Cardiovascular System

Vena Cavas:

- There are 2 vena cava: inferior and superior
- These veins carry blood, transporting CO2 to the right atrium.
- The Superior vena cava carries blood from the head, neck, arm, chest
- The Inferior vena cava carries blood from the legs, back, abdomen, pelvis
- The Superior Vena Cava formed by joining of brachiocephalic veins
- The Inferior Vena Cava formed by joining of common iliac veins
  - Travels along the spine
  - Blood enters posterior of right atrium
- Have 3 layers of tissue
  - Tunica adventitia (aka tunica externa)
    - Made of collagen and elastic fiber connective tissues to strengthen vena cavas and improve flexibility
  - Tunica media
    - Made of smooth muscle to receive nervous system input
  - Tunica intima
    - Has an endothelium lining to secrete molecules to prevent clots and help blood move smoothly
- Veins typically have low pressure (to cause flow)
- **Superior Vena Cava Syndrome:**
  - Results from constriction/obstruction of Superior Vena Cava
  - Caused by swelling of surrounding tissue/vessels (thyroid, thymus, aorta, lymph nodes, tissue) in chest area
  - Most often caused by lung cancer and lymphoma (cancer of lymphatic system)
- **Inferior Vena Cava Syndrome:**
  - Results from constriction/obstruction of Inferior Vena Cava
  - Caused by tumors, deep vein thrombosis, congestive heart failure, kidney disease, pregnancy

Right Atrium:
• Receives blood from the vena cavae— from **systemic circulation**
• Pumps blood into right ventricle via **tricuspid valve**
  o Tricuspid valve (aka right atrioventricular valve):
    ▪ Contains 3 flap-like cusps
    ▪ **Prevents backflow** of blood
    ▪ **Tricuspid regurgitation** occurs when blood flows backwards from right ventricle into right atrium
• Located on the posterior side of heart
• **Auricle** expands and fills with blood to increase total volume
• Divided from Left atrium by **interatrial septum**
• **Less myocardium** than ventricles since less force is needed to pump blood— therefore thinner walls
• **Contains AV (atrioventricular) and SA (sinoatrial) node**
  o SA node located in upper wall of atrium
  o AV node located in right side of interatrial septum
• **Atrial fibrillation**: when AV node receives signals from other sources (ex: pulmonary veins) in addition to SA node, causing atria to not contract fully/contract irregularly
• **Atrial flutter**: when SA node impulses are not delayed long enough, causing atrium to beat very fast
• Supplied with blood from **Right coronary artery**

**Right Ventricle:**

• Pumps blood through **pulmonary circulation system via pulmonary trunk**
• Divided from Left ventricle by **interventricular septum**
• Begins the **pulmonary circuit** to oxygenate blood
• Supplied with blood from **Right coronary artery**

**Left Atrium:**

• Receives oxygenated blood from lungs
• Empties into left ventricle through mitral valve
• Supplied with blood from **circumflex artery**— a branch of the **left main coronary artery**

**Left Ventricle:**

• Pumps out blood to **systemic organs**
• Pumps blood out through aorta— when contracting, the **aortic valve opens** to allow blood flow
• Supplied with blood from **Posterior Descending Artery** -- branch of right coronary artery, and **left anterior descending artery** -- branch of left main coronary artery

**Wall of the heart:**

• **Visceral Pericardium** (epicardium)
  o Made of connective tissue and deep adipose tissue
  o **Reduces friction**
  o **Produces pericardial fluid**
• **Myocardium**
  o Cardiac muscle tissue
Contains capillaries and nerve fibers
- Contracts to **pump blood out** of chambers in the heart
- Thickest layer of the heart
- Controlled by the **peripheral nervous system**
- **Purkinje fibers** carry electrical impulses through the myocardium to cause contraction

**Endocardium**
- Innermost layer
- Endothelium
- Has Smooth muscle
- Has Elastic fibers
- Infection is known as **endocarditis**

**Role of the Heart in Maintaining Homeostasis**

- **Homeostasis**: the process of maintaining a **constant, controlled internal environment** (ex: temperature, O2 concentration, pH)
- **Total Body water** (making up 60% of body weight):
  - **Intracellular** water (inside cells) 67%
  - **Interstitial** body water (between cells) 27%
    - Immediate environment of cells
    - Cells draw nutrients from this
    - **NOT a reservoir of nutrients for cells** due to small volume
  - **Plasma** volume 6%
    - Only fluid outside cells which circulates in CV system
    - Communicates with interstitial fluid to pass necessary elements for cell function
    - Constantly gives **interstitial fluid nutrients**, which are then used by cells
    - Solutes from plasma diffuse to interstitial fluid in capillaries
    - **Net result**: interstitial fluid takes on composition of blood in plasma
- In order for homeostasis to effectively work through circulation:
  - There must be **adequate blood flow** through tissues
  - Composition of solutes in arterial blood must be **able to be altered** to fit tissue needs

**Major components of CV System:**

- **Pulmonary circulation**: right heart pump and lungs
  - Takes deoxygenated blood and **oxygenates** it
- **Systemic circulation**: left heart pump
  - **Pumps out oxygenated blood** to other organs
- **Cardiac Output**: volume of blood outputted by the heart/minute= 5-6 Liters in normal resting person
- All systemic organs receive the same arterial blood (blood with oxygen)
- Flow through each systemic organ can be **controlled independently**
  - CV system can alter how much blood certain organs receive without changing amount of blood in other organs
- Organs which recondition blood composition often receive more blood than necessary to function (ex: kidneys, lungs)
  - Therefore, reductions of blood flow are **tolerable** for these organs
• Distribution of cardiac output:
  o Heart pumps: 100%
  o Lungs: 100%
  o Heart muscle (myocardium): 3%
  o Brain: 14%
  o Skeletal muscle: 15%
  o Bone: 5%
  o GI system, spleen: 21%
  o Liver: 6%
  o Kidney: 22%
  o Skin: 6%
  o Other: 8%

• Reductions of blood flow to organs which **do not recondition blood** is not well tolerated since they receive only slightly more blood than necessary (ex: brain, heart muscle, skeletal muscle)
  o These organs are high priority in CV system operation

**Basic Physics of CV Transport:**

**Blood Flow:**

• **Flow** = Pressure difference/resistance
• There **must be a pressure difference** for flow
• Vascular resistance is the **friction** which develops between the fluid and the wall of the tube
• Flow equation can be applied to networks of tubes
  o Numerator is total pressure difference across entire network
  o Denominator is sum of individual resistances (overall resistance)
    - Overall Resistance = R₁ + R₂ + … + Rₙ
• Flow is affected by:
  o Changing vascular resistance
  o Changing the **total pressure difference**
• French physician **Jean Leonard Marie Poiseuille** notable for flow experiments
• Poisueille’s equation: (this equation takes into account all factors of flow)
  o \( Q = \Delta P \left( \pi r^4 / 8L \right) \)
  o \( Q = \text{flow} \)
  o \( \Delta P = \text{pressure difference} \)
  o \( r = \text{radius of tube} \)
  o \( L = \text{length of tube} \)
  o \( n = \text{fluid viscosity} \)
• Changing the radius has a HUGE effect on flow—halving the radius increases resistance **16-fold**; doubling radius will reduce resistance **16-fold**
• In CV system, length and viscosity usually are constant (artery/vein length and blood viscosity are set)
• Capillaries can constrict or dilate to change radius
• Pressure difference can be affected by cardiac output to certain tissues
• Changing the radius of an artery/vein/capillary is the most effective way for flow to be manipulated in the body

**Bulk Transport:**
Bulk transport: the process of substances being swept along with the flowing fluid

**Transport rate** = **flow rate** * **concentration**

- Transport rate is altered by
  - Increasing/decreasing the flow rate to an organ
  - Change in the composition of arterial blood

**Fick Principle:**

- Helps show how much of the substances transported to the tissue is used

\[ X_{tc} = Q([X]_a - [X]_v) \]

- \( X_{tc} \) = transcapillary efflux rate of X substance (unit: mass/time)
- \( Q \) = flow rate (unit: volume/time)
- \([X]_a, [X]_v\) = arterial and venous concentrations of X substance

**Transcapillary Solute Diffusion:**

- Diffusion occurs in **capillaries**
- Diffusion is affected by:
  - Concentration difference
  - Surface area available
  - Diffusion distance
  - Permeability of diffusion surface
- **Fick’s First Law of Diffusion:**
  - \( X = DA \Delta[X]/\Delta L \)
  - \( D \) = diffusion coefficient
  - \( A \) = surface area
  - \( \Delta[X] \) = concentration difference
  - \( \Delta L \) = diffusion distance
- **Capillaries** have a very large surface area to volume ratio
  - Has a lumen (diameter) of ~5µm (small volume)
  - Wall thickness of 1µm (small diffusion distance)
  - Length of 0.5mm
  - Results in 400 cm^2 of surface area available for diffusion in one cubic cm of heart muscle
- **Polar molecules** cross the diffusion barrier very easily
- **Nonpolar molecules** do not cross the diffusion barrier as easily

**Basic Cardiac Structure and Function**

- Heart lies in the center of **thoracic cavity**
- Lies within the **pericardium** (thin fibrous sac)
- Fluid from pericardium lubricates the heart
- Sole purpose of the heart is to **provide energy to circulate blood**
- Blood flow is **passive** through ALL organs due to **decreasing pressure to cause flow** (arterial pressure > venous pressure)
- **Path of blood circulation:**
  - Vena Cavae -> Right Atrium -> Tricuspid valve -> Right Ventricle -> Pulmonic Valve -> Lungs (pulmonary arteries and veins) -> Left atrium -> mitral valve ->
Left Ventricle -> Aortic valve -> Aorta -> Systemic organs (arteries and veins) -> Vena Cavae

- Valves designed to allow flow in **one direction only** -- failure to do so results in backflow and/or regurgitation
- Valves **passively open** as pressure difference increases; **closes as pressure difference falls**
- Valves **open as soon as pressure in ventricle exceeds aortic pressure** to pump blood out of ventricle
- Ventricular pressure then **falls below atrial pressure to allow blood flow in** to ventricle
- Cardiac muscle cells contract/relax to cause ventricles to pump
  - Ventricles have the most cardiac muscle (Left ventricle has more than right ventricle)
  - Contractions decrease volume to raise pressure
  - Higher pressure difference causes valves to open
  - Open valves cause blood to quickly flow in
    - High flow rate due to high pressure difference
    - As pressure difference falls, flow slows and valve closes
- Systole: when the ventricle is contracting
- Diastole: when the ventricle is filling

Excitation of the Heart/Electrical System:

- Individual cardiac muscle cells must contract together precisely
- Contraction is caused by electrical signals exciting the **action potential** of each cell
- Gap junctions connect cells to conduct action potentials
- Signals come from **SA node**
  - Causes atria to contract
  - The SA node is the heart’s **pacemaker**
- SA node signals travel to **AV node** where **signals are delayed** to allow blood from atria to flow to ventricles
- Signals travel to **Bundle of His and Purkinje Fibers to excite action potentials** and contract ventricles
- Different areas of the heart have muscle cells with different action potentials
- Cardiac muscle action potentials differ from skeletal cells because:
  - They are self-generating
  - They can be conducted directly to other cells
  - Have long durations
- **Membrane Potentials**: the voltage across a cell’s membrane
  - Caused by difference in ionic concentration between cell and interstitium; ions diffusing creates electrical gradients
  - Important ions: Potassium ion (K+), Sodium ion (Na+), Calcium ion (Ca^2+)
  - Equilibrium Potential: when the forces attracting an ion = force driving ion out
• Results in no net movement
• Potassium Equilibrium Potential: -90 mV (mV = millivolts)
• Sodium Equilibrium Potential: 60 mV
• Calcium Equilibrium Potential: 100 mV
  o Since a cell is not ONLY permeable to one type of ion, the membrane potential will vary
  o Membranes can be more or less permeable to certain ions
    • If more permeable to K⁺, membrane potential will be close to -90 mV
    • If more permeable to Na⁺, membrane potential will be closer to 60 mV
    • If equally permeable to K⁺ and Na⁺, membrane potential will be somewhere in the middle of 2 equilibriums
  o Membrane potential is usually closer to -90 mV
    • Na⁺ is partially inhibited by low membrane permeability to Na⁺ and sodium pump
      • Sodium pump removes sodium and also pumps in more potassium
      • The pump is electrogenic because more Na⁺ is removed than K⁺ is added
      • If pump is inhibited, membrane potential is slightly less negative
  o **This membrane potential causes the cell to be polar and usually negatively charged**
    • Some cells have fast action potentials, others have slow action potentials
    • Some special cells act as pacemakers and can activate action potentials
      o Normal cardiac cells cannot activate action potentials
    • Fast Action potentials:
      o Response to stimuli can be separated into 4 phases:
        • Phase 0: the cell membrane is **rapidly depolarized** (the “fast” part of the action potential)
        • Phase 1: as a result of the rapid depolarization, it overshoots and the **has a positive voltage**
        • Phase 2: a **plateau** forms as the cell slowly diffuses ions
        • Phase 3: a **rapid repolarization** occurs as the membrane potential quickly falls back to its original state
        • Phase 4: a **stable resting membrane potential** is achieved
      o **Cell contracts when depolarized**
      o As action potential is conducted rapidly other cells, the result is many cells **contracting almost simultaneously** in a certain area of the heart
    o **ERP (effective refractory period) or ARP (absolute refractory period):**
      • Period of time in which the cell cannot initiate a new action potential
      • ERP/ARP occurs in between phases 0 and 4 since the cell is actively contracting
    o **Relative refractory period:**
      • The action potential can be re-excited by an abnormally large stimulus
Supra normal period:
- Action potential can be easily excited
- These periods are assumed to be present in slow action potential cells too, but are not as obvious

- Slow Action Potentials:
  - Have a slower depolarization rate, resulting in less of an overshoot and less positive voltage
  - Plateau is shorter and unstable
  - Repolarization is slower
  - Resting membrane potential is unstable
    - This resting membrane potential in slow action potential cells is also called:
      - Phase 4 depolarization
      - Diastolic depolarization
      - Pacemaker potential

EKGS (Electrocardiograms):
- First created by Willem Einthoven in 1901
- Contraction is caused by depolarization; causing the myocardium to become positive, causing waves detected by EKG
- Repolarization: when the myocardium regains its original negative charge
- P wave: caused by atrial contraction
- PR interval: pause as blood from atria flows into ventricles
- QRS complex: caused by depolarization of myocardial cells of ventricles
- ST segment: pause as blood from ventricles is pumped out and ventricles relax again
- T wave: caused by repolarization of ventricles
- QT interval: interval between ventricular depolarization and repolarization
- A single cardiac cycle is represented by one of each of these waves
- EKG is recorded on graph paper with one mm squares, with heavy lines every 5mm
  - Height of the wave represents voltage
  - Length of the wave represents time (1mm=0.04 seconds, 5mm=0.2 seconds)
  - Upward waves represent positive voltage
  - Downward waves represent negative voltage
- 12 Lead EKGS:
  - 6 Chest leads and 6 limb leads
  - Limb leads are placed on arms and left leg to create Einthoven’s triangle
Each lead is “bipolar” so right arm has 2 negative electrodes, left leg has 2 positive electrodes, left arm has positive and negative electrodes

- **AVF Lead**
  - Arms have negative electrodes, left foot has positive electrodes

- **AVL Lead**
  - Left arm electrodes positive, others negative

- **AVR Lead**
  - Right arm electrodes positive, others negative

- **AVF, AVL, AVR leads are considered “unipolar”** due to same polarity

- These 6 limb leads allow **6 different views** of cardiac activity

- **Chest Leads:**
  - Numbered V1 to V6
  - Sensor of each chest lead is always **POSITIVE**
  - Centered around the **AV node**

Formulas:

**Heart Rate** (HR): beats/minute

**Stroke Volume**: blood pumped out of heart/beat; SV=end diastolic volume-end systolic volume

**Pulse Pressure**: PP= systolic pressure-diastolic pressure; pressure difference from systole to diastole

**Cardiac Output**: blood pumped out of heart/minute; CO= stroke volume*heart rate

**Mean Arterial Pressure**: average arterial pressure throughout 1 cardiac cycle; MAP=\(\frac{2}{3}\) diastolic pressure + \(\frac{1}{3}\) systolic pressure; OR; MAP= Diastolic pressure + \(\frac{1}{5}\) pulse pressure
Excretory/Urinary System:

Major Organs:

- **Kidneys**—excrete waste through urine
- **Lungs**—excrete waste (CO2) through exhalation
- **Skin**—excrete waste through sweat glands
- **Liver**—excrete waste (filters toxins) through urea
- **Large Intestine**—excrete waste through fecal matter

Kidney Functions:

- **Maintaining homeostasis**: kidneys regulate the amount of a substance in our body by controlling how much is excreted (more intake results in more output of that substance) and can control each substance independent of other substances
- **Excretion of Metabolic Waste**: kidneys help excrete not only what we eat, but also byproducts of our body functions (urea is waste product of protein, uric acid is waste product of nucleic acids, creatinine is waste product of muscle creatine, etc.)
- **Excretion of Toxins**: kidneys help (along with liver) to remove drugs and hormones we may ingest which are harmful to body function
- **Regulation of Blood Pressure**: Kidneys regulate water and sodium levels, which in turn regulates blood volume, which causes a certain blood pressure to be reached
- **Regulation of Erythrocyte (red blood cells) Production**: kidneys create erythropoietin (a peptide hormone) which stimulate bone marrow to increase erythrocyte production
- **Gluconeogenesis**: if carbohydrates are not ingested for long periods of time, kidneys will begin to synthesize glucose from other sources since glucose is necessary for the central nervous system to function

Kidneys: Overview

- Part of the **urinary system**
- Filters waste/excess water from blood and excretes it
- Located towards the **back**, each the **size of a fist**
• 2 main functions: **Filtration and collection/excretion of urine**
• Normally, we have 2 kidneys on each side
• ~1 liter of blood passes through kidneys per minute
• Blood enters through **renal arteries**
• Waste products (urine) exit the kidney to bladder via **ureters**
• Renal veins collect reabsorbed nutrients and send them away for further use
• Kidneys have 2 parts: the **renal cortex** and **renal medulla**; there are **nephrons** in between these layers
• Renal Medulla is **very salty** due to ion reabsorption
• Renal calyces collect urine in the **renal pelvis**
• **Hilum** composed of renal artery, renal vein, ureter

**Nephrons**

• **Glomerulus** receives blood from **afferent arterioles** of the renal artery
• **Glomerulus is where filtration occurs**—waste and extra ions are pushed out, remaining blood flows on out of efferent arteriole
• **Filtrate** is collected in **Bowman’s capsule/Bowman’s space**
• Glomerulus is lined with **endothelial cells, which are fenestrated** (have holes to allow all but red blood cells/platelets to leak into Bowman’s capsule)
• **Basement membrane** is semi-permeable, allowing smaller particles to enter Bowman’s capsule but not larger proteins
• **Podocytes** are epithelial cells which have **pedicels** which “grab” the basement membrane; **slit diaphragms** fill space between pedicels, effectively filtering out large proteins which went past the basement membrane
• **Mesangial cells** help remove trapped material from basement membrane; can contract like smooth muscle
• Together, the glomerulus and Bowman’s capsule is known as the **renal corpuscle**
• **Filtration rate** is controlled by changing diameter of afferent and efferent arterioles
• Smaller afferent arteriole diameter causes **less filtration** due to less blood inflow, and vice versa
• Smaller efferent arteriole diameter causes **more filtration** due to less blood outflow, and vice versa
• **Renal artery stenosis**: when the renal artery becomes very **narrow**
• **Proximal Convoluted Tubule and Proximal Straight Tubule**: reabsorbs filtrate coming from Bowman’s capsule (~65% of fluid is reabsorbed here)
• **Loop of Henle**: has 2 parts (**descending/ascending limbs**) which dip from renal cortex into renal medulla and back up
• **Descending Thin Limb** reabsorbs water passively; impermeable to ions
• **Ascending Thin Limb** reabsorbs sodium, chloride, potassium actively; impermeable to water; found in the **renal medulla** or is **absent in short loops**

• **Thick Ascending Limb** also reabsorbs the same substances as the thin limb, but is located in the **renal cortex**

• **Macula Densa**: specialized cells in the beginning of the distal convoluted tubule in between afferent and efferent arterioles

• **Countercurrent multiplication**: due to ascending limb’s impermeability to water, renal medulla becomes salty, prompting descending limb to reabsorb more water passively

• **Distal Convoluted Tubule**: reabsorbs sodium and chloride

• **Juxtaglomerular Apparatus**: controls blood pressure in the kidney

• **Collecting Tubule/Collecting Duct**: reabsorbs water, urea (sometimes); many DCTs (from other nephrons) filter into a single collecting duct

• **Collecting-duct system**: connecting tubule-> Cortical collecting duct (located in cortex) -> Outer medullary collecting duct (located in medulla)->Inner medullary collecting duct->Papillary duct-> Calyx

• Once **urine enters a renal calyx, its composition is not altered**: the rest of the urinary system is merely storage space

• Efferent arteriole branches into **peritubular capillaries** which weave through interstitium to collect reabsorbed particles and diffuse oxygen

• **Renal Vein** transports nutrients to rest of the body for further use

• Nephrons mostly located in cortex are classified **cortical nephrons**; nephrons with loop of Henle mostly in medulla are **juxtamedullary nephrons**

• ~1 million nephrons per kidney

**Blood Supply to the Kidney Cont’d:**

• Renal artery-> interlobar arteries-> arcuate arteries -> interlobular/cortical radial arteries->afferent arterioles->efferent arterioles->peritubular capillaries/Vasa Recta->venules->renal vein

• The **afferent and efferent arterioles enter/exit the same side of Bowman’s capsule**, allowing the thick ascending limb to pass between the two

• **Peritubular capillaries** are distributed in the **cortex** and deliver oxygen to the kidney

• **Vasa Recta** differ from peritubular capillaries by **descending to the medulla** and are present in arteriole systems **going to juxtamedullary glomeruli** (in between cortex and medulla)

• **Vasa Recta (descending)** later become regular capillaries and **supply blood flow to the Loop of Henle and collecting ducts of the medulla**

• **Vasa Recta (ascending)** also **act as veins** as another set brings blood up

• **Vasa Recta (ascending)** are also **fenestrated** unlike vasa recta (descending), and participate in the **exchange of solutes and water**

**Urination/Micturition**

• After urine is concentrated in nephrons, urine from **collecting ducts lead to renal calyces**: many renal calyces coalesce into renal pelvis

• Urine is transported from **calyces to bladder via ureters**

• **Valves prevent backflow** from bladder to ureter

• Bladder lined with **transitional epithelium**—allowing bladder to expand to hold 300-500mL of urine

• Bladder connects to **urethra, where urine is expelled**
• **Internal urethral sphincter** prevents urine from leaking out of bladder into urethra; involuntary muscle and smooth muscle
• **External urethral sphincter** located in membranous urethra and is under voluntary control
• **Stasis**: when backflow of urine occurs; infection is more likely since bacteria can come up the urethra and is not expelled (since the bacteria end up in ureters, rather than the bladder)

Secondary Active Transport in the Nephron
• Nephron uses a **sodium pump** to actively transport sodium from the cell into bloodstream—the sodium in the lumen now wants to diffuse into the basolateral membrane (the other side of the cell) due to lowered sodium levels; other nutrients capitalize on the lowered sodium levels in the basolateral membrane to cross into the bloodstream via **symporters**, which allow other nutrients to accompany sodium
• The sodium pump works by using a **protein to cause sodium to attach along with nutrient X**; ATP is used to actively cross into the bloodstream and changes the protein configuration; the changed protein now causes the sodium along with nutrient X to detach and enter the blood flow; **potassium then attaches to the new protein** and is taken inside the cell, where the protein reverts to its original state and potassium detaches
• Potassium levels do not become astronomically high in the basolateral membrane because potassium can “leak” in and out of the bloodstream into the basolateral membrane

Types of Nephrons
• **Superficial cortical nephrons**: the renal corpuscle (glomerulus and Bowman’s Capsule) is 1mm below the surface of kidney; all have a short Loop of Henle
• **Midcortical Nephrons**: located in the cortex, deeper than superficial cortical nephrons yet not near the medulla; can have a short or long Loop of Henle
• **Juxtamedullary Nephrons**: the renal corpuscles are located in between the cortex and medulla; all have a long Loop of Henle

Juxtaglomerular Apparatus
• **Has 3 cell types**: Granular cells, Extraglomerular cells, Macula Densa Cells
• **Granular cells** secrete renin, which helps control blood pressure
• **Extraglomerular cells** help clear filtrate which is caught
• **Macula densa cells** help control renin secretion and glomerular filtration rate

Glomerular Filtration and Renal Blood Flow:
• Kidneys receive about **20% of total cardiac output**, much more than the kidney needs
• All blood flows through glomeruli in the cortex
• **Most blood flow** continues to peritubular capillaries
• ~5-10% flows through the **Vasa Recta to the medulla**
• ~20% of blood flow through the glomerulus **enters Bowman’s space**
• **Filtration fraction**: ratio of glomerular filtration rate to renal blood flow (usually about 20%)
• About 10% of the endothelial layer is made of fenestrations
• Filtration is **dependent on molecular size and electrical charge**
• Molecules weighing **under 7000 Daltons** can usually pass through the filtration barrier
• Molecules **over 7000 Daltons gradually decrease in the amount filtered through** the filtration barrier (ex: albumin weighs ~66,000 Daltons and ~0.02% of its plasma concentration passes through the barrier)
• **Small molecules bound to larger proteins may not be able to pass the barrier**, even if they can on their own
• Negatively charged molecules are **not as likely** to be filtered
• Positively charged molecules are **more likely** to be filtered
• Polyanions are found everywhere on the filtration barrier and repel negative charges
• Most proteins are **negatively charged**, restricting their passage even further (they cannot be filtered through)
• Mineral ions and low molecular weight solutes are **still filtered through** despite their negative charge due to their small size (negative charges hinder larger molecules the most)

**Autoregulation:**

• **Pressure Natriuresis:** a rise in blood pressure=increased salt/water excretion, and vice versa
• **Autoregulation** is needed to help control the glomerular filtration rate (GFR)
• Arterial pressure varies greatly throughout the day, which need to be balanced via autoregulation mechanisms
• Greater blood pressure is counteracted by **more vascular resistance** to control blood flow
• Although **higher pressure leads to more flow, it is not proportional**; therefore by increasing resistance, more pressure is created, yet flow does not increase as much as if flow was not impeded, thus controlling the GFR
• Reactions of smooth muscle, the **myogenic response**, helps control short term fluctuations of pressure
• **Tubuloglomerular feedback:** feedback from tubules to the glomerulus; the amount of solute X which is reabsorbed varies according to the filtration rate—the macula densa is **able to detect the presence of sodium and chloride** and gives feedback to the glomerulus as to slow or speed up filtration rate
• The Macula Densa secretes transmitter agents into the interstitium, which affect the filtration rate in the glomerulus by causing vasoconstriction of the afferent arteriole or cause contraction of mesangial cells
• Vasoconstriction of the afferent arteriole decreases filtration rate by reducing flow
• Contraction of mesangial cells increases filtration rate by allowing more filtrate to pass through (think of a clogged drain vs. an unclogged one—water will flow past the unclogged one faster than the clogged one)

**Clearance (ridding the body of a substance):**

• **Metabolic Clearance:** general clearance of a substance **from the whole body** (includes clearance from feces, transformation in the liver, etc.)
• **Renal Clearance:** clearance of a substance by **removing it from blood** and excreting it in urine
**Rate of clearance** is expressed by: the time taken to reduce the concentration of substance X in plasma by ½, volume of plasma per unit time in which all of substance X is removed.

**Unit** of clearance is volume of plasma/time, not amount of substance X (if 5mg of substance X is cleared from 200mL of plasma per hour, unit is 200mL/hour, not 5mg/h).

Amount of clearance equation: \( Cx = \frac{(V \times Ux)}{Px} \)

- \( Cx \): volume of plasma cleared/time
- \( V \): urine flow rate (how much is excreted)
- \( Ux \): concentration of substance X in urine
- \( Px \): concentration of substance X in plasma

The amount cleared from plasma is equal to the amount excreted in urine.

**Excretion rate:** the product of urine flow rate and urine concentration.

**Inulin** is present in urine which is a very good indicator of GFR since it is not reabsorbed or secreted—all the inulin which is filtered into Bowman’s space is excreted, making it the GFR measurement gold standard.

Substances which are reabsorbed by the body will result in a smaller clearance rate.

Substances which are secreted by the body in addition to being freely filtered will result in a greater clearance rate.

These substances are not good indicators of GFR.

**Para-aminohippurate (PAH)** is secreted by the body in the proximal tubule epithelium, and ~90% of PAH entering kidney is excreted, giving an accurate reflection of plasma flow through the kidneys; this is known as effective renal plasma flow.

Knowing the clearance and the GFR tells us whether there was net secretion or reabsorption of substance X.

Net secretion or reabsorption can change under different circumstances.

Creatinine clearance is often used to measure GFR instead of inulin due to ease and low cost (inulin requires infusion to yield accurate results, creatinine is produced naturally by the body and does not require infusion).

Transport:

- **In the Cortex:** tubular epithelium determines secretion/absorption (due to extremely low resistance of vascular endothelium to movement of substances); the interstitium has the composition of blood plasma.

- **In the Medulla:** secretion/absorption is dependent on tubular epithelium and vascular endothelium (due to increased vascular resistance to movement since it is not all fenestrated); the interstitium composition is not like the plasma.

- **Paracellular Route:** transport of a substance around the cells—by crossing through tight junctions (the space in between cells).

- **Transcellular Route:** transport of a substance through the cells—by first crossing apical membrane, then crossing basolateral membrane.
- **Transport through Diffusion**: occurs when a concentration gradient or potential gradient is present and barrier is permeable; applies to substances being transported paracellularly (in particular, lipid soluble substances cross the barrier easily)

- **Transport through Channels**: porous proteins on either side of the membrane which allow certain solutes to diffuse through membrane but not others; are named for the solute they diffuse (ex: sodium channel, potassium channel, aquaporins)

- **Channels may open and close, changing the membrane permeability to solutes at any given time**

- **Transport through channels is passive**

- **Transport through channels allow faster movement of larger quantities of substances than regular diffusion**

- **Channels can be gated** (to increase or decrease the probability of being open) by: changing the membrane potential, mechanical distortion, and reversible binding of molecules which make up signaling systems

- **Transport through Transporters**: alike to channels, but the solute transport rate is less due to stronger bond of solutes to transporter proteins

- **Transport through Uniproters**: transport a single solute through the membrane by causing the solute to bind once on one side of the membrane, then **again on the other side**; differs from a channel because while channels are driven solely by diffusion through the membrane, uniproters require solutes to bind and diffuse through a protein—this is known as **facilitated diffusion**

- **Transport through Symporters**: 2 or more solutes bind to the same protein and **cross the membrane together**; this is known as **cotransport**

- **Transport through Antiporters**: 2 or more solutes **cross the membrane in opposite directions** and bind to the same protein

- **Molecular transport which moves **up the electrochemical gradient is considered active transport**

- **Molecular transport which moves **down the electrochemical gradient is not active transport**

- **Symporters/Antiporters** do not directly hydrolyze ATP, so are known as **secondary active transport**

- **Energy for symporters/antiporters** comes from **movement of solute X down the electrochemical gradient, which powers movement of solute Y up its electrochemical gradient** (but only if energy obtain from moving solute X is greater than the energy needed to move solute Y)

- **Primary Active Transporters **directly hydrolyze ATP for energy** (ex: Na-K-ATPase; aka sodium pump, mentioned earlier)

- As more transcellular transport occurs, the concentration of solutes which cannot be diffused through the membrane rises due to decreased volume, causing them to move through tight junctions more; in this way, **transcellular transport helps to drive paracellular transport**
Lymphatic System

Why We Need It:

- **Extracellular fluid leaks into the interstitium from blood vessels** (mainly capillaries)
- The lymphatic system **collects** the extracellular fluid and **brings it back to the bloodstream**
- Extracellular fluid **needs to escape** the blood flow in order to **transport other essential nutrients like glucose to cells**
- Lymph is deposited at the **subclavian veins, due to lower pressure** (veins have lower pressure than arteries)
- Some lymph will leak back into the cell due to osmosis and lower pressure, since the pressure which forced lymph out of the vessel will now be lowered and suck lymph back in

How Lymphatic Vessels Move Fluid;

- Lymph Vessels are **not closed loops**, so they do not go in a full circle
- Lymph Vessels **do not have a pump** to drive lymph motion
- Lymph Vessels use **valves** to prevent backflow of lymph and to continue forward motion
- **Smooth muscle** lining the lymph vessels contract to cause movement of lymph throughout the vessel
- **Skeletal muscles**, when moved, can also cause motion in the lymph vessels
- The beginning of lymph vessels (the part which collects lymph) is actually **closed**
- The beginning of lymph vessels are **porous** to allow lymph in, **yet close when pressure rises, to prevent lymph from going out**

Thoracic Duct:

- **Largest** lymphatic vessel in the body
- Also known as **left lymphatic duct or alimentary duct**
- Drains lymph into left subclavian vein
- Drains ~4 liters of lymph each day
• Movement is **aided by breathing**—movement of intercostal muscles help squeeze lymph up the duct
• **Nearly all lymph** from the body enters the thoracic duct to be transported back into the bloodstream
• **~16 inches long**

Right Lymphatic Duct:

• Drains **upper right quadrant** of body
• Drains lymph into **right subclavian vein and jugular vein**

Waldeyer’s Ring

• Refers to lymphatic tissues which **ring the oropharynx and nasopharynx**
• Contains tonsils
• **Pharyngeal tonsil** protects the **nasopharynx**
• **Lingual tonsils** and **palatine tonsils** protect the **oropharynx**
• Is able to initiate an immune response immediately before pathogens penetrate deep into the body—since the mouth and nose can serve as a portal of entry for pathogens

Role in Immunity:

• Bacteria or other pathogens are sucked into lymph vessels, which lead to lymph nodes, which shelter **B and T cells**
• **Macrophages** in the tissues may fight pathogens, but **B and T cells in lymph nodes are much more effective**
• Lymph Nodes help filter lymph and prevent pathogens from spreading into the bloodstream and into other tissues
• Lymph Nodes are **not considered organs**
• We have **~600 lymph nodes** in the body

Lipid and Protein Transport

• Fats from the small intestine are consolidated into **chylomicrons**, which cannot diffuse into capillaries, but can diffuse into lymphatic vessels (lacteals) which deposit fats into the bloodstream
• Proteins and waste products which cannot enter blood vessels directly also enter lymphatic circulation and enter the bloodstream later

Lymph Composition

• Lymph is only called such after it has entered lymphatic vessels, before that it is known as **extracellular fluid**
• **No red blood cells** are present in lymph
• **Less protein concentration** in lymph than blood
• Greater ratio of small proteins (ex: albumin) to large proteins (ex: immunoglobulin) in lymph than blood
• **~3 L of lymph per day**
• **~20 L of extracellular fluid leaves the bloodstream**
• Lymph composition varies depending on what sort of extracellular fluid the lymphatic vessel is surrounded by

Lymphatic Cells:

• Include T and B cells
• Originate in bone marrow but migrate to lymph nodes, spleen, thymus
• Each cell can only recognize a specific pathogen
• Two different types of T cells: helper T cells and killer T cells
• T cells mature in the thymus
• B cells mature in bone marrow
• Macrophages which have consumed a pathogen displays an antigen fragment (antigen presentation) to activate the Helper T cell
• Helper T cells activate killer T cells and B cells by multiplying and producing proteins
• Killer T cells identify infected cells by detecting antigens on the cell surface and destroy them
• B cells search for antigens which match its receptors
• Once activated (by helper T cell proteins), B cells multiply into 2 types: plasma cells and memory cells
• Plasma cells create antibodies which attach to infected cells to signal phagocytes to come destroy the infected cell
• Memory cells have a long life span and “remember” certain pathogens so the immune system can react faster if the same pathogen infects the body again

Thymus

• Produces hormones to support T cell progenitors
• Two lobes: the cortex and medulla
• Reticular epithelial cells in cortex secrete thymosin, thymulin, thymopoietin
• Thymosin stimulates development of T cells
• Thymulin helps T cells mature
• Thymopoietin helps differentiate T cells into helper and killer T cells
• Cortex contains more lymphocytes than medulla
• Contains only efferent lymphatic vessels to transport T cells out to lymph nodes
• Contains Hassall's Corpuscles

Lymph Nodes

• Covered by a capsule of connective tissue
• Trabeculae provide support for afferent lymphatic vessels
• Afferent lymphatic vessels enter node, pass through subcapsular sinus to cortical sinus to medullary sinus and out efferent lymphatic vessels
• Blood sinuses lined by simple squamous endothelium
• Blood sinuses contain T cells, B cells, plasma cells, and antibodies
• Germinal centers populated with B cells, plasma cells, macrophages, dendritic cells, and some T cells
• Inner cortex contains mostly T cells
• Lymphocytes enter mostly from blood vessels, but ~10% enter via lymph
• Deep cortex is lined with simple cuboidal epithelium
• T cells are activated in the deep cortex

Peyer’s Patches

• Large patches of mucosa associated lymphoid tissue (MALT)
• Contain mostly T cells
• Have germinal centers with B cells and macrophages
• No afferent lymph vessels
• Lymphocytes exit to lymph nodes via efferent lymph nodes

Spleen:

• Largest mass of lymphatic tissue in the body
• Filters blood rather than lymph
• Only has efferent lymph vessels
• Removes defective red blood cells/platelets from circulation
• Main source of circulating antibodies
• Stores large quantities of platelets
• Receives blood from the splenic artery
• Contains two main specialized tissues
• White pulp contains many lymphocytes
• Red pulp contain many sinusoids
• Sinusoids help filter out damaged red blood cells, which undergo phagocytosis by macrophages
• A ruptured spleen can be fatal due to the large amount of blood that leaks out
• A splenomegaly occurs if spleen becomes swollen and enlarged
• A splenic infarction occurs if the spleen does not have enough oxygen and splenic tissue dies
• Autosplenectomy occurs if malformed cells disrupt blood flow to the spleen and cause it to waste away

Appendix:

• Plays a minor role in immunity
• Stores good bacteria

Diffuse Lymphatic Tissue:

• Prominent near GI, respiratory, urinary tracts
• Generally known as) MALT (mucosa-associated lymphoid tissue
• If associated with GI tract, known as **GALT** (gut-associated lymphoid tissue)
• If associated with respiratory tract, known as **BALT** (bronchi-associated lymphoid tissue)
• Contains **reticular tissue and reticular fibers**
• Cells of lymphatic tissue can be **fixed** or **free**
• **Fixed cells** are reticular cells which **form and maintain** reticular fibers
• **Free cells** are **lymphocytes, macrophages and plasma cells** which play an active role in the immune system
• Lymphocytes can be split into 3 distinct groups based on size
• **Small lymphocytes** are 4-8 microns in diameter
• **Medium lymphocytes** (prolymphocytes) are 8-12 microns in diameter
• **Large lymphocytes** (lymphoblasts) are 15-20 microns in diameter
• Especially prominent near the epithelium of the **intestines**

**Lymphadenitis:**

• **Bacteria, viruses, or fungi** cause inflammation and swelling of lymph nodes, often after the pathogen has caused infection in another part of the body.

• **2 types:** **Localized lymphadenitis**—only one or a few lymph nodes are swollen near the site of initial infection; **Generalized Lymphadenitis**—two or more lymph nodes are swollen in separate areas of the body; often caused by a spreading infection

• **Symptoms:** tender lymph nodes and cause pain when touched; redness of skin above lymph nodes; abscesses form; fluid from nodes drain to skin

• **Treatment:** antibiotics; pain and fever medicine; swelling and inflammation medicine; surgery to drain abscesses

**Hodgkin lymphoma (HL)**

• One of two types of lymphoma
• Often begins in **upper part of the body** (chest, neck or underarms)
• **Spreads** through lymph vessels from **node to node**
• Rarely, lymphoma will spread to the liver, lungs, or bone marrow if it invades the bloodstream

**Classic Hodgkin Lymphoma (cHL)**

• Accounts for more than 90% of Hodgkin Lymphoma cases in developed countries
• Cancer cells in cHL are **Reed-Sternberg cells**; an **abnormal kind of B cell**
• 4 subtypes:
  • **Nodular sclerosis Hodgkin Lymphoma (NSCHL):** most common type of HL; accounts for ~70% of cases; tends to begin in neck or chest
  • **Mixed cellularity Hodgkin lymphoma (MCCHL):** accounts for ~40% of cases; mostly occurs in individuals with HIV; tends to begin in upper body
  • **Lymphocyte-rich Hodgkin lymphoma:** uncommon kind of HL; tends to begin in upper body; usually confined to a few lymph nodes
• **Lymphocyte-depleted Hodgkin lymphoma**: rare form of HL; mainly occurs in the elderly and individuals with HIV; aggressive form of HL; often found in lymph nodes in the abdomen, spleen, liver, and bone marrow

**Nodular Lymphocyte-predominant Hodgkin Lymphoma (NLPHL):**

- Rare form of HL (~5% of cases)
- Not considered a subtype of cHL, but still a subtype of HL
- Cancer cells in NLPHL are known as popcorn cells (a variant of Reed-Sternberg cells) or lymphocytic and histiocytic (L and H) cells
- Usually starts in lymph nodes in the neck and underarms
- More common in men than women
- Grows slowly

**Non-Hodgkin Lymphoma**

- **Indolent lymphomas**: lymphoma which grows and spreads slowly; may not need to be treated immediately but monitored closely instead
- **Aggressive lymphomas**: lymphoma which grows and spreads quickly; rapid treatment is necessary

**Diffuse Large B-Cell Lymphoma (DLBCL):**

- Most common type of NHL in the US (~33% of NHLs)
- Occurs mostly in the elderly
- Aggressive lymphoma
- Responds well to treatment (3 out of 4 people have no signs of DLBCL after treatment)
- Usually begins in the chest/abdomen area
- Primary Mediastinal B-cell lymphoma: subtype of DLBCL which occurs mostly in young women; can cause trouble breathing and block the superior vena cava

**Follicular lymphoma:**

- 1 in 5 lymphomas in the US are follicular lymphomas
- Indolent lymphoma
- Average age of cases is ~60 years old
- Rare in young people
- Respond well to treatment but hard to cure
- Follicular lymphoma could develop into DLBCL
- Occurs in multiple lymph nodes around the body and in bone marrow

**Chronic lymphocytic leukemia (CLL) and Small lymphocytic lymphoma (SLL):**

- Both indolent lymphomas
- Cancer cells are known as small lymphocytes
- Cancer cells in CLL are found mostly in blood and bone arrow
- Cancer cells in SLL are found mostly in lymph nodes and spleen
- Treatment is the same for both CLL and SLL
Mantle Cell Lymphoma (MCL):

- ~5% of lymphomas are MCLs
- More common in men than women
- Often appears in elderly
- Hard to treat since it grows faster than most indolent lymphomas, yet does not respond to treatment for aggressive lymphomas very well

Hairy Cell Leukemia (HCL)

- Cancer cells are small B cells, causing it to be considered a type of lymphoma despite its name
- Rare, only ~700 are diagnosed with HCL annually
- Cancer cells have projections deeming them “hairy”
- Indolent lymphoma
- Treatment is usually very effective

Primary Central Nervous System (CNS) lymphoma:

- Tends to spread throughout the central nervous system
- Sometimes found in tissues around the eye and/or spinal cord
- Rare overall—but more common in the elderly and immunosuppressed individuals

Precursor T-lymphoblastic Lymphoma/Leukemia:

- Accounts for ~1% of all lymphomas
- Considered a lymphoma/leukemia depending on how much bone marrow is involved
- Cancer cells are early form of T cells
- Often begins in the thymus and grows into a large tumor in the mediastinum
- Can cause trouble breathing and swelling in arms and face
- Most common in teens
- More common in males than females
- Aggressive lymphoma