Kaplan Biochem

Ch1: Amino Acids, Peptides, Proteins
-Amino acids are chiral on alpha carbon thus are optically active (except G → achiral)
-Eukaryotic a.a. are L and (S) except Cys: L and (R)
-In Fischer projection: -NH2 on the left (L-amino acids) and -NH2 on right (D-amino acids)

1) Nonpolar, Aliphatic (GAVILMP)
-G: flexible vs P: rigid
-M: one of two a.a. with S in the side chain but nonpolar since S attached to methyl

2) Aromatic (WFY)
-F = nonpolar but Y = polar

3) Polar (STNQC)
-S and T: -OH in side chains = highly polar, good for H bonding
-N and Q: amide N does not gain or lose protons with changes in pH; NO CHARGE
-C: reactive thiol (-SH bond weaker than -OH because S is larger and more EN)

4) Negatively Charged (Acidic) Side Chains (DE)
-Carboxylate ($-COO^-$) groups as side chains
-D before E (1 CH2 < 2 CH2)

5) Positively Charged (Basic) Side (HRK)
-K: terminal amino
-R: 3 N's in side chain
-H: imidazole side chain (with 2 N's), pKa 6

Hydrophobic: AILVF (long alkyl side chains)
Hydrophilic: DERHKNQ (acidic, basic, or amides)
Remaining amino acids are neither particularly hydrophilic nor hydrophobic

Amphoteric species: can either accept or donate protons
Zwitterion: both (-) and (+) charges but overall *0 charge*

pKa is when 50% protonated, 50% deprotonated: [HA] = [A-]
pKa COOH = 2.34
pKa NH2 = 9.60

When pH is close to pKa value, a solution is acting as a buffer, thus titration curve is flat
pH starts to increase after since solution stops acting like buffer

At pI, amino acid electrically neutral, exists only as zwitterion

pI neutral amino acids = (pKa -NH3+ + pKa -COOH) / 2
E.g. pI of glycine = (2.34 + 9.6)/2 = 5.97

When molecule is neutral (at pI), it is sensitive to pH changes, thus titration curve is vertical

pI acidic amino acid = (pKa R + pKa COOH) / 2
pI basic amino acid = (pKa R + pKa NH3+) / 2

Peptide bond formation = dehydration or condensation rxn (-H2O)
C-N bond has partial double bond character because amides have delocalizable pi e-: this restricts rotation of the protein backbone

Peptide bond hydrolysis catalyzed by *trypsin* and *chymotrypsin* in living organisms by reverse rxn to dehydration: add -H to amino and -OH to carboxyl

- Trypsin cleaves at carboxyl end of R and K
- Chymotrypsin cleaves at carboxyl end of F,W,Y

Primary and Secondary Protein Structure:
1^o: stabilized by covalent peptide bonds, codes folding of 2^o, 3^o, 4^o, can be found by sequencing
2^o: H bonding between NH2 and COOH of backbones of neighboring amino acids

- alpha helix: clockwise coils, n and n+3 (between 1^{st} and 4^{th} amino acid), important in *keratin* (fibrous structural protein found in human skin, hair, and fingernails)
    - Ala, leu, his, arg, lys, glu, gln, met
    - Gly not found bc too flexible to be in helix
    - Pro not found INSIDE (too rigid, breaks apart helix) EXCEPT usually found at start
- B-pleated sheet: parallel or antiparallel, side chains point up and below plane, important in *fibroin* (primary protein component of silk fibers)
    - Ile, val, thr, tyr, trp, phe, cys (ramification beta, aromatique, aa encombrés lourds avec grosses chaines latérales)
    - Pro is found in B-pleated sheets to introduce change in direction

Fibrous proteins (e.g. collagen) = sheets or long strands
Globular proteins (e.g. myoglobin) = spherical

Tertiary and Quaternary Protein Structure:
3^o: hydrophilic (H bonding, electrostatic) hydrophobic interactions, S-S between R groups of aa

- 2 Cys forming S-S : -SH + -SH = *cystine* + 2H+ + 2 e- (oxidation)
- Hydrophilic (polar or charged) aa on surface of protein, hydrophobic on inside
- Molten globules = intermediate states during protein folding
- Denaturation = loss of 3^o structure

Folding and Solvation Layer
-Hydrophobic residues in aqueous sln = H2O form solvation layer (highly organized) to maximize H bonding = delta S < 0 and non-spontaneous so delta G > 0
-Hydrophilic residues on surface or exposed in aqueous sln allows H2O more positions = delta S > 0 and spontaneous so delta G < 0

4^{O}: *Not all proteins have 4^{o} structure!!* Only proteins with more than 1 polypeptide chain

- Important for **cooperativity** or **allosteric effects**

Conjugated Proteins
Need covalently attached molecules called **prosthetic groups** to function (can be organic molecules like vitamins or metal ions like Fe)

1B 2B 3C 4D 5D 6A 7C 8C 9C 10C 11B 12A
13D 14D 15C

5: Number of possible tripeptides: n!
15: Collagen has carbon backbones very close so need aa with small side chain so Gly

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Ch2: Enzymes
Catalysts do not affect overall deltaG of rxn (don't alter deltaH or K)
Catalysts are pH and temperature-sensitive (have optimal activity at specific pH and temp)

Enzymes with *dehydrogenase* or *reductase* in their names are usually **oxidoreductases**
Kinases are **transferases** (transfer phosphates from ATP to another molecule)
Phosphatases, peptidases, nucleases, and lipases = **hydrolases** (break down with H2O)
Lyases = break 1 into 2 without water or combine 2 into 1 (synthases)
Isomerases catalyze rxns between stereoisomers as well as constitutional isomers (same molecular formula, different connectivity)
Ligases catalyze addition or synthesis rxns, between large molecules (e.g. nucleic acid synthesis)

Exergonic rxns = give off energy (deltaG < 0) vs endergonic rxns = need energy (deltaG > 0)

Lock and Key Theory: active site (lock) already in conformation for substrate (key) to bind, no change in 3^{o} or 4^{o} structure
Induced Fit Theory: enzyme and substrate adjust to fit each other well, the shape of active site is only complementary after substrate begins binding

[Cofactor] = low so that it's only recruited when needed
Cofactors can attach with diff. bonds, including weak noncovalent to strong covalent interactions
Prosthetic groups: tightly bound cofactors or coenzymes necessary for enzyme function
Cofactors: inorganic molecules, metal ions
Coenzymes: organic groups, vitamins (e.g. NAD+, FAD, CoA, H2O soluble BC, fat soluble ADEK)

Enzyme Kinetics
-Once enzyme is at **saturation**, can only increase v_{max} by increasing [E]
-Michaelis-Menten equation: $v = (v_{max}[S]/ K_m + [S])$
-Michaelis constant: $Km = ½ v_{max}$ (half enzyme occupied)

- Km = intrinsic property, cannot be altered by changing [E] or [S]
- $v_{max} = [E]k_{cat}$ (units: mol/s)
  k_{cat} measures # of substrate molecules "turned over" per second

Catalytic efficiency: k_{cat}/K_m
Large kcat (high turnover) or small Km (high affinity) = high catalytic efficacy = more efficient E

Cooperativity: sigmoidal (S-shaped) kinetics on Michaelis-Menten plot, binding of substrate encourages transition from T state (low-affinity tense) to R state (high-affinity relaxed) state

- **Hill's coefficient:** indicates nature of cooperative binding
  - Hill's coefficient > 1 = positive cooperative binding
  - Hill's coefficient < 1 = negative cooperative binding
  - Hill's coefficient = 1 = no cooperative binding

Michaelis Menten plot = v versus [S]
Lineweaver-Burk plot = 1/v versus 1/[S]

- Decreased Km = left shift vs increased Km = right shift on x-intercept

Local Effects on Enzyme Activity
Temperature: increase T = increase enzyme activity until denaturation = sharp decrease
Ideal T in body: 37^OC (98.6F or 310K)

pH: optimal pH in blood = 7.4, lower than 7.35 = acidemia
optimal pH for gastric enzymes = 2; optimal pH for pancreatic enzymes/small intestine = 8.5

Salinity: increase [salt] = disrupt H and ionic bonds in 3^o and 4^o = denaturation

Feedback regulation = products inhibit enzyme (e.g. feedback inhibition)
Feedforward regulation = intermediates preceding enzyme inhibit it

Reversible Inhibition
Inhibitor binds to S and ES complex with same affinity = **non-competitive inhibitor**

- Adding substrate won't lead to formation of ES complex if inactive
- Decreased vmax since less enzyme active/available but those active still have same Km

inhibitor binds to S and ES complex with different affinity = **mixed inhibitor**
Inhibitor binds to only ES complex and lock substrate = **uncompetitive inhibitor**

Irreversible inhibition = permanently altered; only way to overcome it is making more enzyme

	Competitive	Non-competitive	Mixed	Uncompetitive
Binding Site	Active site	Allosteric	Allosteric	Allosteric
Impact on Km	Increase	None	Increase or Decrease	Decrease
Impact on vmax	None	Decrease	Decrease	Decrease

Regulated enzymes:
1) Transient modifications → allosteric activation or inhibition
2) Covalent modifications → phosphorylation, glycosylation

1A 2A 3B 4A 5A 6D 7A 8A 9C 10B 11D 12D 13D 14A 15B

1: A rxn will proceed with or without enzyme; it will just be slower without enzyme
11: Conversion of ATP → AMP + Pi = example of lyase (no water required)

Ch3: Nonenzymatic Protein Function and Protein Analysis

Structural Proteins
Collagen: trihelix, makes ECM of connective tissues, role = strength/flexibility
Elastin: makes ECM of connective tissues, role = stretch then recoil
Keratins: intermediate filament proteins in hair and nails, role = mechanical integrity of cell
Actin: makes up microfilaments and thin filaments in myofibrils, are polar (+ and -) which allows motor proteins to travel in 1 direction along actin
Tubulin: makes up microtubules, have polarity: (-) close to nucleus, (+) close to periphery of cell

Motor Proteins
Myosin: thick filament in myofibril that interacts with actin, also involved in cell transport, have head and neck; mvt at neck is responsible for power stroke of sarcomere contraction
Kinesins and dynein: associated with microtubules, have 2 heads, 1 remains attached to tubulin at all times

- Kinesin = role in aligning chromosomes during metaphase and depolymerizing microtubules in anaphase
- Dyneins = role in mvt of cilia and flagella
- Both important for vesicle transport in cell, but have opposite polarities:
    - Kinesin brings vesicles toward (+) end of microtubule
    - Dynein brings vesicles toward (-) end of microtubule

Cytoskeletal proteins tend to be fibrous with repeating domains, while motor proteins tend to have ATPase activity and binding heads. Both types of proteins function in cellular motility.

Binding Proteins
Act to transport or sequester molecules by binding to them (e.g. hemoglobin, calcium-binding proteins, DNA-binding proteins)

Cell Adhesion Molecules (CAMs)
CAMs = allows cells to bind other cells or surfaces

3 major families:
1) Cadherins: 2 cells of same or similar type using calcium
2) Integrin: 1 cell to protein in ECM
3) Selectin: 1 cell to carbs, usually on surface of other cells

Immunoglobulins (aka antibodies)
S-S and non-covalent bonds hold 2 light and 2 heavy chains together
Within **antigen-binding region**, specific polypeptide sequences will bind one antigenic sequence
3 possible outcomes of antigen-antibody interaction:
1) Neutralize antigen
2) Opsonization = marking pathogen for destruction by white blood cells
3) Agglutination = clumping together antigen and antibody in large insoluble complexes

Biosignaling

Ion Channels
Facilitated diffusion is used for large, polar, or charged molecules
3 types of ion channels:
1) Ungated: no regulation, always open
2) Voltage-gated channels: regulated by membrane potential change
E.g. voltage-gated Na channels open and close quickly as voltage increases
E.g. voltage-gated K+ channels in SA node of heart bring cell back to threshold
3) Ligand-gated channels: binding of specific ligand causes channel to open or close
E.g. GABA binds to chloride channel and opens it

Enzyme linked receptors = catalytic receptors: receptors where ligand binding causes activity
3 domains: *membrane spanning-domain*, *ligand-binding domain* binds ligand and induced conformational change that activates *catalytic domain*
E.g. RTK; dimer = active form that phosphorylates other enzymes, including itself

GPCR: binding of ligand increases affinity of heterotrimeric G protein to receptor
- G_s stimulates AC = increased cAMP
- G_i inhibits AC = decreased cAMP
- G_q activates phospholipase C which cleaves phospholipid in membrane to form PIP2 → PIP2 is cleaved into DAG and IP3 → IP3 can open Ca+2 channels in ER = increase calcium

Protein Isolation
Proteins and other biomolecules are isolated from body tissues by cell lysis or **homogenization** (crushing, blending, grinding tissue or cell cultures into evenly mixed solutions)
Centrifugation can isolate proteins from smaller molecules before other isolation techniques

2 main methods of protein separation = **electrophoresis** and **chromatography**

Electrophoresis
Cathode attracts cations (charged -) and anode attracts anions (charged +)
Migration velocity = Ez/f (E = electric field, z = net charge, f = frictional coefficient)
Molecules move faster is small, highly charged or placed in large electric field

Native PAGE: analyze proteins in native states but limited by varying mass-to-charge ratios
Useful to compare molecular size or charge of proteins similar in size

SDS-PAGE: separates proteins based on mass alone
SDS = denatures by disrupting all non-covalent interactions + coats proteins with (-) charge

Isoelectric Focusing → separates based on pI
Proteins placed in gel with pH gradient (acidic gel at positive anode and basic gel at negative cathode and neutral in the middle) then electric field is applied;

- Positive proteins move to cathode; negative proteins move to anode
- Proteins stop moving where pH = pI
- Proteins with high pI focus at cathode, proteins with low pI focus at anode

Chromatography
Preferred when large amounts of proteins are being separated

Column chromatography: adsorbent = silica or alumina beads, different fractions collected
Less polar compounds = elute faster = shorter retention time

Ion-Exchange Chromatography: beads are charged, salt gradient used to elute
Size-Exclusion Chromatography: slow compounds move slower, bigger elute first
Affinity Chromatography: coat beads with receptor (e.g. nickel to separate proteins with nickel tags, antibodies and antigens, enzymes substrate analogues)

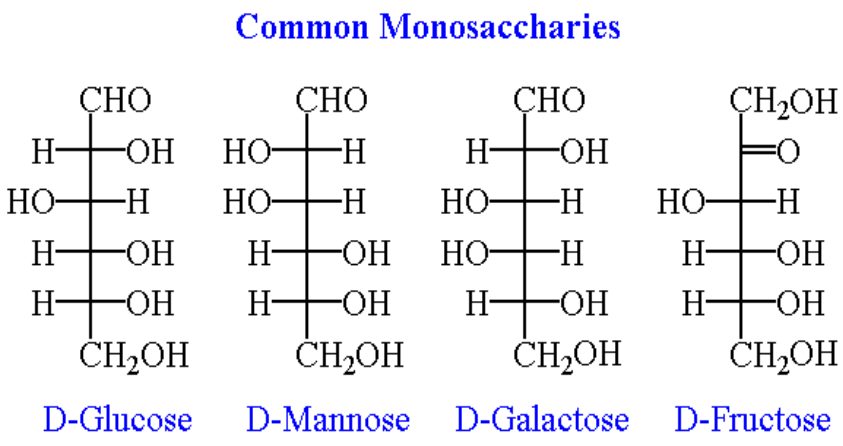
Protein structure can be determined through **X-ray crystallography** (measures e- density, can be used for nucleic acids, generates diffraction pattern) and **NMR spectroscopy**

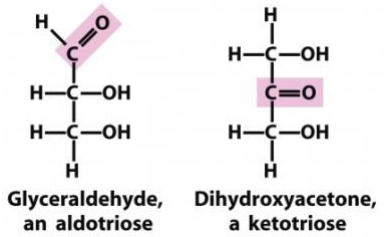
Amino Acid Composition → **Edman degradation** (cleaves N-ter of sequence proteins of 50-70 aa then analyze by mass spectroscopy). For larger proteins, can digest with *chymotrypsin* or *trypsin*. Their position cannot be determined by these methods. Protein activity can be analyzed by **UV spectroscopy** (but it is sensitive to contaminants), **BCA assay**, **Lowry reagent assay**, and **Bradford protein assay** (Coomassie dye + basic aa = blue; less accurate when more than 1 protein present)

1D 2B 3C 4C 5C 6D 7A 8B 9C 10B 11C 12C
13C 14C 15A

3: actin allows for motor protein travel, centrioles are not involved in cell migration, but mitosis
8: ungated or "leak" channels allow free flow of ions to maintain resting membrane potential, while ligand-gated or voltage-gated are involved in cell signaling or pacemaker potentials
9: G alpha, beta, and gamma are in all G proteins; Gi is not in all proteins
14: protein activity and concentration are generally correlated. Protein elutes off of an affinity column by binding free ligand. In this situation, the binding may not have been reversed so this would lower its activity. It was still detected by Bradford so that means it's not stuck to column.

Ch4: Carbohydrate Structure and Function $(C_n(H_2O)_n$





D-sugars have OH on C5 towards right.

Aldoses can participate in glycosidic bonds at C1, ketoses at C2.

Stereochemistry

Stereoisomers (optical isomers) = same chemical formula, different spatial arrangement

- **Enantiomers** = nonidentical, nonsuperimposable mirror images (opposite configurations)
- **Diastereomers** = not mirror images (differ at 1+ carbons)
- **Epimers** = differ at exactly 1 chiral center

Number of stereoisomers with common backbone = 2^n, n = # of chiral carbons
Fischer projection: horizontal lines = wedges (out of page); vertical lines = dashes (in page)

Cyclic Sugars
6-membered = pyranose (form pyranosides); 5-membered = furanose (form furanosides)
Cyclic glucose hemiacetal formation by C1 and C5

Anomers differ at the anomeric carbon: alpha = trans, down vs beta = equatorial, up (for D)
Rule of thumb: alpha means that C1 OH and C5 OH are on opposite sides, beta means same side

Mutarotation = spontaneous shift between one anomeric form and another in presence of H2O

Monosaccharides
Reducing sugar = any sugar with hemiacetal ring, aka free oxygen on anomeric carbon
Lactone = cyclic ester that is made by oxidizing aldose, carbonyl is on anomeric carbon
Reagents used to detect reducing sugars:
1) Tollen's reagent: silver oxide dissolved in ammonia = $[Ag(NH_3)_2]^+$, reduced to silver
2) Benedict's reagent: sln of $Cu(OH)_2$ reacts with aldoses or ketoses to form copper(I) oxide (red)
   - Ketoses react more slowly

Ketoses cannot be oxidized directly to COOH like aldehydes but they can tautomerize to aldose under basic conditions.

When aldehyde group of aldose is reduced to alcohol, it's an **alditol**

Esterification
Hemiacetal + COOH → ester

Glycoside Formation
Hemiacetal + R-OH → acetal (glycoside, alkoxy group formed) + water
Resulting C-O bond = glycosidic bonds

Complex Carbohydrates
Glycosidic bond between 2 -OH groups of 2 monosaccharides = **disaccharide**

Sucrose (glucose-α-1,2-fructose) → NON REDUCING!!
Lactose (galactose-β-1,4-glucose)
Maltose (glucose-α-1,4-glucose)

Polysaccharides
Cellulose: homopolysaccharide of 1,4-linked β-D-glucose in plants, indigestible by humans
Starches: in plants; can be *amylose* (linear 1,4-linked α-D-glucose polymer) or *amylopectin* (branched with both α-1,4 and α-1,6 glycosidic bonds)
   - Amylose is broken down by **β-amylase** (cleaves amylose at nonreducing end) and **α-amylase** (cleaves randomly along the chain to yield shorter polysaccharide chains)
   - Amylopectin is highly branched thus needs **debranching enzyme**

Glycogen: carb storage unit in animals, more branched than starch (more α-1,6 glycosidic bonds)
   - Its high branching = allows for storage of more glucose
   - **Glycogen phosphorylase** cleaves glucose at nonreducing end of glycogen (produces G1P)

1D 2D 3A 4B 5A 6B 7B 8C 9A 10D 11C 12C 13A 14C 15D

1: Glucose has 4 chiral centres so $2^n = 2^4 = 16$ possible stereoisomers

3: Aldonic acids form after aldehyde group on reducing sugar reduces other compound, becoming oxidized in the process

7: B-amylase cleaves amylose at non-reducing end = maltose only
alpha-amylase cleaves anywhere along chain = short polysaccharides, maltose, glucose
Debranching enzyme removes oligosaccharides from a branch in glycogen or starch
Glycogen phosphorylase yields G1P

9: B-anomer has less nonbonded strain than alpha since equatorial not axial -OH

15: Monosaccharides can only be hemiacetals or hemiketals

Ch 5: Lipid Structure and Function

Amphipathic: both hydrophilic and hydrophobic regions

Structural Lipids
Phospholipids: phosphate + alcohol + fatty acid

- **Glycerophospholipids** = glycerol backbone (3-carbon alcohol), ester linkages to 2 fatty acids, phosphodiester bond to polar head group
- **Sphingolipids** = sphingosine backbone
    - Not all are phospholipids (having phosphodiester link): some contain glycosidic links to sugars forming **glycolipids**

4 classes of sphingolipids
1) *Ceramide* = simplest, just H as polar head group
2) *Sphingomyelins* = also phospholipids, either phosphatidylcholine or phosphatidylethanolamine as head group (contains phosphodiester bond) as neutral head groups, present in plasma membranes of cells producing myelin (oligodendrocytes and Schwann cells)
3) *Glycosphingolipids* = mainly on outer surface of plasma membrane, can be classified as *cerebrosides (single sugar)* or *globosides (2+ sugars)*, no net charge at physiological pH
4) *Gangliosides* = glycolipids have a polar head group composed of oligosaccharides with terminal N-acetylneuraminic acid (NANA) and negative charge, play a role in cell recognition

Unsaturated fats' double bonds introduce kinks = difficult to stack/solidify = liquid at room T
Phospholipids with unsaturated fatty acids make up fluid regions of the phospholipid bilayer

Waxes = esters of long-chain fatty acids with long-chain alcohols

- Used for protection for both plants and animals

Signaling Lipids

Terpenes = class of lipids built from *isoprene* (C_5H_8) moieties

- Monoterpene = 2 isoprene units, sesqui- = 3, di = 4, tri = 6, tetra = 8 (e.g. carotenoids like B-carotene)

Terpenoids = derivatives of terpenes that have undergone oxygenation or rearrangement of carbon skeleton, aromatic properties

Steroids = 4 rings (3 cyclohexane + 1 cyclopentane), nonpolar

Steroid hormones = steroids that act as hormones, secreted by endocrine glands into blood and travel by protein carriers to far sites (e.g. testosterone, estrogens, cortisol, aldosterone)

- **Cholesterol** = major component of phospholipid bilayers, amphipathic
    - At low temperatures, keeps cell membrane from solidifying (fluid)
    - At high temperature, holds membrane intact, prevents from being too permeable
    - Precursor to molecules, including steroid hormones, bile acids, vitamin D

Prostaglandins = 20 C unsaturated COOH derived from *arachidonic acid*, with 1 5C ring

- Act as paracrine or autocrine signaling molecules
- In many tissues, function of prostaglandins is to regulate synthesis of cAMP
- Effects on smooth muscle function, sleep-wake cycle, body temp
- Nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin inhibit enzyme *cyclooxygenase* (COX) which aids in production of prostaglandins

Fat-Soluble Vitamins (ADEK)

Vitamin = essential nutrient that cannot be made by body, must be consumed in diet

- **A (carotene)**: as retinal: vision; as retinoic acid: epithelial development
- **D (cholecalciferol)**: as calcitriol: calcium and phosphate regulation (increases uptake in intestines), promotes bone production
    - Lack of vitamin D = *rickets* (underdeveloped bones)
- **E (tocopherols and tocotrienols)**: biological antioxidants, using aromatic rings
- **K (phylloquinone and menaquinones)**: posttranslational modification of *prothrombin* (an important clotting factor in blood), addition of calcium-binding sites on proteins

Some characteristics of hormones: they travel in the blood, are active at low concentrations, have high-affinity receptors, and affect gene expression + metabolism

Energy Storage

Lipids are more energy-dense (yield more energy/gram) than carbs (more reduced C atoms)
They also do not require hydration for stability, so they are lighter than polysaccharides
Dual purpose: energy storage + insulation

Triacylglycerols = 3 fatty acids ester-bonded to glycerol, hydrophobic (n-p), storage for fatty acids

- Travel bidirectionally between liver and adipose tissue

Adipocytes = cells that store large amounts of TGs and fats

Free Fatty Acids and Saponification
Free fatty acids = unesterified, with free carboxylate group, circulate in blood bonded noncovalently to serum albumin

Saponification = ester hydrolysis of triacylglycerols using strong base
Triacylglycerol + 3 NaOH → glycerol + soap (fatty acid salt)

Soaps can act as **surfactants** (lower surface tension)
Colloids = 2 phases appear to form 1 - this is bc formation of **micelles** (hydrophobic core can dissolve hydrophobic compounds, and can wash away with water due to hydrophilic outside)

1D 2B 3B 4B 5C 6C 7C 8C 9C 10C 11B 12C 13B 14D 15B

9: not all sphingolipids have sphingosine as their backbone, some have sphingoid compounds

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Ch 6: DNA and Biotechnology

Nucleoside = pentose + base (C1) (end in "sine" for AG and "idine" for TCU)
Nucleotide = pentose + base (C1) + phosphate (C5)

- High energy phosphodiester bonds due to repulsion of (-) charges

Ribose = -OH at C2; deoxyribose = -H at C2

Sugar-Phosphate Backbone
3'-OH makes bond with 5' phosphate group = 3'-5' phosphodiester bonds
Thus DNA is polar: 5' end has -OH or phosphate group bonded to C5 and 3' end has -OH on C3

Purines = 2 rings = AG
Pyrimidines = 1 ring = TCU
} Aromatic => follow **Huckel's rule (4n + 2 pi e-)**

Watson-Crick Model: 2 antiparallel strands of DNA, wound in right-handed double helix (**B-DNA)**, sugar-phosphate backbone on outside, bases on inside, AT (2 H bonds), GC (3 H bonds)

- **Chargaff's rules (DNA ONLY)**: A = T and G = C (1:1 ratio)
- B DNA has turn every 10 bp
- Major and minor grooves = binding sites for regulatory proteins

Denaturation and Reannealing

- Can disrupt hydrogen-bonding and base-pairing to **denature** 2 strands (but not backbone since sugars and phosphates are covalently bonded) using urea, pH, temp, etc.
- DNA can be **reannealed** if denaturing condition removed
    - e.g. PCR probe binds DNA = detect presence of gene of interest

Eukaryotic Chromosome Organization

DNA is wound around **histones** (proteins with 2 x H2A, H2B, H3, H4 = core), forming **nucleosomes**, organized into **chromatin**

Heterochromatin = compact chromatin; appears dark
Euchromatin = dispersed chromatin; appears light

Telomeres and Centromeres

- DNA replication cannot continue until end = loss of genetic info
- Solution = **telomeres** (TTAGGG) at end of DNA replaced by **telomerase**
- Centromeres are made of heterochromatin
- Telomeres and centromeres stay tightly raveled due to high GC

DNA Replication

Strand Separation and Origins of Replication

- **Replisome** or **replication complex** = set of proteins that help DNA polymerases
- DNA unwinds at **origins of replication**, creating **replication forks**
- Bacteria = 1 circular dsDNA chromosome
    - 1 origin of replication = 2 replication forks meet = 2 identical circle DNA
- Eukaryotes = many origins of replication; as forks move towards each other, chromatids remain connected at centromere

Process of Unwinding

- **Helicase** unwinds DNA and makes 2 ssDNA template strands ahead of the polymerase
- **ss-DNA binding proteins** keep the 2 strands apart
- **DNA topoisomerases** prevent **supercoiling** of DNA by introducing negative supercoils
- **Semi-conservative replication** since new dsDNA = ½ parental, ½ replicated

Synthesis of Daughter Strands

- **DNA polymerase** can only read template in 3’ to 5’ and synthesize 5’ to 3’
    - This is no problem for **leading strand**
    - For the **lagging strand**, **Okazaki fragments** are added 5’ to 3’
    - The gaps are filled in by DNA ligase

Process of DNA Replication

- **Primase** synthesizes short primers in 5’-3’ direction (many on lagging, 1 on leading)

- **DNA polymerase III** (prokaryotes) or **DNA polymerases α, δ,** and **ε** synthesize 5'-3'
- **DNA polymerase I** (prokaryotes) or **RNase H** (eukaryotes) remove RNA
- **DNA polymerase I** (prokaryotes) or **DNA polymerase δ** (eukaryotes) add DNA nucleotides where the RNA primer was
- **DNA ligase** seals ends of DNA molecules together

DNA Repair

- **Oncogenes** = mutated genes that cause cancer, encode proteins that are active more than normal (**proto-oncogenes** = before these genes are mutated)
- **p53** = tumor suppressor gene, encode proteins that inhibit cell cycle
- **Proofreading**: incorrectly paired bases = instability detected by polymerase
    - Can distinguish parent & daughter strand since parent is more heavily methylated
- **Mismatch repair**: enzymes encoded by *MSH2* and *MLH1* detect and remove errors missed during S phase in the G2 phase
- **Nucleotide excision repair (e.g. UV thymine dimers):** proteins scan DNA for bulge, an **excision endonuclease** makes nicks in phosphodiester backbone and removes oligonucleotide, DNA pol fills in the gaps
- **Base excision repair (e.g. deamination of C = U):** a glycosylase removes the incorrect base forming an **abasic site** where DNA pol and ligase fill the gap and seal the strand

Recombinant DNA and Biotechnology

DNA cloning: insert DNA of interest into **vector** to form **recombinant vector**

- Vectors are usually bacterial or viral plasmids, transferred into bacteria
- Bacteria grown in colonies, colony containing recombinant can be isolated (this can be done by ensuring the recombinant has gene for antibiotic resistance and that other colonies that do not are killed off)
- **Restriction enzymes (endonucleases)** recognize specific palindromic dsDNA sequences

DNA Libraries and cDNA

- **DNA libraries** = large collections of known DNA sequences
    - Can be made of *genomic DNA* or *cDNA*
    - **Genomic libraries** contain large DNA with exons (coding) and introns (noncoding)
    - **cDNA** is reverse transcribed from mRNA, lack noncoding introns, only exons

Hybridization

- Joining of complementary base pair sequences, uses 2 single-stranded sequences
- Can be used in PCR and in Southern Blotting

Southern Blot: used to detect presence and quantity of DNA strands

- DNA is cut by restriction enzymes, separated by gel electrophoresis
- DNA fragments are transferred to membrane, while retaining their separation
- Membrane is probed with ssDNA, **probe** labelled with radioisotope will bind to complementary sequences

DNA Sequencing

- Uses ddNTP (which has -H on 3') and when incorporated, polymerase can no longer add
- Fragments separated by size using gel electrophoresis
- Last base for each fragment is read in order

1B 2D 3A 4C 5B 6C 7B 8A 9D 10D 11C 12A
13B 14D 15D

5: an aromatic compound doesn't need alternating single and pi bonds; it can have 1 triple bond which would allow 1 unhybridized p-orbital

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Ch 7: RNA and the Genetic Code

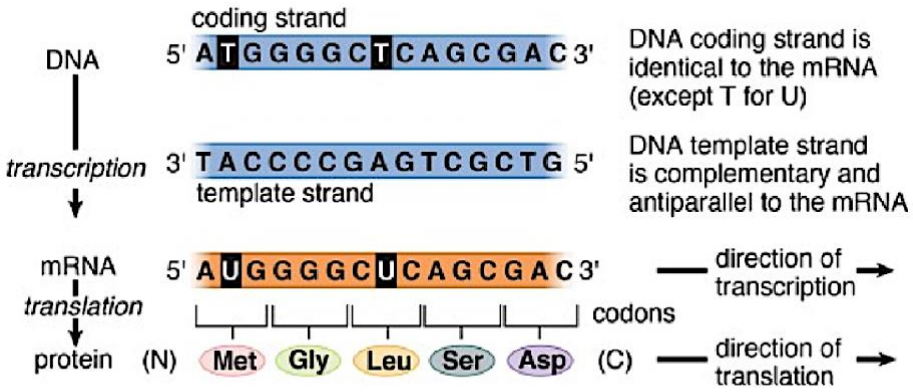


Figure 7.2. Flow of Genetic Information from DNA to Protein

Types of RNA

1) mRNA: transcribed by *RNA polymerase*, contains groups of 3 nucleotides called **codons**
   - In eukaryotes, mRNA = **monocistronic** (codes only 1 protein)
   - In prokaryotes, mRNA = **polycistronic** (codes for many different proteins)

2) tRNA: has **anticodon** that pairs with codon and brings in new amino acid during translation
   - Amino acids are activated by **aminoacyl-tRNA synthase** and requires 2 high-energy bonds from ATP; the enzyme transfers the a.a. to the 3' end of the correct tRNA

3) rRNA: synthesis in nucleolus, part of ribosomal machinery during protein assembly
   - Many rRNA function as **ribozymes** (catalyze peptide bond formation + help splice introns)

AUG = start codon

UAA, UGA, UAG = stop codons

Mutations

Degeneracy and Wobble

- The genetic code is **degenerate** because >1 codon for each amino acid
- For codons for the same a.a., usually only 3rd base is variable → **wobble position**
- Mutations in the wobble position tend to be silent or degenerate

Types of Mutations

- **Missense mutation** = mutation where 1 nucleotide substitutes for another
- **Nonsense mutation** = mutation where stop codon introduced
- **Frameshift mutations:** when nucleotides are added or deleted from mRNA

Mechanism of Transcription

- mRNA is synthesized from the **template strand** (or the **antisense strand**)
- **RNA pol II** (eukaryotes) locates genes by searching for **promoter regions**
- Its binding site in the promoter is the **TATA box**
- **Transcription factors** help RNA pol locate and bind to this promoter region
- RNA pol transcribes mRNA in 5'-3' direction but does not proofread like DNA pol
- RNA pol continues until it reaches termination sequence or stop signal
- DNA double helix reforms, primary transcript = **heterogenous nuclear RNA (hnRNA)**
- mRNA is derived from hnRNA via posttranscriptional modifications

Posttranscriptional Modifications

1) Splicing: remove introns and ligate exons. Uses **small nuclear RNA (snRNA)** and **small nuclear ribonucleoproteins (snRNPs)** in the **spliceosome** to create a lariat, which is degraded.
2) 5' cap: a **7-methylguanylate triphosphate cap** is added to 5'
3) 3' poly-A tail: a **polyadenosyl (poly-A) tails** is added to 3', protects against degradation

Translation

Ribosomes

- The **ribosome** is composed of proteins + rRNA,
- 3 binding sites: A (aminoacyl), P (peptidyl), E (exit)
- Eukaryotic ribosome = 80S (60S + 40S)
- Prokaryotic ribosome = 70S (50S + 30S)

Mechanism of Translation

- In prokaryotes, ribosomes start translating before mRNA is complete
- In eukaryotes, transcription and translation occur at different times and locations
- 3 stages of translation: **initiation, elongation,** and **termination**
- Specialized initiations factors (IF), elongation factors (EF), and termination or release factors (RF), as well as GTP, are required for each step

1) Initiation

- Small ribosomal unit binds mRNA;
  - In prokaryotes, binds to the **Shine-Dalgarno sequence** in 5' UTR of mRNA
  - In eukaryotes, binds to 5' cap structure
- The charged **initiator tRNA** binds to AUG **start codon** in P site
  - In prokaryotes, initial amino acid = fMet
  - In eukaryotes, initial amino acid = Met
- Large subunit binds to small subunit assisted by IF to form initiation complex

2) Elongation

- 3 step cycle, ribosome moves 5'-3' along mRNA, synthesizes proteins from N-ter to C-ter
- The **A site** hold incoming aminoacyl-tRNA complex (holds next a.a. to be added)
- The **P site** holds tRNA that carries growing polypeptide chain. Peptide bond is formed when peptide in P site moves to tRNA in A site (by *peptidyl transferase* which uses GTP)
- The **E site** is where uncharged tRNA pauses transiently before exiting ribosome

Elongation factors (EF) help locate and recruit aminoacyl-tRNA along with GTP

3) Termination

- When any stop codon moves into A site, a protein called **release factor (RF)** bind to stop codon, causing water molecule to hydrolyze peptide
- The peptide is release from tRNA in P site, 2 subunits dissociate

Posttranslational Processing

- **Chaperones** assist in proper protein-folding
- **Cleavage** of proteins or signal sequences
- **Phosphorylation, carboxylation** (adding COOH), **glycosylation**

Control of Gene Expression in Prokaryotes

Operon Structure

- **Operons** are clusters of genes transcribed as a single mRNA (*trp* in *E. Coli*)

Jacob-Monod Model describes structures and function of operons;

- **Structural gene** codes for protein of interest
- **Operator site** (upstream of structural gene), can bind repressor proteins
- **Promoter site** (further upstream) provides place for RNA pol to bind
- **Regulator gene** (even further upstream) codes for **repressor** protein

2 Types of Operons

1) Inducible Systems

- Repressor bonded tightly to operator, blocks mvt of RNA pol from promoter to structural
- To remove that block, inducer binds repressor: inducer-repressor complex can't bind operator = structural genes are transcribed (**negative control**)

Example of Inducible System = *lac* operon, which contains the gene for *lactase*

- Bacteria only want to digest lactose if high lactose, low glucose (since costs energy)
- *lac* operon is induced in presence of lactose, genes only transcribed when useful

2) Repressible Systems

- Constant production of protein product so always active initially
- Repressor is inactive until it binds **corepressor** (often end product)
- This complex will bind operator = no transcription

Example of Repressible System = *trp* operon

- When Trp high, acts as a corepressor

Control of Gene Expression in Eukaryotes

Transcription Factors

- **Transcription factors** = transcription-activating proteins that search the DNA for specific binding motifs
- Tend to have 2 domains;
    1) **DNA-binding domain** binds specific nucleotide sequence in promoter
    2) **Activation domain** binds transcription factors

Gene Amplification

Enhancers

- Allow to control gene expression by multiple signals
- Expression amplified when enhancers bind to their transcription factors
- Enhancer far from promoter can still interact (since enough space for DNA to fold)

Regulation of Chromatin Structure

Histone acetylation (by *histone acetylases*) = open chromatin = gene expression

DNA methylation (by *DNA methylases* to C and A nucleotides) = silencing of gene expression

1D 2C 3A 4D 5A 6C 7B 8B 9C 10C 11B 12B
13B 14B 15B

2: all 3 stages of protein synthesis (initiation, elongation, termination) require lots of energy
4: all codons for Val start with GU so we know by base pairing that the anticodon must *start* with AC in 5'-3' (rather than "CA" for 3'-5') so we look for anticodons that start with AC
10: the C-terminus or reading frame will not change since we deleted exactly 3 bases
13: RNA pol I = rRNA; RNA pol II = hnRNA; RNA pol III = tRNA

Ch 8: Biological Membranes

Plasma membrane = semipermeable phospholipid bilayer

Fluid mosaic model = membrane is made of lipids, proteins, carbs that give it fluidity

Membrane Dynamics

- **Lipid rafts** are collections of similar lipids that are attachment points for biomolecules
- **Flippases** assist in the flip of phospholipids between layers (otherwise unfavorable)

Membrane Components

Lipids

- Main component of membranes, mainly phospholipids with few fatty acids

1) Fatty Acids and Triacylglycerols

- **Unsaturated fatty acids** have double bonds = liquid at room T = membrane fluidity
- **Saturated fatty acids** decrease membrane fluidity
- Essential fatty acids are transported as triacylglycerols from intestine in **chylomicrons**

2) Phospholipids (MAIN LIPID IN MEMBRANE)

- Replacing 1 fatty acid on phospholipid with phosphate group = **glycerophospholipid**
- Phospholipids spontaneously assemble into **micelles** or **liposomes** (bilayered vesicles)
- Phosphates = attachment for water-soluble groups

3) Sphingolipids

- Important component of membrane, contain hydrophilic region + 2 fatty acid tails

4) Cholesterol and Steroids

- At low temp: increases fluidity but at high temp: decreases fluidity

Proteins

- 3 types of membrane proteins;
  1) Transmembrane proteins pass completely through bilayer
  2) Embedded proteins are on interior (cytoplasmic) or exterior (extracellular) surface
  3) Membrane-associated (peripheral) proteins are bound to bilayer with ionic bonds

Carbohydrates

- Generally attached to proteins on outer surface, cell signaling, recognition (ABO)
- Glycoproteins and water can form coat around cell

Cell-Cell Junctions

- Generally made of **cell adhesion molecules (CAM)** aka proteins that allows cells to recognize each other

1) Gap Junctions
- Called **connexons**, allow direct cell-cell communication
- Allow rapid exchange of molecules between adjacent cells (intercellular transport)

2) Tight Junctions
- Prevent solutes from leaking by paracellular route but don't allow intercellular transport

3) Desmosomes
- Bind adjacent cells by anchoring cytoskeletons

Membrane Transport

Osmosis
- **Hypotonic solution** = inner [solutes] > outer [solutes] = water rushes in cells = lysis
- **Hypertonic solution** = inner [solutes] < outer [solutes] = water rushes out cell
- **Isotonic solution** = inner [solutes] = outer [solutes]
    - Does not prevent mvt but rather *net* mvt (cell will neither gain or lose H2O)

Osmotic pressure = **colligative property** (depends on concentration but not identity of particles)
$\pi = iMRT$

where M = molarity of solution, R is the ideal gas constant, T is absolute temp (in Kelvins) and I is number of ions in solution (e.g. i = 2 for NaCl)

Active Transport

Secondary Active Transport: "Coupled transport". Harnesses the energy released by one particle going down its electrochemical gradient to drive a different particle up its gradient.
- **Symport** = both particles flow the same direction
- **Antiport** = particles flow in opposite directions

Endocytosis
- **Pinocytosis** = endocytosis of fluids and dissolved particles
- **Phagocytosis** = ingestion of large solids (e.g. bacteria)

Membrane Potential (V_m)
- Requires energy since ions can passively diffuse across cell membrane thus **Na+/K+ ATPase** regulates concentration gradients (pumps 3 Na^+ out for every 2 K^+ in)
- **Nernst equation** is used to determine V_m from intra and extracellular ion concentrations

$$E = \frac{R\,T}{z\,F} \ln\left(\frac{[ion]_{outside}}{[ion]_{inside}}\right) = \frac{61.5}{z} \log\left(\frac{[ion]_{outside}}{[ion]_{inside}}\right)$$

where R is ideal gas constant, T is temp in Kelvins, z is charge of ion, and F is Faraday constant (96,485 C/mol e-) → simplification to 61.5 assumes body temp of 310 K

- The **Goldman-Hodgkin-Katz voltage equation**:

$$V_m = 61.5 \log \left(\frac{P_{Na^+} \times [Na^+]_{outside} + P_{K^+} \times [K^+]_{outside} + P_{Cl^-} \times [Cl^-]_{inside}}{P_{Na^+} \times [Na^+]_{inside} + P_{K^+} \times [K^+]_{inside} + P_{Cl^-} \times [Cl^-]_{outside}}\right)$$

1C 2C 3D 4B 5A 6B 7C 8C 9A 10B 11D 12B 13D 14A 15D

7: membrane receptors are likely to be transmembrane proteins with catalytic activity
11: the resting membrane potential is unlikely to be 0 mV because that means no gradient at all!

Ch 9: Carbohydrate Metabolism I: Glycolysis, Glycogen, Gluconeogenesis, and PPP

Glucose Transport
GLUT 2: low-affinity transporter (high Km) in liver (for storage) and pancreatic B-islet cells (as part of glucose sensor for insulin release)

- Low affinity means that liver will pick up glucose in proportion to its concentration

GLUT 4: high-affinity transporter (low Km) in adipose tissue and muscle

- Saturated at slightly higher than normal blood glucose (constant rate of glucose influx)
- Rate of glucose transport is **increased by insulin**
- Muscles store glucose as glycogen; adipose tissue uses glucose to form DHAP

GLUT 4 saturated at levels slightly above 5 mM, so glucose entry can only be increased by increasing number of GLUT 4 transporters. Insulin promotes fusion of vesicles containing GLUT 4 with the cell membrane.

Glycolysis (ALL CELLS)

- For red blood cells, only energy-yielding pathway since no mitochondria in erythrocytes
- **Glycolysis** = cytoplasmic pathway, converts glucose to pyruvate
    - If cell has mitochondria and O_2 (aerobic), can use NADH in ETC
    - If cell in anaerobic condition, it can still make energy

Important Enzymes for Glycolysis
1) Hexokinase and Glucokinase: phosphorylate glucose to G6P to prevent leaving

- **Hexokinase** = in many tissues; inhibited by G6P, low Km
- **Glucokinase** = in liver cells and pancreatic B-islet cells; activated by insulin, high Km

2) Phosphofructokinase (PFK-1 and PFK-2)

- **PFK-1** = rate-limiting enzyme, main control point in glycolysis
    - Inhibited by ATP and citrate, activated by AMP and F2,6-BP
- Insulin stimulates, glucagon inhibits PFK-1 in hepatocytes
    - It stimulates PFK-2 = more F2,6-BP = activates PFK-1

3) Glyceraldehyde-3-Phosphate

- Input: Pi and NAD+ → NADH; also produces 1,3-bisphosphoglycerate

4) Phosphoglycerate mutase aka 3-phosphoglycerate kinase

- Transfers phosphate from 1,3-BPglycerate to ADP, forming ATP and 3-phosphoglycerate (**substrate-level phosphorylation**)

5) Pyruvate kinase

- Substrate level phosphorylation using PEP to form ATP and pyruvate
- Activated by F1,6-BP **(feed-forward reaction)**

Fermentation

- In absence of oxygen, pyruvate → lactate by *lactate dehydrogenase*
- Replenishes NAD+ for glyceraldehyde-3P dehydrogenase
- W/O mitochondria and oxygen, glycolysis would stop since no more NAD+
    - Lactate dehydrogenase prevents this! (NADH → NAD+)

Important Intermediates of Glycolysis

1) DHAP: used in liver and adipose tissue for TG synthesis

2) 1,3-BPG and PEP: high-energy intermediates, make ATP by substrate-level phosphorylations

Irreversible Enzymes: glucokinase/hexokinase, PFK-1, pyruvate kinase

Pyruvate Dehydrogenase (PDH)

- Pyruvate from aerobic glycolysis → may be converted to **acetyl-CoA** for entry in TCA or fatty acid synthesis if enough ATP **(acetyl-CoA = negative feedback on PDH)**
- **PDH = irreversible** (can't convert acetyl-coA to pyruvate or glucose)
- **Requires:** TPP, lipoate, CoA, NAD+
- Activated by insulin (insulin signals to liver that the person is in a well-fed state so should burn glucose and store energy as fatty acids)

3 POSSIBLE FATES OF PYRUVATE:

1) Conversion to acetyl-coA by PDH
2) Conversion to lactate by lactate dehydrogenase
3) Conversion to oxaloacetate by pyruvate carboxylase

If there is build-up of acetyl-coA, pyruvate is no longer converted to acetyl-coA (to enter TCA) but rather into oxaloacetate (to enter gluconeogenesis)

Glycogenesis and Glycogenolysis

- Glycogen synthesis occurs in **liver** and **skeletal muscle**: stored in cytoplasm as granules
    - In liver = source of glucose easily mobilized between meals
    - In muscle = stored as energy reserve for muscle contraction

Glycogenesis

- Synthesis of glycogen granules
- Glucose → G6P → G1P → UDP-Glucose → Glycogen (via *glycogen synthase* and *branching enzyme*)

Glycogen synthase: rate-limiting enzyme, forms alpha-1,4 glycosidic bonds

- Activated by G6P and insulin, inhibited by epinephrine and glucagon

Branching enzyme hydrolyzes alpha-1,4 bond and reattaches sugar unit via alpha 1,6 bond

Glycogenolysis

- Degradation of glycogen via *glycogen phosphorylase* and *debranching enzyme*
- Glycogen → G1P → G6P

Glycogen phosphorylase breaks glycogen by adding PPi

- Activated by glucagon (in liver), and AMP and epinephrine (in muscles)
- Inhibited by ATP

Debranching enzyme moves block of glucose from branch to end of chain via alpha 1,4 bond

Gluconeogenesis

- Activated by glucagon and epinephrine, inhibited by insulin
- Activated during fasting conditions
- important substrates:
    - Glycerol 3-phosphate (from TG, adipose tissue)
    - Lactate (from anaerobic glycolysis)
    - Glucogenic amino acids (from muscle proteins)

Glucogenic amino acids (all except Leu and Lys) can be converted into intermediates that feed into gluconeogenesis, while **ketogenic amino acids** can be converted into ketone bodies (alternative during periods of prolonged starvation).

Important Enzymes for Gluconeogenesis

1) Pyruvate Carboxylase

- Mitochondrial enzyme activated by acetyl-CoA, converts pyruvate to oxaloacetate (OAA)
- OAA cannot leave the mitochondrion so it is reduced to *malate* and then leaves
- Once in the cytoplasm, malate is oxidized to OAA

2) PEPCK

- Induced by glucagon and cortisol, converts OAA to PEP
- Rxn requires GTP

3) Fructose-1,6-BPase

- Rate-limiting enzyme of gluconeogenesis, removes phosphate from F-1,6-BP
- Reverses action of PFK-1
- Activated by ATP, inhibited by AMP and fructose-2,6 BP

4) Glucose-6-Phosphatase

- Only found in liver not muscle : muscle glycogen cannot serve as source of blood glucose
- Converts G6P to glucose, opposite of glucokinase/hexokinase activity

Gluconeogenesis requires spending ATP that is provided by B-oxidation of fatty acids. This means that hepatic gluconeogenesis is always dependent on B-oxidation of fatty acids in the liver.

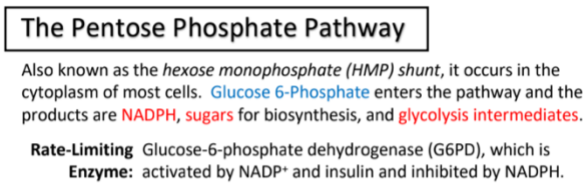
KEY CONCEPT: Because gluconeogenesis requires acetyl-CoA to occur (to inhibit PDH and stimulate pyruvate carboxylase), gluconeogenesis is inextricably linked to fatty acid oxidation. The source of acetyl-CoA cannot be glycolysis because this would just burn the glucose that is being generated in gluconeogenesis! (It would make a futile cycle!)

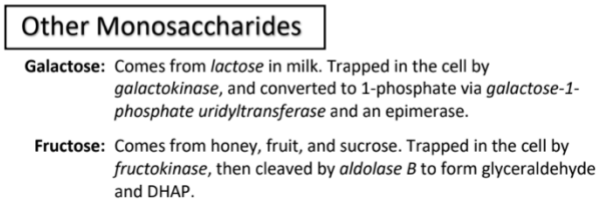
Bottom line: acetyl-CoA inhibits PDH and activates pyruvate carboxylase. Net effect = shifting from burning pyruvate in the citric acid cycle to creating new glucose molecules for the rest of the body. The acetyl-CoA come from B-oxidation, not glycolysis.

Although acetyl-CoA from fatty acids cannot be converted to glucose, can be converted to ketone bodies (low blood sugar = high [ketones] in blood)

Pentose Phosphate Pathway (PPP)

- Occurs in cytoplasm of all cells
- 2 major functions: production of NADPH and source of *ribose 5-phosphate* for nucleotide synthesis





1A	2D	3B	4B	5C
6C	7D	8C	9A	10D
11B	12A	13B	14A	15B

3: hexokinase = in muscles (GLUT4)
9: pyruvate would be high after exercise to activate PDH
14: NADPH functions; biosynthesis of lipids, produce bactericidal bleach, maintain glutathione
15: hexokinase = irreversible step but not rate-limiting step

Ch 10: Carbohydrate Metabolism II: Aerobic Respiration
The **citric acid cycle** or **Krebs cycle** or the **tricarboxylic acid (TCA) cycle** is in the mitochondria.
Main function: oxidize acetyl-CoA to CO_2 and H_2O, produce NADH and $FADH_2$

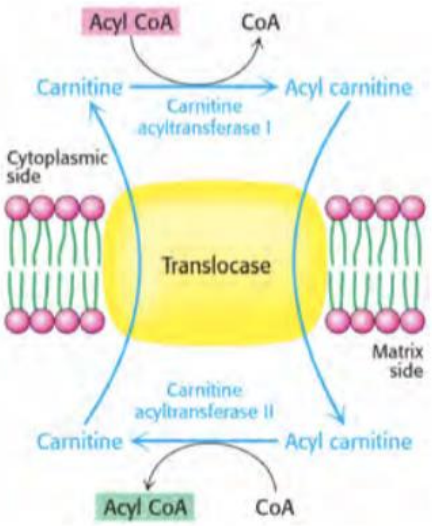
Recall: once pyruvate forms, it enters mitochondria via active transport and is oxidized and decarboxylated: pyruvate + CoA-SH + NAD+ → acetyl-CoA + NADH + CO_2 + H^+ (by PDH complex)

*The SH is part of CoA - this forms a thioester (acetyl-CoA) = high energy released

5 Enzymes in PDH Complex, but 3 of them implicated in forming acetyl-CoA:
1) Pyruvate dehydrogenase (PDH): oxidizes pyruvate, creates CO_2; requires TPP and Mg^{2+}
2) Dihydrolipoyl transacetylase: oxidizes the remaining two-carbon molecule using lipoic acid, and transfers the resulting acetyl group to CoA, forming acetyl-CoA.
3) Dihydrolipoyl dehydrogenase uses FAD to reoxidize lipoic acid, forming FADH2. This FADH2 can later transfer electrons to NAD+, forming NADH that can feed into the electron transport chain.

The 2 other enzymes:
4) Pyruvate dehydrogenase kinase: phosphorylates PDH when ATP or acetyl-coA high = turn off
5) Pyruvate dehydrogenase phosphatase: dephosphorylates PDH when ADP high = turn on

Pathways Other Than Glycolysis That Form Acetyl-CoA
<u>1) Fatty acid oxidation:</u> shuttle acyl group from cytosolic CoA-SH to mitochondrial CoA-SH via carnitine, then undergo B-oxidation



Acyl Carnitine Translocase: Mechanism for Acyl CoA to enter the mitochondrial matrix. The mitochondrial matrix is where Acyl CoA can undergo β-oxidation to form Acetyl-CoA.

<u>2) Amino acid catabolism:</u> transaminate to lose nitrogen, convert carbon skeleton to ketone body, which can then be converted into acetyl-CoA
<u>3) Ketones:</u> reverse of ketone body formation
<u>4) Alcohol</u>: *alcohol dehydrogenase* + *acetaldehyde dehydrogenase* convert alcohol to acetyl-CoA

Reactions of the Citric Acid Cycle (check summary sheet)

Electron Transport Chain
The inner mitochondrial membrane is essential for generating ATP using **proton-motive force**

- Protons are moved from matrix → intermembrane space
- Formation of ATP = endergonic, ETC = exergonic pathway
- Electrons donated by NADH and $FADH_2$

Step 1: Complex I (NADH-CoQ oxidoreductase): $NADH + H^+ + CoQ \rightarrow NAD+ + CoQH_2$
Fe-S (iron-sulfur) clusters are used to transfer electrons from NADH to FMN (flavin mononucleotide) then from FMN to CoQ, forming $CoQH_2$. 4 H+ are displaced.

Step 2: Complex II (Succinate-CoQ oxidoreductase): $succinate + CoQ + 2H^+ \rightarrow fumarate + CoQH_2$
Electrons come from succinate. The Fe-S is used to transfer electrons from $FADH_2$ made in the CAC to CoQ, forming $CoQH_2$. No hydrogen pumping (no contribution to proton gradient).

Step 3: Complex III ($CoQH_2$-cytochrome c oxidoreductase):
$CoQH_2$ + 2 cytochrome c [with Fe^{3+}] → CoQ + 2 cytochrome c [with Fe^{2+}] + $2H^+$
4 H+ are displaced.

Step 4: Complex IV (cytochrome c oxidase): cytochrome oxidase gets oxidized as oxygen is reduced (transfer of electrons using H-) and forms water, 2 H+ are displaced

4 cytochrome c [with Fe^{2+}] + $4H^+ + O_2$ → 4 cytochrome c [with Fe^{3+}] + 2 H_2O

Cytosolic NADH formed from glycolysis cannot directly cross the inner mitochondrial membrane. Thus needs **shuttle** - transfers the e- of NADH to a carrier that crosses inner membrane

The range of 30-32 ATP depends on which shuttle mechanism used:

1) Glycerol 3-phosphate shuttle: electrons transferred from NADH to DHAP forming glycerol-3-phosphate (using cytosolic *glycerol 3-phosphate dehydrogenase*). These electrons can be transferred from glycerol-3-phosphate to mitochondrial FAD, forming $FADH_2$. $FADH_2$ gives its electrons to ETC via Complex II, generating 1.5 ATP for every cytosolic NADH.

2) Malate-aspartate shuttle: electrons transferred from NADH to OAA (can't cross inner membrane) forming malate (which can). Malate crosses to matrix, and gives its electrons to mitochondrial NAD+, forming NADH. NADH gives its electrons to Complex I, generating 2.5 ATP for every cytosolic NADH.

Goal of ETC = generate proton-motive force (aka electrochemical gradient)
Goal of Oxidative Phosphorylation = ATP synthesis (via ATP synthase)

Oxidative Phosphorylation
Chemiosmotic Coupling

- Proton-motive force interacts with F_0 portion of ATP synthase
- **Chemiosmotic coupling** uses energy of gradient to phosphorylate ADP, forming ATP

2 regulators
1) Oxygen: if limited = rate of oxidative phosphorylation decreases, NADH and $FADH_2$ increase, inhibiting CAC

In presence of oxygen, rate depends on ADP:
2) ADP activates isocitrate dehydrogenase = increased rate of CAC = increased NADH/$FADH_2$ = increased rate of oxidative phosphorylation

1C 2B 3B 4C 5A 6D 7C 8C 9B 10B 11B 12C
13A 14B 15B

1: PFK-1 can function without oxygen; CAC enzymes cannot
6: fatty acids enter the catabolic pathway as acetyl-CoA: the fatty acyl-CoA becomes acetyl-CoA

Ch 11: Lipid and Amino Acid Metabolism

B-Oxidation (aka fatty acid catabolism, releases molecules of acetyl-CoA)
Activation: *fatty-acyl-CoA-synthetase* attaches fatty acid to CoA to form acyl-CoA
Fatty acid entry into mitochondria: transport via carnitine shuttle

- *Carnitine acyltransferase I* is the rate-limiting enzyme of fatty acid oxidation

B-oxidation = 4 step cycle
Each step releases 1 acetyl-CoA (2C), 1 NADH, 1 $FADH_2$

In a fasting state, the liver produces more acetyl-CoA from B-oxidation than is used in the CAC
This can be used to form ketone bodies (2 acetyl-CoA molecules linked together)

4 Steps of B-oxidation
1. Oxidation of fatty acid to form double bound (+ 1 $FADH_2$)
2. Hydration of double bond to form -OH group
3. Oxidation of hydroxyl group to form carbonyl (B-ketoacid) (+ 1 NADH)
4. Splitting of B-ketoacid into acyl-CoA and acetyl-CoA

Process continues until chain has been shortened to 2C which is the final acetyl-CoA

Fatty acids with odd number yield one acetyl-CoA and 1 *propionyl-CoA* at the end

Ch 12: Bioenergetics and Regulation of Metabolism

Open systems = exchange matter + energy with environment (e.g. humans)
Closed systems = exchange only energy with environment (changes in internal energy due to heat usually since pressure and volume are constant in most living systems)

Standard free energy (ΔG°) is the energy change that occurs at standard concentrations of 1M, pressure of 1 atm, and temperature of 25 ^oC:

$$\Delta G = \Delta G^\circ + RT\ln(Q)$$

where R is universal gas constant, T is the temperature, and Q is rxn quotient

$\Delta G^{\circ\prime}$ adjusts for pH → pH = 7 so $[H+] = 10^{-7}$ M

Rxns with negative ΔG = more products than reactants

	+ ΔH	- ΔH
+ΔS	Spontaneous at high temp	Spontaneous
- ΔS	Nonspontaneous	Spontaneous at low temp

ATP is a mid-level energy carrier. It provides energy through *hydrolysis* and *coupling* to energetically unfavorable rxns. ATP = 30 kJ/mol

Metabolic States

Postprandial (Absorptive) State (~3-5h after meal)

- More anabolism (synthesis of biomolecules for storage), less catabolism
- Nutrients from gut go to liver via hepatic portal vein
- After a meal, blood glucose levels are higher, and insulin released
- Insulin has 2 main targets: liver, muscle, and adipose tissue
    - In liver and muscle, promotes glycogen synthesis
    - In adipose tissue, promotes TG synthesis
- 2 types of cells are insensitive to insulin: nervous tissue and RBC
    - Brain: oxidizes glucose to CO2
        - Glucose → pyruvate → acetyl-CoA → CO2
    - RBC: only use glucose anaerobically
        - Glucose → pyruvate

Postabsorptive (Fasting) State

- Glucagon, cortisol, epinephrine, norepinephrine, and GH oppose insulin
    - In liver, stimulate glycogen degradation and release of glucose into blood
    - Also stimulates gluconeogenesis in liver (but slower response than glycogenolysis)
    - In muscle and adipose tissue, decreases insulin and increased epinephrine stimulate release of amino acids

Prolonged Fasting (Starvation)

- High levels of glucagon and epinephrine
- Increased glucagon = rapid degradation of glycogen stores in liver
- After 24h, gluconeogenesis (which was still happening) becomes main source of glucose
- Lipolysis is rapid = increased acetyl-CoA = synthesis of ketone bodies
- Muscles will use fatty acids; brain will use ketones (so as to not degrade too many aa)
- After 2-3 weeks, brain's energy comes from 2/3 ketone, 1/3 glucose
- However, RBC continue to rely on glucose (they have no mitochondria!)

Hormonal Regulation of Metabolism

Insulin (beta cells of pancreas)

- Tissues that require insulin for glucose uptake: adipose tissue and skeletal muscles
- Tissues in which glucose uptake is NOT affected by insulin:
    - Nervous tissue
    - Kidney tubules
    - Intestinal mucosa
    - RBC
    - B-cells of pancreas

Insulin increases:

- Glucose and TG uptake by fat cells
- Glycogen synthesis (by *glucokinase* and *glycogen synthase*)
- *Lipoprotein lipase* activity, which clears VLDL and chylomicrons from blood
- TG synthesis (lipogenesis) in adipose tissue and liver from acetyl-CoA

Insulin decreases:

- TG breakdown (lipolysis) in adipose tissue
- Formation of ketone bodies by liver

For glucose to promote insulin secretion it must not only enter the B-cell but also be metabolized, increasing intracellular [ATP] = calcium release in cells = promotes exocytosis of preformed insulin from vesicles

Glucagon (alpha cells of pancreas)

- Primary target for action is liver (hepatocyte), secreted in response to low plasma glucose and basic amino acids

Glucagon results in:

- Increased liver glycogenolysis (activates *glycogen phosphorylase*)
- Increased liver gluconeogenesis (by increasing activity of *pyruvate carboxylase* and *PEPCK* and *fructose-1,6-BPase*)
- Increased liver ketogenesis and decreased lipogenesis
- Increased liver lipolysis (activates *HSL*)

Glucocorticoids (adrenal cortex)

- **Cortisol** promotes mobilization of energy stores, increased lipolysis
- Cortisol inhibits glucose uptake in most tissues, increased liver gluconeogenesis

Catecholamines (adrenal medulla)

- Increase activity of liver and muscle glycogen phosphorylase (promote glycogenolysis)
- Because muscles lack G6Pase, the muscles metabolize the glucose itself
- Increase lipolysis by activating HSL
- Epinephrine increases basal metabolic rate

Thyroid Hormones

- Increase basal metabolic rate (increased O_2 consumption and heat production)
    - T_3 = more rapid increase in metabolic rate, shorter duration of activity
    - T_4 = slower but lasts for several hours or days
- Accelerate cholesterol clearance from plasma

Tissue-Specific Metabolism

Organ	Well-fed	Fasting
Liver	Glucose and amino acids	Fatty acids
Resting skeletal muscle	Glucose	Fatty acids, ketones
Cardiac muscle	Fatty acids	Fatty acids, ketones
Adipose tissue	Glucose	Fatty acids
Brain	Glucose	Glucose (ketones if starved)
RBC	Glucose	Glucose

Respiratory Quotient (RQ) = CO2 produced/ O2 consumed

Regulation of body mass
Ghrelin increases appetite and stimulates secretion of orexin
Orexin further increases appetite and is involved in alertness, sleep-wake cycle
Leptin is a hormone secreted by fat cells, decreases appetite and suppresses orexin production

Body mass index (BMI) = mass/height^2

1C 2B 3C 4A 5B 6C 7C 8C 9B 10B 11B 12B
13B 14A 15B

1: work cannot be done in closed living systems because pressure and volume are constant
3: ATP hydrolysis relies on pH because an ATP that has a proton has less negative charge and less repulsion. The hydrolysis of ATP is energetically favorable because there are repulsive charges that are relieved when hydrolyzed. True for both ATP and ADP.

6: Skipping a single meal is not a prolonged fast - postabsorptive state
8: hormonal controls regulate metabolism of the entire organism (systemic) and they do so by phosphorylating/dephosphorylating (covalent)
10: short term glucocorticoid exposure causes a release of glucose and lipolysis. However if this glucose is not used for metabolism, it can cause an increase in glucose level which promotes fat storage under insulin stimulation.
13: leptin suppresses orexin which is responsible for alertness so it would cause drowsiness
15: during starvation: glucagon secretion = enzyme phosphorylation/dephosphorylation → glycogen storage halted → proteins broken down → ketones made

Kaplan Biology

Ch 1: The Cell
Eukaryotic cells: nucleus enclosed in membrane; membrane bound organelles
Prokaryotic cells: no nucleus or membrane bound organelles, genetic material in nucleoid

Membrane-Bound Organelles
Nucleus: surrounded by nuclear membrane or envelope (double membrane) that has pores

- Allows compartmentalization of DNA transcription separate from RNA translation
- Nucleolus → rRNA synthesis

Mitochondria: has 2 membranes; outer (barrier between cytosol and inside) and inner with foldings called *cristae* (contains enzymes and molecules for ETC)

- *Intermembrane space* = space between inner and outer membrane
- *Matrix* = space inside inner membrane
- Pumping protons from matrix to intermembrane space generates proton-motive force
- Mitochondria = semi-autonomous: replicate independently of nucleus via **binary fission**; they are examples of **extranuclear inheritance**
- Are thought to have evolved from anaerobic prokaryote engulfing and aerobic prokaryote and establishing symbiotic relationship
- Can kill cells by release of enzymes from ETC → kickstarts **apoptosis**

Lysosomes: contain hydrolytic enzymes to break down substrates from endocytosis and cellular waste products. Release of these enzymes causes **autolysis** and apoptosis. Work in conjunction with **endosomes** which transport, package, sort cell material travelling to and from membrane.

Endoplasmic reticulum (ER): rough ER → ribosomes for protein translation
Smooth ER → no ribosomes; lipid synthesis, drug detox, transport proteins from RER to Golgi

Golgi apparatus: stacked membrane-bound sacs, modification of cell products and sorting

Peroxisomes: contain H_2O_2 for breakdown of long chain fatty acids via B-oxidation

Cytoskeleton
3 components: microfilaments, microtubules, intermediate filaments
Microfilaments: solid polymerized rods of actin, can interact with myosin in muscle contraction, forms the cleavage furrow (role in cytokinesis)

Microtubules: hollow polymers of tubulin, provide pathways for motor proteins kinesin/dynein

- Compose cilia and flagella (9+2 structure)
- Centrioles = organizing centres of MT (9 triplets with hollow structure); migrate to opposite poles of dividing cell and organize mitotic spindle

- Kinetochores = MT emanating from centrioles that attach to chromosomes, pulling sister chromatids apart

Intermediate filaments: filamentous proteins involved in cell-cell adhesion, cell structure integrity and rigidity (e.g. keratin = vimentin, desmin = lamin)

Tissue Formation
4 types of tissues: epithelial, connective, muscle, nervous

Epithelial: line cavities, involved in absorption/secretion, joined to underlying layer of connective tissue called **basement membrane**, constitute **parenchyma** or functional part of an organ (e.g. acid-producing cells in stomach)

- Simple epithelia: one layer of cells
- Stratified epithelia: multiple layers
- Pseudostratified epithelia: looks multiple but really just 1 layer

Cuboidal cells = cube-shaped; *columnar* cells = long, thin; *squamous* cells = flat, scale like

Connective: main contributors to **stroma** or support structure (e.g. bones, cartilage, tendons, ligaments, adipose tissue, blood)

- Cells produce + secrete materials like collagen and elastin to form **extracellular matrix**
- Examples of cells: fibroblasts, chondroblasts, osteoblasts

Classification and Structure of Prokaryotic Cells

3 domains of life: archaea, bacteria and eukarya

Archaea

- Often extremophiles
- Similar to eukaryotes: start translation with Met, associate DNA with histones
- Similar to bacteria: single circular chromosome, divide by binary fission

Bacteria

- Contain cell membrane, cytoplasm and some flagella
- **Mutualistic symbiotes**: both humans and bacteria benefit from relationship
- **Pathogens, parasites**: no benefit to host
- Shapes: cocci (spherical), bacilli (rod-shaped), spirilli (spiral)

Obligate aerobes: need O_2 to survive
Anaerobes: don't need O_2 to survive (can ferment)
Obligate anaerobes: cannot survive around O_2
Facultative anaerobes: toggle between aerobic/anaerobic
Aerotolerant anaerobes: can't use O_2 for metabolism but can survive around it

Prokaryotic Cell Structure

Cell wall: outer barrier, allows mvt of solutes (maintain concentrations)

- Gram +: thick peptidoglycan/lipoteichoic acid cell wall
- Gram -: thin peptidoglycan + outer membrane (of phospholipids and lipopolysaccharides)

Cell membrane: composed of phospholipids, just like eukaryote

envelope

Chemotaxis: to detect chemical stimuli and move toward/ away from them

Prokaryotes have no mitochondria, so they use cell membrane to make ATP. They have ribosomes but different ones (30S, 50S) than eukaryotes (40S, 60S).

Genetics and Growth of Prokaryotic Cells

Binary fission = asexual reproduction in prokaryotes where cell grows inward, divides

Genetic Recombination

Transformation: gets genetic material from environment into host genome

Conjugation: transfer of genetic material from donor male (+) to recipient female (-) by forming a conjugation bridge (e.g. F factor: F+ replicates and donates its copy to F- cell, converting it to F+)

Transduction: requires a *vector* (virus that carries genetic material from one bacterium to another), transfer of genetic material using *bacteriophage* (bacteria virus, infects by tail sheath)

Transposons are genetic elements that can insert or remove themselves from genome

Bacterial Growth

Lag phase: bacteria adapt to new conditions

Exponential phase (aka log phase): growth increases

Stationary phase: less resources, slows reproduction

Death phase: environment cannot support bacteria, so they die

Viruses = obligate intracellular parasites → must replicate using host cell

Viruses = 3 parts: genetic material (ss or ds DNA or RNA), protein coat (aka capsid) and envelope with lipids (very sensitive thus enveloped viruses = easier to kill)

ssRNA viruses may be positive sense (genome directly translated to proteins) or negative sense (RNA replicase makes complementary strand to negative sense RNA which is then translated)

Retroviruses = enveloped, ssRNA viruses, containing *reverse transcriptase* which makes DNA from ssRNA which then integrates into host cell genome

Lytic cycle: virus reproduces until cell lyses; they are termed *virulent*

Lysogenic cycle: virus goes into host genome and replicates until triggered to lytic cycle

Subviral particles = **prions** (infectious proteins that cause misfolding of other proteins) and **viroids** (small pathogens with circular ssRNA that infect plants and silence their genes)

1D 2A 3D 4B 5B 6C 7A 8D 9C 10C 11C 12C
13D 14C 15D

5: mitochondria is single circular chromosome of dsDNA that can replicate during binary fission

8: lysosomes have a single membrane; ribosomes have no membrane (they are in prokaryotes)

13: a bacterial cell that does not rapidly cause a phenotypic change in the rest of colony is likely not F+ so the cell is not able to form a sex pilus for conjugation

15: a virus that requires transport to nucleus to produce viral protein likely requires use of nuclear RNA polymerase to make mRNA for protein translation

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Ch 2: Reproduction
Autosomal cells are **diploid (2n = 46)** while germs cells are **haploid (n = 23)**

Cell cycle
Interphase = G_1, S, G_2 (longest part of cycle, individual chromosomes not visible with light microscopy but in less condensed form of **chromatin** to allow gene transcription)
Cells that do not divide spend time in **G_0** (simply living out its function)

During mitosis, DNA condensed to avoid loss during cell division

G_1 Stage: Presynthetic Gap: cells create organelles, increase in size, quality checkpoint
S Stage: Synthesis of DNA: replicates genetic material: chromosome → 2 identical **chromatids** bound at **centromere** (ploidy doesn't change: still have 46 chromosomes but 92 chromatids)

- Cells entering G_2 have 2x DNA as in G_1

G_2 Stage: Postsynthetic Gap: control checkpoint (check if enough organelles and DNA for division + if DNA replication proceeded correctly)
M Stage: Mitosis: division + cytokinesis (splitting of cytoplasm and organelles in 2 daughter cells)

Control of the Cell Cycle
G_1/S checkpoint: check if DNA is in good enough condition for synthesis (restriction point)

- If not, cell cycle arrest by protein **p53**

G_2/M checkpoint: check if enough organelles + DNA for division + if proper replication occurred

Cyclins and **cyclin-dependent kinases (CDK)** = molecules responsible for cell cycle

- [cyclin] varies through cycle;
- Cyclins bind CDKs = active complex that phosphorylates **transcription factors** that promote transcription of genes required for next stage of cell cycle

Cancer = mutations of *TP53* (when this gene mutated, cell cycle not stopped = accumulation of mutations = uncontrolled cell division = **tumors**)

- **Metastasis** = distant spread of cancerous cells through blood

Mitosis (occurs in somatic cells → 2 identical daughter cells)
1) Prophase: chromatin condenses = chromosomes, centriole pairs in **centrosome** migrate to opposite poles and form **spindle fibers** (microtubules), nuclear membrane dissolves, nucleoli disappear, **kinetochores** appear at centromere (protein attach. points for **kinetochore fibers**)

2 microtubule organizing centers = centrosome and basal body of flagellum or cilium

2) Metaphase: centriole pairs at opposite ends of cell, chromosomes aligned at **equatorial plate**
3) Anaphase: centromeres split, sister chromatids separate and pulled towards opposite poles
4) Telophase: spindle fibers disappear, nuclear membrane reforms, chromosomes uncoil, nucleoli reappear, cytokinesis

Meiosis (occurs in **gametocytes** aka germ cells → 4 nonidentical sex cells aka **gametes**)

Mitosis	Meiosis
1 round replication, 1 round division Ploidy doesn't change (2n → 2n) Homologous chromosomes don't pair No crossing over	1 round replication, 2 rounds of division Ploidy changes (2n → n) Homologous chromosomes pair/align opposite ends Crossing over

Meiosis I (Reductional Division)
Prophase I: tetrads form (pair of homologous chromosomes), crossing over occurs, which explains **Mendel's 2nd law (of independent assortment)** (inheritance of one allele has no effect on likelihood of inheriting certain alleles for other genes)

Metaphase I: homologous chromosomes lined up across from each other at metaphase plate

Anaphase I: homologous pairs separate → called **disjunction** and accounts for **Mendel's 1st law (of segregation)** (paternal homologue separates from maternal homologue, can end up in either daughter cell). **Segregation** = separating 2 homologous chromosomes

Telophase I: nuclear membrane forms, interkinesis (partial uncoil), 2n → n (23)

Meiosis II (Equational Division)
Prophase II: nuclear membrane + nucleoli disappear, centrioles migrate, spindle apparatus forms
Metaphase II: chromosomes align at equatorial plate
Anaphase II: sister chromatids separate and pulled towards opposite sides
Telophase II: nuclear membrane + nucleoli reappear, spindle disappear, **interkinesis** occurs (chromosomes may or may not condense as cell prepares for meiosis II)

The Reproductive System

Sex is determined by 23rd pair of chromosomes (XX = female, XY = male)

X chromosome carries lots of genetic info, mutations in X = **sex-linked** disorders

- Males are **hemizygous** with respect to genes on X since they only have 1 copy
- Thus, if they have disease-causing allele on X they **will** express it, whereas females can be **carriers**

Y = little genetic info, has **SRY (sex-determining region Y)** which codes formation of male gonads

Male Reproductive Anatomy

- **Testes** (gonads in **scrotum**) have **seminiferous tubules** + **interstitial cells (of Leydig)**
- **Sperm** are produced in seminiferous tubules and nourished by **Sertoli cells**
- Cells of Leydig secrete **testosterone** and other male sex hormones (**androgens**)
- Sperm formed pass to **epididymis** where flagella gain motility and stored until **ejaculation**
- During ejaculation, sperm travel through **vas deferens** to **ejaculatory duct** and out through **urethra**
- As sperm pass through tract, they are mixed with **seminal fluid** which is produced by:
    - Seminal vesicles: give fructose to nourish sperm
    - Prostate gland: fluid milky alkaline properties for sperm survival in female
    - Bulbourethral gland: clear viscous fluid during sexual arousal to clean urethra
- **Semen** = sperm + seminal fluid

Acronym for pathway of sperm: SEVE(N) UP

Seminiferous tubules → **E**pididymis → **V**ans deferens → **E**jaculatory duct → **U**rethra → **P**enis

Spermatogenesis (formation of haploid sperm via meiosis)

- Diploid cells = **spermatogonia**
- After S stage = diploid **primary spermatocytes**
- After meiosis I = haploid **secondary spermatocytes**
- After meiosis II = haploid **spermatids**
- Spermatids undergo maturation to form **spermatozoa**

Sperm = head (genetic info) + midpiece (mitochondria → ATP) + flagellum (motility)

- Sperm heads are covered by **acrosome** (derived from Golgi apparatus, needed to penetrate **ovum**)

Female Reproductive Anatomy

- **Ovaries** (gonads) produce estrogen and progesterone; each consists of 1000s of **follicles** (sacs that contain and nourish **ova** - eggs)
- 1 egg **ovulated** per month into **peritoneal sac** → then drawn into **fallopian tube** or **oviduct**, lined with cilia to propel egg to **uterus** → **cervix** → **vaginal canal**

Oogenesis (formation of haploid ovum via meiosis)

- By birth, all of the **oogonia** have undergone DNA replication and are considered **primary oocytes** and are arrested in prophase I
- Once a woman reaches **menarche** (1st menstrual cycle), one primary oocyte per month will complete meiosis I, producing **secondary oocyte** (big cytoplasm) and a polar body
- Secondary oocyte remains arrested in metaphase II and does not continue until fertilized

Oocytes surrounded by **zona pellucida** (mix of glycoproteins that protect oocyte) and **corona radiata** (outside the zona pellucida, layer of cells adhered to oocyte during ovulation)

The ovum contributes nearly everything to zygote (half DNA + all cytoplasm, organelles)

Upon completion of meiosis II, the haploid **pronuclei** of sperm and ovum join = diploid **zygote**

Sexual Development
Before puberty, **hypothalamus** blocks production of **gonadotropin-releasing hormone (GnRH)**

At start of puberty, restriction is lifted, hypothalamus releases GnRH triggering **anterior pituitary gland** to make and release **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** → these hormones trigger production of other sex hormones and maintain reprod. system

Male Sexual Development

- Y chromosome leads to producing androgens (production low during childhood)
- **Testosterone** increases during puberty (maintain reprod. system + 2ndary sex traits + has a negative feedback on hypothalamus and anterior pituitary gland to limit production)
    - **FSH** stimulates Sertoli cells and triggers sperm maturation
    - **LH** causes interstitial cells to produce testosterone

Female Sexual Development

- Ovaries produce estrogens and progesterone
- **Estrogen** secreted in response to FSH, maintains reprod. system + 2ndary sex traits + lead to thickening of lining of uterus (**endometrium**) in preparation of implantation of zygote
- **Progesterone** is secreted by **corpus luteum** (remnant follicle after ovulation) in response to LH - it's involved in *maintaining* the thick endometrium and it's supplied by placenta after 1st trimester of pregnancy

E*strogen* ***e****stablishes and* ***p****rogesterone* ***p****rotects endometrium*
*Note: estrogen can have both positive AND negative feedback effects

Menstrual Cycle
<u>1) Follicular Phase:</u> begins with menstrual flow, higher [GnRH] = increased FSH and LH = production of estrogen = negative feedback = decrease in GnRH, LH, FSH + regrow endometrium

2) Ovulation: peak in estrogen = spike in GnRH, FSH, and LH (surge in LH induces **ovulation**)
3) Luteal Phase: after ovulation, LH causes ruptured follicle to form corpus luteum which secretes progesterone - rise in progesterone = negative feedback = decrease in GnRH, LH, FSH
4) Menstruation: progesterone declines = removes block on GnRH = next cycle can begin

High levels of estrogen and progesterone inhibit GnRH secretion, thus preventing LH and FSH secretion and thus the onset of a new menstrual cycle

Pregnancy: zygote develops into a blastocyst that implants in uterine lining and secretes **human chorionic gonadotropin (hCG)**, which maintains corpus luteum until placenta is independent

Menopause: as woman ages, ovaries less sensitive to FSH and LH = ovarian atrophy, negative feedback removed on FSH and LH = high blood levels

1B 2C 3B 4B 5C 6C 7A 8B 9A 10D 11D 12D 13C 14C 15D

3: the initial connection of the microtubule to the kinetochore occurs in prophase
4: to ensure the labeled deoxyadenine will be incorporated into the **DNA** of one of the daughter cells, it should be inserted before DNA replication has been completed
7: can inhibit cell division during S, prophase, or metaphase
9: the cells are diploid until cytokinesis that happens in telophase I

Ch 3: Embryogenesis and Development

Fertilization

- Occurs in the **ampulla**, widest part of fallopian tube
- Sperm's acrosomal enzymes penetrates corona radiata and zona pellucida of oocyte
- Sperm injects pronucleus after meiosis II done, forms **diploid zygote**
- After penetration of sperm, **cortical rxn** (release of calcium ions) depolarizes membrane of ovum, makes it impenetrable

Twins

- **Dizygotic or fraternal twins**: 2 eggs fertilized by different sperm
- **Monozygotic or identical twins**: 1 egg splits into 2 and then fertilized
    - Incomplete division can cause **conjoined twins**

Cleavage
Process where zygote undergoes fast mitotic cell divisions when moving to the uterus to implant

- **Indeterminate cleavage** results in cells that can still develop into complete organisms
- **Determinate cleavage** means the cells have fates already determined (differentiate)

Blastulation

- After several divisions, embryo becomes **morula** (solid ball of cells)
- Morula undergoes **blastulation** which forms **blastula** (hollow ball of cells with fluid-filled cavity called the *blastocoel*), which consists of *trophoblast cells* and *inner cell mass*
    - **Trophoblast cells** give rise to chorion (extraembryonic membrane that becomes placenta)
    - **Inner cell mass** gives rise to organism itself

Implantation

- Blastula moves through fallopian tube to uterus and burrows into endometrium
- Chorionic villi develop into placenta → support maternal-fetal gas exchange
    - Umbilical vein carries oxygenated blood to embryo
    - Umbilical arteries carry deoxygenated blood to placenta

Gastrulation

- Once cell mass implants, it can begin **gastrulation** (generation of 3 distinct cell layers)
- **Gastrula** is formed by invagination of blastocoel called **archenteron** (develops into gut)
- Opening of the archenteron is the **blastopore**
    - In **deuterostomes** (e.g. humans), the blastopore becomes the anus
    - In **protostomes**, it becomes the mouth

Primary Germ Layers
Ectoderm = epidermis, hair, nails, epithelia of nose, mouth, lens of eye
Mesoderm = muscoskeletal system, circulatory system, digestive and respiratory systems
Endoderm = epithelial linings of digestive, respiratory tracts, pancreas, thyroid, bladder

Differentiation

- **Selective transcription**: when only the genes needed for cell type are transcribed
- **Induction**: ability of one group of cells to influence fate of nearby cells

Neurulation

- Once 3 germ layers formed, **neurulation** (development of nervous system) begins
- Nervous system is derived from ectoderm
- Mesoderm develops a **notochord → neural folds → neural tube**
    - ↓ neural crest cells → ↓ PNS (ganglia, Schwann cells, adrenal medulla)
    - ↓ CNS

IMPORTANT: The adrenal cortex is derived from the mesoderm, but the adrenal medulla is derived from the ectoderm

Teratogens = substances that interfere with development, causing defects or death of embryo

Mechanisms of Development

Specification: cell is reversibly designated to specific cell type, cell can still become any cell type

Determination: commitment of cell to particular function, irreversible

- Can be influenced **morphogens** which cause nearby cells to follow particular pathway

Differentiation: assumes structure and function of cell type

Cells that have not yet differentiated are **stem cells**

Potency

Totipotent = can differentiate into any cell type, like stem cells (primary germ layers + amnion, chorion, placenta)

Pluripotent = cells can differentiate into any cell except those in placenta (primary germ layers)

Multipotent = cells within a particular lineage (e.g. hematopoietic stem cells)

Cell-Cell Communication

Autocrine = signal acts on itself

Paracrine = signal acts on local cells

Juxtracrine = signals don't diffuse but rather stimulate receptors of adjacent cell directly

Endocrine = hormones travel in bloodstream to distant targets

Inducers are commonly **growth factors** (peptides promoting differentiation or mitosis in tissues)

- Only function on specific cell types

Cell Death

Apoptosis: programmed cell death; **apoptotic bodies** digested by other cells, no release

Necrosis: cell death due to injury, internal substances can be leaked

Regeneration: ability of organism to regrow parts of body; stem cells migrate to area for repair

- **Complete regeneration** = tissues replaced with identical tissues
- **Incomplete regeneration** = new tissues are not identical to lost tissue

Senescence = biological aging, result of failure of cells to divide, may be due to shortened **telomeres** (ends of chromosomes)

- Telomeres reduce loss of genetic info and help prevent DNA from unraveling; high [GC]
- *Telomerase* = reverse transcriptase able to synthesize telomeres, preventing senescence, plays a role in cancer

Fetal Circulation

Placenta = organ where nutrient, gas, and waste exchanges occur by diffusion (this requires gradient which means higher partial pressure of oxygen in maternal blood than fetal blood)

It is important maternal and fetal blood do not mix because they can have different blood types

Fetal hemoglobin (HbF) has greater affinity for oxygen than adult hemoglobin (HbA)

Arteries = away and veins = towards HOWEVER exception: **umbilical arteries** carry deoxygenated blood and the **umbilical vein** carries oxygenated blood

3 fetal shunts (since babies in the womb don't use lungs or liver)
Skip Lungs: Foramen Ovule: R atrium → L atrium
Ductus Arteriosus: Pulmonary artery → Aorta
Skip Liver: Ductus Venosus: Umbilical vein → inferior vena cava

Gestation and Birth
1st trimester: major organs develop, brain fairly developed, embryo becomes **fetus** (~8 weeks)
2nd trimester: lots of growth, takes on human appearance
3rd trimester: rapid growth, selective transport of antibodies + less mvt before birth

3 phases of birth
1) Water breaking (amniotic sac breaks)
2) Strong uterine contractions = birth
3) **Afterbirth** (placenta and umbilical cord expelled)

1C 2C 3C 4D 5C 6C 7D 8D 9A 10A 11B 12A 13C 14D 15C

3: while the neural tube forms from ectoderm, the notochord itself is mesodermal
10: if cell determination or differentiation failed, there wouldn't even be anorectal structures, which means the error is most likely due to failed apoptosis

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Ch 4: The Nervous System

Neurons (sensory, motor, or mixed)

- Have nuclei located in the **cell body**, also called the **soma** (ER + ribosomes)
- **Dendrites** emanate from the soma and receive incoming messages from other cells
- **Axon hillock** sums signals and plays role in **action potentials** (aka transmitting electrical impulses down the **axon**)
- Most nerve fibers are insulted by **myelin** to prevent loss of signals + speed
    - Produced by **oligodendrocytes** in CNS; **Schwann cells** in PNS
    - Breaks in myelin sheath = **nodes of Ranvier**
- End of neuron has **nerve terminals** (release **neurotransmitters**)
    - Space between neurons = **synaptic cleft**
    - **Synapse** = nerve terminal + synaptic cleft + postsynaptic membrane
- **Glial cells** support neurons

Astrocytes nourish neurons and form blood-brain barrier
Ependymal cells produce cerebrospinal fluid (shock absorber)
Microglia are phagocytic cells that ingest/break down waste products in CNS

Collection of cell bodies in CNS = nucleus
Collection of cell bodies in PNS = ganglion

Transmission of Neural Impulses
Action potentials = "all or nothing" messages

Resting potential = -70 mV, inside of neuron (-) relative to outside, maintained by K+ and Na+

- K+ leaks out of cell through **potassium leak channels** due to [ ] gradient
    - Cell leaves behind small amount of (-) charge, outside slightly (+)
- K+ will be drawn back in due to (-) charge inside until equilibrium is reached at **equilibrium potential of potassium** (-90 mV)
- Na+ leaks into cell by **sodium leak channels** and the **equilibrium potential of sodium** is ~60 mV

The resting potential is a tug of war! Potassium pulls cell potential toward -90 mV while sodium pulls it towards 60 mV. But neither ion wins - there is a balance reached at around -70 mV which is known as the **resting membrane potential** - it is closer to potassium's equilibrium potential because the cell is slightly more permeable to potassium.

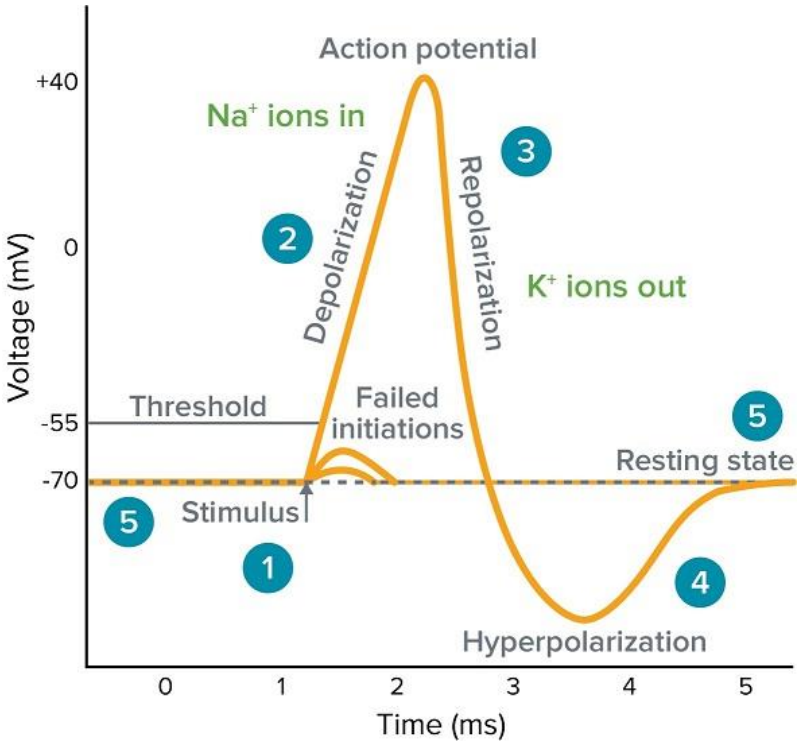
Na^+/K^+ ATPase pumps Na+ and K+ back to where they started (against gradients)

The Axon Hillock
Excitatory input causes **depolarization** (raising membrane potential V_m from resting potential)
Inhibitory input causes **hyperpolarization** (lowering membrane potential from resting potential)

If axon hillock receives enough excitatory input to depolarize to the **threshold** value (-55 to -40 mV), an action potential is fired.

Summation = additive effect of multiple signals (excitatory + inhibitory)

- **Temporal summation** = multiple signals integrated in short time
- **Spatial summation** = additive effects based on # and location of incoming signals



- Depolarization = sodium channels open = Na+ influx = membrane potential becomes more (+) and finally sodium channels inactivated ~+35 mV
    - Na+ channels **closed** (before cell reaches threshold), **open** (threshold to ~35 mV) and **inactive** (35 mV to resting potential)
- After depolarization, K+ efflux favored to restore (-) membrane potential = **repolarization** or hyperpolarization, which makes neuron refractory to another action potential
    - **Absolute refractory period** - no amount of stimulation can cause another a.p.
    - **Relative refractory period** - *greater than normal* stimulation required for a.p.
- Na+/K+ ATPase restores resting potential, as well as Na+ and K+ gradients

Impulse propagation = the action potential travels down the axon as proximal Na+ channels open and depolarize and induce nearby channels to open too and K+ channels hyperpolarize

- After the a.p. has fired in one segment, that segment is refractory, which makes the movement of the a.p. unidirectional towards the nerve terminal

Speed of propagation depends on:
1) Length of axon: increased length = slower conduction (more resistance)
2) Cross-sectional area of axon: greater area = faster propagation (less resistance)

Saltatory conduction = signal "hops" from node to node

Increased intensity of a stimulus DOES NOT result in increased potential difference but rather increased frequency of firing

Synapse
Effector = neuron that signals to gland or muscle rather than another neuron

Neurotransmitters (NTs)

- NTs are stored in vesicles in the nerve terminal
- When a.p. reaches nerve terminal, voltage-gated calcium channels open = influx of calcium
- Increased intracellular [calcium] = fusion of membrane-bound vesicles with cell membrane = exocytosis of NTs

3 ways to get rid of NTs in the synaptic cleft
1) Break down by enzymes (e.g. AChE or *acetyl-cholinesterase* breaks down Ach)
2) Reuptake carriers, back into presynaptic neuron (e.g. 5-HT, DA, NE)
3) Diffusion out of synaptic cleft

Organization of Nervous System
Sensory neurons: transmit sensory info from receptors to CNS (AFFERENT FIBRES)
Motor neurons: transmit motor info from CNS to muscles and glands (EFFERENT FIBRES)
Interneurons: between other neurons, located mainly in CNS, reflexes

In the CNS:
White matter (myelinated axons) and **grey matter** (unmyelinated cell bodies and dendrites)

- Brain = white deep/grey outer
- Spinal cord = white outer/grey deeper

In the PNS:
Somatic nervous system = sensory and motor neurons, regulates mvt of muscles, joints
Autonomic nervous system = regulates involuntary (e.g. heartbeat, respiration, digestion)

Difference between SNS and ANS is that the peripheral component of ANS contains 2 neurons:

- A motor neuron in the SNS goes directly from spinal cord → muscle
- In the ANS, 2 neurons work to transmit messages from spinal cord: 1st = **preganglionic neuron**, 2nd = **postganglionic neuron**
    - The soma of the preganglionic neuron is in CNS and its axon travels to ganglion in PNS

2 Subdivisions of ANS
Parasympathetic nervous system = decrease heart rate, increase digestion

- Ach is responsible for parasympathetic responses, is released by both preganglionic and postganglionic neurons

Sympathetic nervous system = increase heart rate, decrease digestion, blood → muscles

Reflexes
Monosynaptic reflex arc: single synapse between sensory neuron and motor neuron (e.g. knee-jerk reflex)
Polysynaptic reflex arc: at least 1 interneuron between sensory and motor neurons (e.g. withdrawal reflex to stepping on nail)

1C 2C 3D 4C 5A 6C 7B 8D 9D 10A 11B 12B
13B 14A 15B

Ch 5: The Endocrine System

Mechanisms of Hormone Action
At target tissue, **hormones** bind receptors + induce change in gene expression or cell function.

Classification of Hormones by Chemical Structure
Peptide Hormones (e.g. ADH, insulin)

- Cleaved during posttranslational modifications, smaller units activated in Golgi apparatus
- Packaged in vesicles, released by exocytosis
- Charged (cannot cross membrane) thus must bind to extracellular receptor
    - However, water soluble thus can travel in bloodstream without carriers
- 1st messenger that triggers **signaling cascade**
- Common 2nd messengers = cAMP, IP3, calcium
- Rapid but short-lived effect

Steroid Hormones (e.g. estrogen)

- Derived from cholesterol, produced by gonads and adrenal cortex
- Can easily cross cell membrane, receptors usually intracellular (cytosol) or intranuclear
    - Not water-soluble, required protein carriers in blood stream (bound = inactive)
- Direct action on DNA
- Slower but longer-lived effect

Amino Acid-Derivative Hormones (e.g. epinephrine, norepinephrine, thyroxine)

- Derived from 1 or 2 amino acids, with few additional modifications
- **Catecholamines** (E, NE) use GPCR, thyroid hormones bind intracellularly

Direct hormones act directly on target tissue
Tropic hormones require intermediary, only stimulate other endocrine glands (e.g. GnRH and LH)

Mechanism of action: peptide hormones stimulate a receptor (usually GPCR) and affect levels of secondary messengers (commonly cAMP), to initiate a signal cascade. Steroid hormones bind to a receptor, induce conformational change, and regulate transcription at level of DNA,

Endocrine Organs and Hormones

Hypothalamus

- Above pituitary gland (hypo controls pituitary through paracrine release), below thalamus
- Roles: appetite and satiety, sleep-wake cycles, etc.
- Release of hormones regulated by **negative feedback**
- Pituitary gland has anterior and posterior component, each interact differently with hypo

Interactions with Anterior Pituitary

Hypothalamus secretes compounds → **hypophyseal portal system** → anterior pituitary → bind to receptors in anterior pituitary = stimulate release of other hormones

Hormones released by hypothalamus + tropic hormone released by anterior pituitary (response):
GnRH →↑ FSH and LH
GHRH → ↑GH
TRH → ↑TSH
CRF → ↑ACTH
Exception: prolactin-inhibiting factor (PIF aka dopamine) = ↓ prolactin secretion

Each tropic hormone = release of hormone from endocrine gland with negative feedback
e.g. CRF causes release of ACTH which will cause adrenal cortex to increase level of **cortisol** secreted in blood. Cortisol had negative feedback on anterior pituitary and hypothalamus.

Anterior Pituitary (FLAT PEG) → FLAT = tropic, PEG = direct

Interactions with Posterior Pituitary

The posterior pituitary does NOT receive tropic hormones through hypophyseal portal system. Rather, neurons in hypothalamus send axons down pituitary stalk directly into posterior.

- **Oxytocin** = ↑ uterine contraction, ↑ lactation, ↑ bonding (*positive feedback*)
- **ADH** aka **vasopressin** = secreted in response to increased osmolarity or low blood volume
  - ↑ reabsorption of water in collecting ducts of kidneys (↑ water permeability)
  - ↑ blood volume and pressure
  - ↓ H_2O output in urine

Thyroid

- Controlled by TSH from anterior pituitary

1) Sets basal metabolic rate (by release of triiodothyronine T_3 and thyroxine T_4)

- T_3 and T_4 made in **follicular cells** → ↑ basal metabolic rate
- High levels of thyroid hormones = negative feedback = ↓ TSH and TRH
- **Hypothyroidism** = not enough thyroid hormones = ↓ body temp, ↓ heart rate, ↑ weight
- **Hyperthyroidism** = excess thyroid hormones = ↑ body temp, ↑ heart rate, ↓ weight

2) Calcium homeostasis (by calcitonin)

- Calcitonin made in **C-cells** (aka **parafollicular cells**)
- Secreted in response to high [Ca^{2+}] in blood: ↓ plasma Ca^{2+} by ↑ Ca^{2+} excretion from kidneys, ↓ Ca^{2+} absorption from gut, ↑ Ca^{2+} storage in bones

Parathyroid Glands

- Produces **parathyroid hormone (PTH)**
- PTH = antagonist of calcitonin: ↑ plasma Ca^{2+} by ↓ Ca^{2+} excretion by kidneys, ↑ Ca^{2+} absorption from gut, ↓ Ca^{2+} storage in bones (aka ↑ bone resorption)
- PTH also activates **vitamin D** required for absorption of calcium in gut

Adrenal Cortex

- Adrenal glands located on top of kidneys, each consists of a cortex and a medulla
- Each part, the cortex and the medulla, secrete different hormones
- The adrenal cortex secretes **corticosteroids**: **glucocorticoids, mineralocorticoids, cortical sex hormones**

1) Glucocorticoids

- Steroid hormones that regulate glucose levels
- 2 main glucocorticoids: **cortisol** and **cortisone** = ↑ gluconeogenesis = ↑ blood glucose
    - They also ↓ protein synthesis and ↓ inflammation/immune response
- These hormones are under control of ACTH from anterior pituitary (ACTH = release)

2) Mineralocorticoids

- Used in salt and water homeostasis: mainly **aldosterone**
- ↑ Na reabsorption in distal convoluted tubule & collecting duct of nephron, water follows sodium = ↑ blood volume and pressure (DOES NOT AFFECT OSMOLARITY)
- Also ↓ reabsorption of potassium and H+ ions = ↑ output in urine
- Aldosterone Is under the control of the **renin-angiotensin-aldosterone system**:
    - Decreased blood pressure causes **juxtaglomerular cells** to release **renin**
    - Renin cleaves inactive **angiotensinogen** to active **angiotensin I**
    - ACE in lungs converts angiotensin I to **angiotensin II**
    - Angiotensin II stimulates adrenal cortex to release aldosterone
    - Once blood pressure is restored, negative feedback on renin

NOTE: ADH affects osmolarity, aldosterone does not!!!

ADH increases free water absorption, increasing volume but decreasing plasma osmolarity. Aldosterone increases salt reabsorption but also increases volume because with every sodium that is absorbed a water molecule follows. Therefore, it doesn't affect osmolarity, but it does increase total amount of salt in the blood.

3) Cortical Sex Hormones

- Include **androgens** and **estrogens**

Adrenal Medulla

- Secretes the **catecholamines** (E and NE), which are amino acid-derivative hormones
- Effects centered on fight-or-flight response:
    - E = ↑ glycogenolysis and ↑ basal metabolic rate
    - Both hormones = ↑ heart rate, dilate bronchi, ↑ blood to muscles, lungs, heart

Important distinction: cortisol = long-term (slow) stress response, while catecholamines = short-term (fast) stress response

Pancreas

- Has both exocrine function (pancreatic enzymes) and endocrine function
- Endocrine: small clusters of hormone-producing cells grouped into **islets of Langerhans**
- Islets have **alpha (α)**, **beta (β)**, and **delta (δ) cells**
    - α-cells secrete **glucagon**
    - β-cells secrete **insulin**
    - δ-cells secrete **somatostatin**

1) Glucagon (α-cells): secreted during fasting, when low [glucose] = ↑ CATABOLIC PROCESSES
    ↑ degradation of protein and fat
    ↑ gluconeogenesis

2) Insulin (β-cells): secreted when high [glucose] = ↑ ANABOLIC PROCESSES
    ↑ fat and protein synthesis
    ↑ storage of glucose in glycogen

Excess insulin = **hypoglycemia**
Insufficient insulin or insensitivity = **diabetes mellitus** (glucose unable to enter cells)

- In kidneys, excess glucose = nephron can't reabsorb it = ↑ glucose in urine
    - Results in **polyuria** (increased frequency of urination) and increased thirst
    - **Type I (insulin-dependent):** destruction of β-cells = insufficient production
    - **Type II (non-insulin-dependent):** resistance to insulin

3) Somatostatin (δ cells): inhibitor of both insulin and glucagon secretion, secreted when high blood glucose and amino acid concentrations, produced by hypothalamus

Gonads

- Secrete either testosterone (testes), or estrogen and progesterone (ovaries) in response to gonadotropins (LH and FSH)

Pineal Gland

- Located deep within brain, secretes **melatonin** (involved in **circadian rhythms**)

Other Organs

- Gastrointestinal peptides include secretin, gastrin, cholecystokinin
- The kidneys produce **erythropoietin** = ↑ erythrocyte production in response to low O_2
- The heart releases **atrial natriuretic peptide (ANP)** to regulate salt and water balance
    - When excess volume in atria, ANP released = ↑ Na excretion = ↑ urine
- The thymus releases **thymus** important for T-cell development and differentiation

1C 2D 3A 4C 5B 6C 7C 8B 9C 10D 11B 12B
13C 14C 15D

Ch 6: The Respiratory System

Anatomy (Passage of Air)
Nares → nasal cavity (filtered by mucous membranes and hair) → **pharynx → larynx → trachea → bronchi → bronchioles → alveoli**

Pharynx = common passage for air and food
Larynx = only air; the **glottis** (opening of larynx) is covered by **epiglottis** while swallowing

Alveoli = site of gas exchange, covered with surfactant (prevents alveoli from collapsing) and capillaries

Lungs are in the **thoracic cavity**, and are surrounded by a membrane called **pleurae**

- **Visceral pleura** = surface adjacent to lung
- **Parietal pleura** = outer part

The lungs do not fill passively and require skeletal muscle to generate the negative pressure for expansion, the most important muscle being the **diaphragm** (thin muscle that separates thoracic cavity from abdominal cavity)

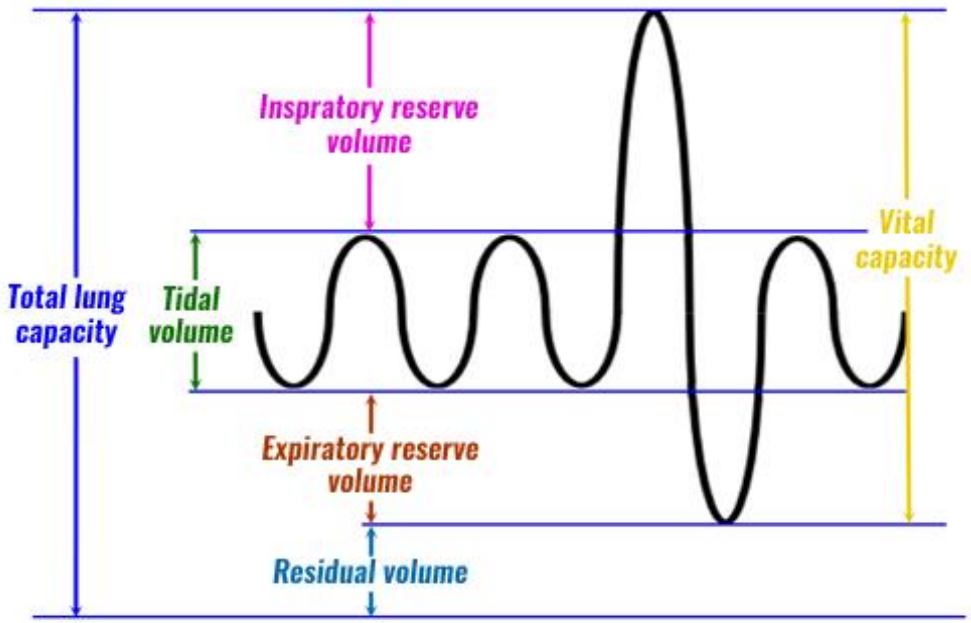
*The diaphragm is under somatic control, while breathing is under autonomic control

Inhalation (active process) = external intercostal muscles contract; diaphragm contracted
Lung expanded = negative pressure = air rushes in

Exhalation (passive process) = external intercostal muscles relax; diaphragm relaxed
Lung deflate = pressure increases = air pushed out (could also be active using internal intercostal muscles to push out air)

Lung Capacities and Volumes

Total lung capacity (TLC): the max volume of air in the lungs (~6-7L)
Residual volume (RV): the max volume of air in the lungs when one exhales completely
Vital capacity (VC): the difference between min and max volume of air in lungs (TLC - RV)
Tidal volume (TV): the volume of are inhaled or exhaled in a normal breath
Expiratory reserve volume (ERV): volume of additional air that can be forcibly exhaled
Inspiratory reserve volume (IRV): volume of additional air that can be forcibly inhaled



Regulation of Breathing

- Regulated by neurons in medulla oblongata, contains **chemoreceptors**

↑ [CO_2] aka **hypercarbia** or **hypercapnia** = ↑respiratory rate (to get rid of CO_2)
↓ [O_2] aka **hypoxemia** = ↑ ventilation (air in/out)

Functions of the Respiratory System

1) Gas Exchange

- **Pulmonary arteries**: bring deoxygenated blood from right ventricle of heart to lungs
- **Pulmonary veins:** bring oxygenated blood from lungs to left atrium
- Driving force for gas exchange = pressure differential of gases (when arrives at alveoli; blood has low partial pressure of oxygen and high partial pressure of CO_2)

2) Thermoregulation

- Vasodilation = allow heat to dissipate
- Vasoconstriction = conserve thermal energy

3) Immune Function

- Nasal cavity has hairs (trap) + enzyme **lysozyme** (attacks peptidoglycan wall of gram +)
- **Mucociliary escalator** propels mucus to oral cavity
- Lungs (mainly alveoli) contain immune cells like:
    - **Macrophages** engulf and digest pathogens
    - **Mast cells** have antibodies on surface: reactive to substance (also cause allergy!)

Bicarbonate Buffer System

CO_2 (g) + H_2O (l) → H_2CO_3 (aq) → H+ (aq) + HCO_3^- (aq)

- Body attempts to maintain pH 7.35-7.45
- pH lower = **acidemia** (higher [H+]) = ↑ respiratory rate to ↓ CO_2 (left shift)
- pH higher = **alkalemia** (lower [H+]) = ↓ respiratory rate to ↑ CO_2 (right shift)

1D 2D 3C 4B 5C 6C 7D 8D 9B 10D 11B 12C 13A
14B 15C

5: the intrapleural space (between parietal and visceral) is normally collapsed; however introduction of fluid (e.g. blood) or air can cause it to expand and to cause lung collapse
8: spirometry cannot determine residual volume so it cannot measure total lung capacity - also increased stiffness of lungs = decrease residual volume
14: with decreased recoil, the patient will have difficulty exhaling completely, increasing RV. Also decreased recoil would increase lung capacity, decrease oxygen, increase carbon dioxide

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Ch 7: The Cardiovascular System

Pulmonary circulation: right side of heart accepts deoxygenated blood from body by **venae cavae** and sends to lungs via *pulmonary arteries*
Systemic circulation: left side of heart accepts oxygenated blood from lungs by **pulmonary veins** and sends to body via *aorta*

Ventricles = more muscular than atria

Atria are separated from ventricles via **atrioventricular valves**
RAT LAB mnemonic → **R**ight **A**trium = **T**ricuspid valve
Left **A**trium = **B**icuspid valve

Semilunar valves
Pulmonary valve = separates right ventricle from pulmonary circulation
Aortic valve = separates left ventricle from aorta

Electrical Conduction of the Heart ("**S**tab **A** **B**ig **P**ickle")
SA node → **A**V node → **B**undle of His → **P**urkinje fibers

SA node = 60-100 bpm (without neurological input)
Parasympathetic signals slow heart rate by **vagus nerve**

Contraction
Systole = AV valves closed, ventricles pump blood
Diastole = semilunar valves closed, blood from atria fills ventricles

Cardiac output = total blood volume pumped by a ventricle in 1 minute

$$CO = HR \times SV$$

where HR = heart rate in bpm and SV = stroke volume or volume of blood pumped per beat

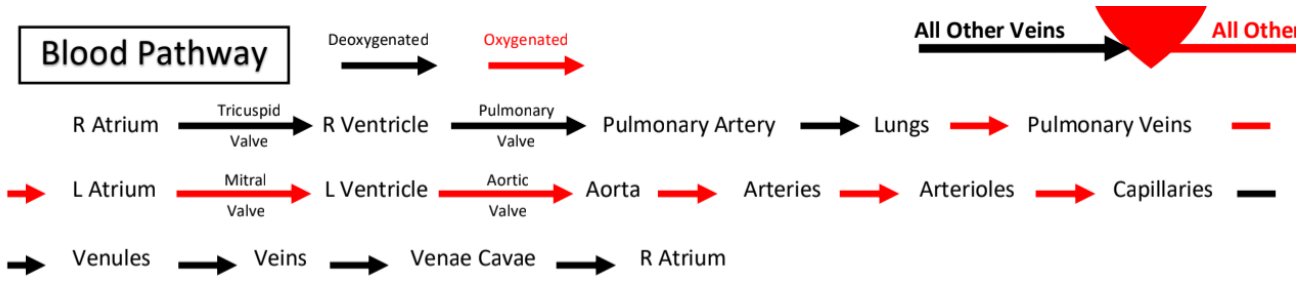
Vasculature
- Blood travels *away* from heart in **arteries → arterioles → capillaries → venules → veins**
- All blood cells lined with endothelial cells - release chemicals to help vasodilate/constrict
- Arteries have more smooth muscle than veins

Arteries
- Thick, highly muscular, elastic = recoil + propel blood forward

Capillaries
- Single endothelial cell layer, RBC pass in single file, thin wall for easy gas exchange

Veins
- Thin, inelastic, less smooth muscle than arteries = less recoil
- Can stretch to hold large amounts of blood
- Unlike arteries, less recoil so must have **valves** to push blood forward (close to prevent blood from flowing back) + surrounded by **muscle** to push blood toward heart

Circulation



3 portal systems where blood passes 2 capillary beds in series before returning to heart:
1) Hepatic portal system: blood travels from capillaries of gut → capillaries of liver
2) Hypophyseal portal system: blood travels from capillaries in hypothalamus → capillaries in anterior pituitary
3) Renal portal system: blood travels from glomerulus to vasa recta through efferent arteriole

Blood (connective tissue)
Plasma = liquid portion of blood: mix of nutrients, salts, gases, hormones, blood proteins
Cellular portion of blood = **erythrocytes, leukocytes, platelets**

- All blood cells formed from hematopoietic stem cells, which originate in bone marrow

1) Erythrocytes (RBC)

- Each RBC = millions of **hemoglobin** that bind 4 oxygen molecules each
- Biconcave (easier travel through tiny capillaries + increase surface area)
- No mitochondria or organelles; recycled by cells in liver and spleen
- **Hematocrit** = % of blood sample that is RBC

2) Leukocytes (WBC)

- **Granulocytes (neutrophils, eosinophils,** and **basophils)**
  - Have granules with contents that attack invaders via exocytosis
  - Inflammatory response
- **Agranulocytes (lymphocytes** and **monocytes)**
  - **Lymphocytes** = specific immune response
  - **Monocytes** = digest foreign matter (if leave bloodstream and enter organ, they are called **macrophages**)
    - E.g. in CNS, called **microglia**
    - E.g. in skin, called **Langerhans cells**
    - E.g. in bone, called **osteoclasts**

3) Thrombocytes (Platelets)

- Cell fragments released from cells in bone marrow
- Blood clotting

Erythropoietin = secreted by kidney, stimulates RBC development
Thrombopoietin = secreted by liver and kidney, stimulate platelet development

Blood Antigens

- Surface proteins on RBC, 2 major families: **ABO antigens** and **Rh factor**

1) ABO Antigens

Blood Type	Genotype(s)	Antigens produced	Antibodies produced	Can donate to…	Can receive from…
A	I^AI^A, I^Ai	A	Anti-B	A, AB	A, O
B	iI^BI^B, I^Bi	B	Anti-A	B, AB	B, O
AB	I^AI^B	A and B	None	AB	Everybody
O	ii	None	Anti-A and -B	Everybody	O only

O = universal donor (will not induce ABO-related hemolysis since no antigens produced)
AB = universal recipients (can receive from all blood types since no antibodies produced)

2) Rh Factor
- Rh^+ (D allele present - only 1 needed since dominant) vs Rh^- (D allele absent)

Physiology of the Cardiovascular System
Blood Pressure
- Measure of force per unit area, measured with **sphygmomanometer**
- Ratio of systolic (ventricular contraction) to diastolic (ventricular relaxation) pressures
    - Normal blood pressure = between 90/60 and 120/80

$$\Delta P = CO \times TPR$$

where ΔP is the pressure differential across the circulation, CO is the cardiac output and TPR is the total peripheral (vascular) resistance.

Atrial natriuretic peptide (ANP) = hormone that helps lose salt in nephron, with loss of fluid

Oxygen = carried by hemoglobin
Carbon dioxide = mainly in blood as bicarbonate HCO_3^-

Bicarbonate Buffer: CO_2 (g) + H_2O (l) → H_2CO_3 (aq) → H+ (aq) + HCO_3^- (aq) (*carbonic anhydrase*)
- **Bohr effect:** ↓ in hemoglobin's affinity for oxygen due to ↓ pH or ↑ $PaCO_2$ or ↑ temp
- These triggers (increased P_aCO_2, increased [H+], decreased pH) = right shift in oxyhemoglobin dissociation curve
    - Left shift = higher affinity
    - Right shift = lower affinity
- These triggers are associated with oxygen demand: high rate of cellular metabolism = increased CO_2 production = allows oxygen to be unloaded at tissues

e.g. If individual hyperventilates, will blow off more CO_2 = shift to left = increased pH

Fluid Balance: 2 opposing pressures (**Starling forces**);
1) **Hydrostatic pressure** = pushes fluid out of vessels
2) **Osmotic pressure** = pulls fluid back into vessels

At arteriole end, hydrostatic pressure (pushing fluid out) > osmostic pressure (drawing fluid in)
At venule end, hydrostatic pressure <<< osmotic pressure
Accumulation of excess fluid in interstitium = **edema**

Coagulation
- When endothelium of blood vessel damaged, collagen and **tissue factor** exposed
- When platelets come into contact with exposed collagen, they sense the injury
- Response = release contents, **coagulation factors** sense tissue factor, initiate cascade
- End of cascade = activate **prothrombin → thrombin** which converts **fibrinogen → fibrin**

- Blood clots broken down by **plasmin** generated from **plasminogen**

1C 2C 3C 4A 5A 6C 7D 8C 9A 10C 11B 12D
13D 14A 15C

11: Plasma proteins like albumin play an important role in generating osmotic pressure. This allows water that is displaced at the arterial end of the capillary bed by hydrostatic pressure to be reabsorbed at venule end. Loss of plasma proteins = decrease in plasma oncotic pressure

14: Cardiac conduction starts at SA node is located at top of right atrium, continues down to AV node, which is between the 2 AV valves, then down to bundle of his located within the wall of the ventricles

14: Greatest amount of resistance provided by arterioles since they are highly muscular and have ability to contract and dilate in order to affect blood pressure

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Ch 8: The Immune System

Structure of the Immune System
innate immunity = defenses always active against infection, but can't target specific invaders (aka **nonspecific immunity** - skin, mucus, stomach acid, tears)
Adaptive immunity = defenses that target a specific pathogen (aka **specific immunity**), slower to act but can maintain immunological memory of an infection to be able to mount faster attack in subsequent infections

Anatomy
Bone marrow = site of immune cell production (B- and T-)
Lymph nodes = filter lymph, site where immune responses are mounted
Thymus = site of T-cell maturation
Spleen = storage for blood, filters blood and lymph

Adaptive Immunity
Humoral immunity: centers on antibody production by B-cells

- **B-lymphocytes (B-cells):** made and mature in bone marrow, activated in spleen and lymph nodes. Express antibodies on cell surface.
- **Antibodies**: 2 light chains, 2 heavy chains (held tg by disulfide and noncovalent bonds)
- **Opsonization:** antibodies mark pathogens for destruction
- **Agglutination:** pathogens clump together into insoluble complexes that can be digested
- **Hypermutation:** mutation of the antigen binding site on the antibody
- **Memory B-cells:** lie in lymph node, waiting to be exposed to the same antigen

Cell-mediated (cytotoxic) immunity: center on T-cells which respond to cells infected by antigen

- **T-lymphocytes (T-cells):** made in bone marrow, mature in thymus, facilitated by peptide hormone *thymosin*. Kill infected cells.
- **Positive selection:** only mature T-cells can respond to cells presenting MHC
- **Negative selection:** apoptosis in T-cells that are reactive
- **Helper T-cells:** T_h or CD4+. Coordinate immune system by secreting **lymphokines** which recruit other immune cells to mount an immune response. Deficiency of these in **HIV**
- **Cytotoxic T-cells:** T_c or CD8+. Inject toxic chemicals in virally infected cells = apoptosis
- **Suppressor or regulatory T-cells:** T_{reg}. Downregulate immune response, defective T-cells can cause autoimmune disease
- **Memory T-cells:** wait to be exposed to antigen

Hematopoietic stem cells form the leukocytes: granulocytes and agranulocytes
Granulocytes = neutrophils, eosinophils, basophils
Agranulocytes = lymphocytes, monocytes (phagocytic cells in blood, macrophages in tissues)

Innate Immune System (Nonspecific Immunity)

Non-Cellular Innate Defenses:

- **Skin:** physical barrier, secretes antibacterial enzymes like **defensins**
- **Mucus:** on mucus membranes, traps pathogens, propelled upwards by *mucociliary escalator*
- **Lysosomes**: antibacterial enzyme in saliva and tears
- **Complement***:* punches holes in cell walls of bacteria, making them osmotically unstable
- **Interferons**: produced by virally infected cells, prevent viral replication and dispersion

Cellular Innate Defenses:

- **Macrophages:** digest pathogens from outside and present them on MHC II molecules;
    - **MHC I** = present in nucleated cells; endogenous pathway = present antigen from inside to cytotoxic CD8+-T cells
    - **MHC II** = present in professional antigen-presenting cells (macrophages, dendritic cells), exogenous pathway = present antigen from outside to helper CD4+-T cells
- **Natural killer cells:** activated by virally infected cells that have no or less MHC
- **Granulocytes:**
    - **Neutrophils:** activated by bacteria; phagocytosis
    - **Eosinophils:** activated by parasites and allergens; release histamine
        - Histamine = inflammatory mediator = vasodilation and increased leakiness of blood vessels = immune cells can move out of blood stream into tissue
    - **Basophils and mast cells:** activated by allergens

Active immunity = the immune system is stimulated to produce antibodies against pathogen
Passive immunity = transfer of antibodies to an individual (transient, don't last forever)

Lymphatic System

- Circulatory system, made of **lymph nodes** and one-way vessels that carry **lymph** (fluid)
- Connects to cardiovascular system via *thoracic duct* in posterior chest
- Allows mounting of immune responses
- Equalizes fluid distribution: lymphatic vessels drain excess fluids in tissues
- Also transports fats packed into *chylomicrons* in **lacteals** (small lymphatic vessels)

1A 2B 3B 4A 5D 6C 7A 8D 9C 10A 11C 12C
13A 14C 15A

12: Clonal selection = only antibodies or T-cells with receptors specific to antigen are activated
14: B cells = humoral immunity

Ch 9: The Digestive System

Intracellular digestion: oxidation of glucose and fatty acids for energy
Extracellular digestion: process by which nutrients are obtained from food, occurs in alimentary canal (mouth to anus)

Mechanical digestion: physical breakdown of food
Chemical digestion: enzymatic cleavage of chemical bonds, such as peptide bonds (proteins) or glycosidic bonds (starches)

Absorption = transport of products from digestive tract → blood

Digestive Pathway: oral cavity (mouth) → pharynx → esophagus → stomach → small intestine → large intestine → rectum → anus

Enteric nervous system = collection of neurons that govern the function of the GI system, trigger **peristalsis**, can function independent of brain and spinal cord but heavily regulated by ANS

Ingestion and Digestion
Oral Cavity

- Mastication begins physical digestion
- *Salivary amylase* (digests starch) and *lipase* (digests lipids) start chemical digestion
- Food is formed into a **bolus** and swallowed

Pharynx

- Connects to the esophagus but also the larynx, covered by the epiglottis

Esophagus

- Top third is made of skeletal muscle and is under somatic (voluntary) control
- Bottom third is made of smooth muscle and is under autonomic (involuntary) control
- The middle and bottom are under autonomic control
- Carries out peristalsis to propel bolus to stomach, passage regulated by sphincters

Stomach

- Located under diaphragm, pH = 2, four parts:
  - Fundus and body (contain gastric glands)
  - Antrum and pylorus (contain pyloric glands)
- Secretory cells that line the stomach:
  - Mucous cells: produce bicarbonate-rich mucus, protects stomach wall from acid
  - Chief cells: secrete pepsinogen (inactive), protease that is activated in acid
  - Parietal cells: secrete HCl and intrinsic factor (glycoprotein that helps in the proper absorption of vitamin B_{12})
  - G-cells: found in the pyloric glands, secrete gastrin (peptide hormone that tells parietal cells to secrete ↑HCl and increases gastric motility)

After food digested in the stomach, called chyme and exits via *pyloric sphincter* → duodenum
Chyme = acidic, semifluid mixture of digested food

There are a few substances absorbed directly from stomach (aspirin and alcohol) but stomach is mainly for digestion.

Small Intestine = duodenum, jejunum, ileum
1) Duodenum (pH = 8.5, where the majority of chemical digestion and some absorption occurs)

Enzymes in Duodenum
Disaccharidases: brush-border enzymes that break down maltose, lactose, sucrose
Aminopeptidase: removes N-ter amino acid from peptide
Dipeptidase: cleave peptide bonds of dipeptides
Enteropeptidase: activates *trypsinogen* → *trypsin* and *procarboxypeptidases*
*Trypsin and carboxypeptidases are secreted in pancreas

Hormones in Duodenum
Secretin: peptide hormone, increases pancreatic secretions, reduces HCl secretion and motility

Cholecystokinin (CKK): peptide hormone, causes release of bile and pancreatic juices

- Bile (released from gallbladder) emulsifies fats and cholesterol into micelles
- Pancreatic juices = mix of enzymes in bicarbonate-rich alkaline solution, bicarbonate helps neutralize acidic chyme
- CKK promotes satiety

Absorption and Defecation

2) Jejunum and Ileum

- Involved in absorption of nutrients, lined with **villi** and each with **microvilli**
- **Villi** has *capillary bed (*absorb water-soluble nutrients) and *lacteal* (lymphatic channels that takes up fats for transport into lymphatic system)
- Absorption (epithelial cells → blood) of simple sugars by secondary active transport and facilitated diffusion → go to liver via hepatic portal circulation
- Fats don't enter bloodstream; they are packaged into chylomicrons and enter lymphatic circulation through lacteals, which converge, enter venous circulation via thoracic duct
- Vitamin absorption
    - Fat-soluble: ADEK → dissolve in chylomicrons, enter lacteals
    - Water-soluble: BC → enter plasma

3) Large Intestine

- Absorbs H_2O + feces
- **Cecum:** accepts fluid from small intestine via **ileocal valve** + site of attachment appendix
- **Colon** = ascending, transverse, descending; absorbs H_2O and salts, concentrates material to form **feces**
- **Rectum**

- **Gut bacteria**: produce vitamin K and biotin (vitamin B7)

Accessory Organs of Digestion (Origin = Endoderm)

Pancreas

- Release of insulin, glucagon, and somatostatin
- Made of **acinar cells** that produce pancreatic juices containing bicarbonate, *pancreatic amylase*, *pancreatic peptidases* (*e.g. carboxypeptidase*) and *pancreatic lipase*

Liver

- Receives blood from abdominal portion of digestive tract via **hepatic portal vein**
- Makes bile (which can be stored in gallbladder or secreted into duodenum)
- Processes nutrients (e.g. takes up excess sugar to make glycogen, stores fats as TGs)
- Detox of compounds (e.g. ammonia, alcohol, medications)

Bile = bile salts (amphipathic molecules that emulsify fat) + pigments (especially bilirubin from breakdown of hemoglobin) + cholesterol

Jaundice of skin may occur due to excess bilirubin that was unprocessed by liver

Gallbladder

- Located just beneath liver, stores and concentrates bile
- Common site of cholesterol or bilirubin stone formation

1B 2B 3B 4D 5C 6B 7B 8B 9B 10C 11A 12B
13A 14C 15A

13: While the capillaries from the intestine come together to form the portal vein, which drains to the liver (water-soluble compounds), the lacteals come together to form the thoracic duct (bypass liver). Therefore, fat-soluble compounds do not pass through the liver before reaching the right heart.

6: Sucrase is a brush-border enzyme, not in the salivary glands.
15: A patient with liver failure would not be able to convert ammonia to urea so they would have high [ammonia] and low [urea]. The liver also synthesizes album and clotting factors so liver failure would mean low concentrations of both in the blood.

Ch 10: Homeostasis

The Excretory System
Urine flow: Bowman's space → proximal convoluted tube → descending loop of Henle → ascending loop of Henle → distal convoluted tube → collecting duct → renal pelvis → ureter → bladder → urethra

Kidney: composed of cortex (outermost layer) and medulla, functional unit = **nephron**

- Produces urine which dumps into **renal pelvis → ureter → bladder → urethra**

Renal Portal System (blood flow): renal artery → afferent arterioles → glomeruli → efferent arterioles → vasa recta → renal vein

Osmoregulation
1) Filtration: mvt of solutes from blood → filtrate (Bowman's capsule)
fluid flows from glomerulus into Bowman's space because the hydrostatic pressure in the glomerulus >> than in Bowman's space and counteracts the pressure due to higher blood osmolarity so net mvt is fluid from glomerulus → Bowman's space

- Buildup of urine could disrupt this flow by increasing the hydrostatic pressure in Bowman's space to the point that filtration can't occur because there is too much pressure opposing mvt of fluid into nephron
- The filtrate that crosses from the blood in glomerulus to nephron has no cells or proteins due to filter size (will not cross if larger than glomerular pores)
- Filtrate is isotonic to blood so no swelling of capsule or capillaries occurs
- Blood remaining after filtrate passed into nephron will then continue to efferent arterioles and empty into vasa recta

2) Secretion: mvt of solutes from blood → anywhere besides Bowman's capsule
3) Reabsorption: mvt of solutes from filtrate → blood

Bladder
Detrusor muscle: muscular lining of bladder, parasympathetic control
Internal urethral sphincter: smooth muscle, involuntary control
External urethral sphincter: skeletal muscle, voluntary control

Micturition reflex = urge to pee (urge to relax your external urethral sphincter)

Nephron
Horizontal (Bowman, proximal, distal) = *keep what the body needs, lose what it doesn't*
Vertical (Loop of Henle, collecting duct) = *concentrate urine to conserve water*

1) Proximal convoluted tubule: reabsorption of glucose, amino acids, soluble vitamins, H_2O and salts + secretion of H+, K+, NH_3 and urea.

2) Descending limb of the loop of Henle: permeable to water, NOT salt: as the loop descends into the osmotically concentrated renal medulla, water is reabsorbed from filtrate into vasa recta

3) Ascending limb of loop of Henle: permeable to salt, NOT water

Countercurrent multiplier system: ascending and descending tubules = opposite directions to maximize reabsorption of water (passive reabsorption of water in descending due to active reabsorption of salts in ascending)

At the beginning of loop of Henle, filtrate is isotonic to interstitium. At the end, the filtrate is hypotonic to the interstitium (since so much salt being pumped out). So there is a slight degree of dilution of the urine that happens at the ascending portion.

4) Distal convoluted tubule: responds to aldosterone = ↑ Na reabsorption
Also site of excretion of waste products, like PCT

5) Collecting duct: responsive to both aldosterone and ADH, reabsorption of water

- If body well hydrated, will remain impermeable to water and salt
- If body is in conservation mode, ADH and aldosterone will ↑ reabsorption of water = less urine output = more retention = more concentrated urine

Function of Excretory System
Aldosterone = steroid hormone secreted by adrenal cortex in response to decreased blood pressure. Increases Na+ reabsorption in the distal convoluted tubule and collecting duct, thereby increasing H2O reabsorption. Result: ↑BP but no change in blood osmolarity

ADH = peptide hormone synthesized by hypothalamus and released by posterior pituitary in response to high blood osmolarity. ↑ water reabsorption = lower blood osmolarity

Key concept: ADH only governs water reabsorption and thus results in lower blood osmolarity. Aldosterone causes both salt and water reabsorption and does not change blood osmolarity.

Osmoregulation
Osmotic pressure - sucking pressure that draws water into blood vessels
Oncotic pressure = attributed to dissolved proteins specifically

The excretory system also plays a role in acid-base balance:

- When blood pH too low, ↑ secretion of H+ and ↑ reabsorption of bicarbonate
- When blood pH too high, ↑ reabsorption of H+ and ↑ secretion of bicarbonate

Skin (derived from ectoderm)

- From innermost to outermost: **hypodermis** (**subcutaneous** layer), **dermis**, **epidermis**

1) Epidermis - multiple layers called **strata**
From innermost to outermost ("**C**ome, **L**et's **G**et **S**un **B**urned)

- **Stratum basale**: proliferation of stem cells → **keratinocytes**
- **Stratum spinosum:** Langerhans cells
- **Stratum granulosum:** keratinocytes die
- **Stratum lucidum:** on thick, hairless skin
- **Stratum corneum:** multi thin flattened keratinocytes

Other Cells of the Epidermis
Melanocytes = cell type derived from neural crest cells, found in stratum basale

- Produce **melanin** = pigment to protect skin from DNA damage by UV radiation
- Skin color is caused by varying levels of activity of melanocytes

Langerhans cells = macrophages, can present antigens to T-cells to activate immune system

2) Dermis: upper layer = **papillary layer**, below = **reticular layer**
Sweat glands, blood vessels, and hair follicles originate in the dermis

Sensory receptors in dermis:

- **Merkel cells (discs)** = deep pressure and texture
- **Free nerve endings** = pain
- **Meissner's corpuscles** = light touch
- **Ruffini endings** = stretch
- **Pacinian corpuscles** = deep pressure and vibration

3) Hypodermis: fat and fibrous tissue, connects skin to body

Thermoregulation

- Sweating = cooling (evaporation of water from skin absorbs body heat)
- Piloerection = warming (hairs stand up on end, trap layer of heat near skin)
- Shivering = warming (energy from ATP → thermal energy)
- Vasodilation/vasoconstriction = cool/warm

1B 2A 3A 4A 5C* 6D 7A 8C 9B 10A 11C 12D
13C 14D 15C

2: sodium is actively transported out PCT and DCT bc concentration of sodium is higher outside of nephron than inside, so it requires active transport. In the inner medulla, passive diffusion of sodium but thick = active transport of sodium out of filtrate
5: ADH increases water permeability of collecting duct; aldosterone increases Na reabsorption from DCT and collecting duct
9: the filtrate is hypotonic to blood before it passes through the collecting duct where it becomes **hypertonic to blood** (because becomes so concentrated)
14: aldosterone serves to increase reabsorption of sodium while promoting excretion of H+ and K+ ions.
15: excess acetylcholine = activation of parasympathetic neurons = increased urination and increased sweating

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Ch 11: The Muscoskeletal System

Types of Muscle

Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Striated	Striated	Nonstriated
Voluntary (somatic)	Involuntary (autonomic)	Involuntary (autonomic)
Multinucleated	1-2 nuclei per cell	1-2 nuclei per cell
Ca^{2+} required for contraction	Ca^{2+} required for contraction	Ca^{2+} required for contraction
No myogenic activity	Myogenic activity	Myogenic activity

Myogenic activity = can contract without nervous input

Different types of fibers in skeletal muscle:
Red fibers: slow twitch, high myoglobin, oxidative phosphorylation, contract slowly but can sustain activity
White fibers: fast twitch, less myoglobin, contract rapidly but fatigue quickly

Microscopic Structure of Skeletal Muscle
Sarcomere

- Basic contractile unit of skeletal muscle
- Made of **actin** (thin filament) associated with proteins **troponin** and **tropomyosin** and **myosin** (thick filament)

Parts of the Sarcomere

Z = end of sarcomere (end of alphabet)
M = middle of sarcomere (middle of myosin filaments)
I = thin filaments only
H = thick filaments only
A = all of the thick filament, overlapping or not

Structure of Myocytes

Sarcomeres are attached end-to-end to form **myofibrils** arranged in parallel which are surrounded by covering called **sarcoplasmic reticulum (SR)** - a modified version of endoplasmic reticulum which has a high [Ca^{2+}] concentration.

The cell membrane of myocytes is the **sarcolemma** which can propagate action potentials and distribute it to all sarcomeres in a system using **transverse tubules (T-tubules)** that are perpendicular to the myofibrils.

A muscle is composed of parallel myocytes and can be called **muscle fibres**.

Muscle Contraction

1) Initiation

- Starts at **neuromuscular junction** where nervous system communicates with muscles via **motor (efferent) neurons**
- Signal travels down efferent neuron where Ach is released into synapse and binds receptors on sarcolemma, causing depolarization
- Depolarization spreads down to T-tubules and triggers release of Ca^{2+} from SR
- Ca^{2+} bind to troponin and trigger change in conformation of tropomyosin
- This change exposes **myosin-binding sites** of actin

2) Shortening of the Sarcomere

- Myosin heads bind exposed sites and form actin-myosin cross bridges where myosin pulls on actin, drawing thin filaments towards M line

In more detail…

- Resting state = ATP on myosin hydrolyzed, leaving ADP and Pi
- Ca^{2+} binds to troponin; myosin binds to actin
- Power stroke occurs; sarcomere contracts, ADP and Pi dissociate from myosin
- New ATP binds myosin = detach from actin

When a sarcomere contracts, both H-zone and I-zone shorten, while A-zone is the same.

3) Relaxation

- Ach degraded in synapse by *acetylcholinesterase* = calcium release ceases, sites covered
- ATP binds myosin = detachment from actin, sarcomere returns to original width

Stimulation, Summation and Muscle Fatigue

- Muscle cells, like neurons, exhibit all-or-nothing response. Max response = when all fibers within a muscle are stimulated to contract simultaneously.

Simple Twitch

- Response of single muscle fiber to brief stimulus above threshold
- Latent period = time between reaching threshold and contraction (time that action potential spreads and calcium is released from SR)

Summation and Tetanus

- Frequent, prolonged simple twitches (summation) so that muscle cannot relax = tetanus

Oxygen Debt and Muscle Fatigue

- Creatine phosphate = transfer of phosphate from ATP→creatine during rest, ATP reserve
- Myoglobin = heme-containing protein that is a muscular oxygen reserve

The Skeletal System

Axial skeleton = skull, vertebral column, ribcage, hyoid bone
Appendicular skeleton = bones of limbs, pectoral girdle, and pelvis

Bone Composition

Bone = connective tissue, derived from mesoderm, harder than cartilage but lightweight

- Compact bone: dense, strong
- Spongy bone: lattice-like structure of bony points known as trabeculae
- Bone marrow: red = hematopoietic cells; yellow = fat
- Long bone: has shafts called diaphysis that swell at each end to form metaphyses and terminate in epiphyses - contain epiphyseal (growth) plate (cartilaginous structure, growth halted during puberty)
- Periosteum: connective tissue surrounding long bone, protects it, attaches muscles
- Bone Matrix: *osteons* are the structural units, each contains circles of bony matrix called lamellae surrounding Haversian channels (longitudinal) and Volkmann's channels (transverse). Between the circles are small spaces called lacunae which contain osteocytes. The lacunae are interconnected by tiny channels called canaliculi that allow exchange of nutrients and wastes between osteocytes and the channels.

Tendons: attach muscle to bone
Ligaments: attach bone to bone

Bone Remodeling

- Osteoblasts build bone, while osteoclasts (macrophages) resorb it
- During formation, calcium and phosphate obtained from blood
- During resorption, these ions are released back into blood

- **Parathyroid hormone (PTH)** = peptide hormone, promotes resorption = ↑ calcium and phosphate in blood
    - **Vitamin D** also promotes resorption (to allow new, stronger bones to form)
- **Calcitonin** = peptide hormone, promotes bone formation = ↓ calcium in blood

Cartilage

- Consists of firm, elastic matrix called **chondrin** secreted by **chondrocytes**
- Difference from bone is that cartilage = avascular, not innervated
- Fetuses = mainly cartilage, until bones form from cartilage (*endochondral ossification*) and from undifferentiated embryonic connective tissue (*intramembranous ossification*)

Joints and Movement

- **Immovable joints** = bones are fused together to form **sutures**
- **Movable joints** = allow bones to move relative to one another, strengthened by **ligaments**, and consist of a **synovial capsule**
    - **Synovial fluid** = secreted by **synovium**, lubricates joints

Classifications of Muscles by Types of Movements
Flexor = decreases angle of joint (e.g. biceps)
Extensor = increases angle (e.g. triceps)
Abductor = moves party of body away from midline
Adductor = moves part of body toward midline

1D 2A 3D 4C 5A 6C 7C 8C 9B 10D 11D 12D 13D 14B 15C

2: the A band has some overlapping thin and thick filaments, but it represents myosin only
7: white fibers do not use aerobic respiration, they are fast twitching too
8: synovial fluid lubricates the mvt but does not stop the bones from contacting one another. The articular surfaces of the bones are covered with a layer of smooth articular cartilage.

Ch 12: Genetics and Evolution
Definitions
Incomplete dominance = red (RR) x white (rr) = pink (Rr)
Penetrance: proportion of individuals in population carrying allele who express the phenotype (full penetrance = 100% of individuals with the allele express it, high, reduced, low, non)
Expressivity: varying phenotypes despite identical genotypes

- If expressivity is constant, then all individuals with given genotype have same phenotype
- If expressivity is variable, then same genotype may have different phenotypes

Genetic leakage: flow of genes between species, can yield **hybrid** offspring
Genetic drift: changes in gene pool due to chance

Founder effect: Bottlenecks that suddenly isolate a small population; inbreeding.

Increased diversity = increased fitness of population (and vice versa)

Mendel's Laws

1) Law of Segregation: An organism has two alleles for each gene, which segregate during Anaphase I. Because of this, gametes carry only one allele for a trait.

- Anaphase I: homologous chromosomes pulled to opposite sides

2) Law of Independent Assortment: The inheritance of one allele does not influence the probability of inheriting a given allele for a different trait (except for linked genes).

- Prophase I: recombination that happens in tetrads

Experiments to Support DNA as Genetic Material

- **Griffith:** Demonstrated transformation. Heat-killed smooth (virulent) strain of bacteria still transformed rough strain into smooth.
- **Avery-MacLeod-McCarty:** Degradation of DNA led to a cessation of bacterial transformation. Degradation of proteins did not.
- **Hershey-Chase:** Confirmed DNA is the genetic material because only radiolabeled DNA could be found in bacteriophage-infected bacteria.

We saw nucleotide mutations or point mutations (e.g. silent, missense, nonsense, frameshift)

Chromosomal Mutations

- **Deletion mutations** = large segment of DNA lost
- **Duplication mutations** = segment of DNA copied multiple times in genome
- **Inversion mutations** = segment of DNA reversed within chromosome
- **Insertion mutation** = segment of DNA moved from one chromosome to another
- **Translocation mutation** = segment of DNA from one chromosome swapped with segment of DNA from another chromosome

Analytical Approaches in Genetics
P generation: PP x pp = 100% Pp
F generation: Pp x Pp = 25% PP, 50% Pp, 25% pp (1:2:1 distribution of genotypes and 3:1 distribution of phenotypes)

Test cross: an organism with unknown genotype is crossed with homozygous recessive organism to identify unknown parental genotype using phenotypes of resulting offspring

E.g. Parental: Px x pp, where x = unknown
If x = P, then PP x pp = 100% Pp (purple)
If x = p, then Pp x pp = 50% Pp (purple), 50% pp (white)

Dihybrid cross: e.g. TtPp x TtPp = 9:3:3:1 ratio

Gene Mapping

- The further apart 2 genes are, the more likely that there is a point of crossing over, called a chiasma, between them
- Recombination frequency: likelihood that 2 alleles are separated from each other during crossing over

Hardy-Weinberg Principle

- Allele frequency = how much an allele appears in a population

- If a population meets certain criteria (aimed at a lack of evolution), then the allele frequencies will remain constant;
    - The population is very large (no genetic drift)
    - There are no mutations that affect the gene pool
    - Mating between individuals in the population is random (no sexual selection)
    - There is no migration of individuals into or out of the population
    - The genes in the population are all equally successful at reproducing
- If all these conditions are met, the population is in Hardy-Weinberg equilibrium

Some Important Equations

$p + q = 1$ (combined allele frequencies = 100%)

$p^2 + 2pq + q^2 = 1$

where p^2 is the frequency of homozygous dominant genotype

$2pq$ is the frequency of the heterozygous dominant genotype

q^2 is the frequency of homozygous recessive genotype

The sum of $p^2 + 2pq$ is the frequency of the dominant *phenotype*

Evolution

Natural selection = certain traits possessed by individuals within species help those individuals to have greater reproductive success, thus passing those traits to the offspring. The tenets are:

1) Organisms produce offspring, few of which can survive
2) Chance variations within individuals in a population are heritable
3) Individuals with greater favorable variations are more likely to survive and reproduce

This level of reproductive success = fitness

Modern synthesis model = mutation or recombination results in change that is favorable to organism's reproductive success, that change is more likely to pass on to next generation - termed differential reproduction. The populations evolve over time - not the individuals.

Inclusive fitness: measure of organism's success in the population, based on # of offspring but also on ability to care for that number of offspring

Punctuated equilibrium: considers evolution to be a very slow process with intermittent rapid bursts of evolutionary activity.

Modes of Natural Selection

Stabilizing selection = keeps phenotypes in narrow specific range, excluding extremes
e.g. normal birth weight is optimal, too large or too little won't survive

Directional selection = moves average phenotype towards extreme
e.g. only the colonies resistant to antibiotic will survive

Disruptive selection = 2 extreme phenotypes selected over the norm
e.g. only birds with large and small beaks survive since they can eat large and small seeds

- Possible due to **polymorphisms** = differences in form between members of population

Adaptive radiation = rapid rise of different species from a common ancestor, each has a niche

Speciation

- **Species** = largest group of organisms capable of breeding to form fertile offspring
- Formation of new species through evolution is called **speciation**
- If we took 2 population from same species and separated them geographically for a long period of time, eventually when we put them back together, they wouldn't be able to interbreed - they would be considered 2 separate species. This is called **isolation**.
- **Prezygotic mechanism** prevents formation of zygote completely
    - Temporal isolation (breeding at different times),
    - Ecological isolation (living in different niches)
    - Behavioral isolation (lack of attraction between members)
    - Reproductive isolation (incompatibility of reproductive anatomy)
    - Gametic isolation (intercourse can occur, but fertilization cannot)
- **Postzygotic mechanism** allows for gamete fusion but yield either nonviable or sterile offspring
    - Hybrid inviability
    - Hybrid sterility
    - Hybrid breakdown (first generation offspring are viable and fertile, second generation inviable or infertile)

Patterns of Evolution