Test Overview

- 2 hours to do the test
- Don’t be surprised if the test takes the whole time.
- Major ideas are emphasized.
- Biomechanics is a portion of it (~3 questions).
- Calculators may be useful.

-Review modified from Payal Kohli's review

What to Study

- Schiller and Olsen!
  - Bone development
  - Cells Involved
- Major diseases
  - Osteoporosis
  - Rheumatoid arthritis
  - Osteoarthritis
- A little bit of biomechanics

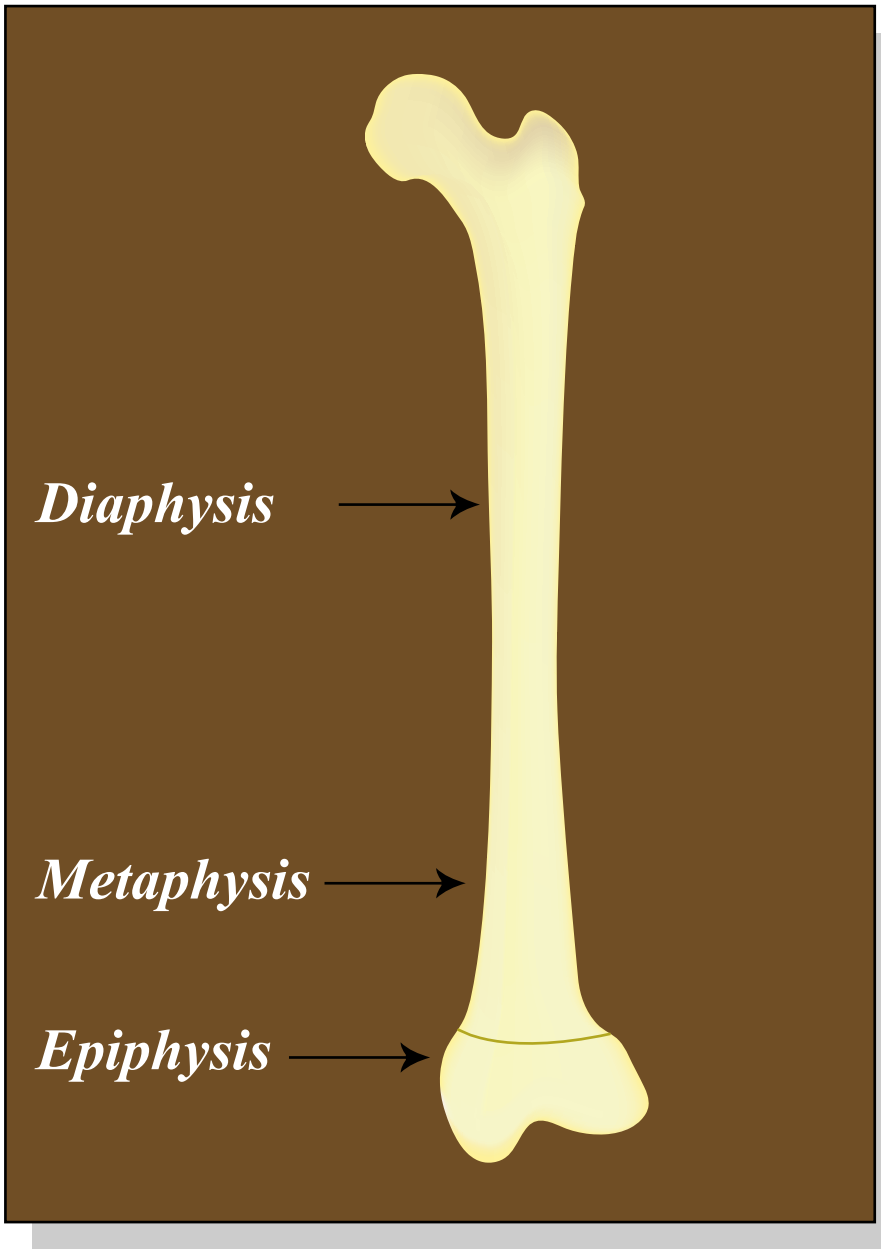


Figure by MIT OCW.

Normal Anatomy of a Long Bone

Long bones are divided into 3 sections.

-The diaphysis is the tubular shaft.

-The metaphysis is the wider part at the extremity of the shaft.

-The epiphysis is at the end of the bone, and in the **young** it is separated from the metaphysis by the growth plate.

What is a synonym for the growth plate?

A synonym for growth plate is **physis**. Note how the anatomic names of the parts of the bone are derived from this word

Schiller/Overview of bone

- Know overview of bone synthesis, anatomy, and vasculature.
  - Nutrient arteries passes through the cortex to the marrow and subsequently reperforates, serving the inner 1/3 of the cortex (the endosteum)
  - Perforant arteries - from the overlying musculature and serve the outer 2/3 of cortex.
  - Osteoid – unmineralized bone
  - Osteon – unit of osteocytes and bone surrounding a Haversian canal
  - Haversian and Volkman's canals. Haversian are parallel to the axis and Volkman's are perpendicular. The 3-D system is the Haversian system
  - *Wolff's Law*: "Use it or loose it" or Bones respond to stress

Schiller/Overview of bone

- Types of marrow
  - red - hematopoeisis
  - yellow – fat
  - white – pathology
- Extent of red and yellow marrow depends on age and site.
- Red marrow disappears from appendicular skeleton (only in axial skeleton) after puberty.
- Sample question: Biopsies (normal/abnormal?)
  - 30M tibia biopsy → red
  - 75F vertebral body → yellow
  - 10M vertebral body → yellow

Schiller/Overview of bone

- Types of bone
  - Woven - Bone found during development, in fracture healing, and at pathological sites. It is characterized by disorganized Type I collagen with many osteocytes of various sizes and shapes. Produced with rapid deposition.
  - Lamellar – Characterized by Collagen I in a parallel arrangement and few osteocytes, which are similar in size. Deposition is slow. Found in mature bone. There are 4 types: trabecular, circumferential, interstitial and concentric.
- Sample question: Differences between woven and lamellar bone.

Bjorn Olsen

- Know the basic process of endochondral ossification.
- Be familiar with the transcription factors and the zones of cartilage.
- Be able to anticipate what a given defect could do.
  - FGFR3 leading to achondroplasia, why?
  - Collagen X leading to Schmid metaphyseal chondroplasia, why?
  - PTHrP activation leading to Jansen's metaphyseal chondrodysplasia, why?

Endochondral vs. Intramembranous Ossification

- Appositional Growth: Placing bone of the surface of pre-existing bone (cells come from outside and deposit ECM) vs. interstitial growth (cells come from within)

- **Intramembranous ossification**
  - Yields the flat bones of the cranium and the medial clavicles
  - Initial mesenchymal condensation (fibrous tissue) and subsequent formation of calcified bone
- **Endochondral ossification**
  - Produces the facial bones, vertebrae, lateral clavicles, and long bones that compose the appendicular skeleton
  - Intermediate step wherein a cartilage template, or anlage, is produced to regulate the growth and patterning of the bone

Endochondral Appositional Ossification

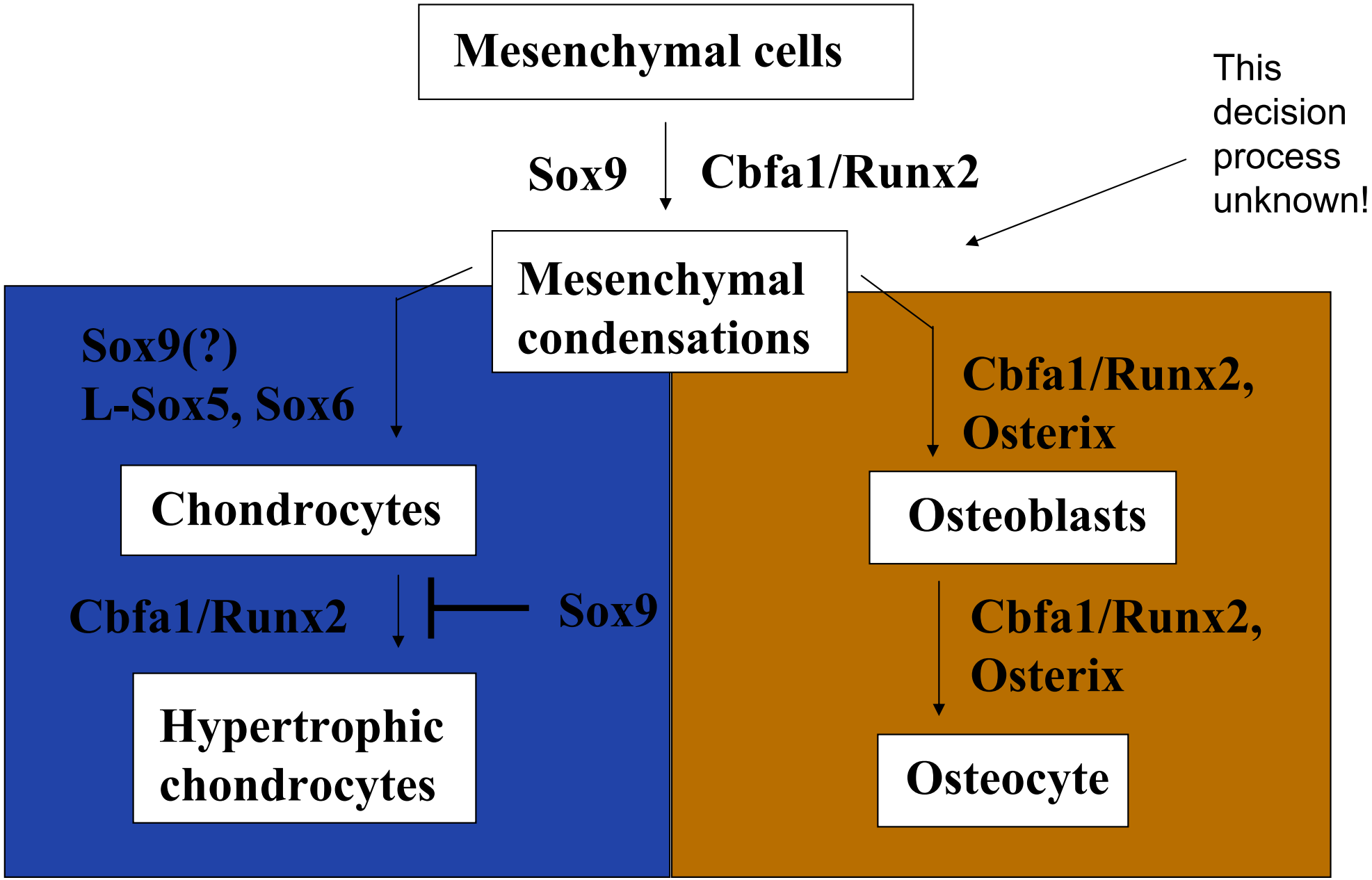
- Beginning with the population most distal to the future diaphysis of the long bone, the pool of condensing mesenchymal cells, known as reserve or resting chondrocytes, differentiates centrally into a proliferative population of chondrocytes that produce type II collagen, and peripherally into perichondrial cells that express type I collagen.

- The central population of cells, known as proliferating chondrocytes, is stimulated near the midpoint of the cartilage anlage to leave the cell cycle, hypertrophy, and initiate the synthesis of type X collagen in place of type II collagen.

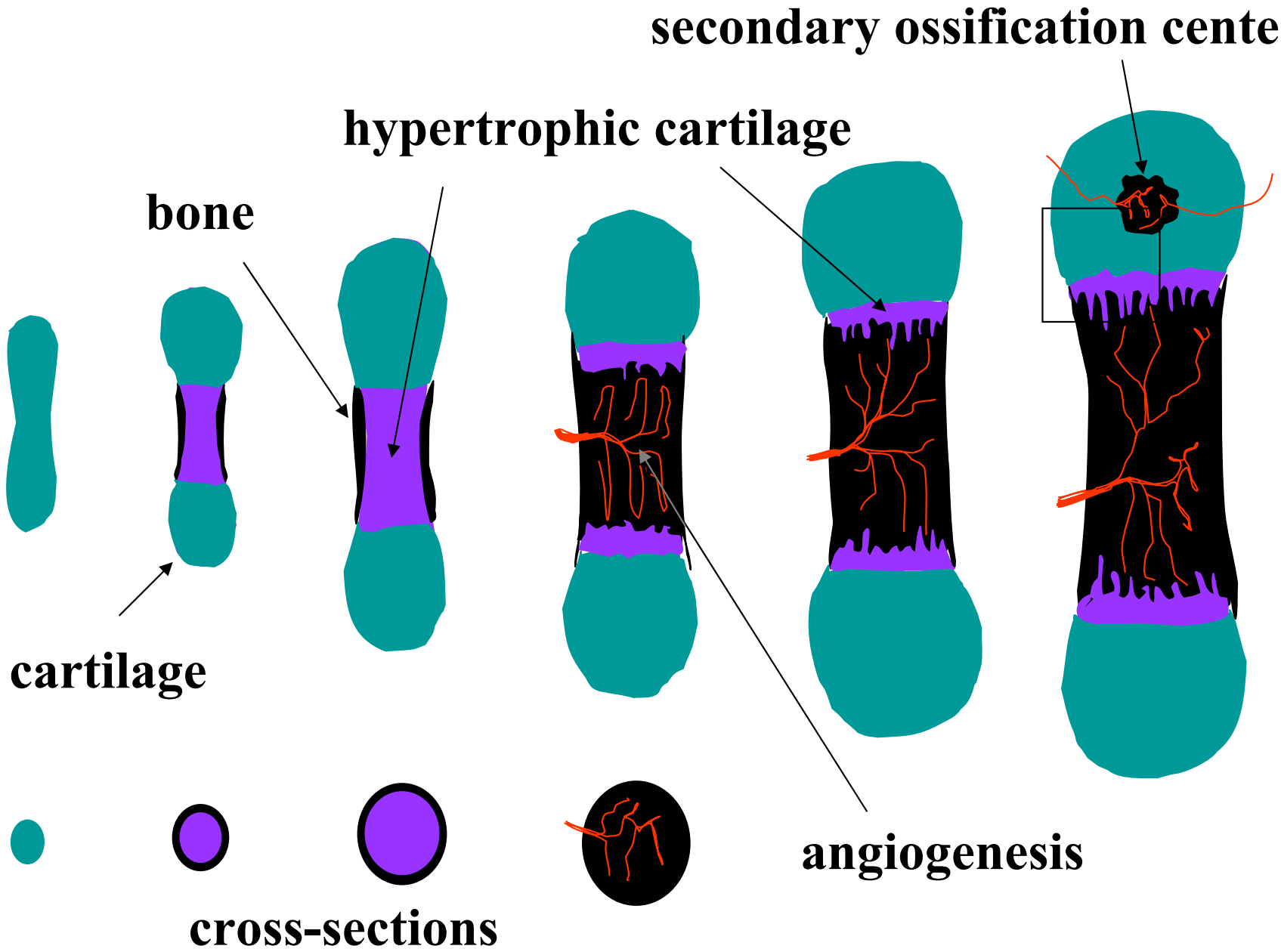
- During this process, these cells differentiate into a transient pool of pre-hypertrophic chondrocytes that become a longer-lived pool of hypertrophic chondrocytes.

- Most proximally, these hypertrophic cells are replaced by trabecular bone as the cells undergo apoptosis.

Transcriptional control of chondrocytic and osteoblastic differentiation pathways



Stages in endochondral ossification-from cartilage to bone



Regulation of growth plate activities maintains global polarity

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Interaction of FGF and BMP signaling in growth plates

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Cells

- ***Osteoblasts***: The master cell. Mensenchymal origin. Controls bone formation and resorption. Has receptors for PTH, estrogen, and prostaglandins. Does NOT have a calcitonin receptor. Releases IL-1 and IL6. Controls osteoclast. Interconnections between osteoblasts through cadherins. Regulation of these cells is by TGF-b, prostaglandins, IGF-I, PDGF, PTH, Estrogen, BMP, cytokines, androgens, insulin, and other growth factors.

- ***Osteoclasts***: Multinucleated giant cells from the macrophage lineage. These cells are responsible for bone resorption. RGD integrin binding allows for the formation of an acidic seal on the bone surface. The cells release calcium salt, phosphate, degradative enzymes, and growth factors from bone. The collagenases are previously made by osteoblasts, stored in the bone matrix, and activated by the osteoclasts. The have receptors for calcitonin, but not for Vitamin D, and only few PTH receptors. Prostaglandin E2 stimulates these cells. *Osteopetrosis* is caused by poorly functioning osteoclasts.

- ***Osteocytes***: Metabolically inactive cells located in the lacunae within the bone matrix; osteoblasts trapped in their own synthetic matrix. They have little ER, and have canaliculi, which are small hair-like connections between the cell and the extraceullar fluid. The function is purported to sense damage or strain.

Bone Diseases

- Be familiar with causes and phenotypes of various diseases.
- Ex. What does Paget's disease look like (excess osteoclast activity), and how could it be caused (anything that causes unregulated osteoclast activity)?
- Don't bother memorizing every bone disease – just the ones on which time was spent!

Schiller: Other things to know…

Fractures:

- Know time-course of fracture healing!
- Fx healing:
- hemorrhage (hrs –2 days)
- inflamm (2-5 days)
- early repair (4-12 days)
- callus (7-40 days)
- remodeling (>50 days)
- Know which cells present at which time, and what bone types present when.
- Read Robbins for review

Heritable Disorders of Connective Tissues (Dr. Krane's Lec)

- *Marfan's Syndrome:* Fibrillin-1 mutation leads to skeletal, ocular, and vascular malformations
- *Ehlers-Danlos*: Collagen III mutation.

  -Hyperextensible skin, joint laxity.
- *Menkes Disease*- X-linked recessive disorder related to Cu metabolism; mutations in copper-transporting ATPase gene (*ATP7A*); lethal during early childhood
- *Autosomal dominant cutis laxa* -dominant negative aberrant tropoelastin; Lax skin, hernias

Biomechanics

- Free-Body Diagram- Determining force by muscle and joint reaction force
- Understand Stress/Strain
  - Structural stiffness
  - Material stiffness

Statics

- Solve for moment = zero (based on $\tau = F \times d$.
- Plug into equations for x and y.
- Use components to get total force and angle.

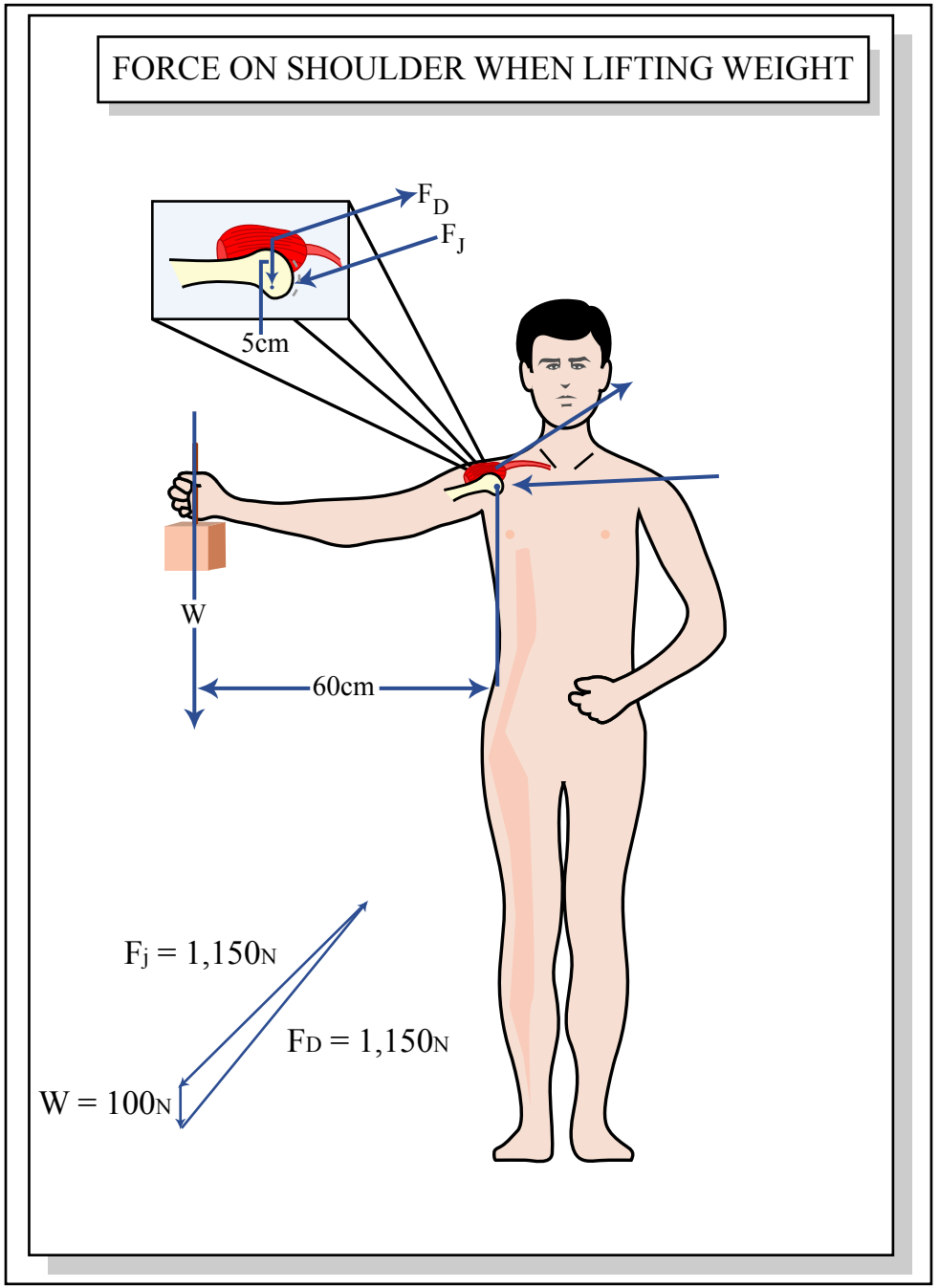

Figure by MIT OCW.

Stress and Strain

- Stress, σ: the intensity of force sustained by a material through its cross section. $\sigma = \frac{F}{A}$

  F: applied force

  A: cross sectional area

- Strain: the extent to which a material deforms under applied load. $\varepsilon = \frac{L_0 - L}{L_0}$

  L_0: Un-deformed length

  L : deformed length

Yield stress and strain define the point at which ultimate deformation occurs

Ultimate stress or strain define the point at which failure occurs

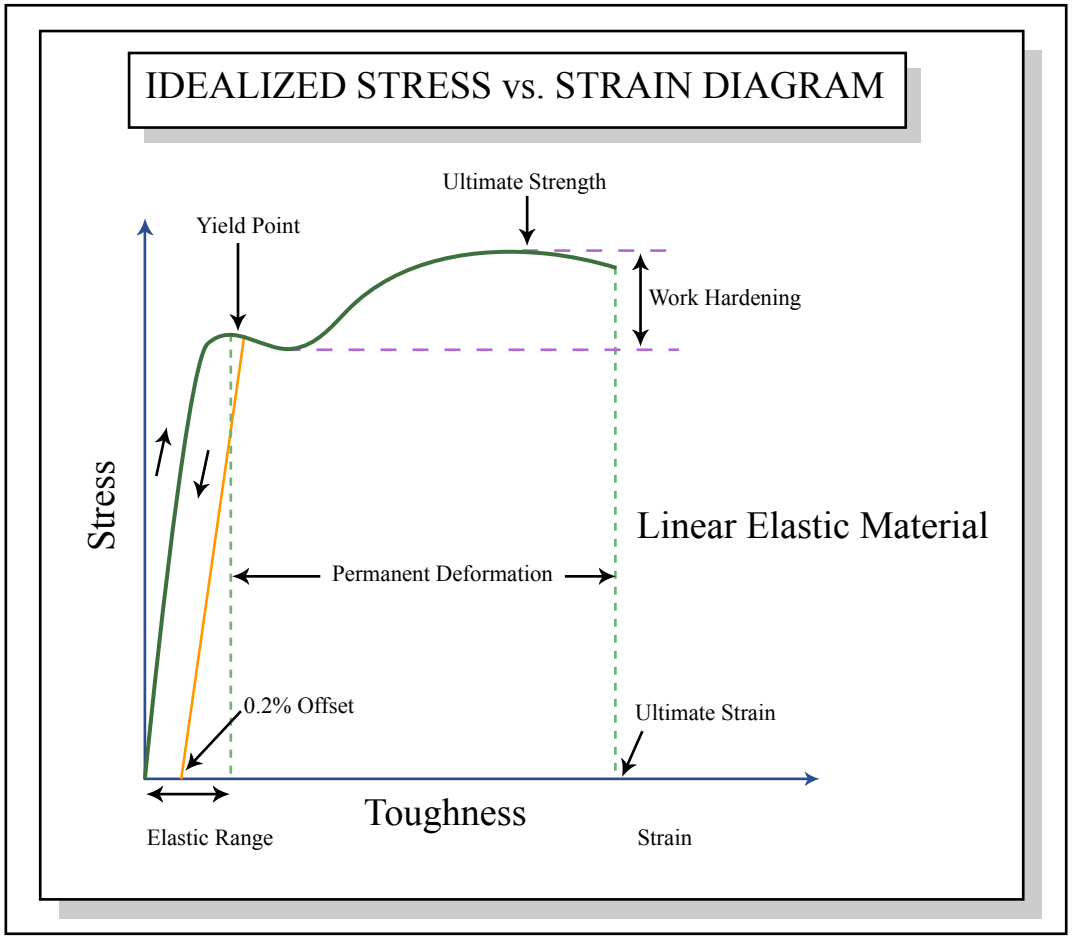

Figure by MIT OCW.

Rheumatic Diseases (Dr. Robinson)

- Focus on pathogenesis from Dr. Anderson's Lec.
- Understand the differential diagnosis for the rheumatic diseases.
- Rheumatic diseases may involve all organ systems. Often this takes place through inflammation in connective tissues and blood vessels.
- Inflammation may be induced by infection due to micro-organisms, by certain crystals, or by autoimmune mechanisms.
- The etiology of many of the rheumatic diseases remains unknown.

Rheumatoid Arthritis

- A chronic, progressive inflammatory arthritis which may involve any joint; polyarticular and symmetrical in distribution; etiology unknown
- It causes pain and limitation of joint function.
- The pathology is that of a chronic inflammatory reaction of joint synovial tissues.
- The inflammation is thought to be an autoimmune reaction, but the stimulus is unknown – understand the basis for this (Dr. Anderson)
- The inflammatory reaction leads to destruction of articular cartilage and other joint structures, producing deformities. This disease varies in severity from one patient to the next, and not all patients develop severe deformities.
- Treatment in early stages may alleviate both pain and the potential for deformity.
- There are several anti-inflammatory drugs available for rheumatoid arthritis.

Rheumatoid Arthritis

- Key words: Pannus, joints affected (MCP, PIP), subcutaneous rheumatoid nodules, ulnar deviation, subluxation
- 80% of patients have positive Rheumatoid factor (anti-IgG)
- Presentation: stiffness/gelling in morning, improving with use
- Symmetric joints affected
- Can see systemic sxs (fever, fatigue, pleuritis, pericarditis)

Treatment

- Nonsteroidal anti-inflammatory drugs
- Glucocorticoids, very effective, but limited in use because of side-effects.
- Hydroxychloroquine, an anti-malarial drug with mild anti-inflammatory effects, mechanism unknown.
- Methotrexate. An inhibitor of de novo purine synthesis with immunosuppressive effects
- Sulfasalazine, a combined sulfa drug-salicylate with anti-inflammatory effects toward rheumatoid arthritis and inflammatory bowel disease.
- Leflunomide, an inhibitor of pyrimidine synthesis.
- Anti-TNFa agents
  - Etenercept, a recombinant human truncated TNF receptor
  - Infliximab, an engineered chimeric monoclonal antibody to TNFa

Other forms of arthritis

- Septic arthritis (tuberculosis, B. burgdorferi – Lyme disease)
- Psoriatic arthritis
- Reactive arthritis/Reiter's syndrome
- (Not mentioned, but be aware of lupus)
- Palindromic Rheumatism: Recurrent episodes of acute arthritis.
- Autoimmune Rheumatic Diseases: Caused by one of several mechanisms including antibodies binding to self antigens (complement, recruitment of inflammatory cells), immune complexes deposited in joints, and delayed type hypersensitivity (T cell mediated cytolysis).

Gout

- A crystal-induced arthritis
- The pathogenesis of the disease is due to the supersaturation of the extracellular fluids with respect to monosodium urate (needle-like, negative birefringence)
- These crystals induce acute inflammation following their ingestion by neutrophils
- Chronic inflammation also leads to tissue destruction around deposits on sodium urate crystals (tophi)

Other forms of Gout

- Acute gouty arthritis: one joint without constitutional symptoms. Triggered by consuming a large meal, drinking alcohol (competitively impair urate secretion), trauma, and drugs/surgery. Self-limiting.
- Chronic gouty arthritis: hyperuricemia. Can lead to renal failure and urate stones. Treatment is NSAIDs or allopurinol.
- Pseudogout: Caused by excessive levels of inorganic pyrophosphate in the synovial fluid. Has CPP crystals, and causes chondrocalcinosis.

- Don't worry about vasculitis

Dystrophies/Inflammatory Myopathies

- **Muscle**: Know about motorneurons, neuromuscular junctions, myofibrils, myofilaments.
- **Muscle fibers**:
- *Type I* (slow twitch, red): Rich in blood supply and mitochondria for oxidation. Optimal for sustained, tonic contractions. Recruited at low frequencies of stimulation and low loading. “one slow, red ox”
- *Type II* (fast twitch, white): Rich in glycogen. Optimal for brief, intense contraction. Recruited at higher frequencies and high loading.
- Diseases often diagnosed with electrical stimulation tests and biopsies.

- **Denervation**: Includes polio, amylotrophic lateral sclerosis, peripheral neuropathy (ex. diabetes), trauma. Characterized by an initial fiber shrinkage and an eventual muscle atrophy. Reinnervation caused by cells converting to the fiber type of the new neuron (fiber type grouping). Subsequent denervation produces group atrophy.
- **Neuromuscular blockage**:
- Presynaptic blockage is generally from drugs.
- *Myasthinia Gravis* – post-synaptic blockade leads to a loss of muscle strength after use. Muscle may show type II atrophy and lymphocyte clusters. Caused by an autoimmine attack on acetylcholine receptors. Treatment is anticholinesterase medication. Muscle fatigue
- **Degeneration**:
- *Rhabdomyolysis* – loss of striations, macrophage invasion, connective tissue replacement, elevated creatine phosphokinase (CPK) and aldolase. Myoglobin can cause acutre renal failure.
- *Segmental Necrosis*

- ***Muscular Dystrophy***: Progressive weakening and wasting.
- *Duchenne's* – X-linked. Hypertrophied calves, segmental degeneration. From the absence of dystrophin protein.
- *Becker's* – mutated dystrophin protein
- *Limb girdle muscular dystrophy* – mutation in a-sarcoglycan.
- *Fascioscapulohumeral muscular dystrophy*
- ***Congenital myopathies***: central core disease, nemaline myopathy
- ***Metabolic myopathies***: Glycogen storage diseases, malignant hyperthermia after halothane injection, mitochondrial defects.
- *McArdle's Disease*: Myophosphorylase deficiency leads to muscle weakness.

Mitochondrial Myopathies

- Maternal inheritance pattern.
- BIG PICTURE
  - Cellular pathology results from relative disproportion of need and capacity for oxidative metabolism
  - Virtually all tissues and organ systems depend on oxidative metabolism and may therefore be affected in these disorders
  - Resultant protean manifestations of mitochondrial disorders
- *Leber's Hereditary Optic Neuropathy* - Subacute, painless central vision loss, mtDNA mutations *(*Optic Neuropathy)
- *Kearns Sayre Syndrome (KSS)* – deletions in mtDNA lead to progressive opthalmoplegia, weakness and short stature. (Ophthalmoplegia)
- *Mitchondrial encephalomyopathy with lactic acidosis (MELAS)* – point mutation in tRNA for leucine leading to weakness, short stature hearing loss with stress-induced stroke-like episodes. (Pigmentary retinopathy)

Potts summary

- ***Calcium***: Absorption in gut. Vitamin D is required for absorption. Excretion is renal, as regulated by PTH, with a maximum reabsorption of 95%. The serum concentration is tightly regulated by PTH.
- ***Phosphate***: Absorption in gut. Renal reabsorption is up to 100%. Primarily store in the skeleton. Principle site of regulation is the kidney. Estrogen and PTH increase phosphate excretion. Growth hormone, glucocorticoids, and vitamin D decrease phosphate excretion.
- ***Vitamin D***: Steroid hormone. Derived from diet as well as from body precursors as induced by UV radiation. Hydroxylated in the liver (25-OH) and again in the kidney (1,25 dihydroxy vitamin D), to produce the physiologically active form. Functions at the gut enabling adequate absorption of calcium, and in the bone where high levels enhance bone resorption.
- ***PTH***: Acts on bone and kidney directly. G-protein mediated. Maintain extracellular fluid calcium concentrations, and is regulated by serum calcium concentrations (calcium low→high PTH). Increases bone reabsorption, reduces renal clearance of calcium, increases gut absorption of calcium, and increases formation of 1,25-OH-vitamin D.
- ***PTHrP***: Paracrine factor important in embryonic bone development by signaling chondrocytes to stop differentiating and start hypertrophying. Induced by Indian hedgehog with signaling though *patched*. The receptor is the same as that for PTH. Secreted by some tumors.
- ***Calcitonin***: Hormone secreted by parafollicular cells of thyroid to inhibit bone reabsorption by inhibiting osteoclasts. Does not appear to have significant role in normal human ion homeostasis, but can be used (salmon derived) for treatment.

Metabolic Bone Disease

- Know hyper/hypo-parathyroidism!!
  - Causes
  - What symptoms it can cause (“bones, stones, moans, and groans”)
  - How diagnosed?
- Renal osteodystrophy
- Sample question: see decreased urinary cAMP (secondary messenger for PTH), decreased urinary Phosp, and increased serum PTH level. What is it?

Osteoporosis

- Net increased resorption relative to deposition:

  Osteoblasts are not depositing enough bone during remodeling (type II) or osteoclasts are resorbing too much (type I).
- Loss of estrogen increases the effects of PTH, decreases calcium absorption, increases local bone IL-1 (potent stimulator of osteoclast activity) and TNF, and increases IL-6 to promote osteoclast activity.
- Vertebral bodies are affected, especially in the cancellous compartments, in the thoracic and lumbar regions.
- What does it do to bone?

Treatment

- Calcium (1-1.5g/day)/vitamin D pills
- Exercise
- Estrogens (inhibit osteoclasts, stimulate osteoblasts)
- Tamoxifen/raloxifene (analog of estrogen with selective effects; also reduces breast and endometrial carcinomas) - SERMs
- Bisphosphonates (ex. Fosamax - inhibit bone resorption at osteoclast resorption front – use of drug has been shown to increase bone mineral density)
- Calcitonin (potent inhibitor of osteoclast mediated resorption), fall prevention.
- Parathyroid hormone

Joint Info (Mankin and others)

- Articular cartilage. A thin layer of hyaline cartilage which provides a nearly frictionless surface between the ends of articulating bones.
- No blood supply, nerves or lymph to cartilage
- Synovium. A layer of specialized cells lining the synovial cavity, containing synovial fluid
- Joint capsule and ligaments. A strong tissue consisting of collagen Type I and providing stability to the joints

Types of Cartilage

- *Hyaline*: Found in articular cartilage, airways, and fracture callus. Composed of type II collagen, and contains proteoglycans and therefore a lot of water. Load (compression) is absorbed by fluid.
- *Fibrocartilage*: Like hyaline cartilage but has a lot of type I collagen. Found in annulus fibrosis, menisci, as well as tendon and ligament insertion sites.
- *Elastic*: Primarily in the ears. Composed of type II collagen with a lot of elastin.

Osteoarthritis

- From irreparable damage to cartilage, often secondary to trauma.
- Chondrocytes are not static, but respond to stresses – activity may reduce the risk.
- Excessive stresses cause apoptosis. Changes in chondrotin sulfate/aggrecans etc. occur over time. This leads to worse overall cartilage.
- Be able to differentiate between rheumatoid arthritis and osteoarthritis.
- Key words: osteophytes, subchondral bone formation/sclerosis, eburnation, thick capsule, Heberden's nodes (DIP), Bouchard's nodes (PIP)

Treatment

- Intrarticular: corticosteroids, hyaluronic acid.
- Systemic: corticosteroids, NSAIDs, Cox2 inhibitors, glucosamine, chonrdoitin sulfate.
- Tests
  - Long term use of glucosamine –barely better than placebo – Mankin doesn't like it.
  - Programmed physiotherapy - mild improvement in pain and function.
  - COX2 inhibitors – mild improvement with problematic side effects
  - Intra-articular hyaluronan – modest effect (disputed)