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
• 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 O2 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

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

Cilia

Ciliated Columnar Epithelial Cells
Diseases of Epithelial Tissue

Simple Squamous Epithelium
Arterial Endothelium Dysfunction
The Beginnings of Atherosclerosis

Tear in endothelial wall
(injury - dysfunction)

Monocyte
(Macrophage)

Cholesterol crystal deposits

Red blood cell

Foam cell
(Lipid filled macrophages)

Fat deposits

Ciliated Columnar Epithelium
Trachea Tissue from a SMOKER

Note Lack of Cilia

Note Disorganization of Columnar Epithelial Cells
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 H₂O
    - Hyaluronic Acid - negative charged slippery polysaccharide
    - Condroitin sulfate
  - Fluid - H₂O, gasses, nutrients for cells (H₂O 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

A Proteoglycan Aggregate

Hyaluronic Acid (a Glycosaminoglycan)

Core Protein + Chondroitin Sulfate (a Glycosaminoglycan) = Proteoglycan
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

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

**Collagen Structure**

- **Collagen Fiber** (Fibril)
- **Microfibril**
- **A Collagen Molecule** (Tropocollagen)
- **Fibril**
- **Microfibril**
- **Tropocollagen**

**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

• **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)

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

Diseases caused by Insufficient or malformed Collagen

• **Osteogenesis Imperfecta** - Brittle bones
  • Bones easily fractured
• **Scurvey** - Vitamin 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 immunosuppressants
  - **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 vertebrates
    - 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

Fibrocyte Nucleus

Collagen Fiber

Elastic Fiber

Fibrocyte Nucleus

Collagen Fiber
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](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**

- **Endosteum**
- **Periosteum**
- **Compact (Cortical) Bone**
- **Trabecular (Cancellous) Bone**
- **Haversian System (osteon)**
- **Haversian Canal** (contain blood vessels)
- **Lamellae** (concentric rings of hard bone)
- **Osteocytes in Lacunae**
- **Volkmans Canal**
- **Canaliculi** (connecting tunnels)
- **Epiphyseal Plates**
- **Marrow**
- **Lamellae** (concentric rings of hard bone)
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 $\rightarrow$ 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

- Zone of resting hyaline cartilage
- Zone of proliferation
- Zone of hypertrophy
- Zone of calcification
- Ossified bone

Hematopoietic Tissue

Epiphysis (bone end)

Diaphysis (bone shaft)

Length Increase (Growth) Occurs Toward Diaphysis

Chondrocytes divide and stack on top of one another

Chondrocytes die upon calcification - blood vessels from diaphysis grow into the area

Red Bone Marrow
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.
  • **Common Fracture Sites:** thoracic vertebra, distal radius (close to wrist), femur neck (Hip Fracture)

http://www.medicinenet.com/osteoporosis/article.htm
**Bone Diseases & Treatments**

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

- **Osteoporosis** – continued)
  - **Causes:**
    - Prolonged treatment with corticosteroids
    - Anorexia nervosa
    - Inadequate diet, especially during pregnancy and breast feeding
    - Amenorrhea $\rightarrow$ ↑ estrogen metabolism disturbances $\rightarrow$ 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) $\rightarrow$ ↑ osteoblast activity
      - **FORTEO** (Teriparatide) a PTH analog: $\rightarrow$ ↑ osteoblast activity
        - Intermittent exposure to PTH will ↑ osteoblast activity more than osteoclast activity
      - Weight bearing exercise can ↑ bone mineral density and ↓ falls

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

- 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

Femur

Bone on bone

Osteophytes

Sclerotic bone

Tibia
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
    - **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

**Normal Joint**

- Synovial Membrane
- Cartilage
- Immune Complex
- Neutrophil

**Rheumatoid Joint**

- Pannus (granulation tissue)
- Leukocyte
- Macrophage
- Interdigitating Cell (“traps” antigens)
- T-lymphocyte or B-lymphocyte
- Capillary Bud (angiogenesis)

Inflamed Synovial Membrane
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

- **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

**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

http://www.webmd.com/rheumatoid-arthritis/guide/biologics
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
    - \( \downarrow \) tissue \( \text{O}_2 \) \( \rightarrow \) \( \uparrow \) erythropoietin from kidneys & liver \( \rightarrow \) \( \uparrow \) RBC’s

• **White blood cells (Leukocytes)**
  - 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) \( \rightarrow \) B cell activation \( \rightarrow \) antibody production
      - Helper T cells cause cytokine production, cytokines mediate immune function
      - Cytotoxic T cells have cytotoxic granules \( \rightarrow \) 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
Plasma (continued)

• **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

+50 mv

rapid voltage change due to influx of Na⁺ ions

depolarization threshold reached and action potential initiates

-67 mv

excitatory post-synaptic potentials

transient potentials (balance of EPSP’s and IPSP’s) moving the fiber toward depolarization threshold

-90 mv

voltage moves back toward resting potential due to the efflux of K⁺ ions

Hyperpolarization due to excess K⁺ conductance (K⁺ channels remaining open) depolarization is not possible during this period

resting membrane potential

threshold
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)** i.e. 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 Ca²⁺ channels in direct proportion to AP frequency. Ca²⁺ 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.

**Terminal Boutons of an Inhibitory Axon**

Chlorine channels open in response to **GABA** release and chloride ions enter the terminal bouton.

**Terminal Bouton of an Excitatory Axon**

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

Sensory Neuron

Free Nerve Endings (type of receptor)

Afferent Signal

Efferent Signal

Motor Neuron

Effector Muscle

Axon Hillock

Higher Neural Processing Centers
Regeneration of Peripheral Nervous Tissue

http://www.answers.com/topic/nerve-regeneration
Nerve Diseases & Associated Therapy

• **Multiple Sclerosis** - an autoimmune disease in which auto-active 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**
    - **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)
    - **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
    - **Tremor therapies:** anticonvulsant drugs
    - **Visual problem therapies:** corticosteroids to reduce ocular inflammation

$34,000 / year (2010) for 1 drug

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:**

- 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
Neuromuscular Junction

Presynaptic Terminal Bouton

Acetylcholine Receptors

Acetylcholine

Mitochondria (ATP Producer) (Ca++ Reservoir)

Saroplasmic Reticulum (Site of Ca++ storage)

T-tubule

Myosin

Actin

Z disk

A

I

H

Acetylcholinesterase

Synaptic Vesicles

Synaptic Cleft

Ca++ (Site of Ca++ storage)
Motor End Plates (Skeletal Muscle)
**Action of Selected Toxins & Drugs Around the NM Junction**

**Black Widow Venom** (Latrodectism)
- Blocks AP transmission
- \( \uparrow \) Ach release

**Botulinium toxin**
- Blocks Ach receptors

**Cobra / Mamba snake Curare**
- Resp. muscles affected

**Ach-ase inhibitors: Nerve gas (Sarin, VX)**
- Blocks Ach receptors

**Local anesthetics**
- Tetrodotoxin (puffer fish)
- Batrachotoxin (S.A. frog)
- 1 frog: toxin to kill 50 men

**Dantrolene**: muscle relaxer used in MS treatment
- \( \downarrow \) CA++ release from SR
- Blocks AP transmission within muscle

**Quinine**: (antimalarial drug)
- Muscle relaxer
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
      - Migraine headache
      - Depression
      - Sleep disturbances
      - Irritable bowel syndrome
      - Restless leg syndrome
      - TMJ syndrome
      - 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**), Opioids (**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

- **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

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

[http://www.cidpusa.org/nerves.htm](http://www.cidpusa.org/nerves.htm)
Muscle Spindles, GTO’s, and the Myotatic Stretch Reflex

**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

**Myotatic Stretch Reflex (MSR)**
- “Smoothes out” or “dampens” movements, stabilizes body during fine motor tasks
- Overactive MSR $\rightarrow$ hyperactivity of cortex $\rightarrow$ upper motor neuron lesion (stroke, tumor, injury)
  - Muscle spasticity (muscle always receives contraction signals $\rightarrow$ ↑ muscle tone)
  - Positive Babinski sign, clasped knife sign (http://www.youtube.com/watch?v=ovQkcw86pMo),
  - ↓ limb strength & dexterity
- Underactive MSR $\rightarrow$ 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 $\rightarrow$ activation $\rightarrow$ GTO signal overrides α motor activity
Mechanisms of the Myotatic Stretch Reflex
The Golgi Tendon Organ

- Tendon Organ Capsule
- Striated Skeletal Muscle
- Type Ib afferent Sensory Nerve Fiber (Myelinated)
- Distribution of Golgi Tendon Organ
- Tendon
- Bone Insertion
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 → ↑ \( \alpha \) motor neuron reflex activity
• Overproduction of reflex \( \alpha \) 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, β₂ agonists (asthma), THORAZINE (anti-psychotic)
  - DANOZOL (corticosteroid for endometriosis), LITHIUM, PREDNISONE, LASIX
Information Included on

Test 1

stops here