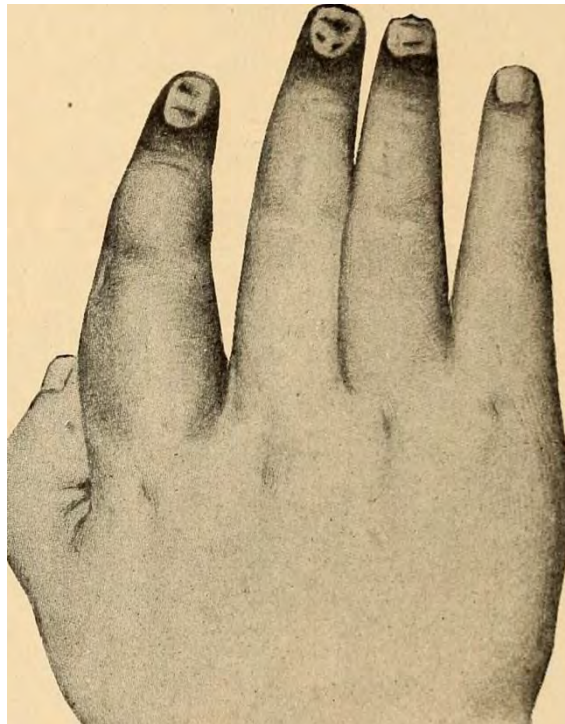
BodyParts3D



Wikipedia/Public Domain

Dactylitis

- Swelling of fingers and toes
- Caused by tendon and soft tissue inflammation

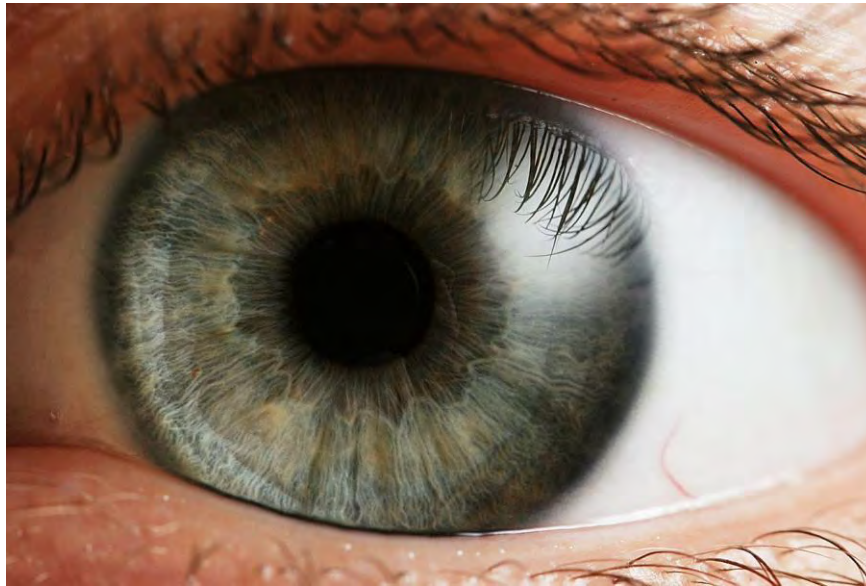


Wikipedia/Public Domain

Ankylosing Spondylitis

Other Features

- Uveitis
- Aortitis
 - Often leads to **aortic regurgitation**



Petr Novák, Wikipedia

Ankylosing Spondylitis

Other Features

- Restrictive lung disease
- ↓ chest wall and spine mobility



Ankylosing Spondylitis

Lab Testing

- Elevated acute phase reactants
- Most patients: **↑ESR and ↑CRP**

Ankylosing Spondylitis

Classic Case

- 25 year old male
- Inflammatory back pain
- Heel pain
- Swollen finger and toes
- Elevated ESR and CRP
- HLA B27 positive
- Treatment: Anti-inflammatory drugs
 - NSAIDs
 - Anti-TNF antibodies (infliximab)

Psoriatic Arthritis

- Arthritis associated with psoriasis
- Occurs in less than 1/3 of psoriasis patients



James Heilman, MD/Wikipedia

Psoriasis

Nail Findings

- Nail pitting
- Onycholysis (separation of nail from nailbed)
- Hyperkeratosis
- 46% of uncomplicated psoriasis cases
- **90% of psoriatic arthritis cases**



Alborz Fallah/Wikipedia

Psoriatic Arthritis

Common Features

- Asymmetric polyarthritis
 - Mimics RA
 - Morning stiffness
 - Improves with use
- Distal interphalangeal (DIP) arthritis
- Sacroiliitis
- **Dactylitis**
 - Sausage digits occur in half of patients
- Heel pain (enthesitis)



Psoriatic Arthritis

Common Features

- Distal interphalangeal (DIP) arthritis
- Classic finding: **“pencil in cup”** deformity DIP joint



Public Domain

Inflammatory Bowel Disease

Crohn's disease and Ulcerative colitis

- Frequently complicated by arthritis
- Type 1 pattern
 - <5 joints
 - Usually large joints: knees, hips, shoulders
 - Symptoms often with flare of GI disease
- Type 2
 - >5 joints
 - Small joints of the hands
 - Independent of GI disease
- Can see spondylitis and sacroiliitis
- Rarely enthesitis and dactylitis

Reactive Arthritis

- Arthritis following **infection**
- Form of spondyloarthritis (autoimmune)
- Occurs **days to weeks after an infection**
- One or multiple joints affected
- Sometimes occurs with dactylitis and enthesitis
- Symptoms usually resolve in 6-12 months

Reactive Arthritis

Triggering Infections

- GI bacteria:
 - Salmonella
 - Shigella
 - Yersinia
 - Campylobacter
 - Clostridium difficile
- Urogenital: **Chlamydia trachomatis**

Reactive Arthritis

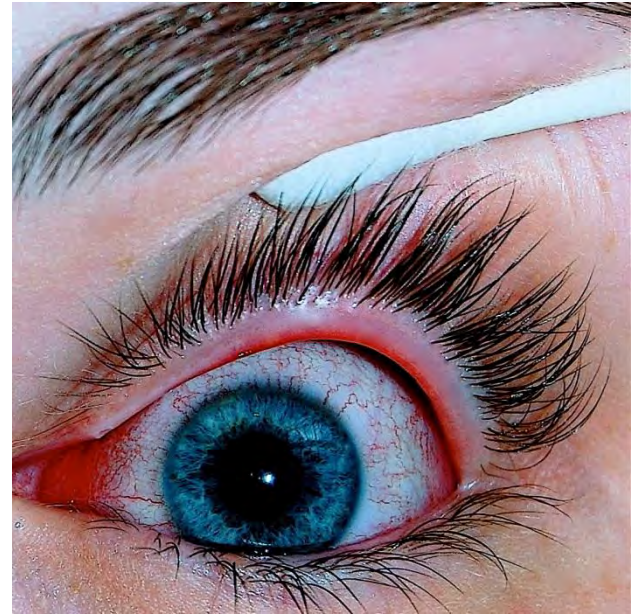
Clinical Features

- **Asymmetric oligoarthritis**
 - Usually 1-4 weeks after infection
 - Most commonly affects lower extremities (knees)
- Enthesitis (heel pain)
- Dactylitis
- Inflammatory low back pain

Reactive Arthritis

Clinical Features

- **Conjunctivitis**
- Urethritis (dysuria)
- Oral ulcers
- Reiter Syndrome
 - Older term
 - Arthritis, urethritis, conjunctivitis following infection



Joyhill09/Wikipedia

Muscle Disorders

Jason Ryan, MD, MPH

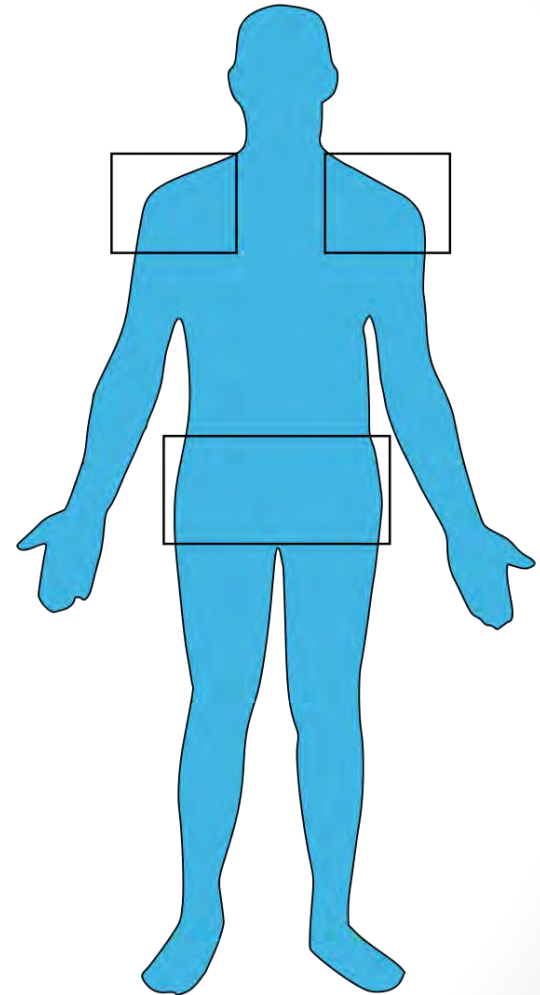
Polymyalgia Rheumatica

- **Inflammatory** disorder
- Unknown cause
- Occurs in **older patients (age > 50)**
- Muscle pain/stiffness
- Diagnosed clinically: no pathognomonic test
- Commonly occurs with **temporal arteritis**

Polymyalgia Rheumatica

Clinical Features

- Bilateral proximal muscle **stiffness**
 - Neck or torso
 - Shoulders/proximal arms
 - Hips/proximal thighs
- Worse in morning
- Often difficulty dressing



Wikipedia/Public Domain

Polymyalgia Rheumatica

Clinical Features

- Does not cause muscle weakness
 - **Strength testing normal**
 - **Normal CK level**
- Muscle pain (myalgias) especially in **shoulder**
- Sometimes malaise, fever, fatigue

Polymyalgia Rheumatica

Diagnosis and Treatment

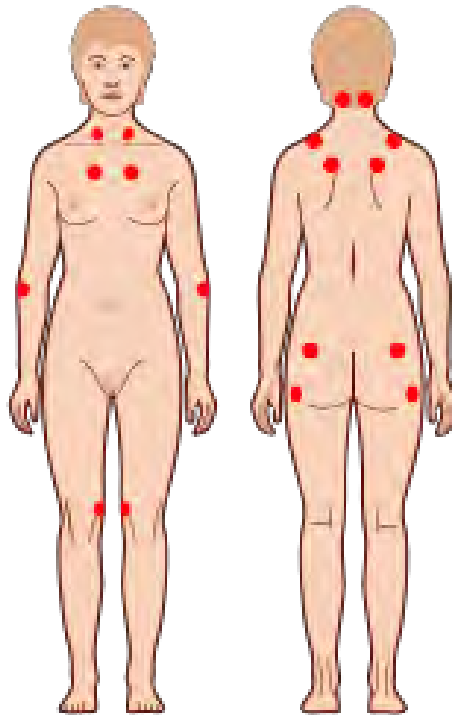
- Characteristic clinical features
- **↑ CRP, ↑ ESR**
- Responds well to **glucocorticoids**

Fibromyalgia

- **Chronic pain disorder**
- Widespread musculoskeletal pain
- Common in women 20 to 55 years old
- Depression/anxiety in 30 to 50% of patients
- Unknown cause
- Diagnosed clinically
- Muscle biopsy: normal
- Normal lab tests

Fibromyalgia

- Point tenderness on exam
- Usually in specific anatomic locations



Sav vas/Wikipedia

Fibromyalgia

- Exercise
- Tricyclic antidepressants (amitriptyline)
- SSRIs

Inflammatory Myopathies

- **Autoimmune muscle disorders**
- Polymyositis
- Dermatomyositis
- Usually involve skeletal muscle (weakness)
- Can involve heart

Inflammatory Myopathies

Diagnosis and Treatment

- Diagnosis: **muscle biopsy**
- Treatment: **immunosuppression**
 - Usually corticosteroids (prednisone) initially
 - Long term treatment with steroid sparing drugs
 - Often azathioprine or methotrexate

Inflammatory Myopathies

Clinical Features

- **Myalgias**
- Slow onset symmetric muscle weakness
- Hallmark: **proximal muscle weakness** at first
 - Muscles closest to midline
 - Difficulty rising from a chair
 - Difficulty climbing stairs
 - Difficulty combing hair
 - Fine hand movements intact
- Distal weakness occurs later in disease

Inflammatory Myopathies

Lab Testing

- Elevated **creatinine kinase (CK)**
- ESR can be elevated (sometimes normal)
- Anti-nuclear antibodies (ANA)
 - Not specific for myopathies
 - Positive in 80-90% of patients
- **Anti-Jo1 antibodies**
 - Histidyl t-RNA synthetase
 - Most common myositis antibody
- Other antibodies (anti-Mi2, anti-SRP)

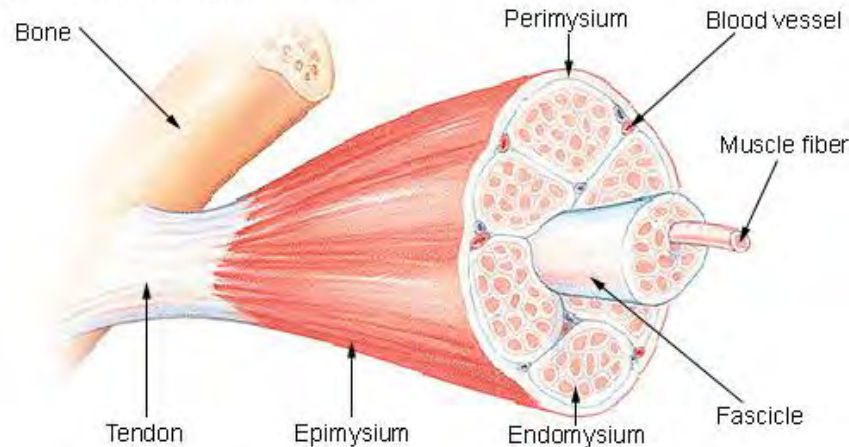
Polymyositis

- Slow onset proximal muscle weakness
- No skin involvement
- Diagnosis: muscle biopsy

Skeletal Muscle

- Perimysium
 - Connective tissue surrounding fascicles (bundles of fibers)
- Endomysium
 - Connective tissue surrounding each muscle fiber (myocyte)

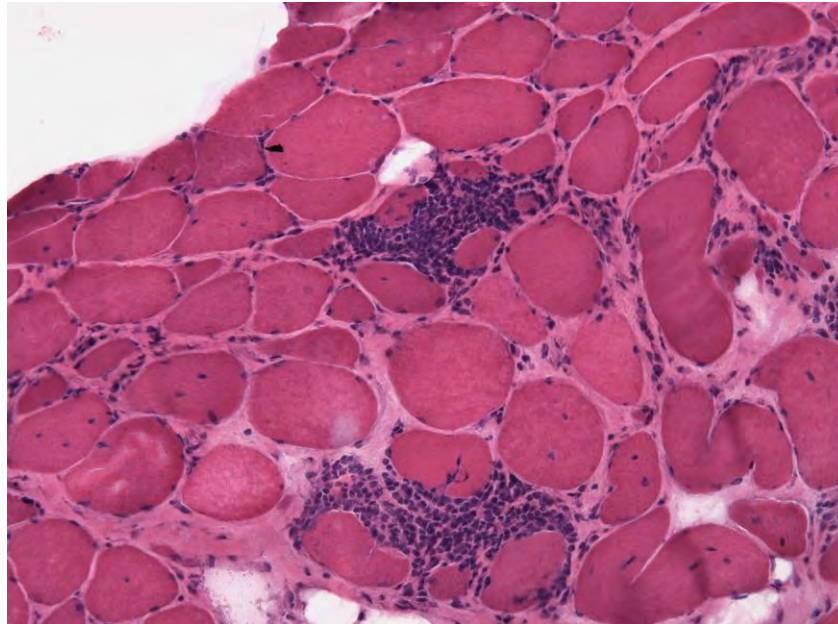
Structure of a Skeletal Muscle



Wikipedia/Public Domain

Polymyositis

- **Endomysial inflammation**
- Predominant cell type: **CD8+ T-cells**



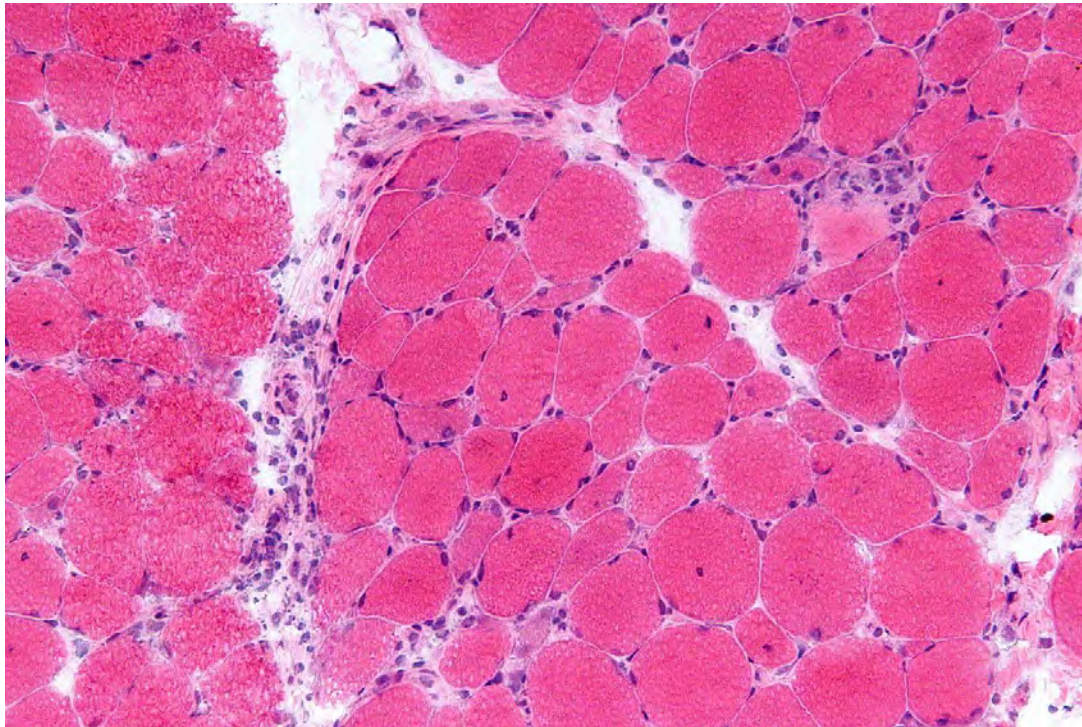
Jensflorian/Wikipedia

Dermatomyositis

- Slow onset proximal muscle weakness
- Skin changes
- Diagnosis: muscle biopsy

Dermatomyositis

- Muscle biopsy: **perimysial inflammation**
- Major cell type: **CD4+ T-cells**



Nephron/Wikipedia

Dermatomyositis

Classic Skin Findings

- **Heliotrope rash**
 - Purple discoloration of upper eyelid
- **Gottron papules**
 - Symmetric red, scaly papules on hand/finger joints
- Both pathognomonic for dermatomyositis



Elizabeth Dugan et al.

Dermatomyositis

Other Skin Findings

- Malar rash (similar to SLE)
- “Shawl and V signs”
 - Red-brown discoloration of skin
 - Occurs in sun exposed area
 - Upper back (like a shawl)
 - Neck/upper chest sparing skin below chin (V sign)
- Mechanic’s hands
 - Cracks/fissures on palms with increased pigmentation

Malignancy

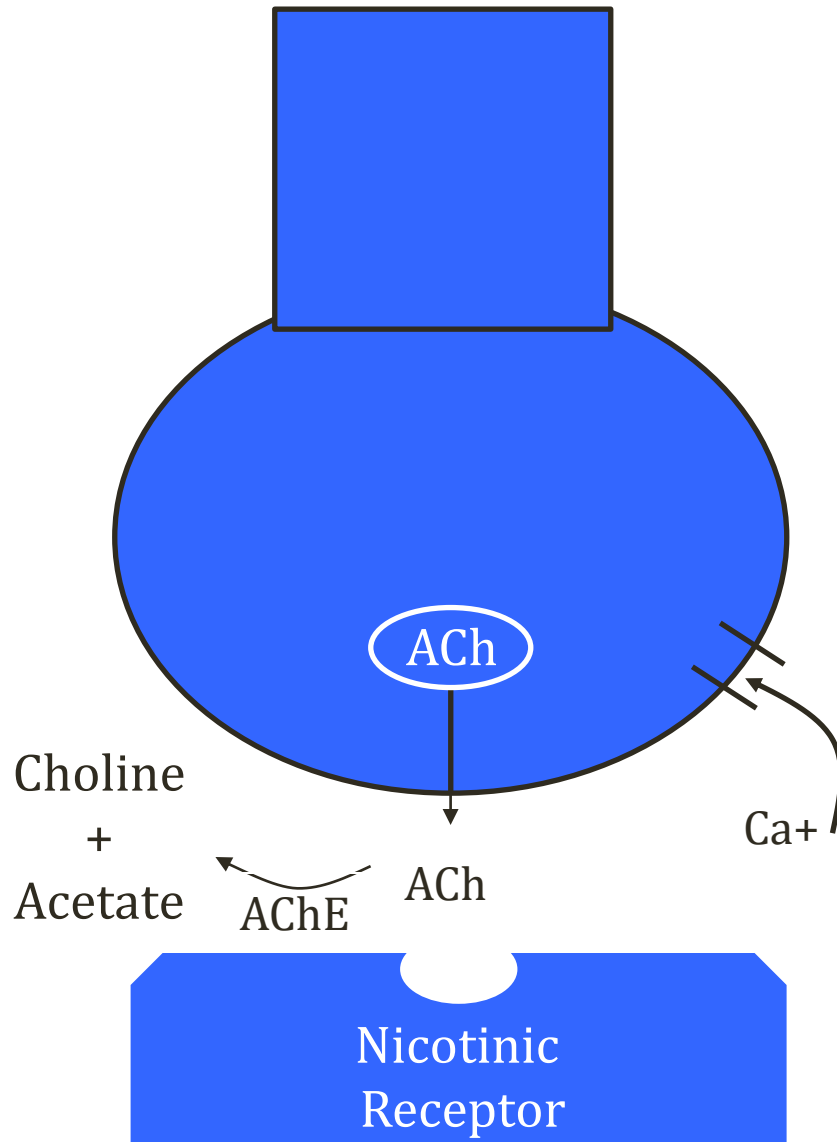
- Associated with inflammatory myopathy
- Mechanism unclear
- Stronger evidence for DM versus PM
- Associated malignancies mostly **adenocarcinomas**
 - Cervix
 - Lung
 - Ovaries
 - Pancreas
 - Bladder
 - Stomach

Neuromuscular Disorders

Jason Ryan, MD, MPH

NMJ Disorders

- Myasthenia gravis
- Lambert-Eaton Myasthenic Syndrome

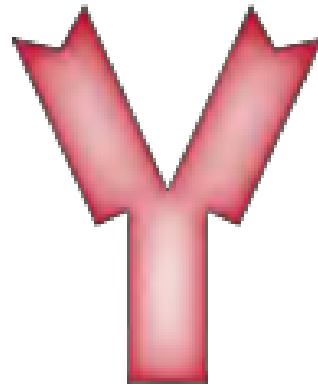


Neuromuscular Junction

- Pre-synapse: nerve terminal
 - Depolarization → calcium influx
 - Release of acetylcholine (ACh) vesicles
- Post-synapse: motor end plate
 - Acetylcholine → nicotinic receptors
 - Muscle depolarization → contraction
- ACh broken down by acetylcholine esterase (AChE)

Myasthenia Gravis

- **Autoimmune disease**
- Antibodies block nicotinic ACh receptors
- Compete with ACh for receptor binding
- Muscles weakness
- Diagnosis: **Acetylcholine receptor antibodies**



Martin Brändli /Wikipedia

Myasthenia Gravis

Clinical Features

- **Muscle fatigability**
 - Repeated nerve stimulation \rightarrow \downarrow ACh release
 - Muscles weaken with use

Myasthenia Gravis

Clinical Features

- **Diplopia and ptosis**
 - Extraocular muscle weakness
 - 50% patients present with eye complaints
- Speech, chewing and swallowing problems
 - 15% patients present with “bulbar symptoms”



Andrewya/Wikipedia

Myasthenia Gravis

Treatment

- Neostigmine, Pyridostigmine, Edrophonium
 - **Acetylcholine esterase inhibitors**
 - ↓ ACh metabolism
 - ↑ ACh levels in synapse
- Immunosuppressants

Myasthenia Gravis

Exacerbations

- Occur for two reasons
- #1: Insufficient dose AChE inhibitor
- #2: Cholinergic crisis
 - Too much medication
 - Muscle refractory to ACh
- Tensilon test: Administer **edrophonium**
 - Short acting AChE inhibitor
- Muscle function improves: ↑ dose AChE inhibitor
- Muscle function fails to improve: ↓ dose

Myasthenia Gravis

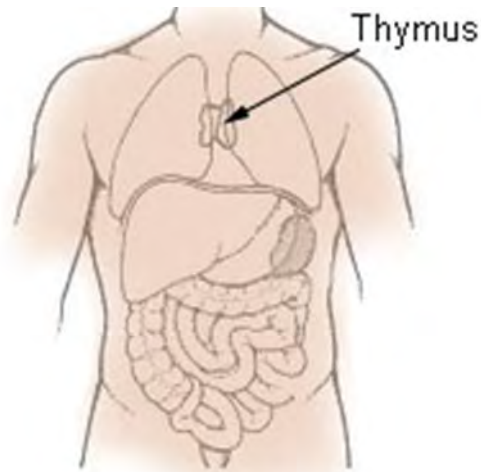
Exacerbations

- Tensilon test may lead to complications
- Caused by diffusely **increased ACh levels**
- Activation of **parasympathetic activity**
- Salivation
- Abdominal cramping (bowel stimulation)
- Asthma (bronchoconstriction)
- Bradycardia

Myasthenia Gravis

Disease Associations

- Most MG patients have **abnormal thymus**
 - Hyperplasia ~85%
 - Thymoma ~15%
- MG often **resolves with thymectomy**
- Key test: Imaging of mediastinum (CT or MRI)



Public Domain/Wikipedia

LEMS

Lambert-Eaton Myasthenic Syndrome

- Also a disorder of NMJ (more rare)
- Paraneoplastic syndrome (small cell lung cancer)
- Antibodies against pre-synaptic Ca channels
- Prevent ACh release
- Diagnosis: VGCC antibodies
 - Antibodies to voltage-gated calcium channel (VGCC)

LEMS

Lambert-Eaton Myasthenic Syndrome

- Slow onset **symmetric proximal muscle weakness**
 - Also seen in myositis
 - Normal CK levels
 - No muscle pain/myalgia
- Difficulty walking or rising from chair
- Difficulty combing hair

LEMS

Lambert-Eaton Myasthenic Syndrome

- **Autonomic dysfunction common**
- Classically **dry mouth** from ↓ salivation
- Erectile dysfunction, constipation

LEMS

Lambert-Eaton Myasthenic Syndrome

- **Muscle use → improved symptoms**
 - Contrast with myasthenia gravis
 - More depolarization → more ACh release
- Tensilon test: mild ↑ in muscle function
 - ↑ ACh → more contraction
 - Much less effective than in MG (reverses symptoms)
- Treat (or locate) underlying malignancy
- Guanidine: inhibits K⁺ channels → ↑ ACh release

NMJ Syndromes

	Myasthenia	Lambert-Eaton
Cause	ACh receptor ab	Calcium channel Ab
Muscle Use	Worsens	Improves
Eye Symptoms	Classic	Less common
Proximal Muscles	Rare	Common
Autonomic Symptoms	Absent	Common
Tensilon Test	Symptom reversal	Mild improvement