Tissue Types in the Human

- **Epithelial**
  - Primarily used for protection
  - Very little extracellular material between cells
  - **Endothelium**: specialized epithelial cells in blood vessels
- **Connective**
  - Primarily used for support
- **Nerve**
  - Primarily used for control
- **Muscle**
  - Primarily used for movement

Epithelial Tissue

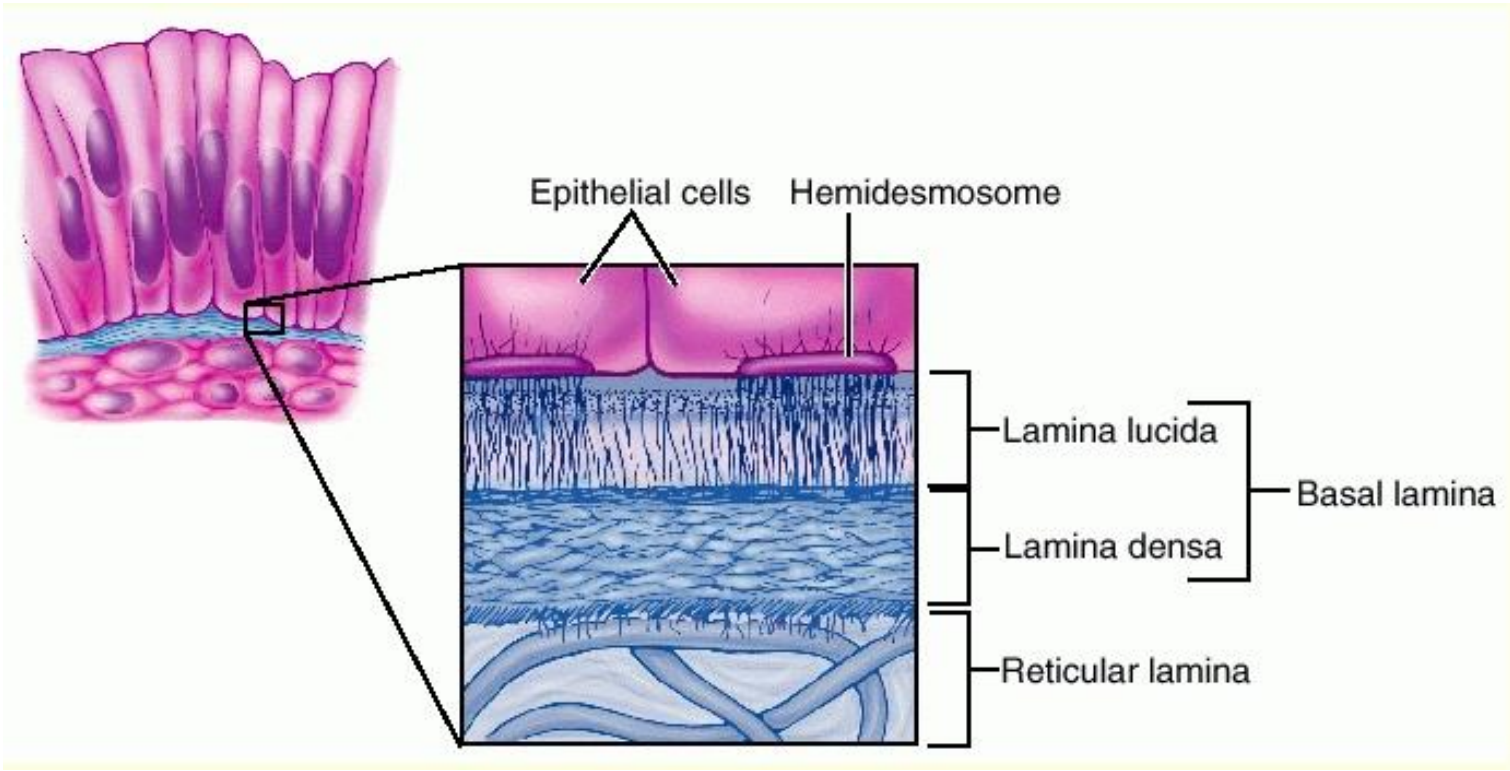
- **Cells are polyhedral (many sided) with little interstitial space**
- **Covers the outermost layer of the skin**
- **Covers innermost layer of most organs and cavities**
  - Lungs, GI tract, Urinary tracts, Reproductive tracts,
- **One side always exposed to:**
  - Body exterior
  - Organ tract or cavity

http://www.britannica.com/EBchecked/topic/190379/epithelium

- **Makes up the exocrine and endocrine glands**
  - Exocrine ("excreting"): sweat glands, digestive glands, mammary glands
  - Endocrine ("hormones"): thyroid, pancreas, adrenal cortex
- **Cells have high regeneration potential but are avascular**
  - Rely on perfusion for O_2 supply
- **Many epithelial cells rest on a "Basement Membrane"**
  - **Basement Membrane = Basal Lamina (2 layers) + Reticular Lamina**
    - Basal Lamina: flat "sheets" of nonliving adhesive-like collagen and glycoprotein
      - secreted by the epithelial cells themselves
    - Reticular Lamina: "foundation" for the Basal Lamina

Three layer structure of the “Basement Membrane”

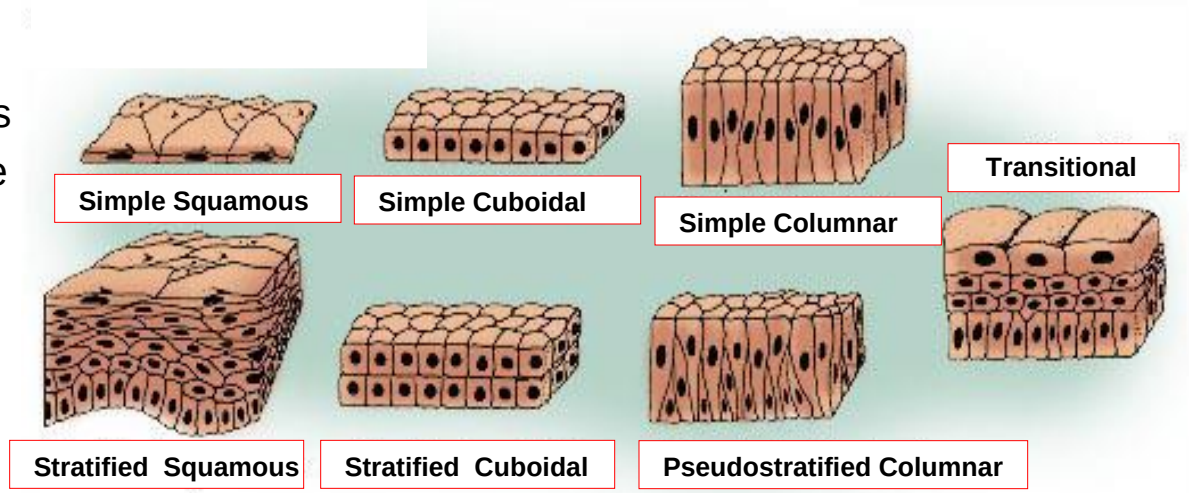
Basement Membrane = Basal Lamina + Reticular Lamina



(Hemidesmosomes function in cell signaling for things such as proliferation & apoptosis)

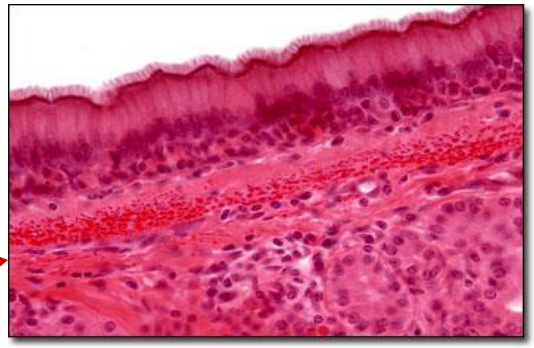
Adjectives Describing Epithelial Tissue

Simple - having a single layer of cells
Squamous (meaning "scale") - flat cells
Cuboidal - cells as tall as they are wide
Columnar - tall and column shaped
Stratified - having stacked layers
Transitional – "dome" surface cells
- capable of stretching (bladder)
Ciliated - cilia on the exposed surface



Examples you should remember:

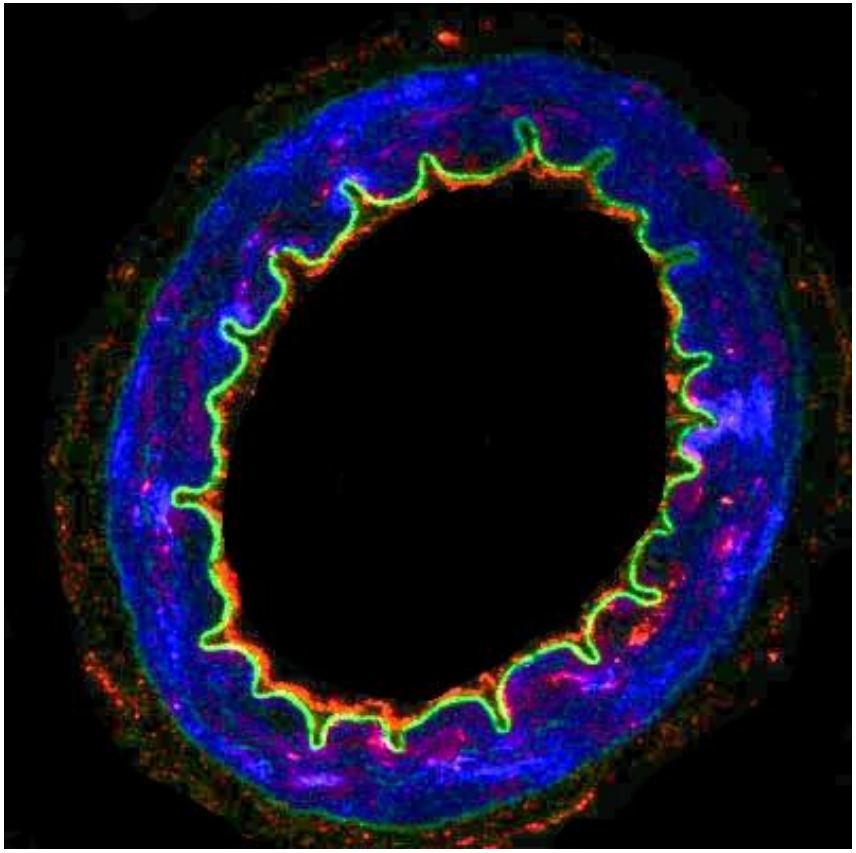
- **SIMPLE SQUAMOUS EPITHELIUM**
  - Permeable cell structure - used for filtration and gas exchange
  - Examples: capillaries, alveoli, kidney glomeruli
- **STRATIFIED SQUAMOUS EPITHELIUM**
  - Used for "protection"
  - Examples: skin, inside of mouth, vagina
- **CILIATED COLUMNAR EPITHELIUM**
  - Used to move substances along a particular direction using the cilia
  - Examples: upper respiratory tract, fallopian tubes



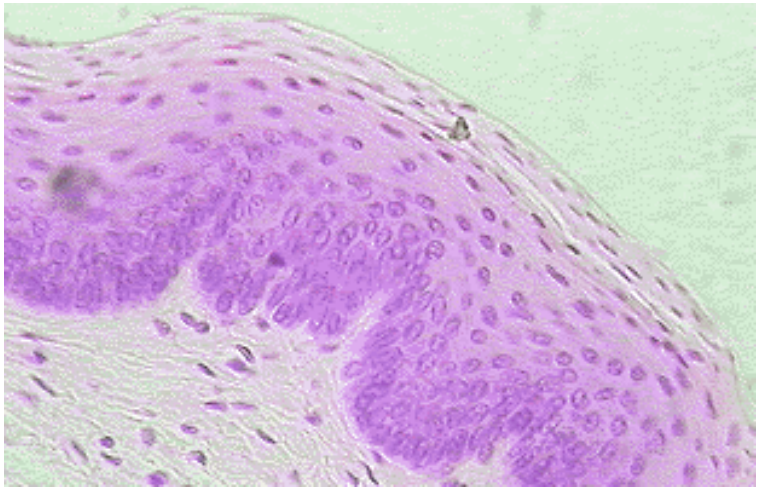
Examples of Epithelial Tissue

Simple Squamous Epithelium
Artery Endothelium

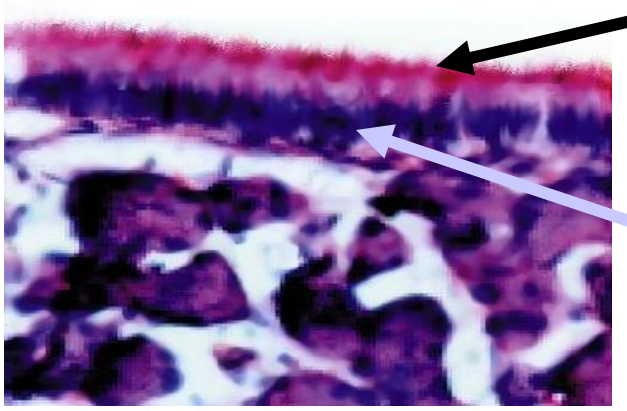
- Orange and brown/green covering: Adventicia
- Blue: Actin in smooth muscle
- Green: Elastic basal membrane (Basil Laminae)
- Innermost Orange: Arterial Endothelium



Stratified Squamous Epithelium
Human Skin



Ciliated Columnar Epithelium
Tracheal Lung Tissue



Diseases of Epithelial Tissue

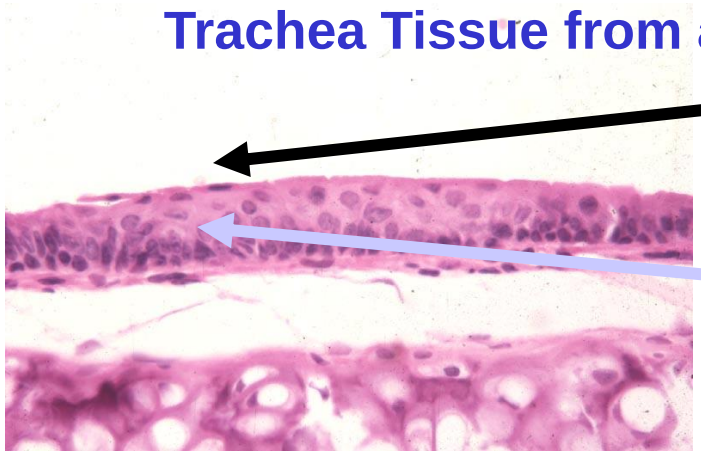
Simple Squamous Epithelium

Arterial Endothelium Dysfunction

The Beginnings of Atherosclerosis

Ciliated Columnar Epithelium

Trachea Tissue from a SMOKER

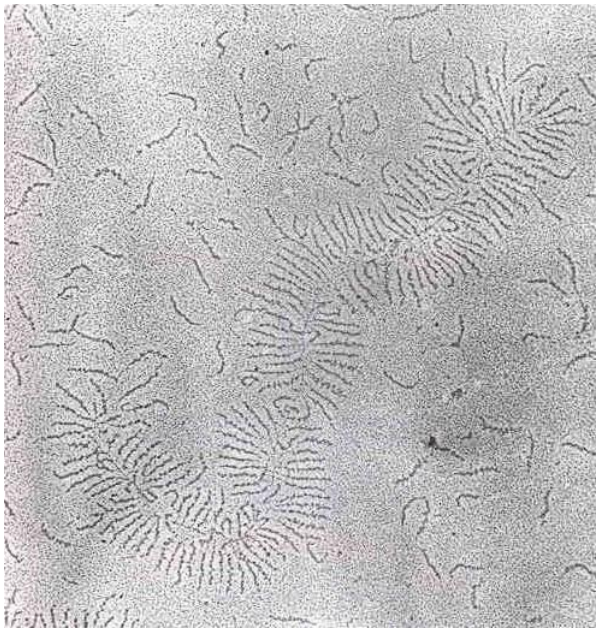


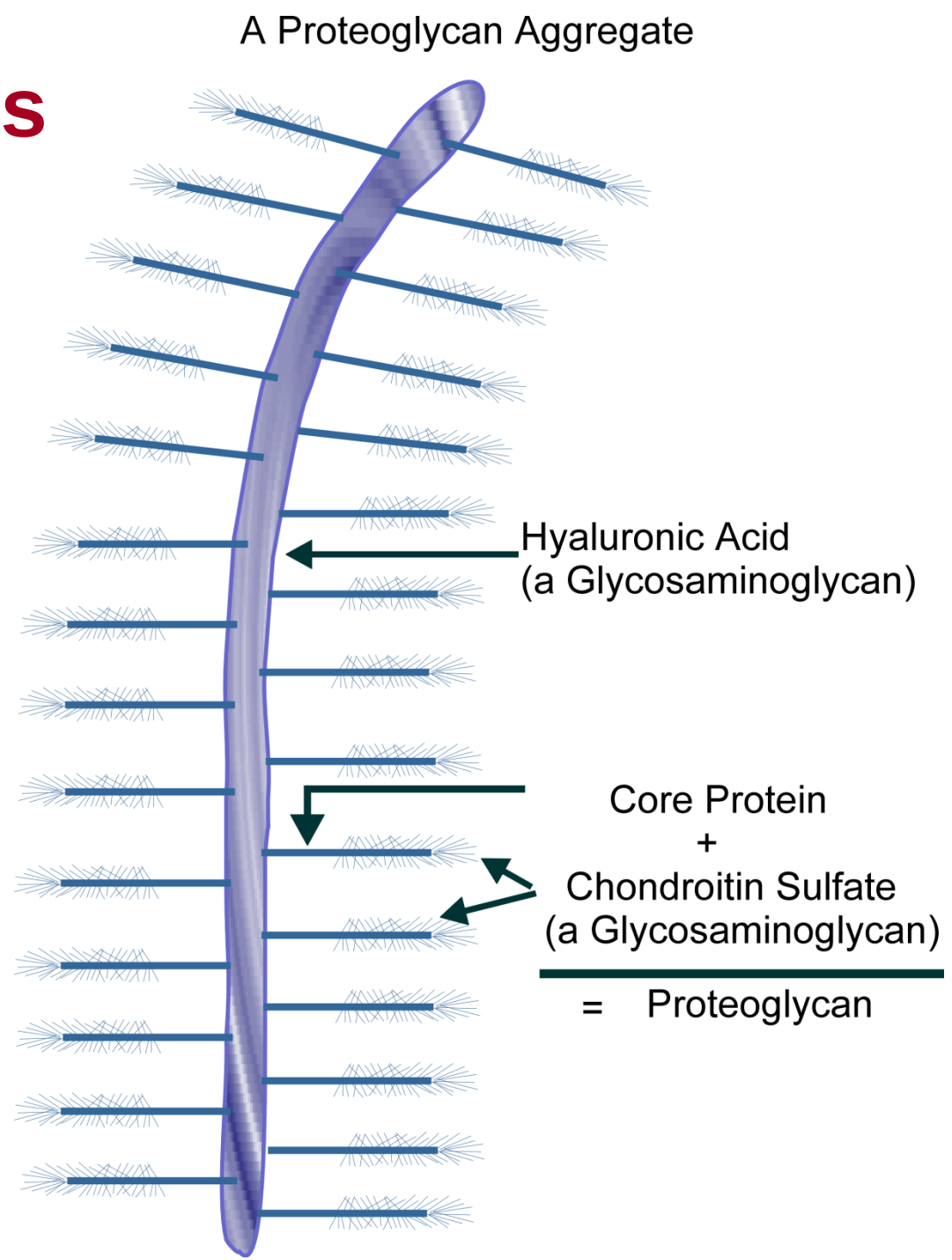
Connective Tissue

- **Matrix - "non-living" component of connective tissue**
  - **Ground Substance**
    - **Proteoglycan aggregates (PGA)** - pine tree shaped molecules
      - Glycosaminoglycans - neg charged → binds Na^+ & K^+ → attract H_20
        - Hyaluronic Acid - negative charged slippery polysaccharride
        - Condroitin sulfate
      - Fluid - H_2O, gasses, nutrients for cells (H_2O facilitates tissue "turgor")
      - Minerals - Calcium salts
    - **Adhesive glycoproteins** – hold PGA's together & to membranes
      - Chondronectin (cartilage), osteonectin (bone), fibronectin (fibrous tissue)
        Laminin (holds epithelial cells to basement membrane)
  - **Fibers**
    - Collagen, Elastin, and Reticular Fibers
- **Cells - "living" component of connective tissue**
  - "Blast" Cells, "Cyte" Cells, "Clast" Cells
  - Macrophages and white blood cells
  - Mast cells containing Heparin & Histamine
  - Adipose tissue

Proteoglycans

Electron Micrograph of actual Proteoglycan Aggregate





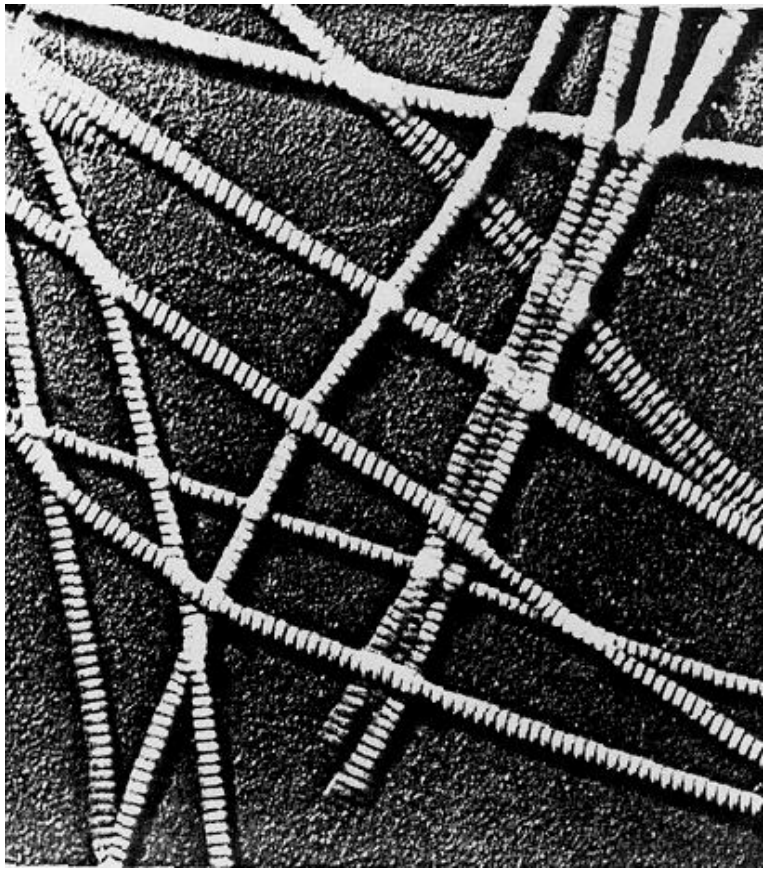
Types of Fibers

Collagen

- Fibrous protein in connective tissue structure
- Derived from Greek word meaning “to glue together”
- Constitutes about 50% of the proteins in man
- Present to some degree in all human organs
- Collagen has a finite life span after which it is degraded to the constituent amino acids and replaced by new fibers.
- Has high tensile strength:
  - 4.5 pound load needed to break collagen fiber 1 mm thick

http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mcb.section.6542

Collagen Fibers



Collagen Structure

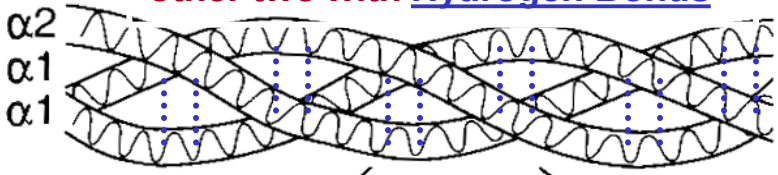
Collagen Fiber (Fibril)

Each collagen molecule (also called a tropocollagen) is connected to others via PYRIDINIUM CROSS-LINK BONDS.

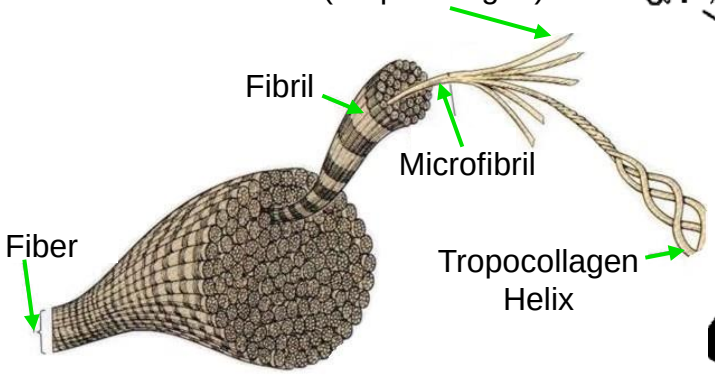
Microfibril

A Collagen Molecule (Tropocollagen)

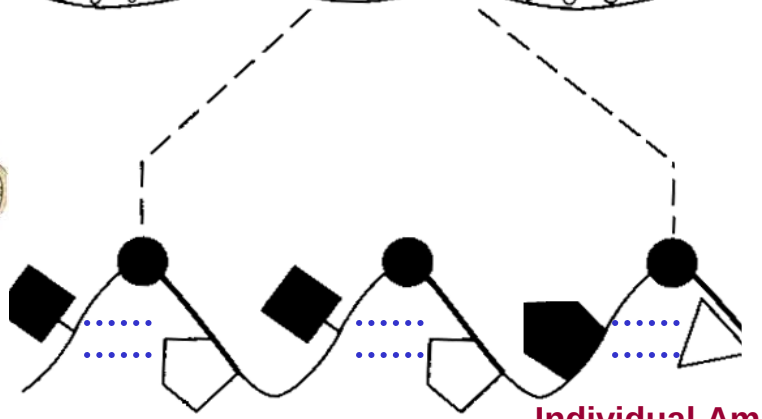
Each chain connected to the other two with Hydrogen Bonds



3 Alpha Helix Chains Within Each Collagen Molecule



Although Hydrogen bonds are weak, the "stacked intertwined" formation of the triple helix give collagen remarkable strength.



Individual Amino Acid Bonds Are Reinforced With Hydrogen Bonds

Diseases that Affect Collagen

Overproduction of Collagen Fibers

- **Lung Fibrosis (Cystic Fibrosis)** – mucous buildup in lungs and pancreas
  - Caused by a mutation in CTFR gene → product of this gene is ion channel
    - This channel is important in creating sweat, digestive juices, and mucous
    - High salt content in sweat is usually present in CF kids – used as a test for CF
  - Life-span used to be limited to 20-30 years….now possibly 40-50 years
  - Fibrous obstructions and fluid in lungs → breathing disorders & numerous infections
  - Fibrous obstructions in pancreas → ↓ digestive enzymes → ↓ nutrient absorption
    - Malnutrition → ↓ growth http://www.kidshealth.org/kid/health_problems/heart/cystic_fibrosis.html
- **Liver Cirrhosis** – fiber deposition → irreversible scarring in the liver
  - Common causes: Hepatitis-C Hepatitis-B, alcoholism
    - Alcohol blocks normal metabolism of protein, fats, and carbs → injury
  - Cirrhosis → edema & ascites (fluid in peritoneal space)
    - Liver cannot make Albumin → blood looses osmotic (sucking) pressure
  - Cirrhosis → ↑ infection risk, jaundice, bruising & bleeding, portal hypertension
  - Cirrhosis will elevate the Aminotransferase Enzymes
    - ALT, AST, GGT(aka SGOT- large elevations associated with alcoholism)
- **Atherosclerotic heart disease** http://www.digestive.niddk.nih.gov/ddiseases/pubs/cirrhosis/

Diseases that Affect Collagen

Autoimmune Disorders that Damage Collagen

- **Lupus Erythematosus** - production of "auto antibodies" that target body tissue
  - 90% of Lupus patients will experience joint and muscle pain
    - Pain caused by collagen damage and destruction in joints & muscles
  - Collagen damage and inflammation can occur anywhere in the body
    - Most common areas affected: articular tissue, skin (rashes that result from sunlight exposure), lungs, blood vessels, liver, kidneys, and nervous system
  - Course of the disease is unpredictable with attacks and remissions
  - Most common in women ages 18 – 40 http://www.hopkins-arthritis.org/arthritis-info/lupus/

Diseases caused by Insufficient or malformed Collagen

- **Osteogenesis Imperfecta** - Brittle bones
  - Bones easily fractured
- **Scurvey** - Vitmain C deficiency
  - Too few hydrogen bonds form in the collagen molecule
  - Inferior tissue formation in bones, blood vessels, skin, and teeth

Therapy for Common Collagen Diseases

- **Cystic Fibrosis**
  - Clearance techniques for excess lung secretions
  - Pancreatic enzyme replacement for pancreatic duct obstruction
  - Healthy diet and exercise
  - Drugs:
    - **Ibuprofin** – slows rate of decline of pulmonary function
    - **Corticosteroids** – ↓ inflammation in lungs, joints, and vasculature
    - **Antibiotics** – used to treat and reduce the incidence of lung infections
      - Drugs are rotated to prevent development of resistance

Therapy for Common Collagen Diseases

- **Lupus**
  - **Drugs:**
    - **Disease Modifying Anti Rheumatic Drugs (DMARDS): ↓ flare-ups**
    - **NSAID's**
    - **Corticosteroids and other immunosuppresants**
    - **Hydroxychloroquine** ↓ inflammation
    - **Experimental drugs**
      - **BENLYSTA (Belimumab)** – antibody that inhibits B-lymphocyte stimulator (BLyS). BLyS turns B-lymphocytes into plasma cells which produce antibodies (first line of defense "foot soldiers" against infection). Overproduction of BLyS results in overproduction of antibodies. Excess BLyS production is noted in Lupus and other autoimmune diseases.

Other Types of Fibers

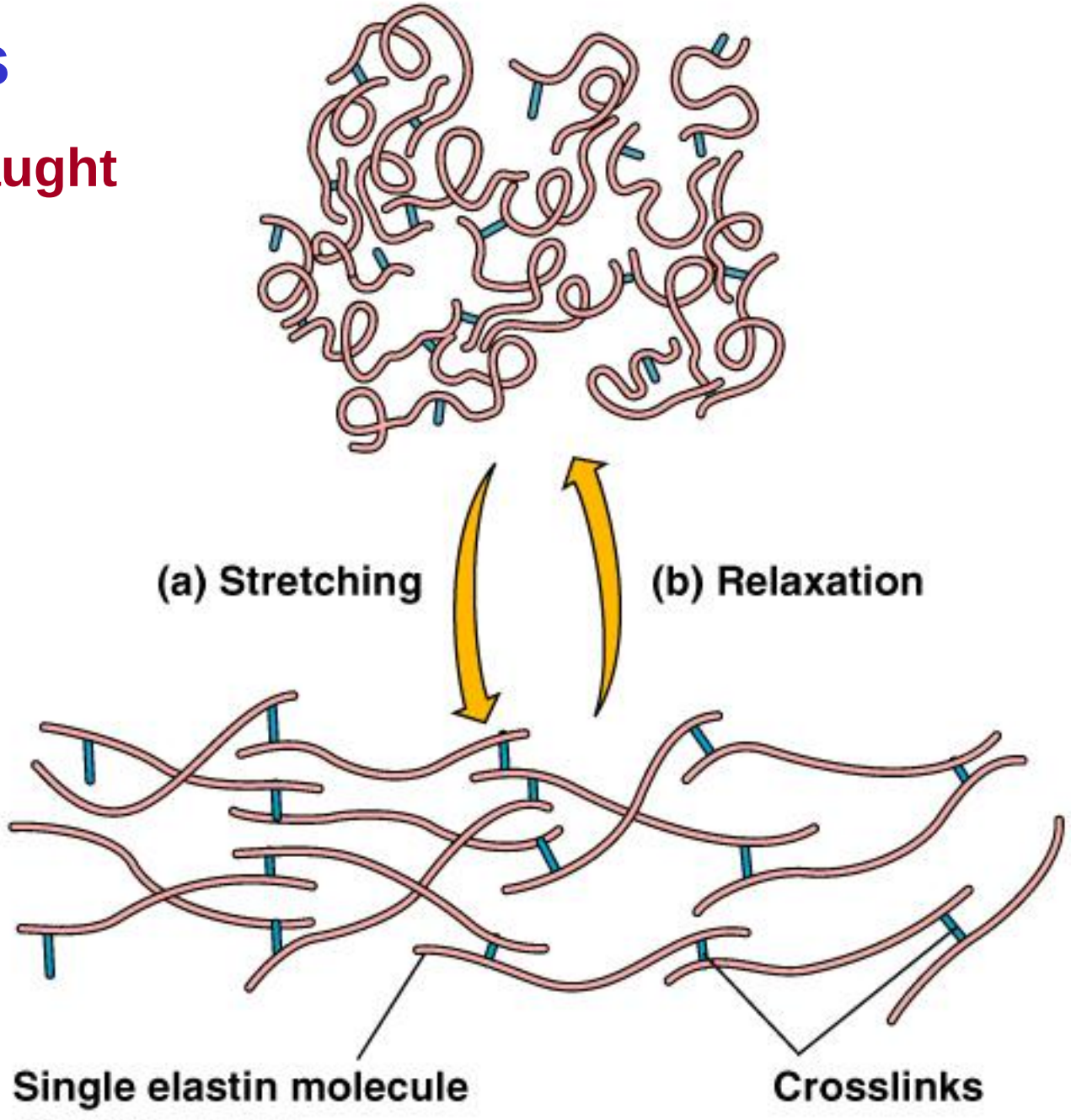
- **Reticular Fibers:**
  - Actually they are very fine collagen fibers
  - Usually form a network
  - Fill “space” between other tissues & organs
  - Contained in the **reticular laminae**

- **Elastic Fibers:**
  - Contain protein called **ELASTIN**
  - Elastin molecules look like “coiled springs”
  - Return to original shape after distortion
  - Found in arteries, skin, alveoli of lungs (prominent in skin)
    - Synthesized by only fetal and juvenile fibroblasts
    - Loss of elastin with age contributes to development of “wrinkles”

Elastin Fibers

(a) Stretched or taught

(b) Relaxed



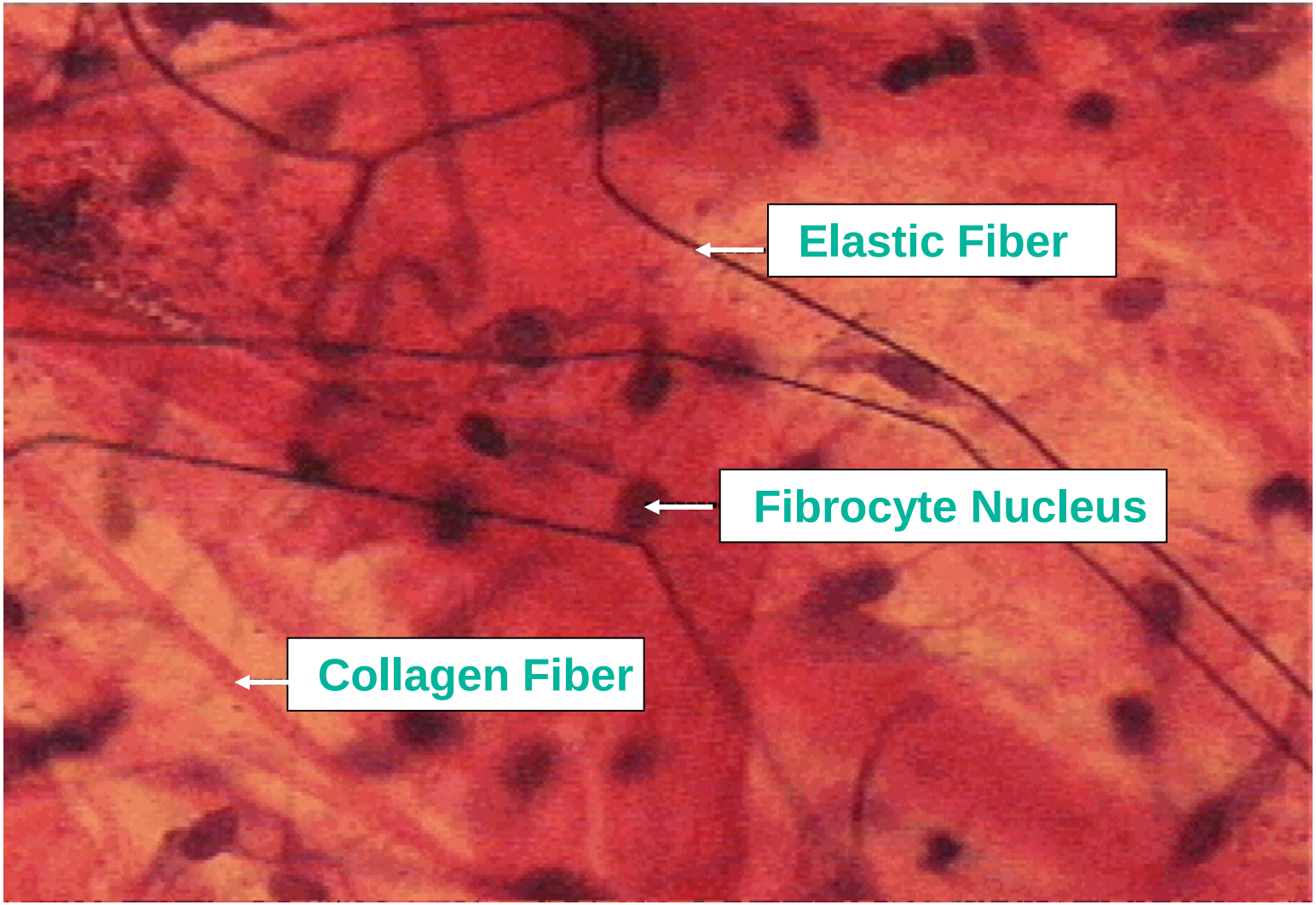
Types of Connective Tissue

- Fibroconnective Tissue
- Cartilage
- Bone

Types of Connective Tissue

- **Fibro connective Tissue** - matrix composed mostly fibers
  - **Areolar** -"Loose connective tissue" "packing material" holds organs in place
    - Most common connective tissue in all vertibrates
    - Component of some basal membranes
    - Separates muscles - allows for muscles to slide over each other
    - Fibers in extracellular matrix are collagen & elastin
    - Extracellular matrix is not well organized
  - **Reticular** - **forms an internal skeleton for lymph, bone marrow, fat, & spleen**
    - Fibers are collagen & elastin
  - **Adipose** - **highly vascular insulator, shock absorber & energy store**
    - Cells account for 90% of tissue mass (little matrix present)
  - **Dense regular** - **closely packed parallel collagen fibers – few cells**
    - Found where tension is exerted in a particular direction
    - Examples: tendons, ligaments
  - **Dense irregular** - **closely packed non-directionalized collagen – few cells**
    - Forms "sheets" where tension is exerted in many directions
    - Examples: dermis of skin, muscle fascia, organ & nerve coverings
  - **Elastic** - **composed of mostly elastin fibers**
    - Examples: vocal cords, vertebral connective tissue

Areolar Tissue

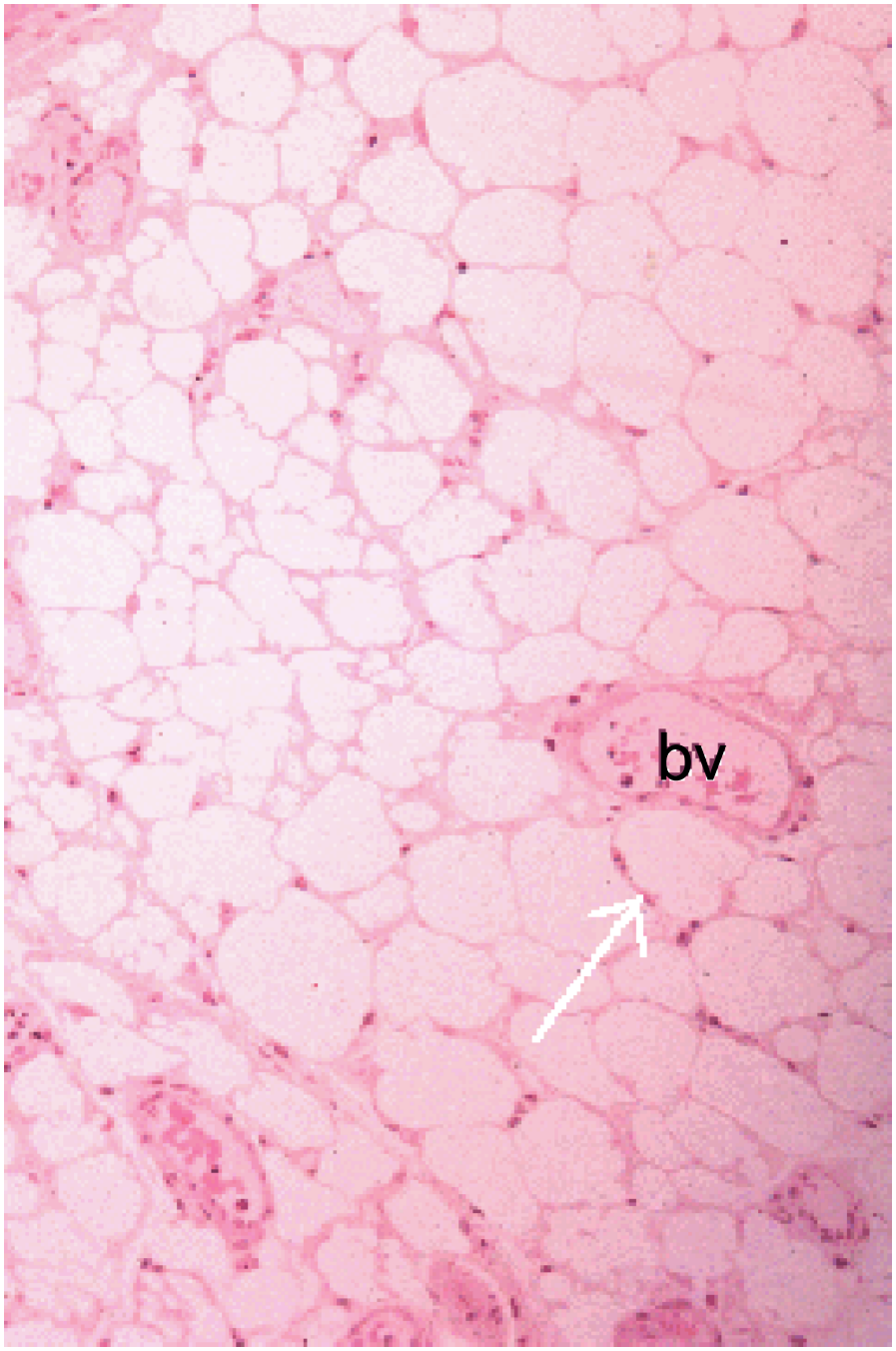


Adipose Tissue

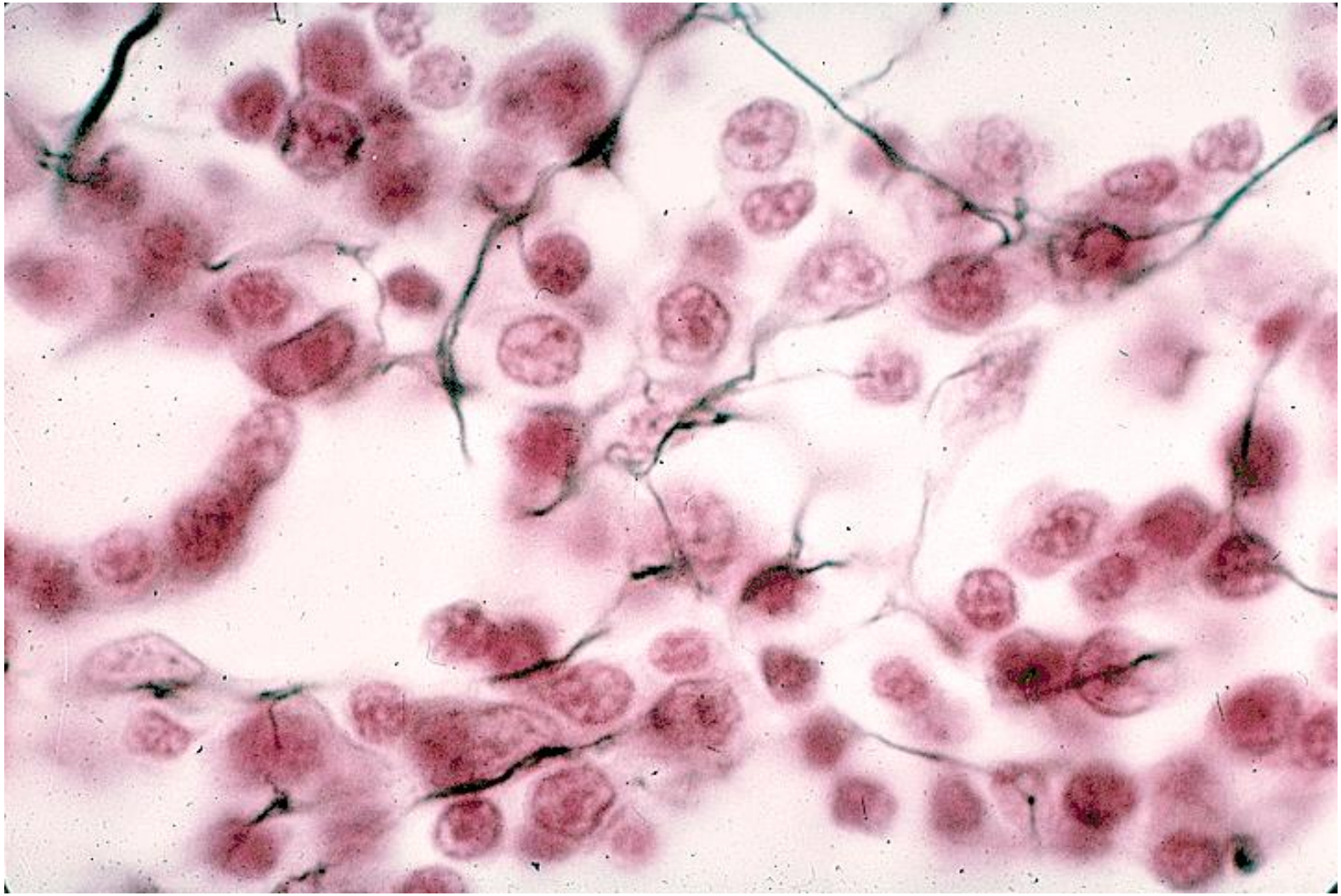
X 200

(bv = blood vessel)

(arrow: adipocyte nucleus)



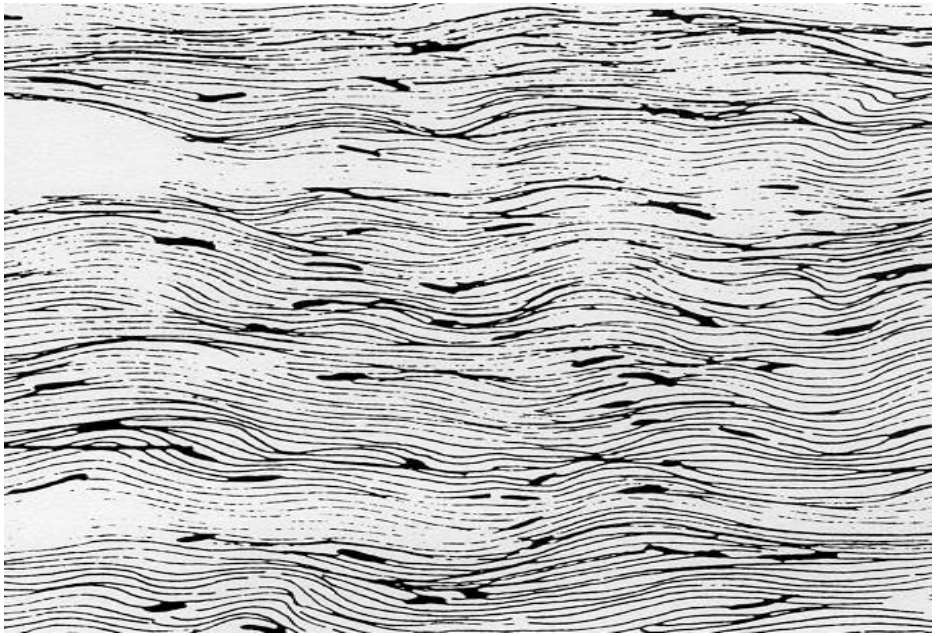
Reticular Tissue

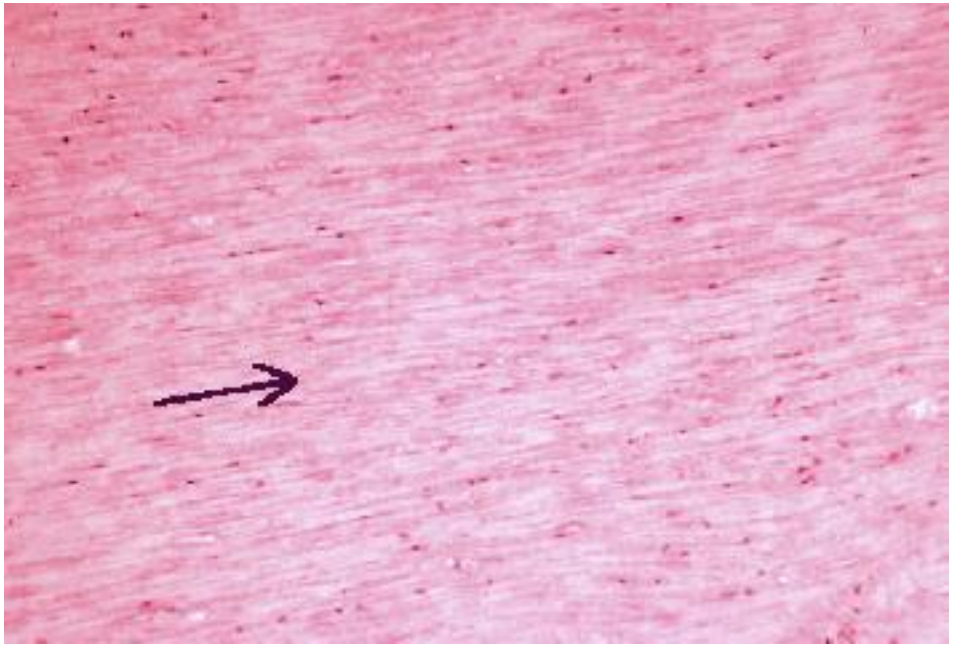


Dense Regular Tissue

(Tendons & Ligaments)

Horse Tendon x100

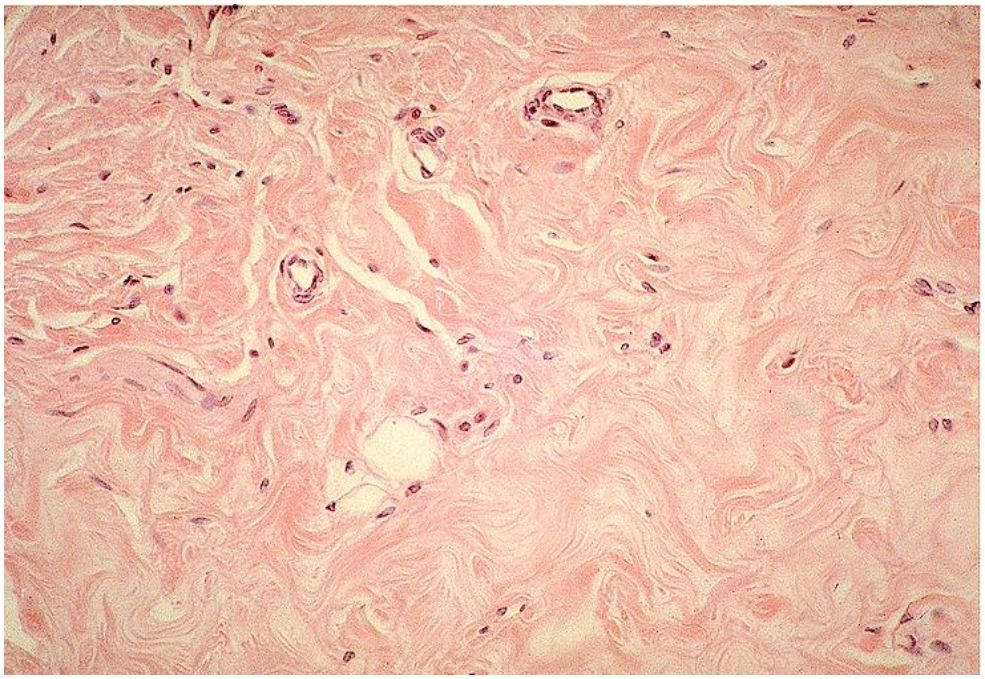




arrow: orientation of collagen fibers

Dense Irregular Tissue

(Dermis of Skin & Muscle Fascia)



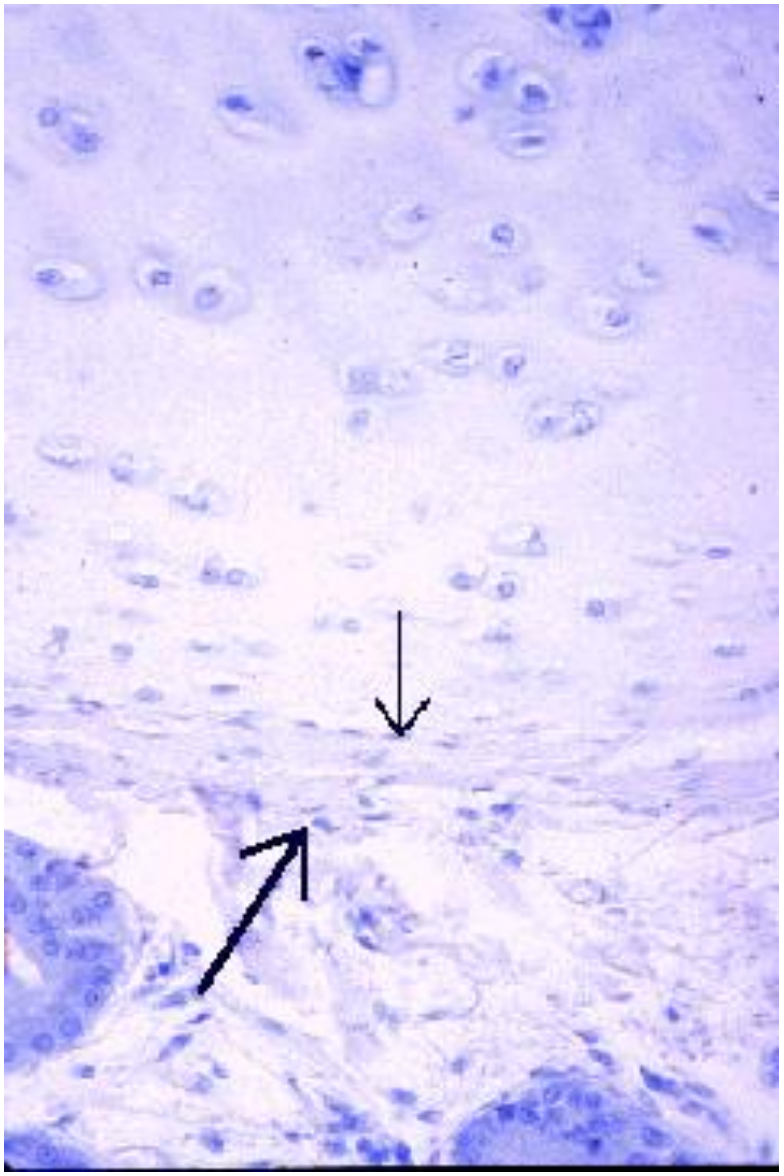
Types of Connective Tissue

- **Cartilage**
  - Avascular (which makes it slow to heal) and not innervated
  - Composition of cartilage matrix:
    - Ground substance: chondroitin sulfate & hyaluronic acid
    - Collagen (the main fiber) & elastin
  - Perichondrium – surrounding tissue from which nutrients diffuse
    - Limits cartilage thickness - nutrients must diffuse entire tissue thickness
    - Gives rise to chondrocytes
  - Types of cartilage:
    - **Hyaline** - tough & flexible - much matrix / few cells - shock absorber
      - Covers ends of long bones (articular cartilage – eroded in OA)
      - Forms the “skeleton” of trachea and bronchi
    - **Fibrocartilage** - less firm than hyaline - more cells and fibers
      - Similar in structure to dense regular tissue
      - Transitional tissue between tendon and articular hyaline cartilage
      - Component of joint capsules and spongy knee menisci
    - **Elastic** - contains more elastin fibers than other types of cartilage
      - Forms ear pinna & epiglottis

http://education.vetmed.vt.edu/curriculum/vm8054/labs/Lab7/lab7.htm

Hyaline Cartilage X 250

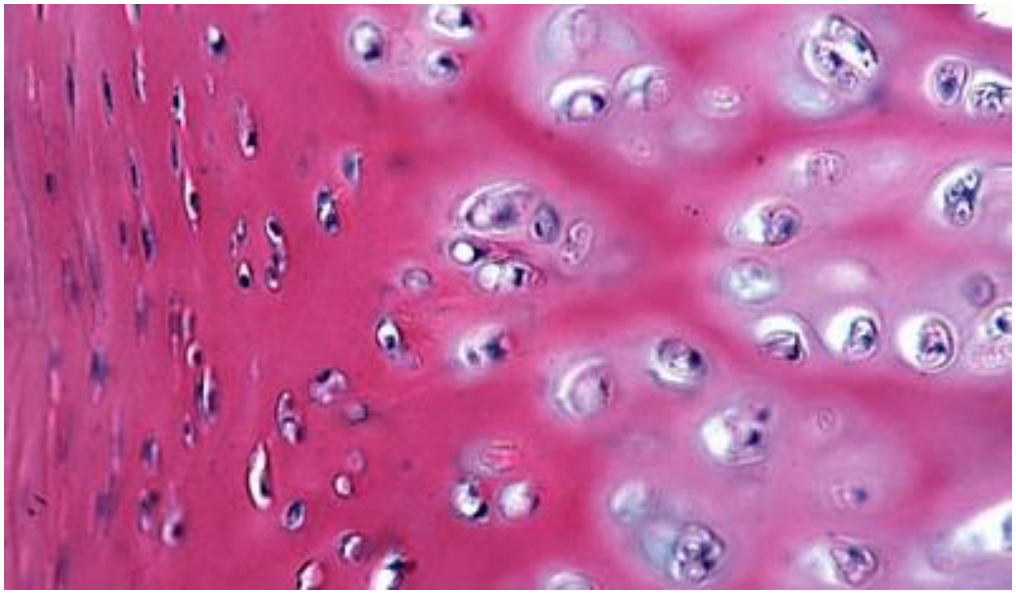
arrows: Perichondrial borders



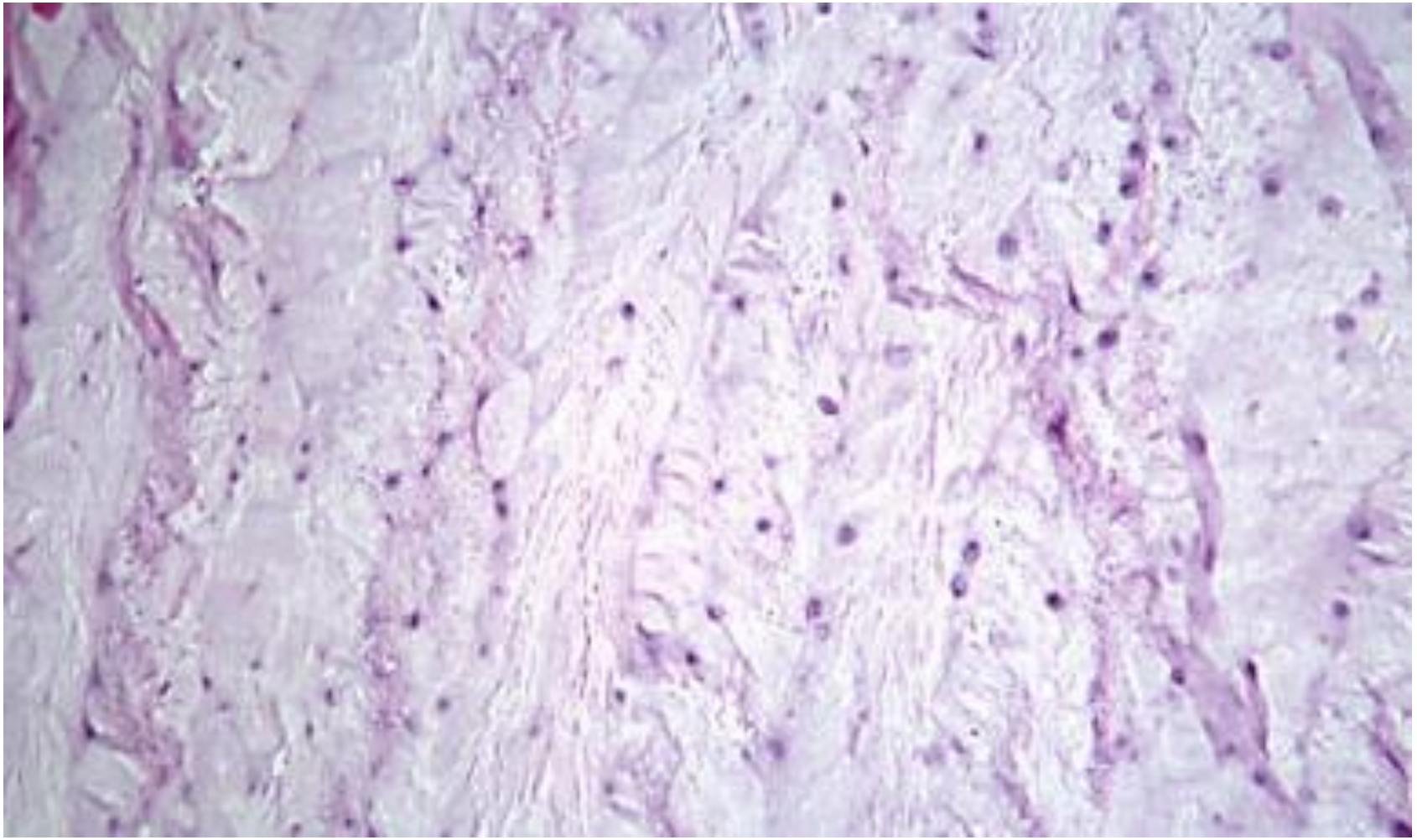
Hyaline Cartilage

Perichondrium on the left

Chondrocytes form in the perichondrium and move out into the tissue

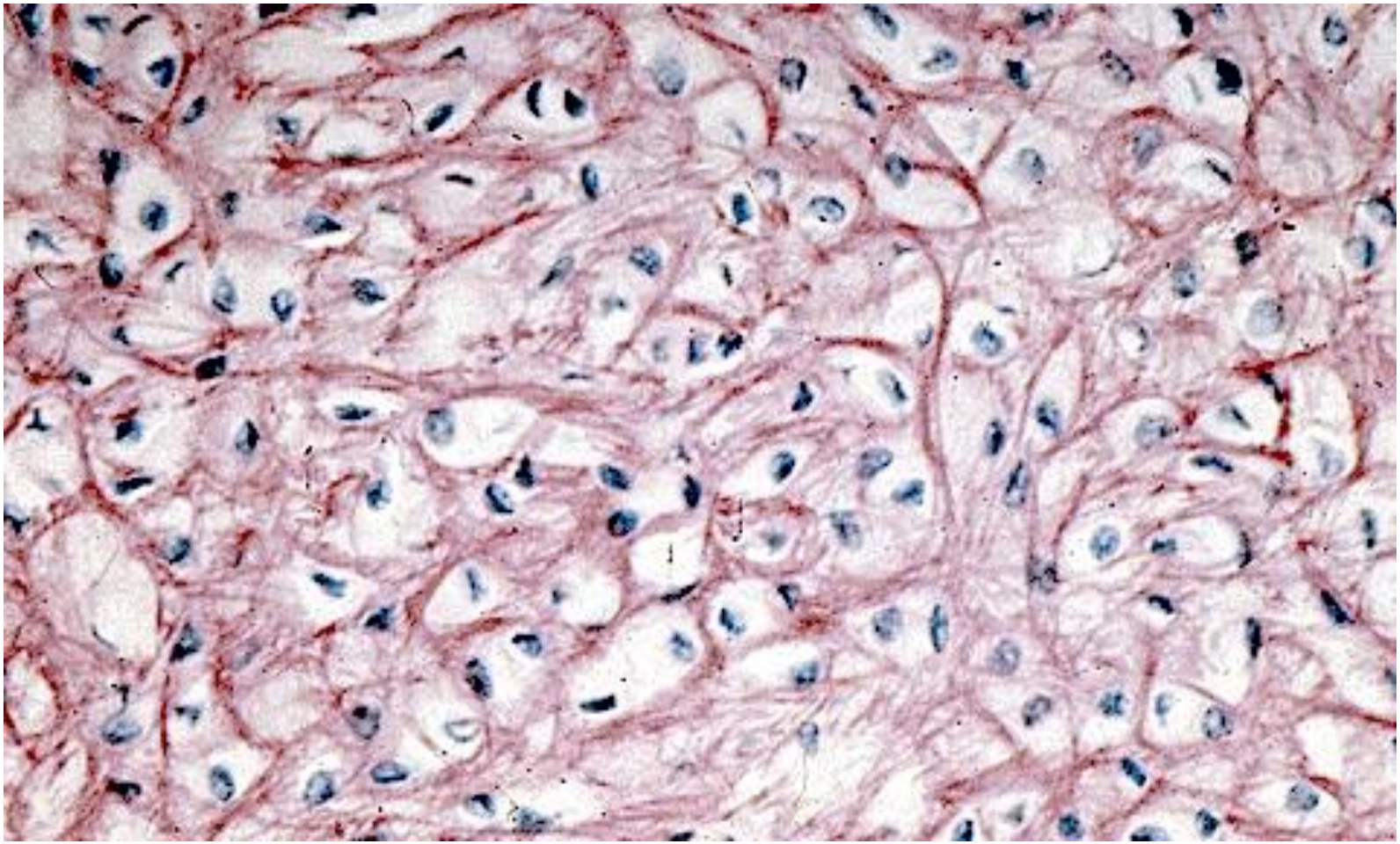


Fibrocartilage



Elastic Cartilage

(note numerous chondrocytes and elastic fibers)



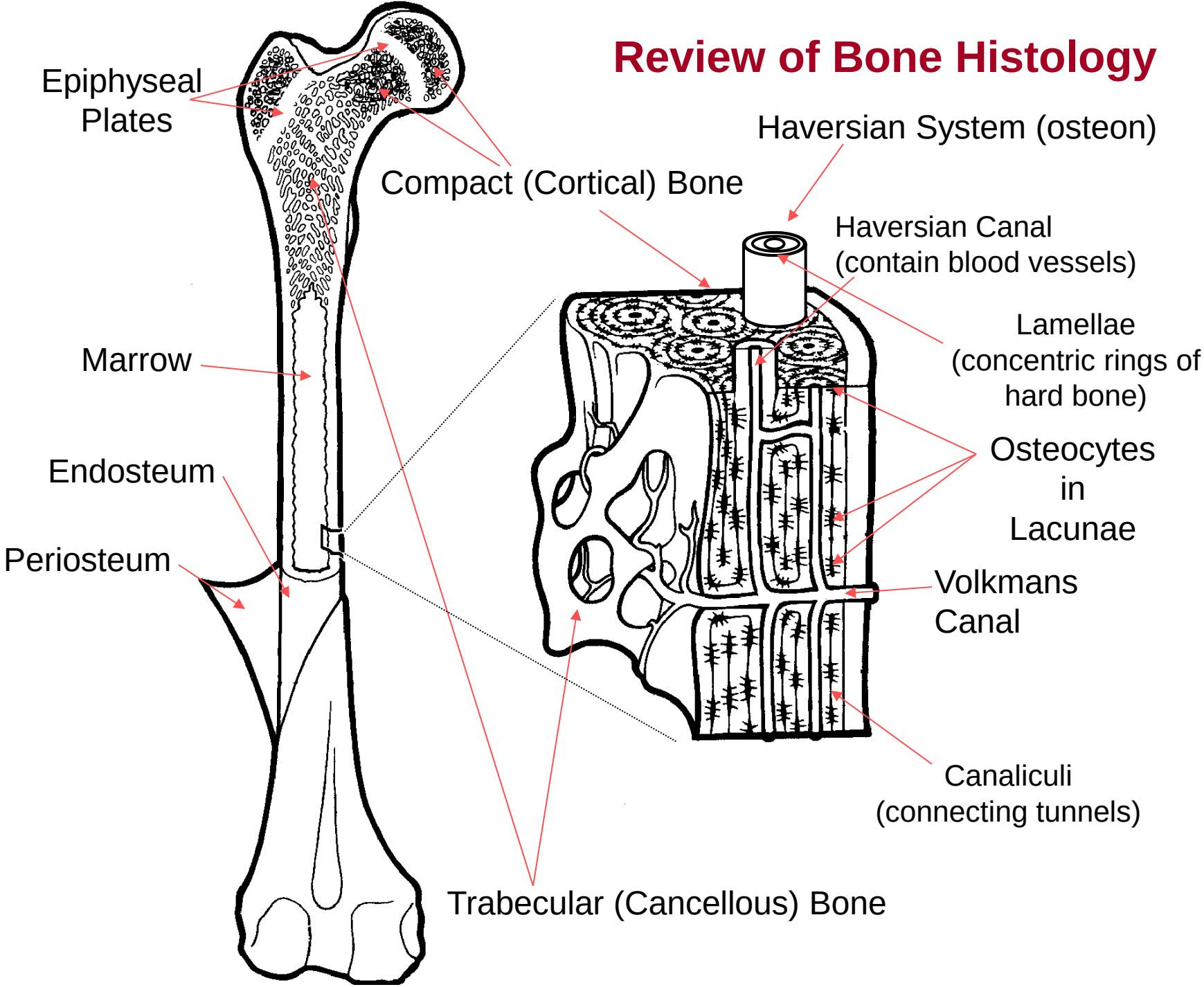
Types of Connective Tissue

- **Bone** - matrix mostly calcium and phosphate
  - 65% of bone weight is **calcium hydroxyapatite**
    - Calcium phosphate, calcium hydroxide, calcium carbonate
  - Contains tropocollagen subunits giving bone elasticity and fracture resistance
    - Bone collagen ↓ with age → ↑ fracture risk
  - Highly vascular and well innervated
  - Contains lymph channels
  - Functions in mineral storage and blood cell production
    - Regulation of Ca^{++} metabolism - bone remodeling (deposition-resorption)
      - ↓ blood Ca^{++} → ↑ Parathormone (PTH) → ↑ osteoclast activity
      - ↑ blood Ca^{++} → ↑ Calcitonin → ↑ osteoblast activity
  - Red bone marrow: contains hematopoietic tissue - produces blood cells

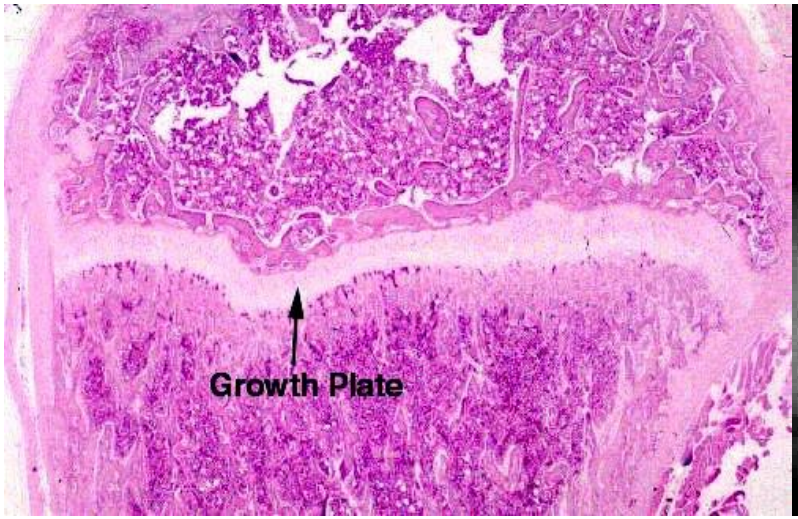
- **Influences on Bone Growth:**
  - Levels of Ca^{++}, Phosphorous, Vitamin D, HGH, estrogen, testosterone

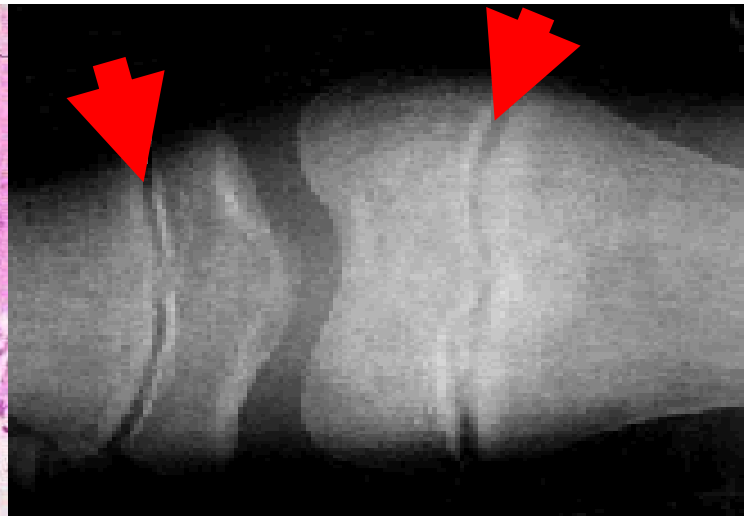
http://emedicine.medscape.com/article/1254517-overview

Review of Bone Histology



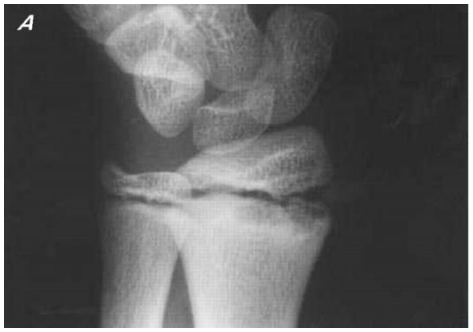
Growth Plates (epiphyseal plate or the physis) in Long Bone

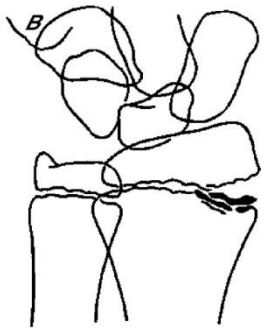




Example: Widening of distal radial epiphysis in young gymnast

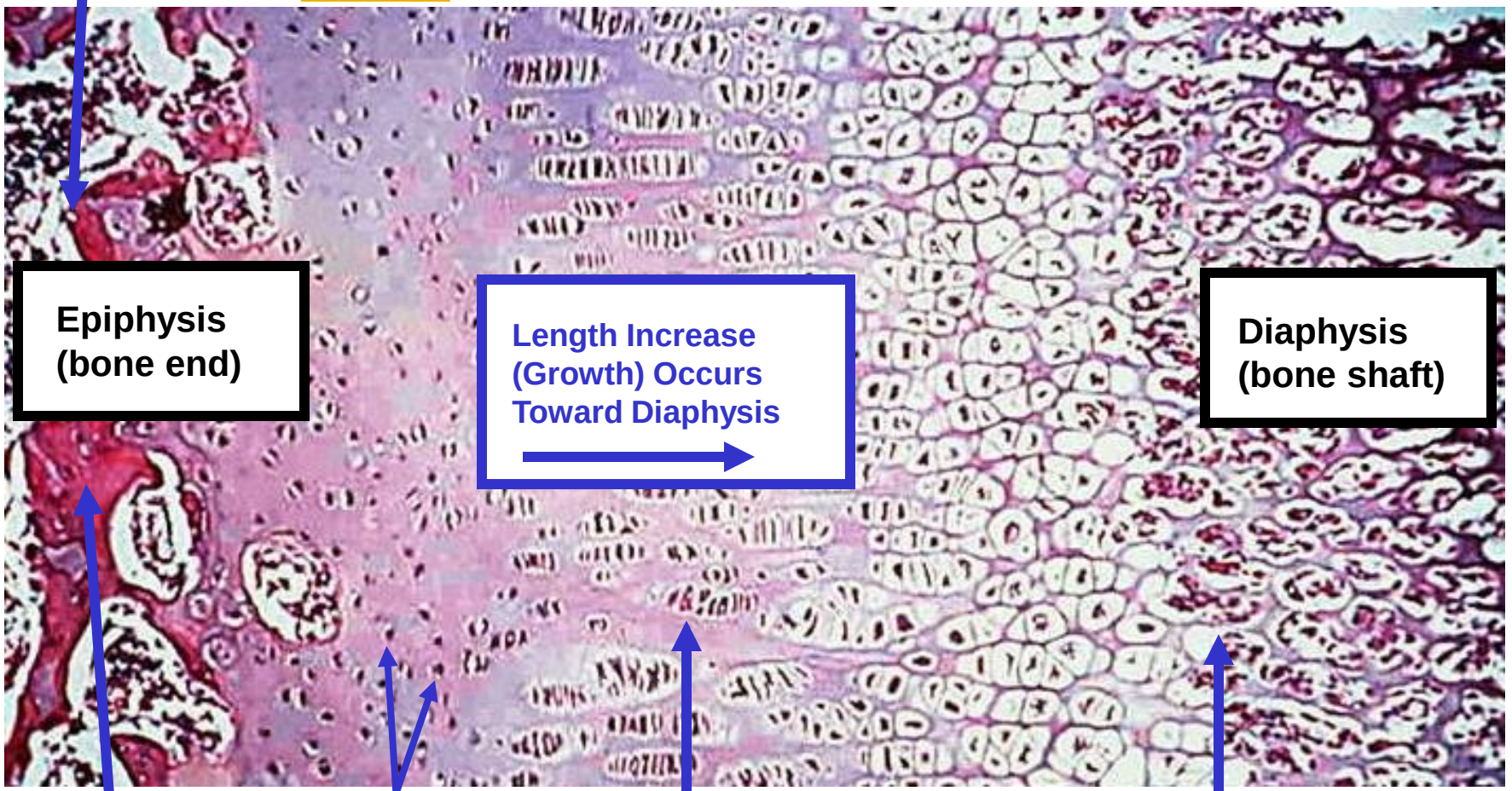
- Widening (breaking) of distal radial epiphyseal plate ➞ ischemia
  - Necrotic changes take place and growth may be asymmetrical
  - Possible premature closing of physis





http://bjsm.bmj.com/cgi/content/full/40/9/749?rss=1

Growth Plate (epiphyseal plate) in Long Bone



Bone Diseases & Treatments

- **Pagets Disease** - enlarged deformed bones
  - ↑ bone resorption and deposition → thick soft bones, bone pain, ↑ fractures, arthritis
  - Bending (bowing) of weight bearing bones
  - Affects about 1% of adults - rarely diagnosed in people under 40 years of age
  - Symptoms: pain, pinched nerves → tingling & numbness, leg bowing, hip & knee pain
  - Bones most often affected: spine, femur, pelvis, skull, clavicle, humerus.
  - Treated with Bisphosphonate drugs (see osteoporosis treatment)

- **Osteoporosis** - ↓ bone density → fracture predisposition
- Osteopenia – bone loss but not as severe as in osteoporosis
  - ↑ bone resorption in the presence of normal bone metabolism
  - ↓ both cortical (thick) and trabecular (porous) bone density, but affects cortical bone more
  - Women start losing bone density about age 40, men at age 60
  - Over 28 million people in the U.S. have osteoporosis
    - **80% of this 28 million are women**
    - **Many women experience up to a 20% ↓ in bone mass by 5 to 7 years after menopause**
  - 1 in 2 women and 1 in 4 men over age 50 will have an osteoporosis related fracture in their lifetime. http://www.medicinenet.com/osteoporosis/article.htm
    - **Common Fracture Sites:** thoracic vertebra, distal radius (close to wrist), **femur neck (Hip Fracture)**

Bone Diseases & Treatments

- **Osteoporosis – continued)**
  - **Causes:**
    - Prolonged treatment with corticosteroids
    - Anorexia nervosa
    - Inadequate diet, especially during pregnancy and breast feeding
    - Amenorrhea → ↑ estrogen metabolism disturbances → bone loss
  - **Treatment:**
    - Estrogen replacement (for postmenopausal women)**??**
    - **EVISTA (Raloxifene)** - Selective estrogen receptor modulator that ↓ bone resorption
    - Calcium supplementation
    - Vitamin D supplementation
    - Bisphosphonate drugs (also called diphosphonates)
      - **FOSAMAX, ACTONEL, BONIVA, AREDIA, RECLAST** – ↓ osteoclast activity
    - **CALCIMAR or MIACALCIN** (**Calcitonin**) → ↑ osteoblast activity
    - **FORTEO (Teriparatide)** a PTH analog: → ↑ osteoblast activity
      - Intermittent exposure to PTH will ↑ osteoblast activity more that osteoclast activity
    - Weight bearing exercise can ↑ bone mineral density and ↓ falls
      - ***Kemmler et al. Arch Intern Med. 2010 Jan 25;170(2):179-85***.

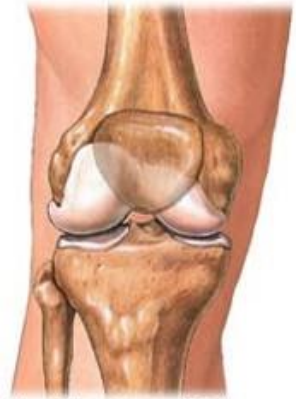
- **Osteomyelitis** - bone inflammation & destruction
  - Caused by bacteria and fungi spreading from other infection sites
  - Symptoms: fever, localized warmth & swelling, localized pain
  - Treated with antibiotics

Bone Diseases & Treatments

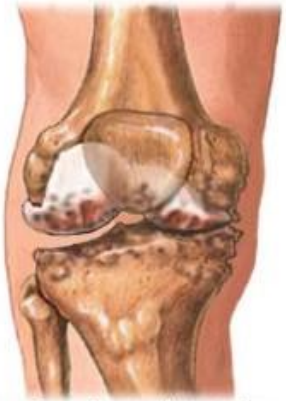
- **Osteoarthritis** - Degenerative changes in cartilage & bone
  - Loss of articular cartilage in hands, hips, and knees
    - Roughening, pitting, & destruction in hyaline cartilage → ↑ joint "stiffness"
  - **IL1β** & **TNFα** from chondrocytes → ↓ collagen production + ↑ catabolism of articular cartilage
  - May result in the formation of **osteophytes** (bone spurs) or **nodes** **(Bouchard's nodes)**
  - 80 – 90 % of people over age 65 have some evidence of osteoarthritis
  - **Causes**
    - Heredity, infection, endocrine disorders, overuse, fracture or ligament injury
      - **Fracture or Ligament Injury → bad joint alignment and instability → ↑ "wear and tear"**
  - **Treatments** http://www.medicinenet.com/osteoarthritis/article.htm
    - Exercise - helps maintain ROM, healthy cartilage, and strength - it also reduces pain
      - ***Rogind et.al. 1998; Gur et.al. 2002***
        - Inactivity can actually worsen the course of the disease
    - Weight loss for OA in weight bearing joints
    - NSAIDS and COX2 inhibitors for pain **(COX 2 inhibitors ??? VIOXX CELEBREX)**
    - Injections of **HYALURONIN** (hyaluronic acid) or other new artificial injectible lubricants
    - Corticosteroid injections may be useful when inflammation is present
    - Joint replacement (when conservative therapy fails)
    - "Tissue engineering" to regenerate articular cartilage has had some success
    - Glucosamine & Chondroitin Supplements??…. .definitive meta analysis study says no benefit

(***Sawitzke et al*, *Arthritis and Rheumatism*, 58: (10), 2008**)

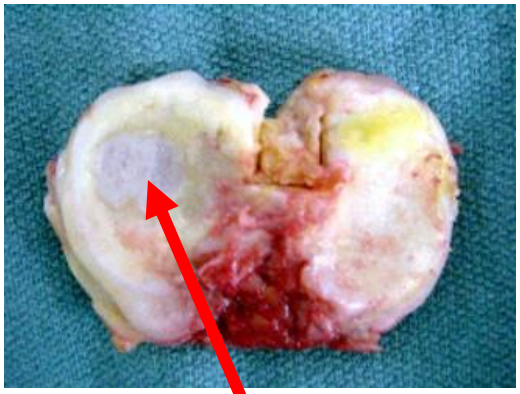
Osteoarthritis of the Knee



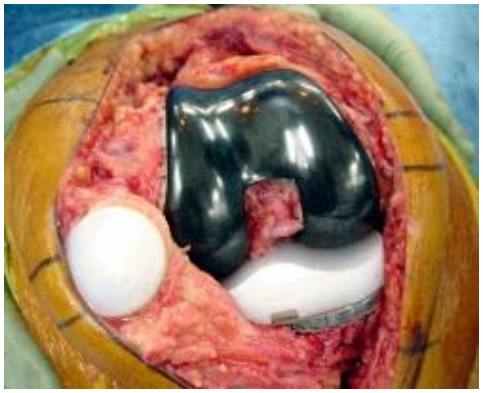
Healthy knee joint



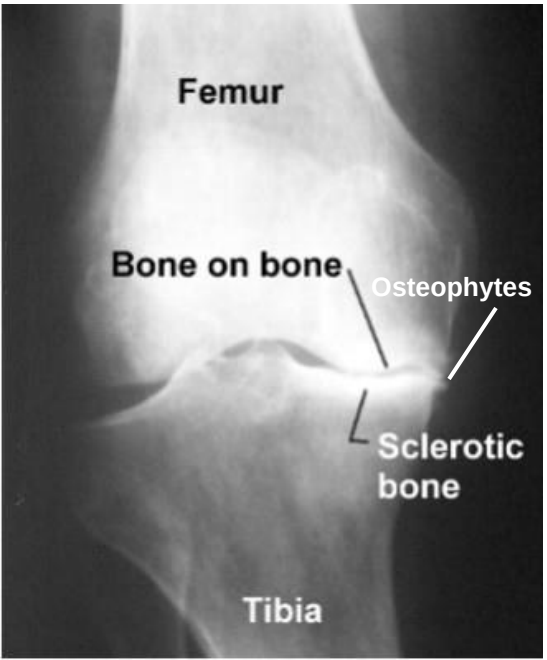
Hypertrophy and spurring of bone and erosion of cartilage



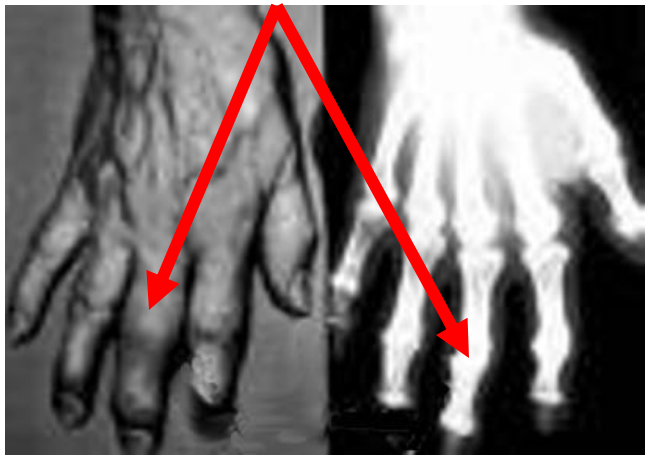
Bone on bone in this resected tibial plateau

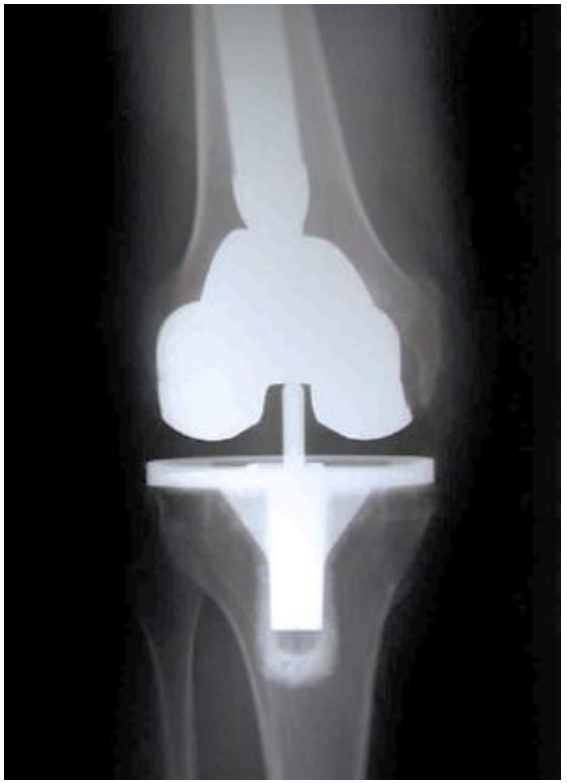


Knee Arthroplasty



Bouchard's nodes





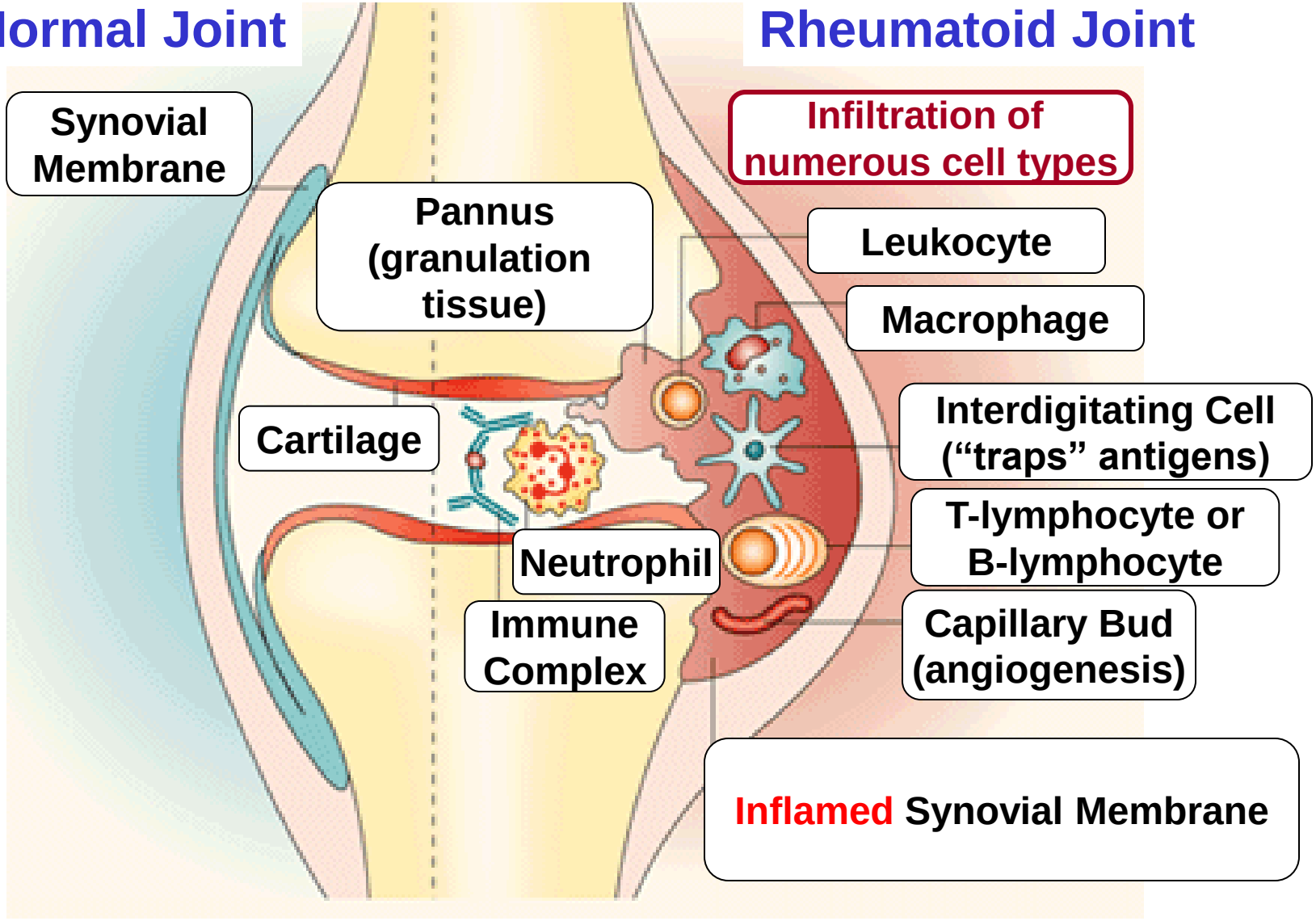
Bone Diseases & Treatments

- **Rheumatoid Arthritis (RA) – Autoimmune inflammatory disease**
  - May be related to genetic factors, environment triggering an autoimmune response, or infectious agents such as viruses, bacteria & fungi
  - Usually occurs between ages 25 & 55 and affects mostly young and middle age females - may fluctuate substantially in severity
  - Rheumatoid factor (autoantibody) + globulins ➞ immune complexes
    - Immune complexes activate the compliment system ➞ **inflammation**
  - Involves synovial membranes of joints (most common manifestation)
    - Inflammation leads to swelling & thickening of synovial membrane
    - Joints most often affected: wrists, fingers, knees, feet, and ankles
    - May also affect: http://www.arthritis.org/disease-center.php?disease_id=31
      - **Heart** – endocarditis, pericarditis, CHF, valvular fibrosis, MI
        - RA and other autoimmune disease patients have an ⬆ risk for CHD
      - **Lungs** – fibrosis
      - **Kidneys** – amyloidosis (deposition of insoluble proteins in kidney tissue)
      - **GI tract** – anemia resulting from constant NSAID use causing bleeding
        - most RA patients are anemic
  - Fibrin deposition (fibrosis) and necrosis are also present in the joint
  - 60% of RA patients are unable to work 10 years after disease onset
  - Most research suggests that life span is reduced 5 – 10 years

Bone Diseases & Treatments

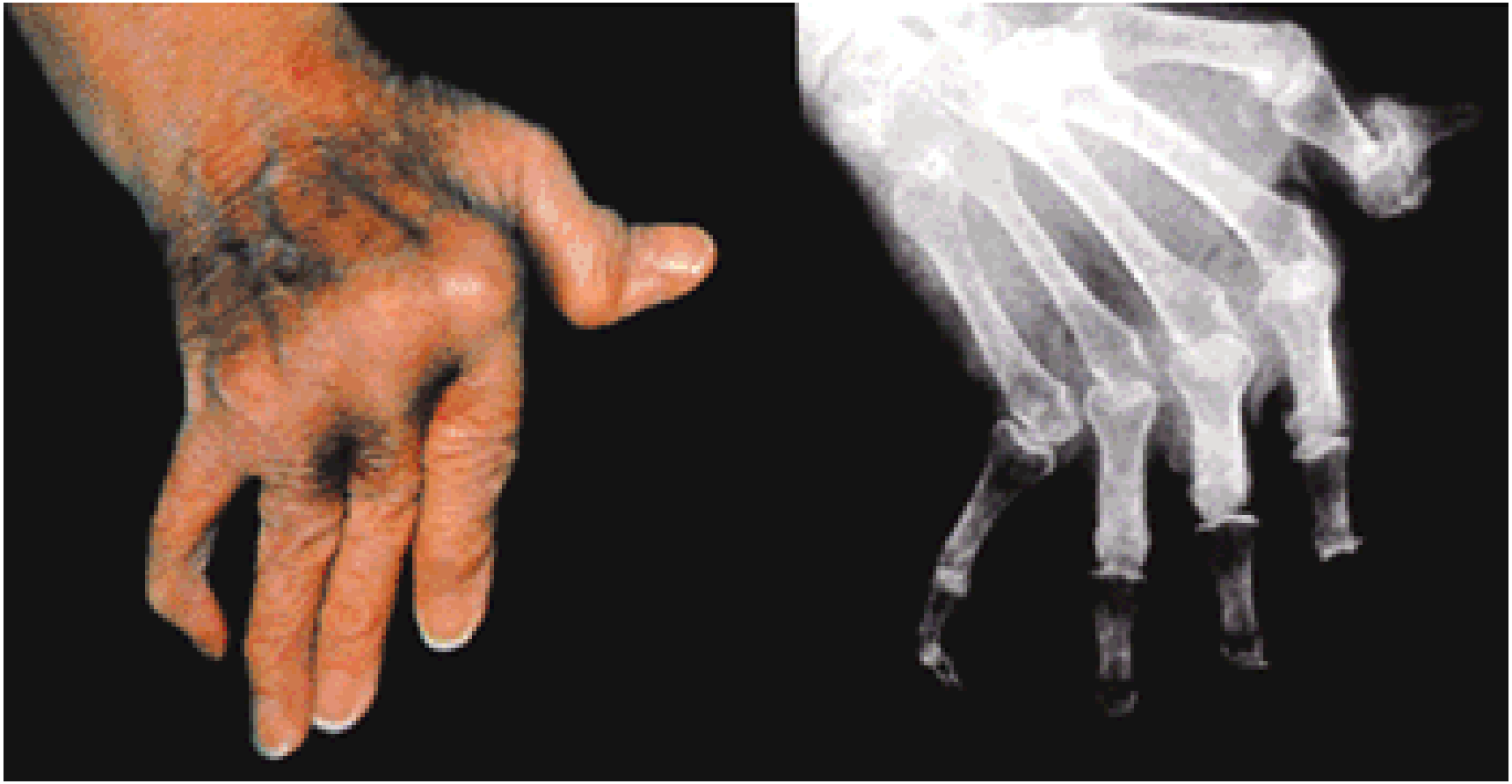
Rheumatoid Arthritis

Comparison of Normal & Rheumatoid Joint



Bone Diseases & Treatments

Rheumatoid Arthritis



Bone Diseases & Treatments

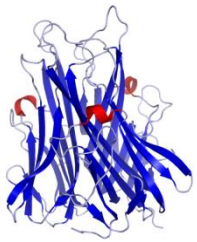
- **Treatments for Rheumatoid Arthritis**
  - NSAID's
  - COX2 inhibitors
  - Corticosteroids
  - **Disease-Modifying Anti-Rheumatic Drugs (DMARD's)**
    - **Methotrexate**
      - ↓ TNF, neutrophils, histamine, lymphocyte number & function
      - ↓ growth of certain cells in blood, skin, GI tract, & immune system
      - Cytotoxicity + inhibition of metabolism → ↓ immune function
    - **Sulfasalazine -** ↓ immune function
    - **PLAQUENIL (Hydroxychloroquine) –** mechanism of action not known
  - Exercise to maintain joint mobility
    - Physiotherapy, physical therapy, water exercise
  - Surgery: synovectomy or joint replacement

New Anti-Arthritic Drugs – "Biological Agents" (or "Biologics")

Tumor Necrosis Factor (TNF) & Interlukin blockers:

- Must be given by subcutaneous injection or IV

TNFα →



HUMIRA adalimumab
REMICADE infliximab
ENBREL etanercept

$15,000 - $45,000 / year (2008)

Mechanism of Action

- Binds to TNF
- Prevents attachment to its receptor
- Inhibits inflammatory mediators
- ↓ inflammation in joint → ↓ pain

http://www.webmd.com/rheumatoid-arthritis/guide/biologics

Indications:

- Rheumatoid Arthritis
  - Effective in 70% of patients who have not responded to Methotrexate
- Ankylosing Spondylitis
- Psoriasis
- Psoriatic Arthritis- 12% of people with psoriasis have psoriatic arthritis
- Chron's Disease - autoimmune inflammatory bowel disease

Adverse effects:

- Immunosuppression !!
  - ↑ risk of infection !!
    - Tuberculosis common
- Allergic reactions

KINERET Anakinra

- **Mechanism**: Injectable man-made protein that blocks interleukin-1 **(IL-1)**
  - IL-1 → cartilage degradation, ↑ bone resorption
- **Adverse Reactions**: Injection site reactions, systemic infections (↓ immunity), malignancies, neutropenia

Blood & Body Fluids

- 62.5% of total body fluid is intracellular (contained within cells) and is abbreviated ICF
- 37.5% of total body fluid is extracellular (outside of cells: blood, interstitial fluid, etc) abbreviated ECF
- Average human blood volume is about 5 Liters
    - 3 Liters plasma + 2 Liters RBC's, WBC's etc
- Hematocrit ("crit"): packed RBC volume – about 45% of total volume for men, 40% for women
    - Anemia: crit < 40% for men or < 30% for women ([Hb] < 14 g/dL for men, < 12 g/dL for women)

      Anemia can lead to fatigue & weakness and may be caused by:
        - Colon Cancer (bleeding), IBS (bleeding), Bleeding Ulcer, Chron's Disease (bleeding)
        - Chemotherapy & Radiation for cancer
            - RBC destruction + ↓ RBC production
        - Kidney disease

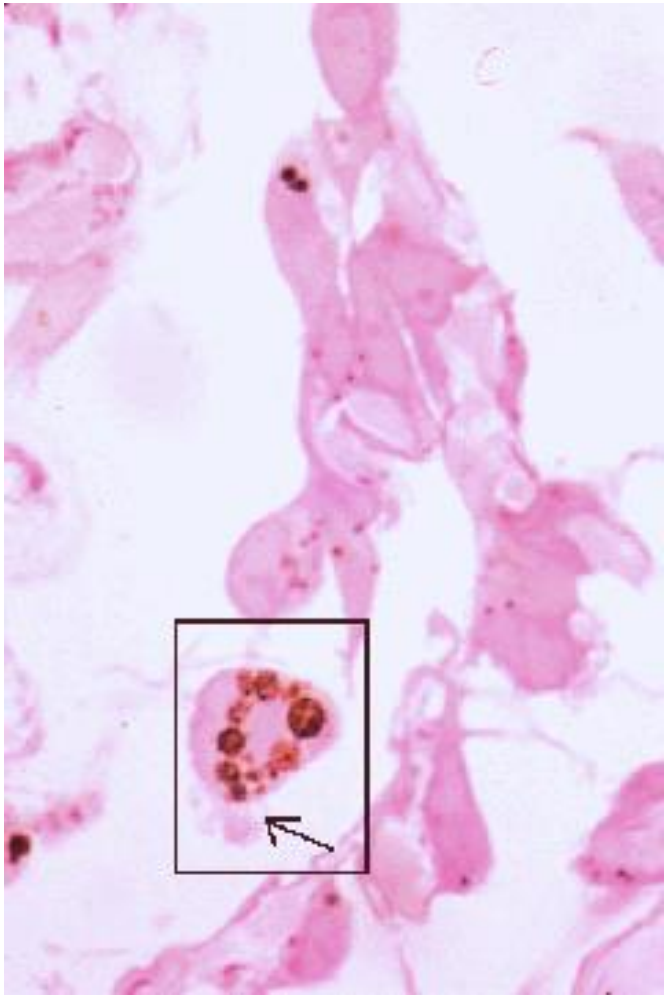
- Blood Components
    - Formed elements: RBC's, WBC's, Platelets
    - Plasma: Plasma = Serum + clotting proteins such as fibrinogen (Serum = Plasma - Proteins)
        - Elevated fibrinogen levels → ↑ risk of stroke and atherosclerotic disease

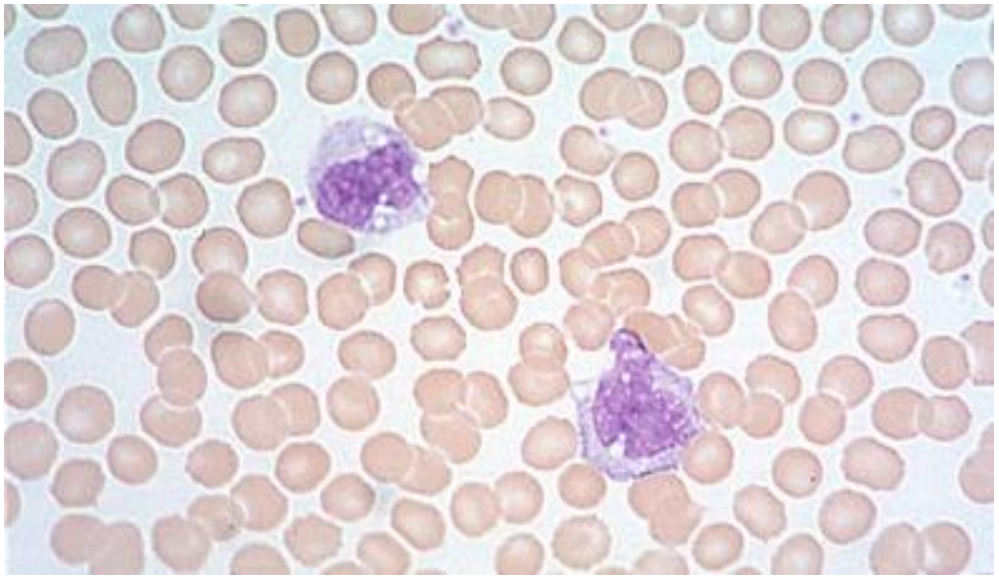
Blood & Body Fluids

- **Red blood cells (Erythrocytes)** - formed in bone marrow
  - Production and homeostasis regulated by tissue oxygenation
    - ↓ tissue O_2 → ↑ erythropoietin from kidneys & liver → ↑ RBC's
- **White blood cells (Leukocytes)** http://thyroid.about.com/library/immune/blimm06.htm
  - Primary effector against infection & tissue damage
  - WBC's engulf foreign substances & lysozomal enzymes digest them
  - **GRANULOCYTES (Polymorphonuclear cells)** - granulated WBC's
    - Neutrophils - 62% of WBC's - 1st to travel & arrive at injury – "kamikazi" phagocytotic
    - Eosinophils - 2% of WBC's - destroy parasites - involved in allergies
    - Basophils - < 1% of WBC's - release histamine & heparin
  - **AGRANULOCYTES** – phagocytotic non-granulated WBC'S
    - **Monocytes** - 5.3% of WBC's - become lysosome filled macrophages
      - Macrophages - monocytes that have left the circulation
      - Macrophages play an important role in removing dust and necrotic tissue in lungs
      - Macrophages release cytokines and compliment proteins (inflam. mediators)
    - **Lymphocytes** – T cells & B cells – 15%-40% of WBC's - function in acquired immunity
      - Antigen (pathogen) → B cell activation → antibody production
      - Helper T cells cause cytokine production, cytokines mediate immune function
      - Cytotoxic T cells have cytotoxic granules → cause death of pathogen infected cells

Macrophage: (in the box)

Arrow: Pedicle for locomotion:

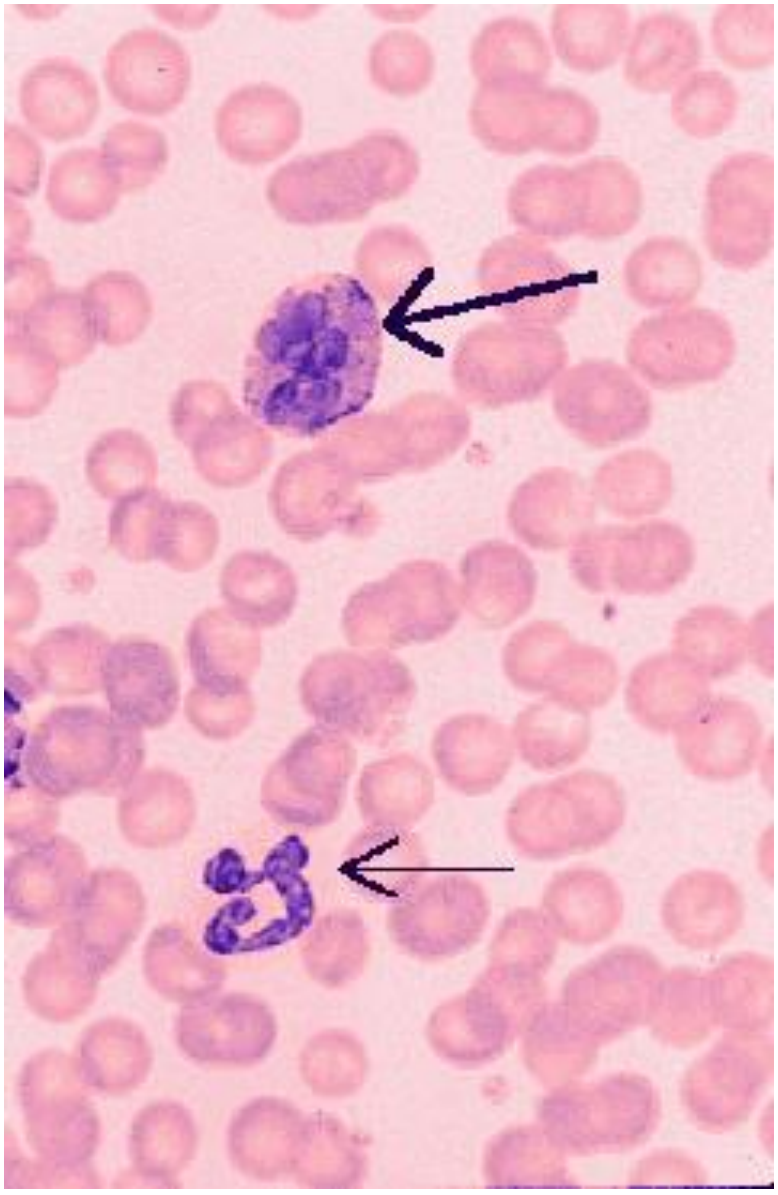




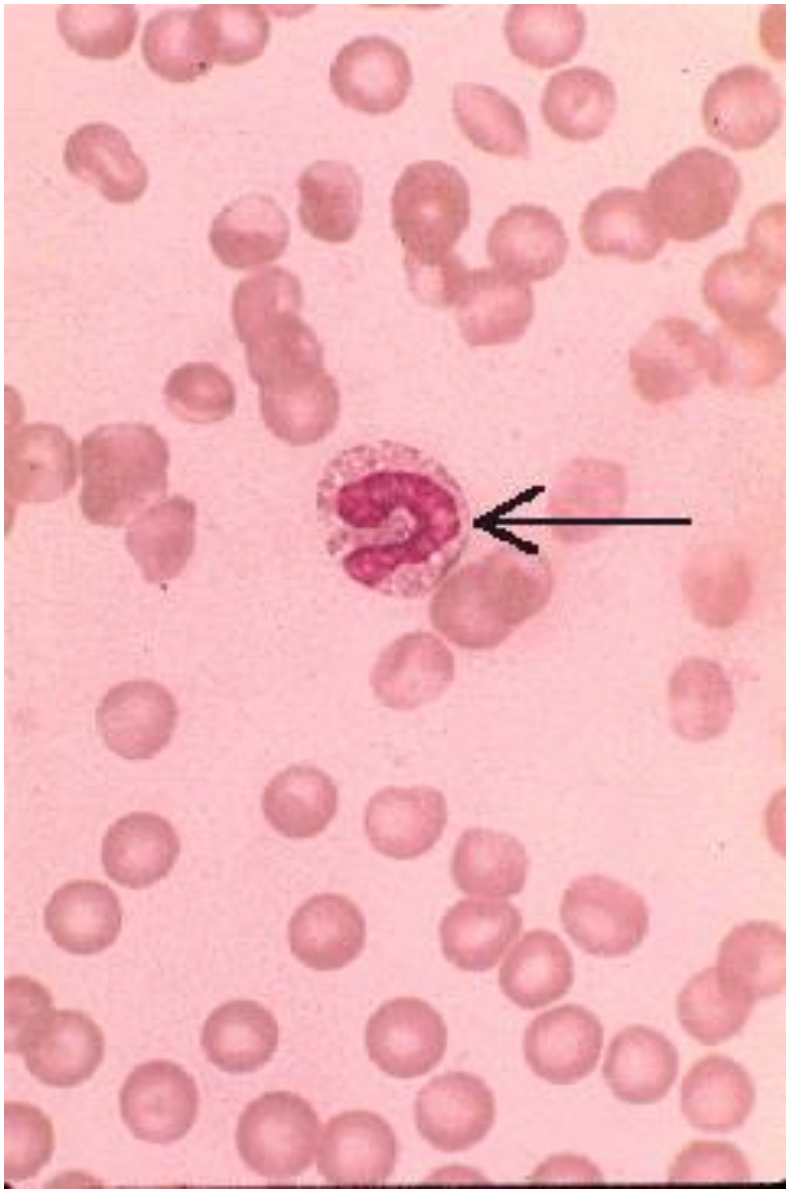
Monocytes

large arrow: Basophil

small arrow: Neutrophil



Arrow: Eisonophil



Blood & Body Fluids

- **Platelets** - Thrombocytes
  - Sticky cells that function in all aspects of hemostasis

- **Plasma**
  - Water (90% of plasma volume)
  - Metabolic by products: lactic acid, urea, creatinine, etc.
  - Nutrients: glucose, FFA's, lipids, cholesterol, vitamins
  - Electrolytes: sodium, potassium, magnesium
  - Gasses: oxygen, nitrogen, carbon dioxide

Blood & Body Fluids

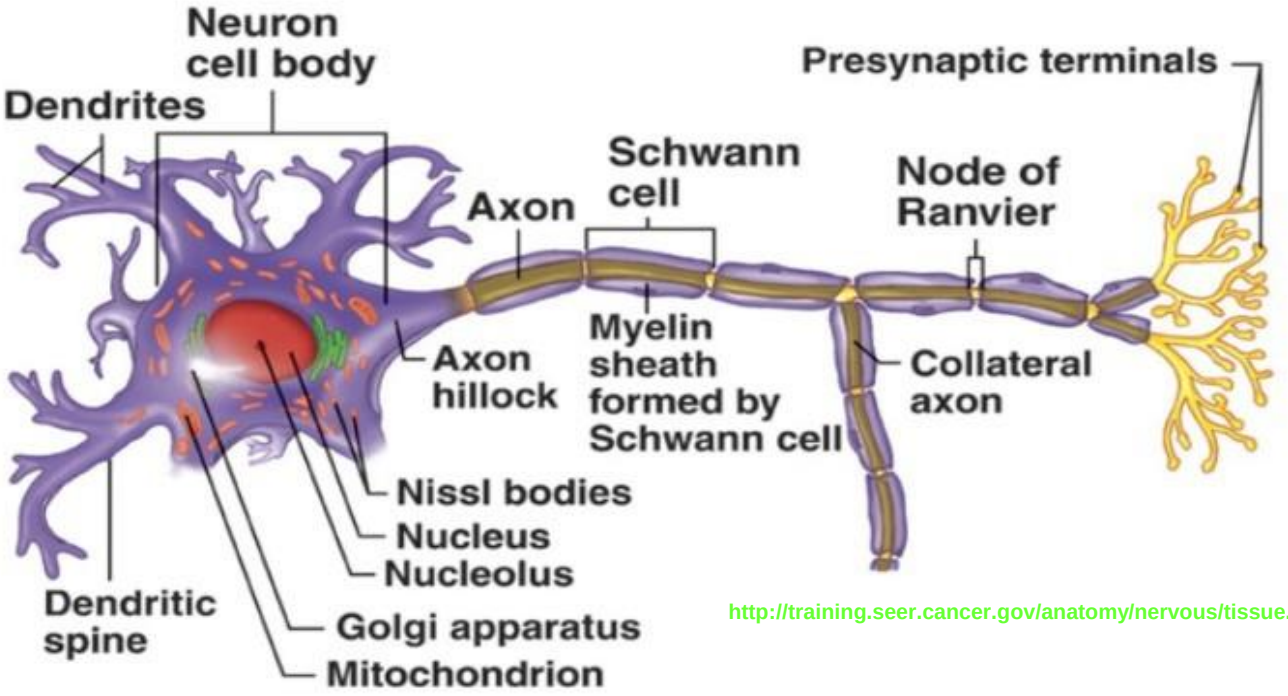
Plasma (continued)

http://www.mckinley.illinois.edu/handouts/immunoglobulin.html

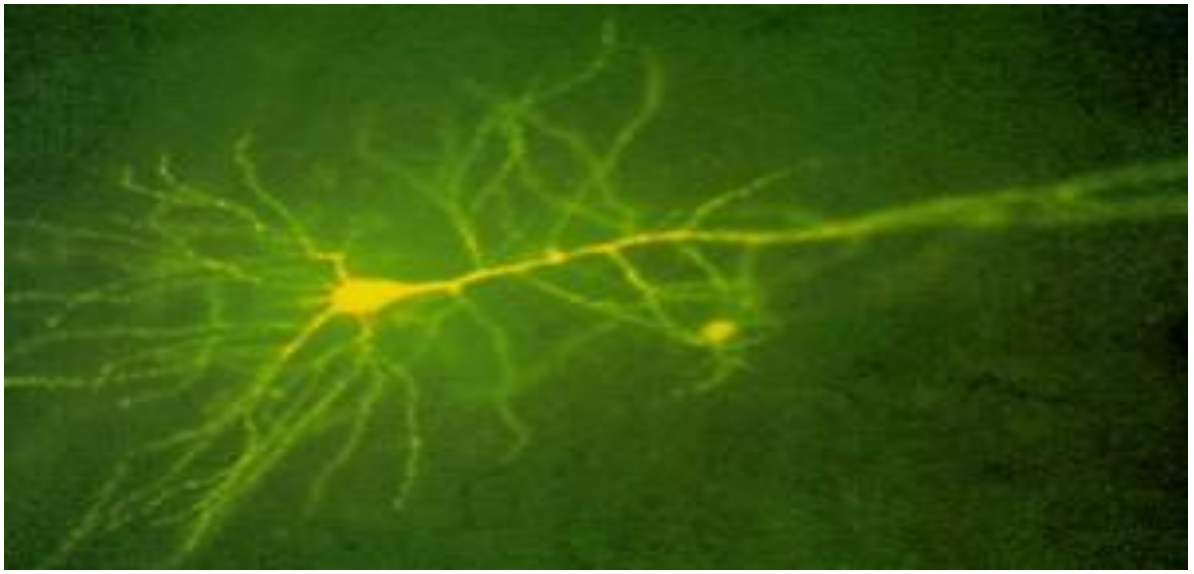
http://thyroid.about.com/library/immune/blimm07.htm

- **Proteins**: Total Blood Protein ≅ Albumin + Globulin
  - **Albumin** - **(60%)** manufactured by the liver
    - Maintains oncotic pressure
    - Transports FFA's, bilirubin, thyroid & other hormones
    - Functions as a free radical scavenger (antioxidant)
  - **Globulins (36%)**
    - **Alpha (from liver)** – transports bilirubin & steroids
    - **Beta (from liver)** – transports Cu and Fe, form lipoproteins (mostly LDL)
    - **Gamma** (or immunoglobulin) – "Ig" – contains antibodies
      - Produced by immune system in response to infection, allergic reaction
      - Provide short term disease protection (GG injections are possible)
  - **Fibrinogen** - **(3%)** functions in hemostasis (the clotting process)
  - **Enzymes** – catalyzes physiological reactions (PFK, citrate synthase….)
  - **Antibacterial Proteins** – CAP18, LL37
  - **Protein Hormones** – Insulin, HGH, LH, FSH, ADH(vasopresin)

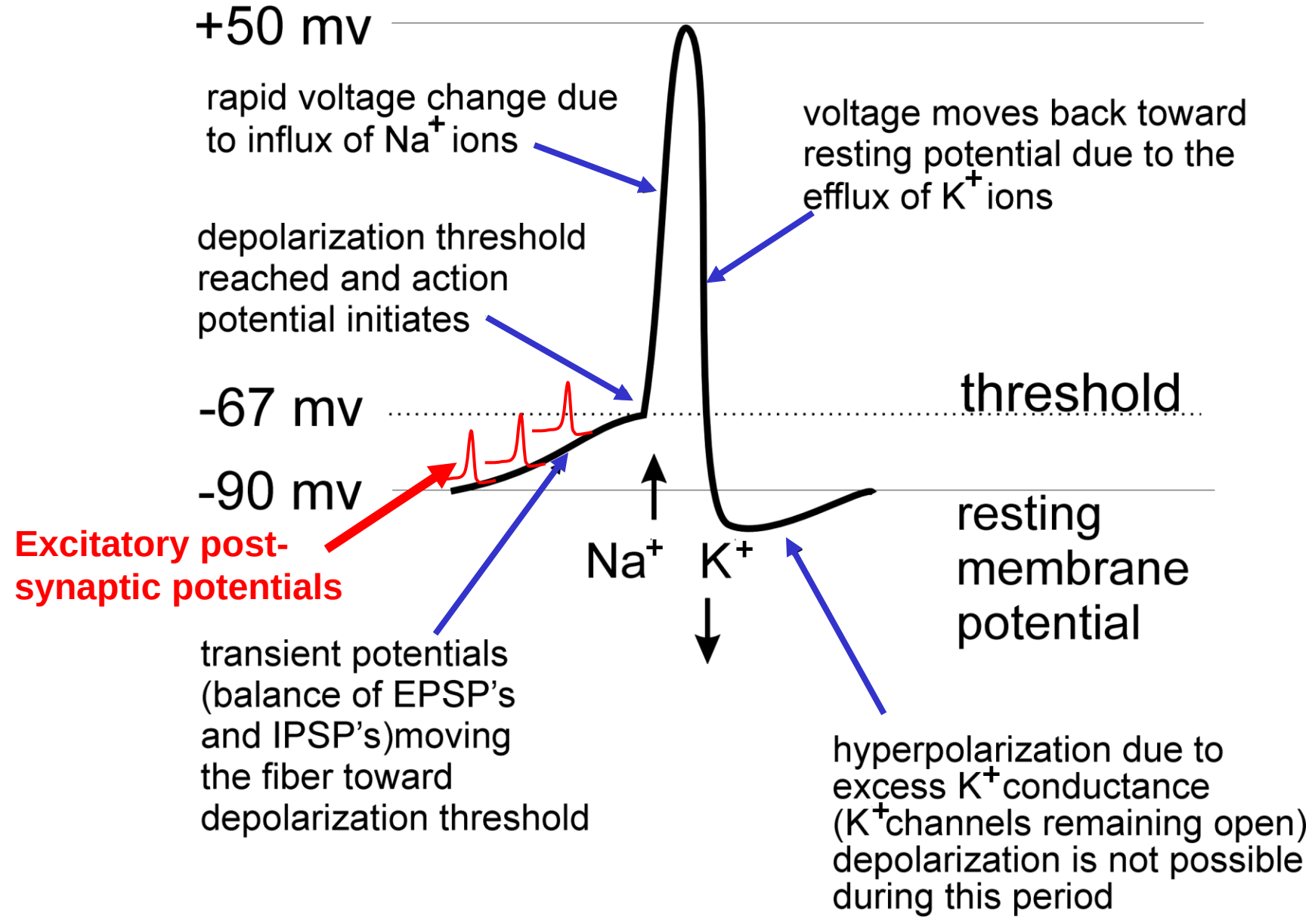
The Basic Unit of Nerve Tissue – The Neuron



http://training.seer.cancer.gov/anatomy/nervous/tissue.html



Skeletal Muscle or Motor Unit Action Potential

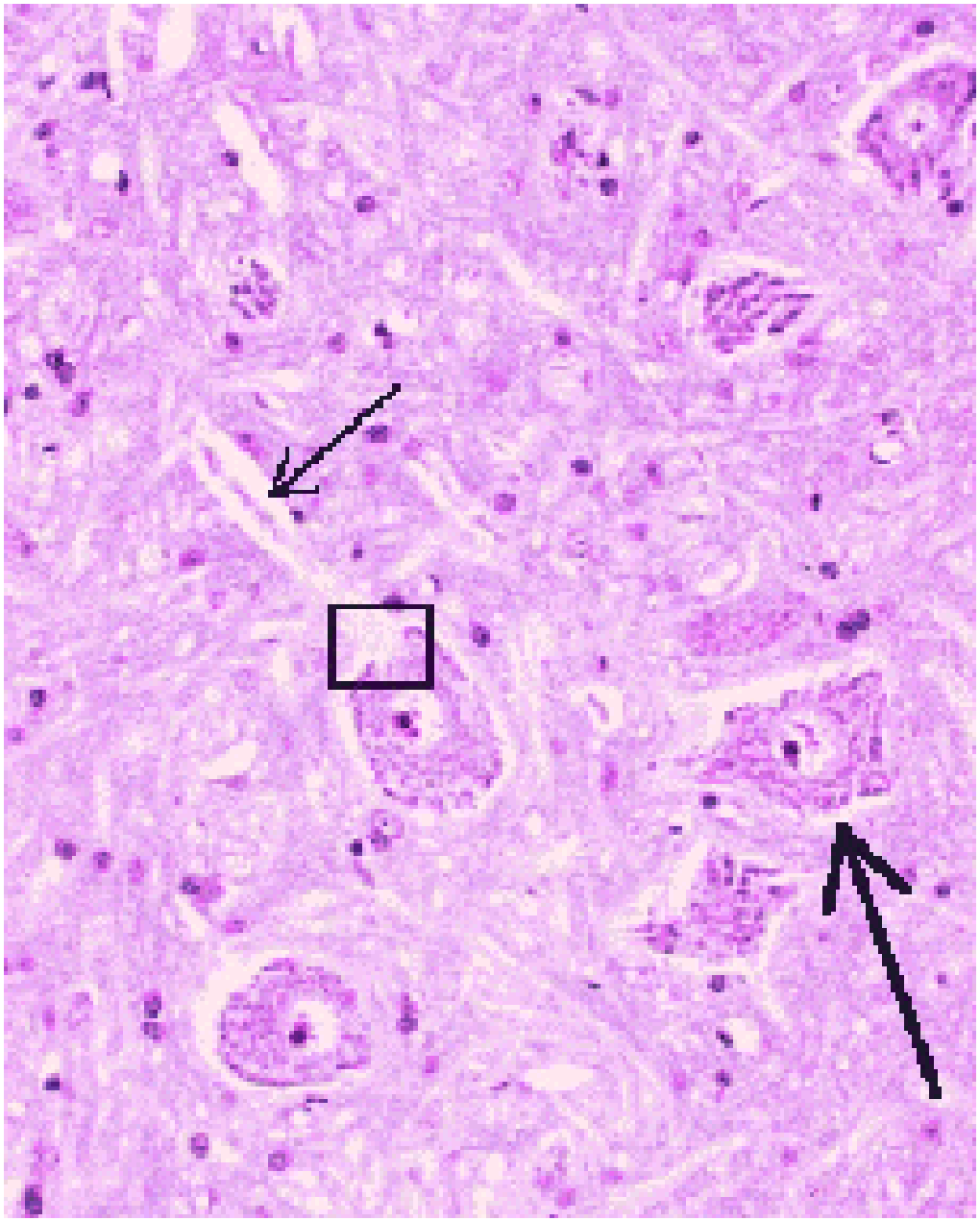


Nerve Tissue X 200

Large arrow: Soma (cell body)

Small arrow: axon body

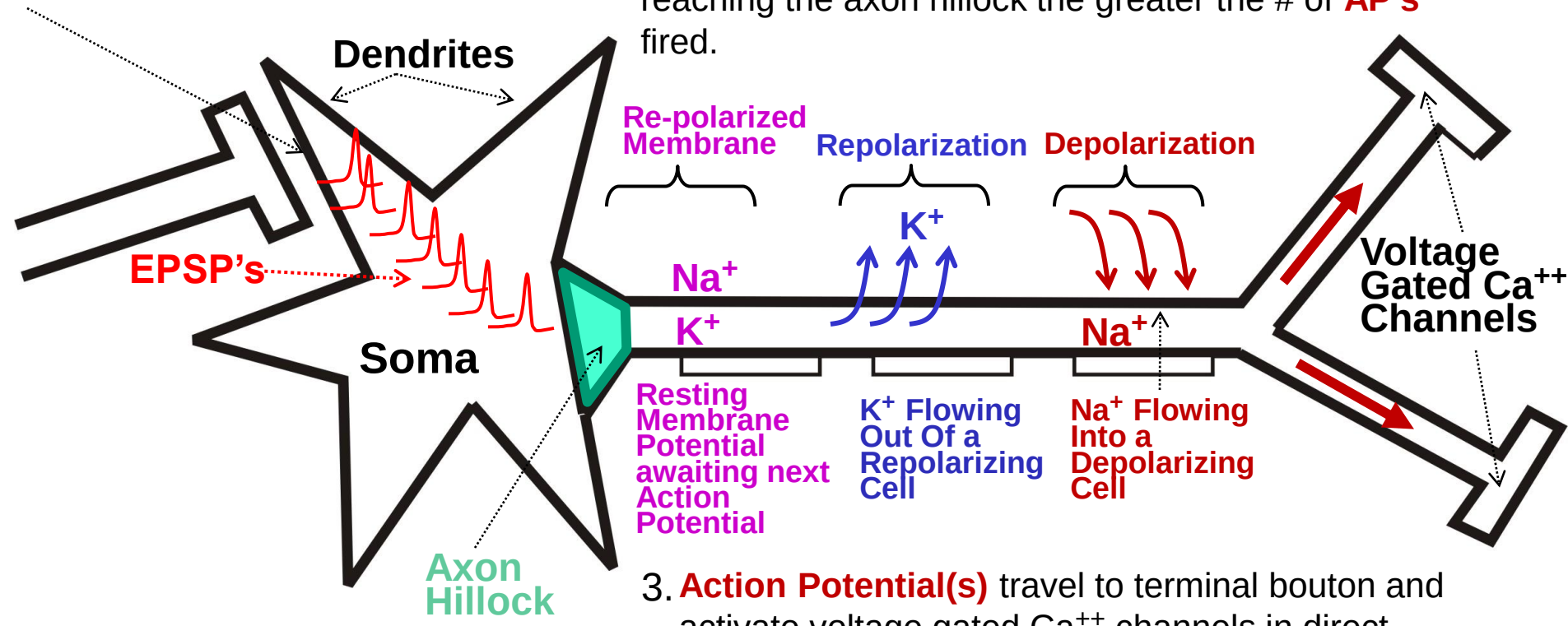
Box: Axon Hillock



Propagation of a Neural Impulse

1. Acetylcholine released from pre-synaptic neuron causes receptor operated (acetylcholine gated) channels to allow Na+ and K+ to pass through. This creates **Excitatory Post Synaptic Potentials (EPSP's)** ie. transient depolarizations

2. **Axon Hillock** fires an AP when enough **EPSP's** depolarize it to threshold. The greater the voltage reaching the axon hillock the greater the # of **AP's** fired.



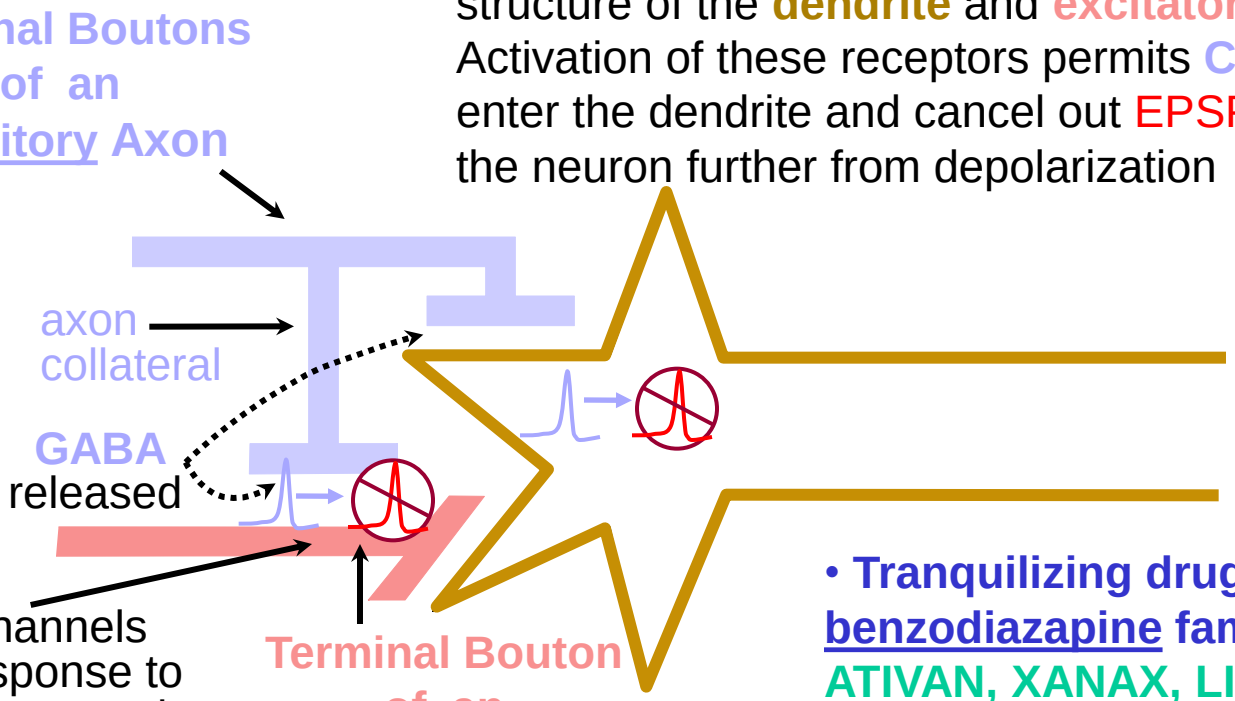
3. **Action Potential(s)** travel to terminal bouton and activate voltage gated Ca^{++} channels in direct proportion to **AP** frequency. Ca^{++} flows in and triggers the release of acetylcholine causing further propagation of the impulse or muscle fiber activation.

http://www.bristol.ac.uk/synaptic/basics/basics-2.html

Inhibition of Neural Transmission via GABA – the inhibitory neurotransmitter

GABA - gamma aminobutyric acid

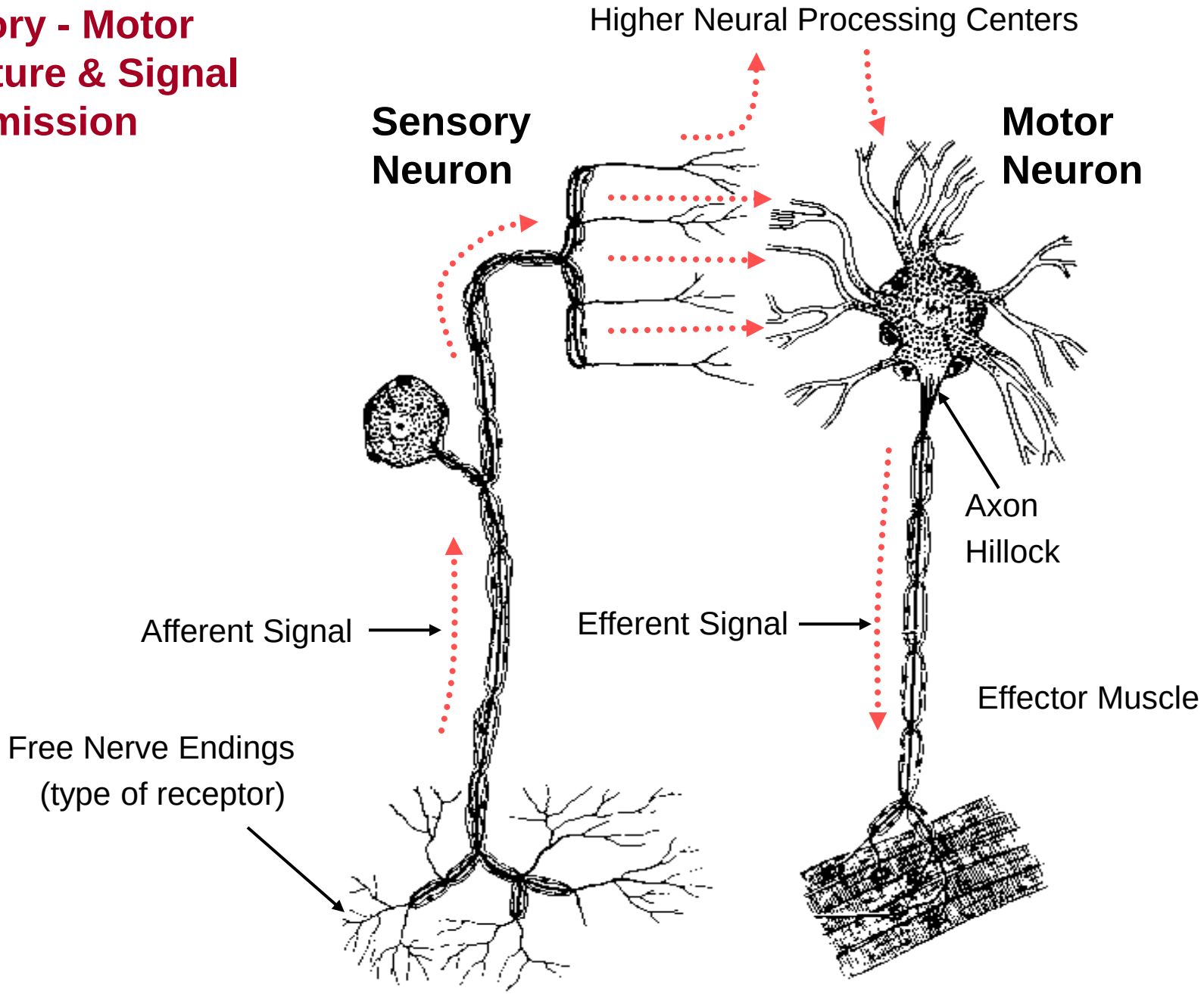
Inhibitory **GABA** receptors exist on the post synaptic structure of the **dendrite** and **excitatory terminal bouton**. Activation of these receptors permits **Chloride ions** to enter the dendrite and cancel out EPSP's. This takes the neuron further from depolarization



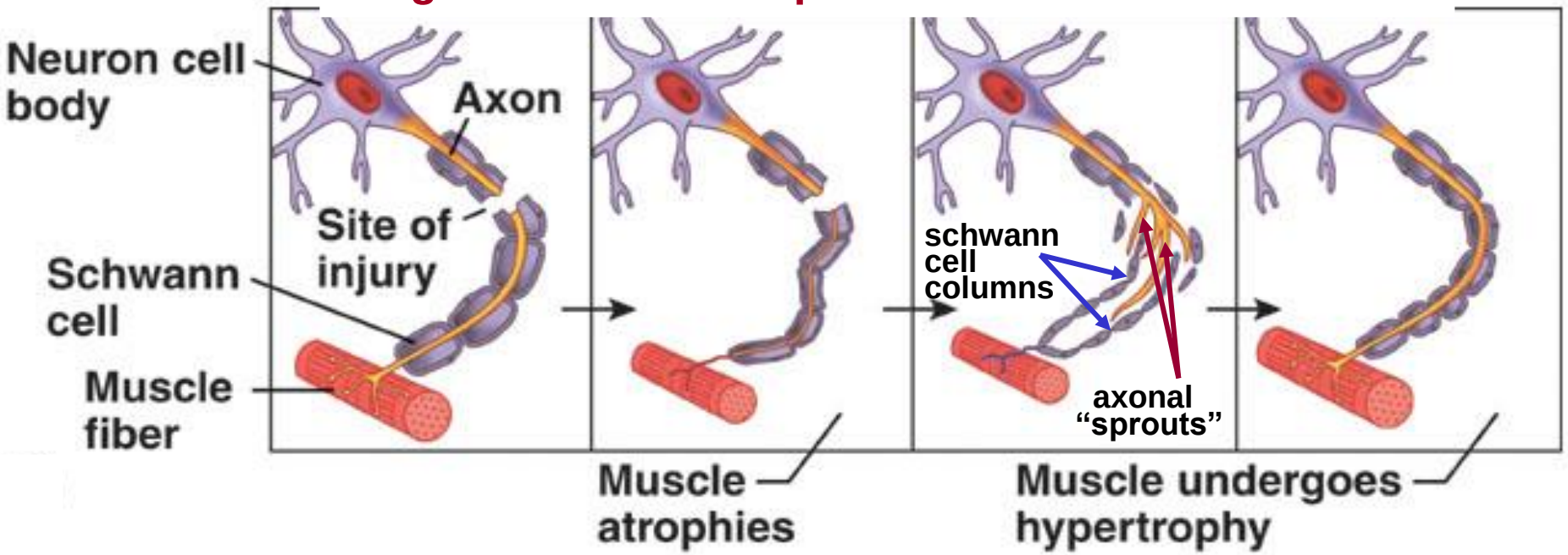
Inward Chloride ions (Cl^-) hyperpolarizes the bouton (less depolarization) so AP's traveling down the axon are inhibited. This causes less Calcium to enter the terminal bouton of the excitatory axon, resulting in less Acetylcholine release (neural transmission is retarded).

- **Tranquilizing drugs of the benzodiazapine family (VALIUM, ATIVAN, XANAX, LIBRIUM, RESTORIL, HALCION, KLONOPIN) bind to receptors in the brain and enhance the affinity of GABA for its receptor. This further promotes the inward chloride current, which reduces anxiety & panic. Also promotes a calming effect.**

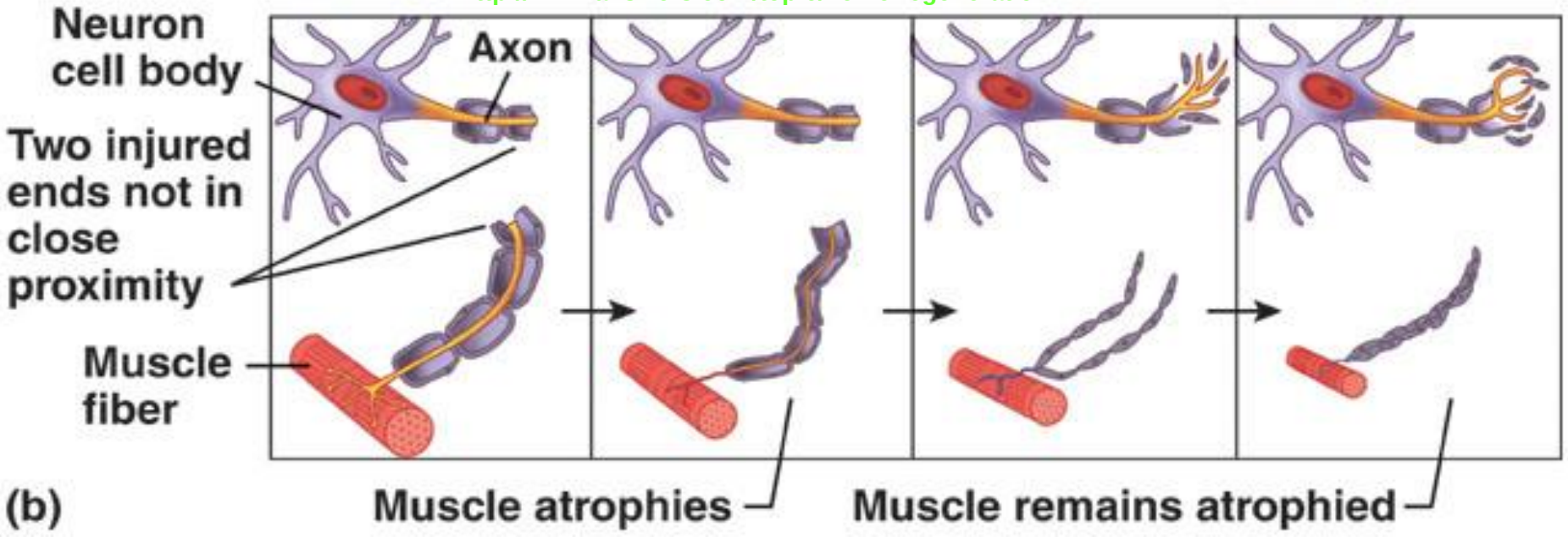
Sensory - Motor Structure & Signal transmission



Regeneration of Peripheral Nervous Tissue



http://www.answers.com/topic/nerve-regeneration

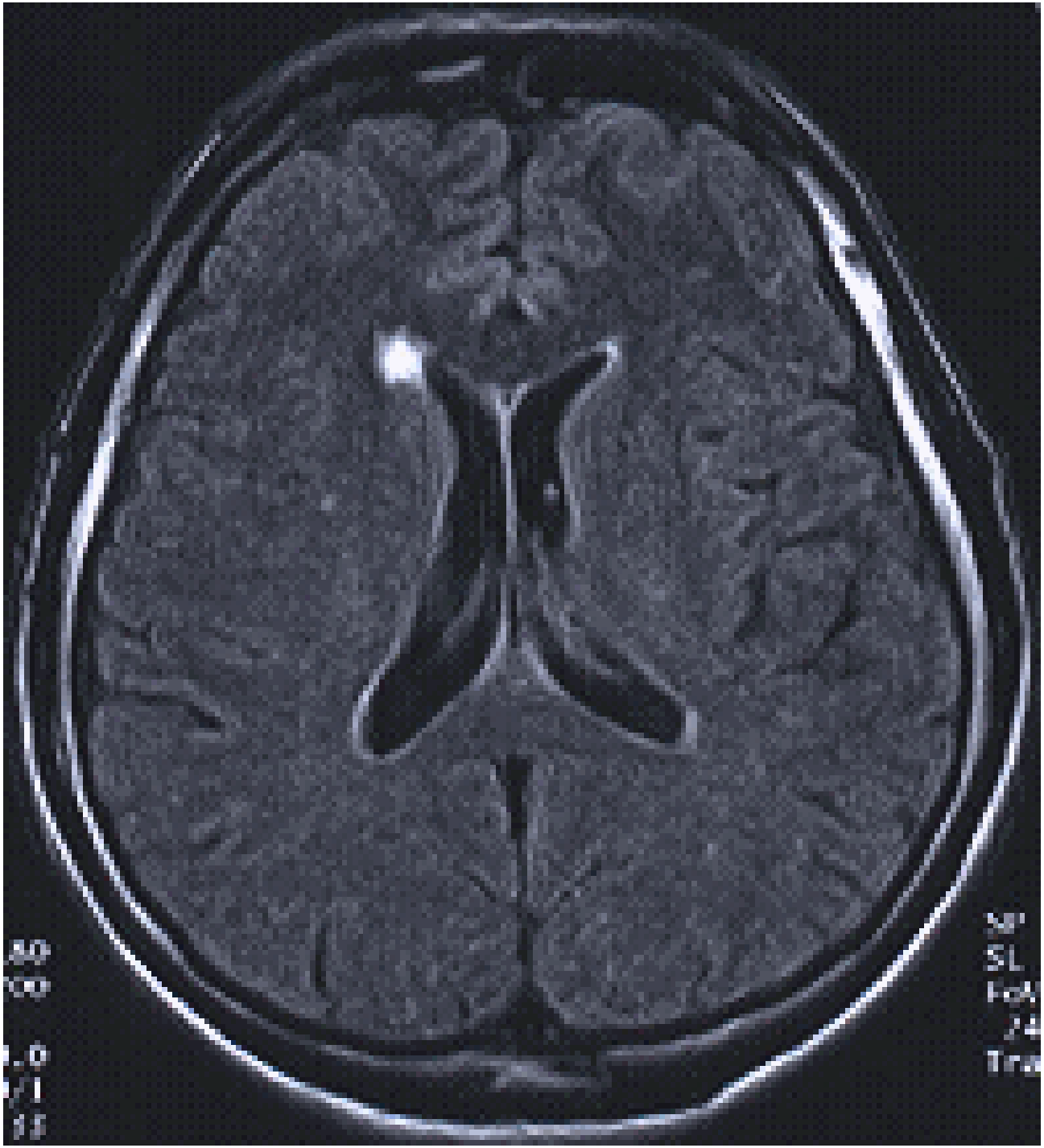


Nerve Diseases & Associated Therapy

- **Multiple Sclerosis** - an autoimmune disease in which auto-reactive T cells (lymphocytes) cross the blood–brain barrier and attack the myelin sheath leading to a cascade of inflammation. The result is de-myelination, acute axonal transection, and axonal degeneration [Trapp *et al.* 1998]. – Of the 4 types of MS, 2 are the most common: **primary progressive (12.5%)** and **relapsing-remitting (85%)**
  - **Causes:** autoimmune factors (exact antigen not identified), virus triggers (theory not proven), possible genetic predisposition, various forms of physical trauma.
  - **Symptoms:** weakness, numbness ("pins & needles"), loss of balance, loss of coordination, bowel & bladder dysfunction, muscle spasticity, optic nerve neuritis. **symptoms are "epidsodic"**
  - **Therapies** http://www.ninds.nih.gov/disorders/multiple_sclerosis/multiple_sclerosis.htm
    - Immunomodulator drugs: ↓ number of lymphocytes and their inflammatory effects
      - inhibit cytokines → ↓ inflammation - cytokine inhibition also ↓ number of episodes
      - **Interferon β (1a & 1b) - AVONEX BETASERON REBIF GILENYA (1st line drugs)**
      - **Glatiramer Acetate - COPAXONE (2nd line drug)**

      $34,000 / year (2010) for 1 drug
    - Immunosuppressants: ↓↓ inflammatory effects of lymphocytes, ↓ inflammation **(3rd line drug)**
      - **Mitoxantrone, Cyclophosphamide, Methylprednisolone, Azathioprine**
      - Side effects: Danger of infection from suppressed immune system
    - **Natalizumab -TYSABRI**- prevents activated lymphocytes from crossing blood–brain barrier
    - Weakness therapies: dopaminergic drugs – similar to drugs for Parkinson's patients, exercise (water exercise & swimming most beneficial)
    - Spasticity therapies: reflex inhibitors, muscle relaxers
    - Tremmor therapies: anticonvulsant drugs
    - Visual problem therapies: corticosteroids to reduce ocular inflammation

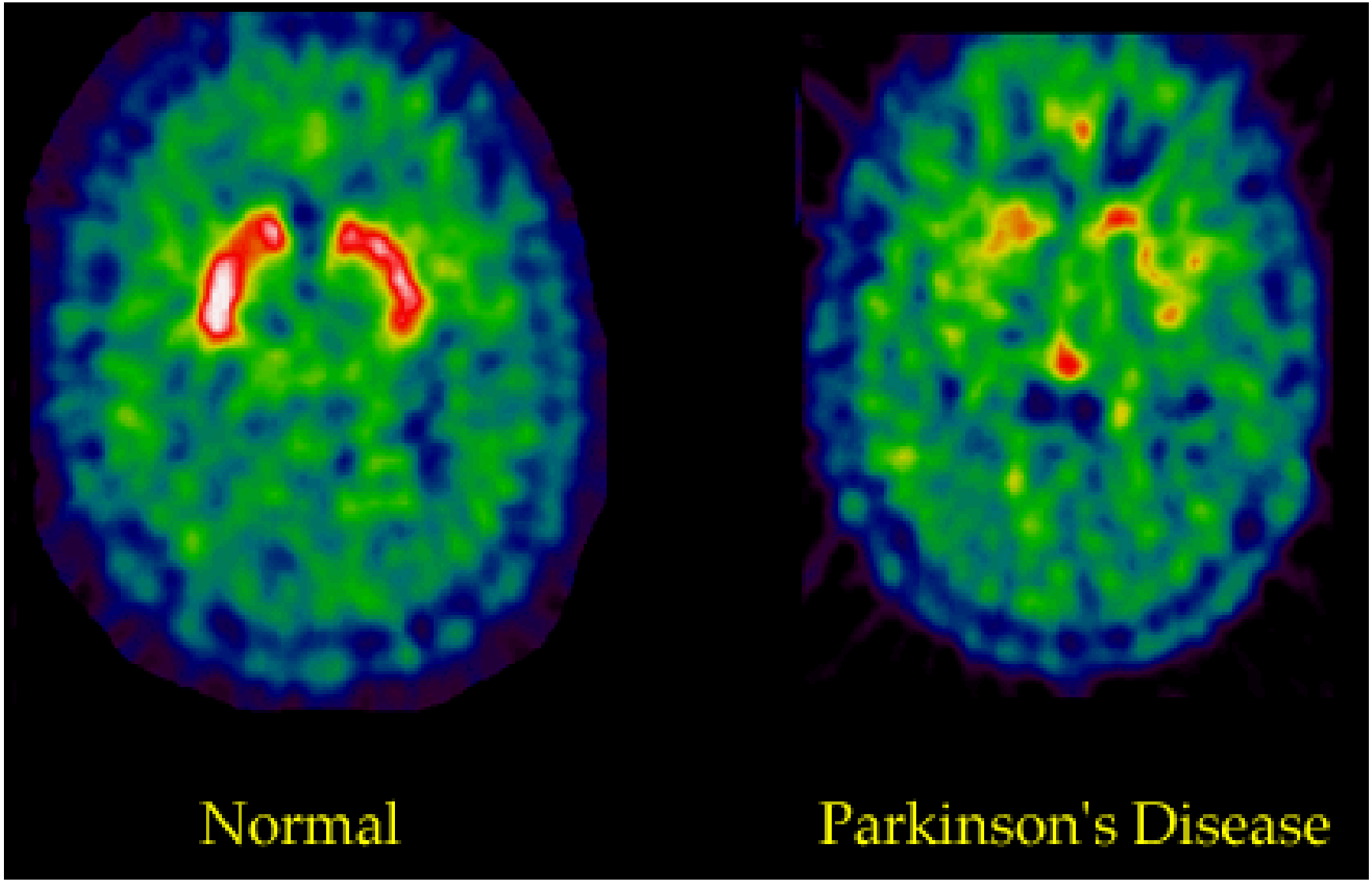
MRI of the brain showing a plaque associated with Multiple Sclerosis



Nerve Diseases & Associated Therapy

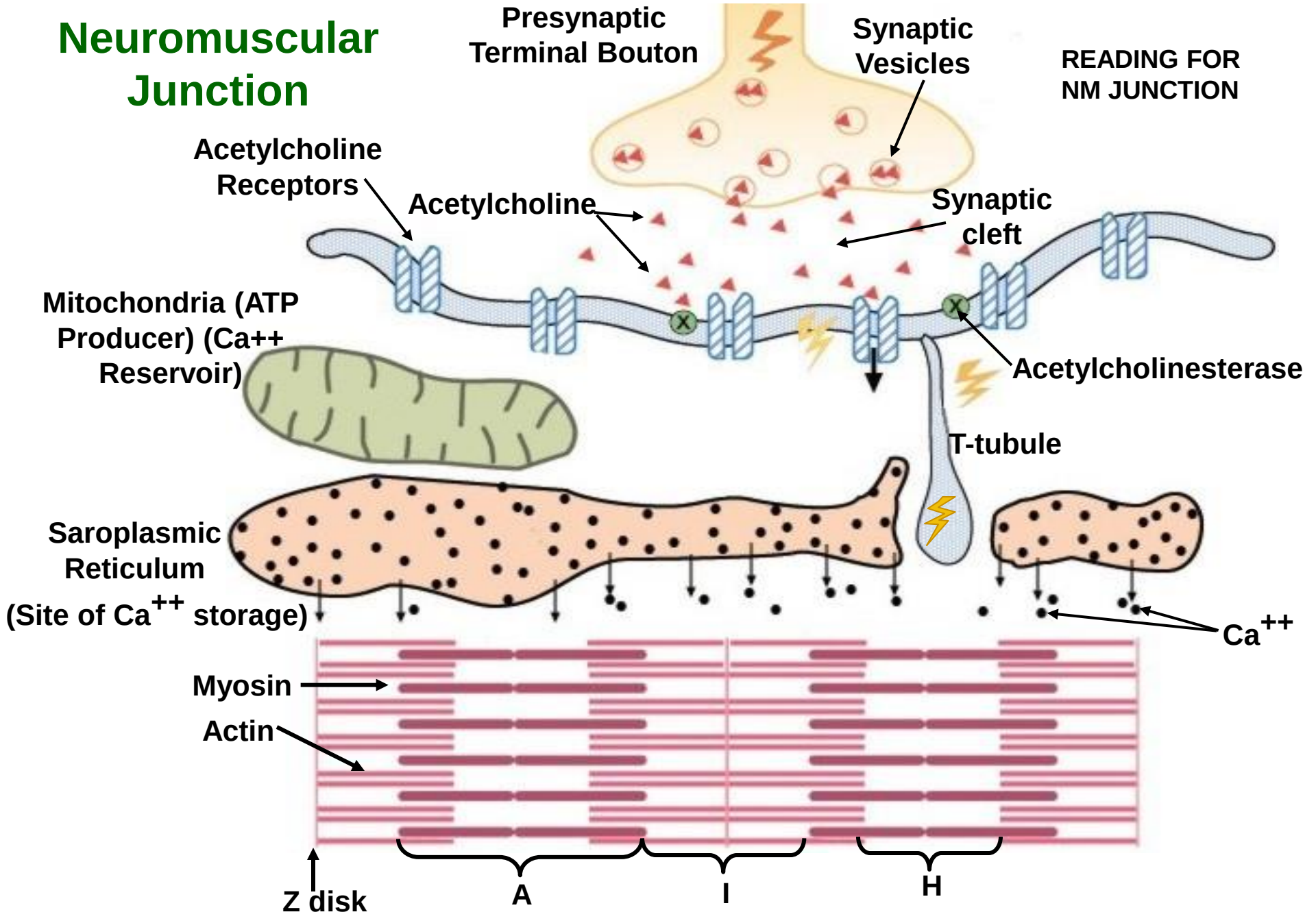
- **Parkinson's** - loss of production of the neurotransmitter dopamine in the basal ganglia (loss of 80% of dopamine producing cells) → disruption of balance between dopamine and Ach → ↓ voluntary movement control
  - **Causes:** free radical damage (theory), toxins (theory), age related ↓ in dopamine producing neurons, genetic predisposition, repeated head trauma (boxing), illegal drug use, hydrocephalus (CSF accumulation in the ventricles of the brain), viral encephalitis (inflammation of white and gray brain matter).
  - **Symptoms:** resting tremor - "pill rolling" motion (70%), bradykinesia (inability to generate movement), rigidity, postural instability, difficulty rising from sitting position, shuffling gait.
  - **Therapy:** http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm http://www.usnews.com/health/articles/2009/01/23/3-ways-that-stem-cells-may-speed-new-cures.html?s_cid=et-0316
    - Levodopa: ↑ dopamine levels in brain (current gold standard of treatment)
    - Catechol-O-methyltransferase inhibitors: (inhibits levodopa's peripheral metabolism → more available for transport across blood brain barrier)
    - Dopamine agonists: stimulate dopamine receptors
    - Monoamine Oxidase B inhibitors: slow dopamine neuron degeneration
    - Embryonic tissue transplantation – not very successful so far
    - DBS Surgery – brain "pacemaker" - sends e^- to parts of brain - promising

PET Scan showing reduced uptake of injected flurodopa (radioactive dopamine) in the dopamine producing neurons in the brain of a Parkinson's Patient



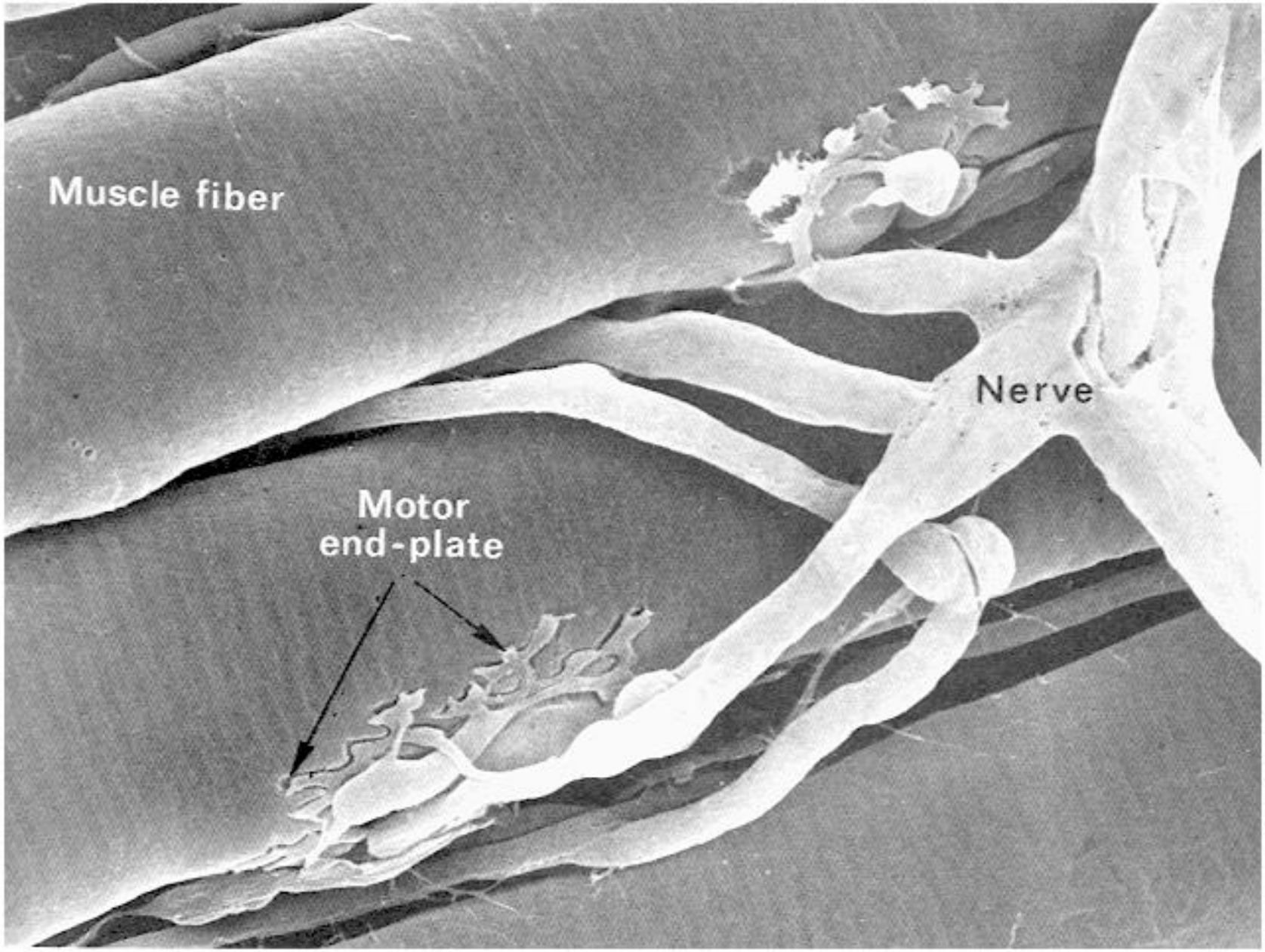
http://www.answers.com/topic/neuromuscular-junction-1

Neuromuscular Junction

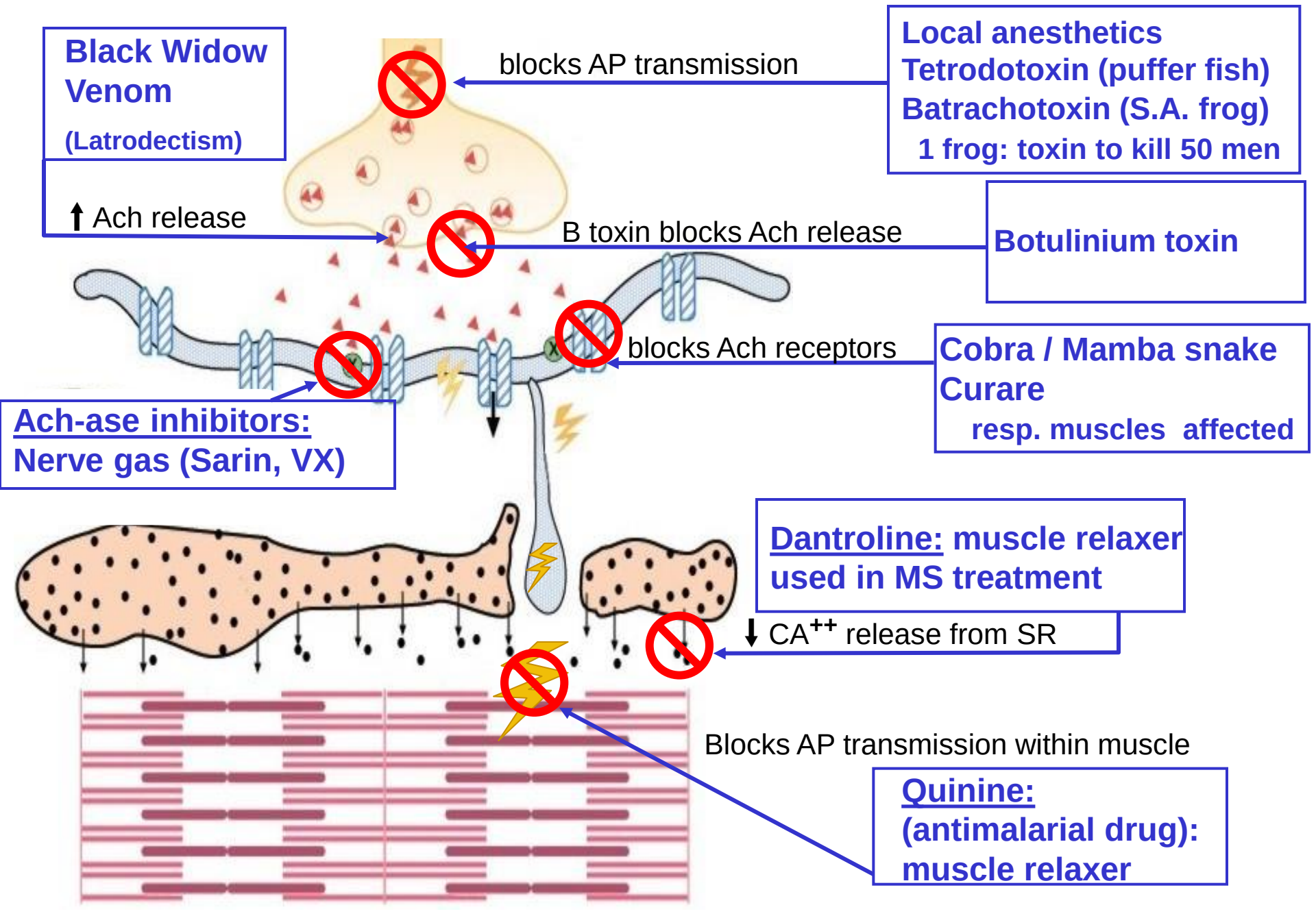


Motor End Plates (Skeletal Muscle)

Neuromuscular Junction (α Motor Neuron)



Action of Selected Toxins & Drugs Around the NM Junction



Muscle Diseases & Associated Therapy

- **Fibromyalgia** – chronic non-inflammatory pain in muscles and connective tissues (affects over 6 million Americans –most are women 20-50 years old)
  - **Theoretical Causes:** Thyroid problems, over growth of yeast bacteria, trauma, stress, hormone malfunction, infection, immune system dysfunction, autonomic NS malfunction, abnormal spinal cord pain processing, ↓ gray matter density & dopaminergic neurotransmission in the brain (*J Pain*, 2009)
  - **Symptoms:** "Aching", "un-refreshed by sleep", GI problems, fatigue, anxiety & depression, "↓ energy", presence of pain "trigger points"
    - Symptoms may be chronic – better one day, worse the next
    - Disease is often associated with other co-morbid conditions:

Anxiety	**Irritable bowel syndrome**
Migraine headache	**Restless leg syndrome**
Depression	**TMJ syndrome**
Sleep disturbances	**Chronic Fatigue Syndrome**

  - **Diagnosis:** one of exclusion
  - **Therapy:** stress reduction, exercise, growth hormone therapy, psychiatric help, acupuncture, NSAID's, Tricyclic Anti-depressants (ELAVIL), Muscle relaxants of the Cyclobenarine family (FLEXERIL), Opiods (ULTRAM), SSRI's (PROZAC), SNRI's (EFFEXOR) (CYMBALTA) (SAVELLA), anticonvulsants (LYRICA) - ↓ number of pain signals from damaged nerves

Muscle Diseases & Associated Therapy

- **Muscular Dystrophy** - an inherited disorder characterized by progressive proximal muscle weakness with destruction of muscle fibers and replacement with connective tissue
  - Diagnosed between 2 & 5, in a wheelchair by 10 or 12, death in 20's
  - Blood creatine kinase is elevated (indicator of muscle damage)
  - Some are mildly mentally challenged

http://www.ninds.nih.gov/disorders/md/md.htm

- **Cause:** genetic related absence of **Dystrophin**, a muscle membrane protein
- **Initial Symptoms:** "waddling" gait, falls, difficulty standing, difficulty climbing or descending stairs, muscle wasting, contractures, cardiac involvement, respiratory muscle weakness with complications (respiratory infections).
- **Therapy:** daily steroids produce long term symptom improvement, exercise should be continued as long as possible, surgery may be done to release contractures, pneumonia vaccine (prophylactic), physical therapy to delay development of contractures.
- Contractures – any condition that affects mobility or range of motion of a joint
  - Usually involves **fiber deposition in the skin, fascia, muscle, or joint capsule**

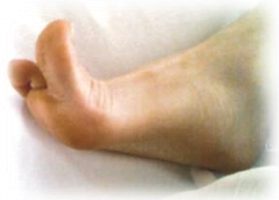
Somata Sensory Neuron Types and Function

Classification	Diameter	Velocity	Receptor	Function / Sensation
Aα (α efferents)	**Largest**	**Highest**	Ia II - - - - - - - - - - - - - - - - Spindle	Reflexes Joint sensation
			Ib - - - - - - - - - - - - - - - - GTO	
Aβ (γ efferents)			Spindle	Fine touch Kinesthesia
			Merkels disks	Joint sensation
			Meisner's corpuscle	Deep tissue sensation
			Pacinian corpuscle	Deep pressure Vibration
			Ruffini's end organs	Touch Pressure
			Hair end organs	Touch
Aδ (γ efferents)			Cold receptors	Temp(cold) Crude touch
			Free nerve endings	Fast (sharp) pain
C (unmylenated)	**Smallest**	**Slowest**	Warm receptors	Temp(warm) Crude touch
			Free nerve endings	Slow(aching) pain
				Joint & muscle aches, Itch
				Deep tissue pain, pressure

http://www.cidpusa.org/nerves.htm

Muscle Spindles, GTO's, and the Myotatic Stretch Reflex

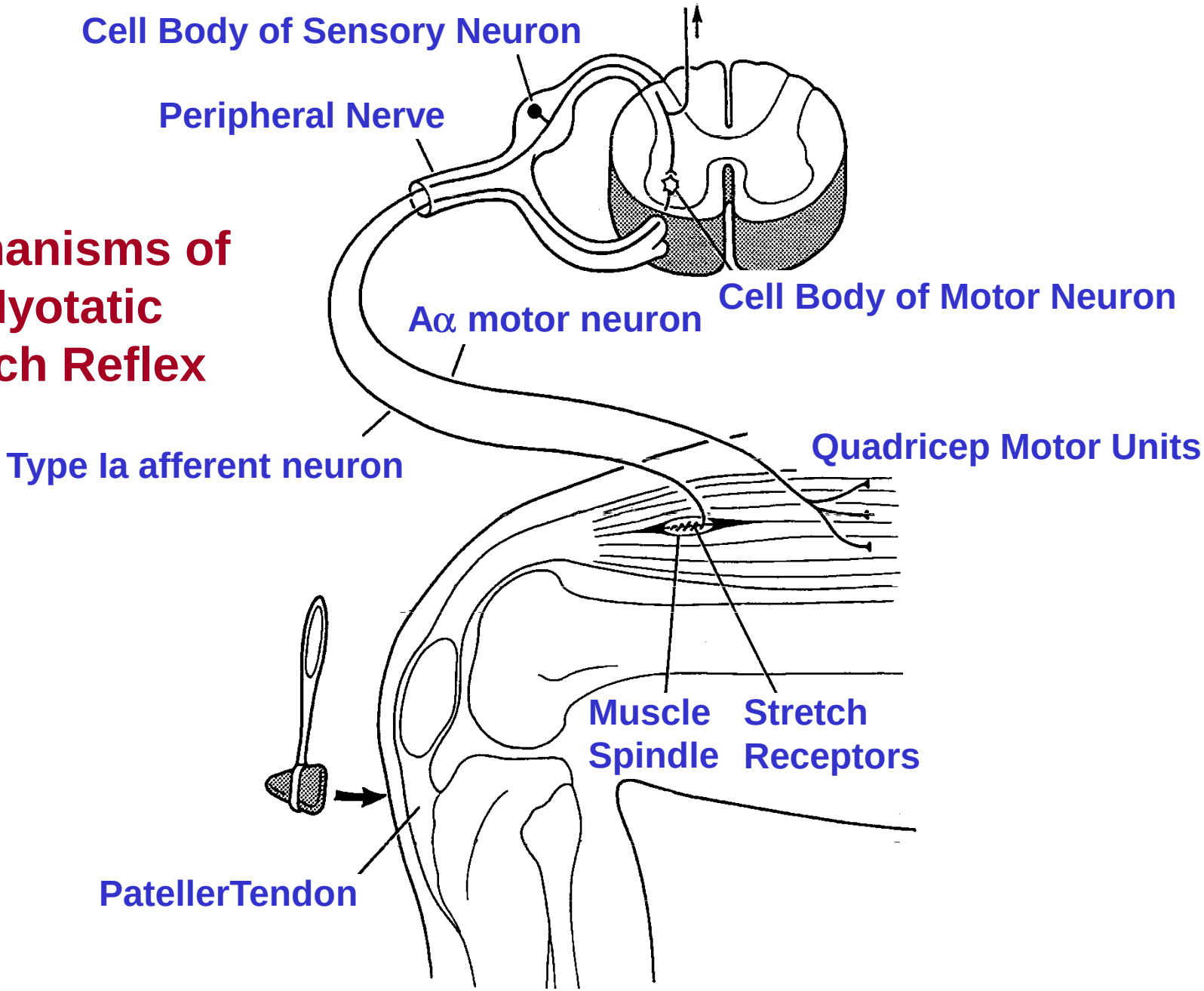
- **Muscle Spindles** http://www.livestrong.com/article/38316-muscle-spindles/
  - Detect change in muscle length and rate of change in muscle length
  - Arranged in parallel with actual muscle fibers
  - Muscle involved in fine motor activity: 120 spindles per gram of muscle
  - Muscles involved in bulk movement: 5 spindles per gram of muscle



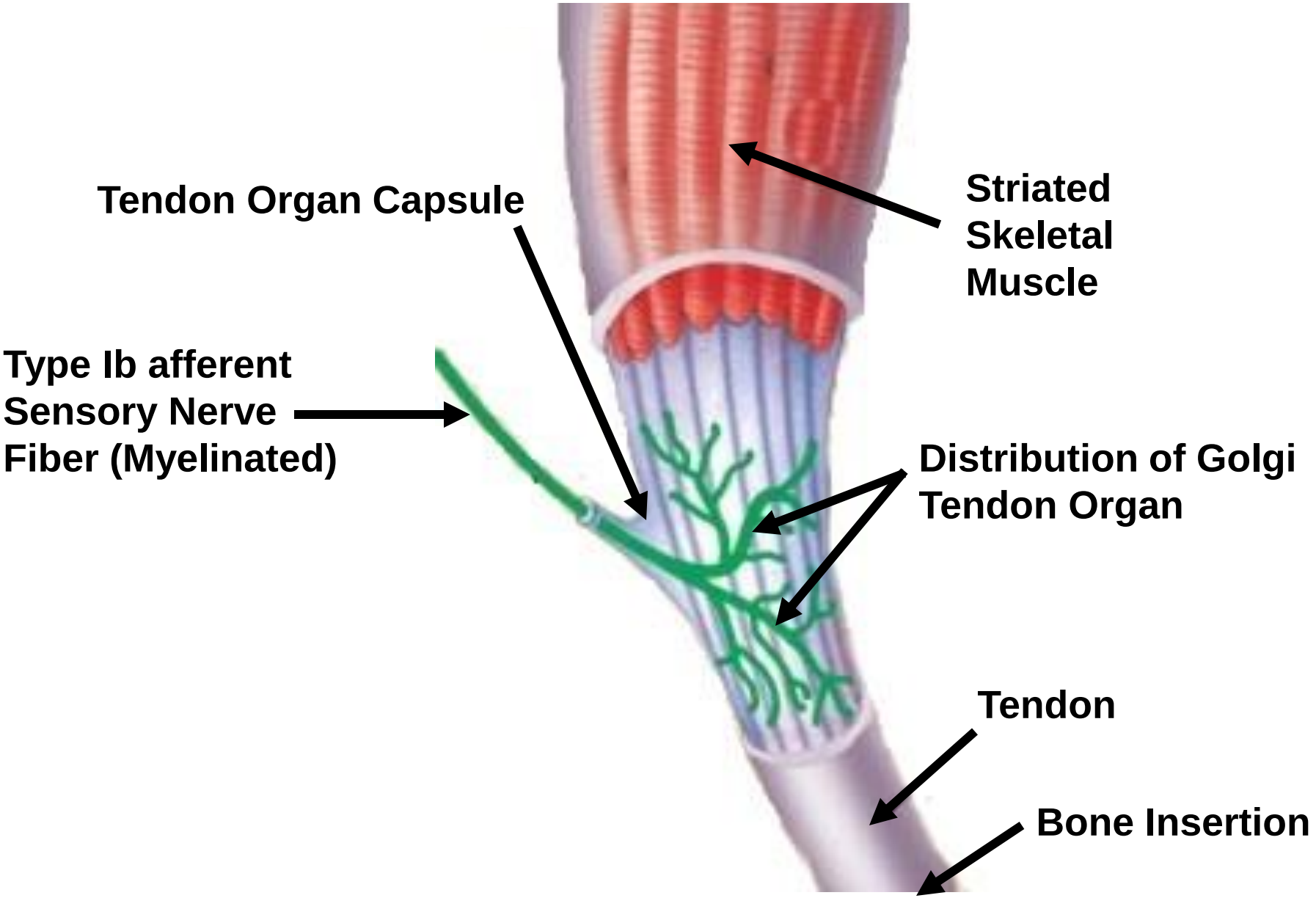
+ Babinski

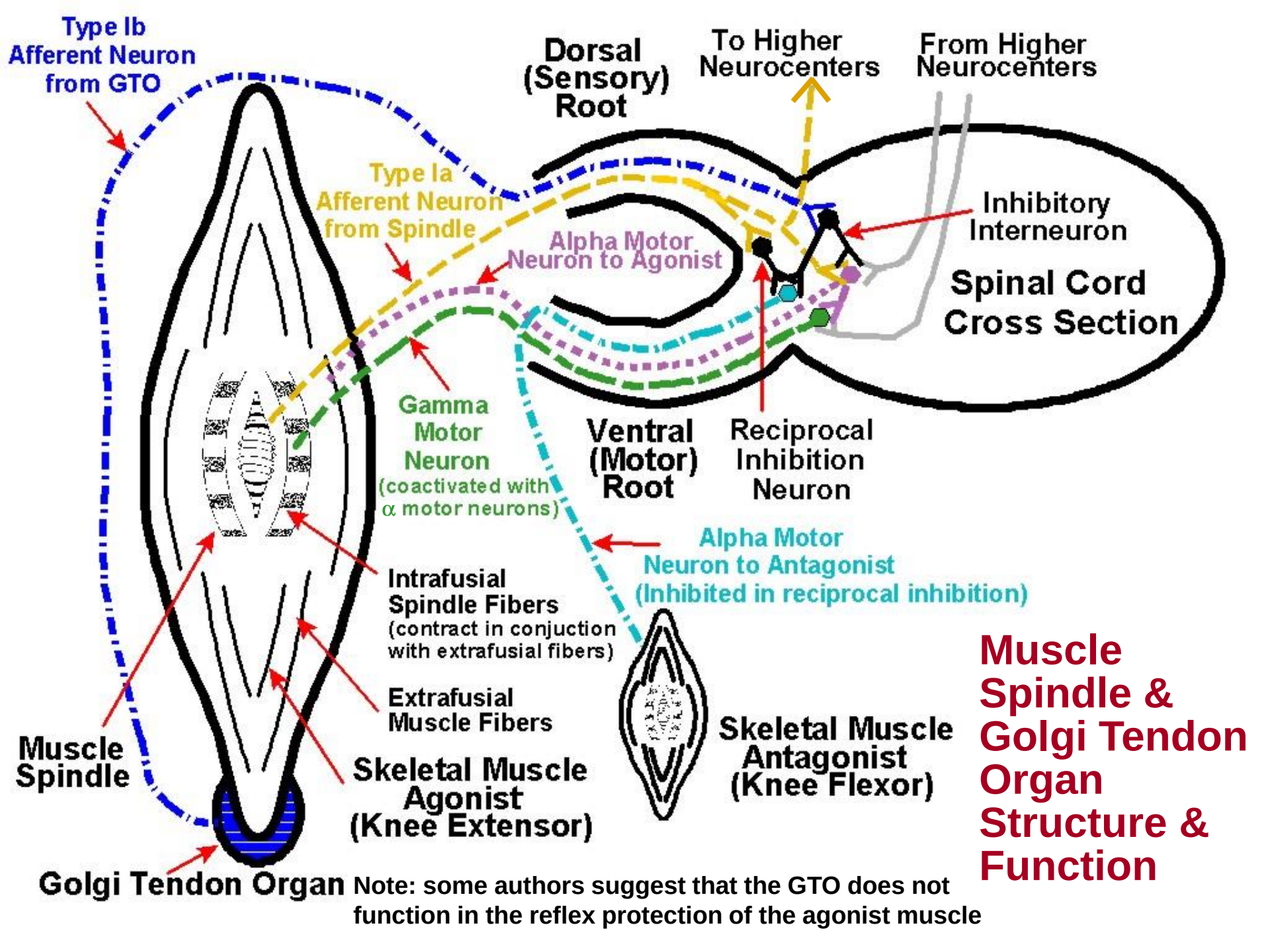
- **Myotatic Stretch Reflex (MSR)**
  - "Smooths out" or "dampens" movements, stabilizes body during fine motor tasks
  - Overactive MSR ➞ hyperactivity of cortex ➞ upper motor neuron lesion (stroke, tumor, injury)
    - Muscle spasticity (muscle always receives contraction signals ➞ ↑ muscle tone)
    - Positive Babinski sign, clasped knife sign (http://www.youtube.com/watch?v=ovQkcw86pMo),
    - ↓ limb strength & dexterity
  - Underactive MSR ➞ lower motor neuron lesion(s) (multiple sclerosis, neuropathy)
    - Loss of strength, ↓ tone, muscle wasting & atrophy, muscle twitches
- **Golgi Tendon Organs**
  - Detect both magnitude and rate of tension development in a muscle
  - Arranged in series with muscle units
  - Less active, less numerous, and slower to react than spindles
  - Are responsible for Autogenic inhibition (inverse myotatic reflex)
    - Excessive stretch / tension ➞ activation ➞ GTO signal overrides α motor activity

Mechanisms of the Myotatic Stretch Reflex



The Golgi Tendon Organ





Muscle Spindle & Golgi Tendon Organ Structure & Function

Note: some authors suggest that the GTO does not function in the reflex protection of the agonist muscle

Etiology & Treatment of Exercise Induced Muscle Cramps

Factors thought to contribute to Fatigue and subsequent EIMC's

- Exercising in hot, humid environments
  - Dehydration
    - Electrolyte deficiencies (possibly from malnutrition also)
      - Hyponatremia, hypokalemia, hypocalcaemia, hypomagnesaemia
- Overexertion (**Fatigue**) → muscle hypoxia
- Disturbances in carbohydrate (hypoglycemia), fat , or protein metabolism
- Nutritional deficiencies
  - Inadequate amounts of electrolytes, vitamins B1(Thiamine), B5 (Pantothenic acid)

Hypothesized cramp mechanisms supported by the recent literature

- **Fatigue** → ↑ spindle firing rate + ↓ GTO firing rate → ↑ α motor neuron reflex activity
- Overproduction of reflex α motor neuron activity in a shortened muscle → CRAMP
  - Further exact mechanisms remain to be elucidated

http://www.medicinenet.com/muscle_cramps/article.htm

Factors Thought to Contribute to Idiopathic Leg Cramps

(No consensus on exact etiology)

- **Metabolic disturbance**
  - **hyponatraemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hypomagnesaemia, hypoglycaemia**
- **Chronic or severe acute diarrhea**
- **Pregnancy, especially in the late months**
- **Cirrhosis of the liver**
- **Renal dialysis**
- **Thyroid disease**
- **Heavy alcohol ingestion**
- **Lead toxicity**
- **Disorders of the lower motor neurons, including amyotrophic lateral sclerosis (ALS), MS, polyneuropathies involving the motor neurons, recovered poliomyelitis, peripheral nerve injury and nerve root compression**

Treatment and Prevention for Cramps

Treatment for Cramps

- Stretching - activation of GTO helps relax the muscle
- Movement - walking allows muscle spindles to "reset"
- Massage
- Cold application - reduces α motor neuron activity
- Transcutaneous electrical nerve stimulation
- **Quinine** (anti-malaria, antipyretic, & analgesic drug) used for chronic cramping
  - ⬇ excitability of motor endplate + ⬆ refractory period of skeletal muscle

Preventing Cramps

- Stretching
- Correction of muscle weaknesses and strength imbalances
- Conditioning to prevent the onset of fatigue
- Strength training - reduced spindle sensitivity ➡ ⬇ reflex α motor activity
- Proper nutrition before and during event:
  - replacement of fluid and energy substrate during exercise ➡ ⬇ fatigue
- Some common drugs that might cause or increase the risk for cramps
  - β-blockers, Ca^{++} channel blockers, β_2 agonists (asthma), **THORAZINE** (anti-psychotic)
  - **DANOZOL** (cortocosteroid for endometriosis), **LITHIUM, PREDNISONE, LASIX**

Information Included on

Test 1

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