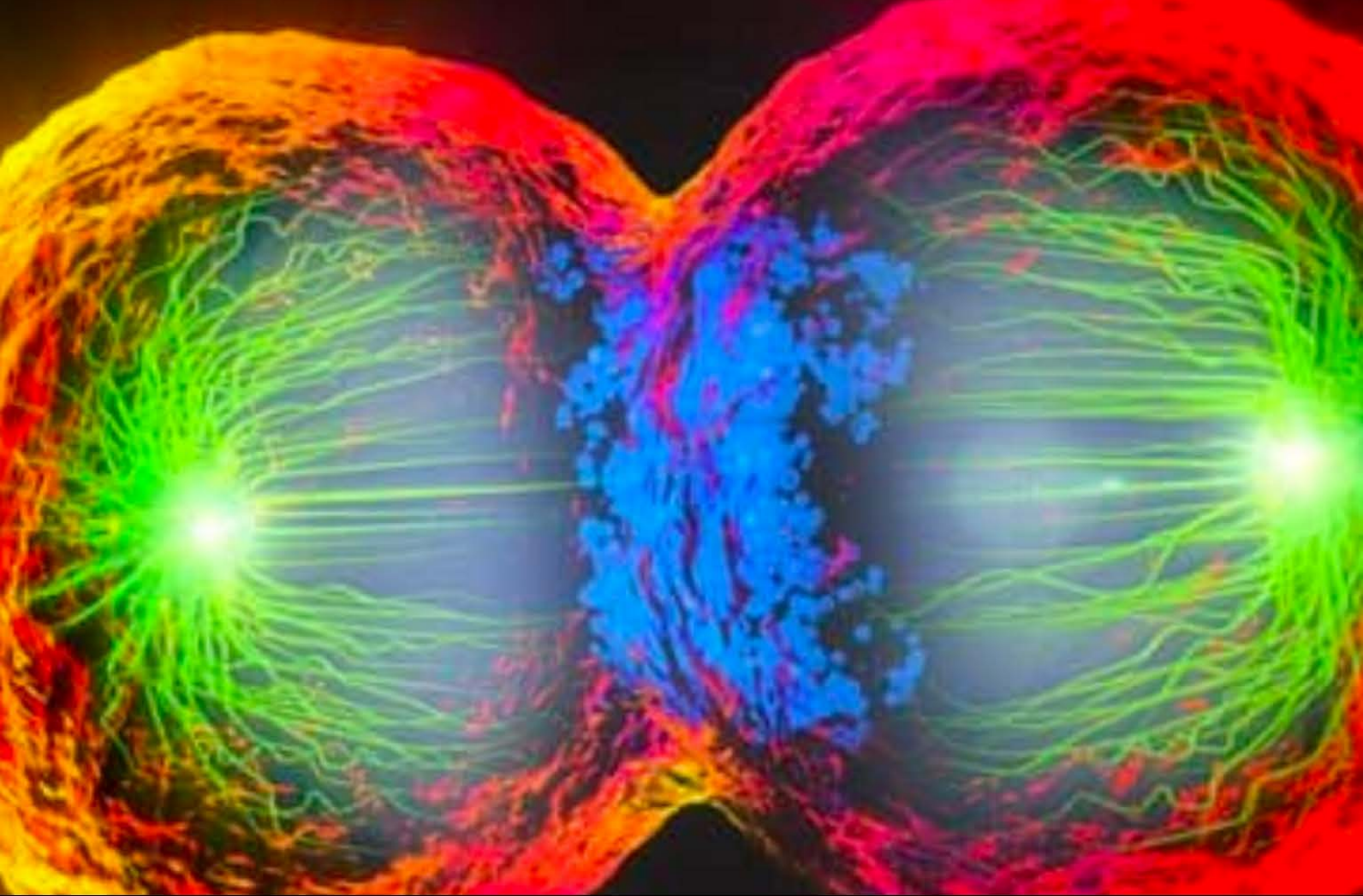


CELLULAR & MOLECULAR BIOLOGY

NOTES

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT



MEDICAL NOTES

(MBBS, MD, MBChB, USMLE, PA, & Nursing)

Anatomy, Physiology, Pathophysiology, Pathology, Histology & Treatments

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Table Of Contents:

What's included: Ready-to-study summaries of cellular & molecular biology presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your ipad or tablet PC.

Free bonuses: 3x Metabolism & Respiration Chapters from Guyton Textbook of Medical Physiology.

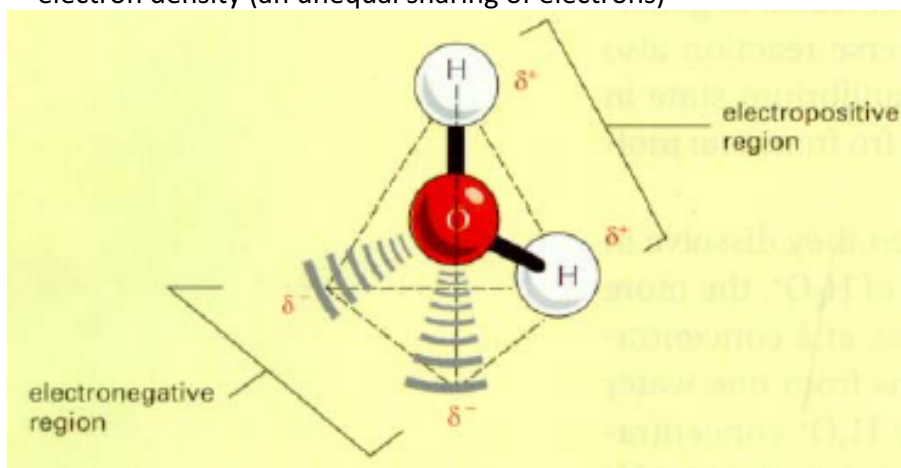
File List:

- The Biological Elements
- The Molecular Building Blocks of the Cell
- Cells Basics
- The Cell Membrane & Transport
- Cellular Signalling
- The Cell Cycle & Division
- Cellular Fate
- Mutation, Cell Death & Ageing
- Very Basic Intro to Microbial Life
- Epithelial Tissues
- Glandular Epithelia & Epithelial Membranes
- Connective Tissue
- Muscle & Nervous Tissue
- Membrane Action Potentials
- Neurotransmission & Receptors
- **Free Bonuses - Metabolism & Respiration Chapters from Guyton Textbook of Medical Physiology:**
 - Metabolism of Carbohydrates & the formation of ATP
 - Lipid Metabolism
 - Protein Metabolism

Essentials of Biochemistry The 'biological elements'

Water:

- Polar covalent bonds
 - When a covalent bond is formed and there is an unsymmetrical distribution of electron density (an unequal sharing of electrons)



- Hydrogen Bonding in H₂O:
 - Due to the polarity of water molecules, there is an electrostatic attraction between molecules.
- Hydrophilic Molecules: are always either polar or ionic (charged) and therefore readily dissolve in water.
- Hydrophobic Molecules: generally either contain non-polar bonds and are usually insoluble in water. (eg. hydrocarbons)
- Hydrogen Ion Exchange: H⁺ ions can spontaneously move from one water molecule to another, creating 2 ionic species: the hydronium ion (H₃O⁺) and hydroxyl ion (OH⁻).

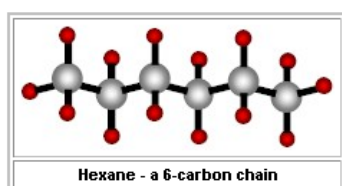
Weak Non-Covalent Bonds:

- Hydrogen bonds
- Hydrophobic Forces
- Ionic Bonds
- Van der Waals Forces

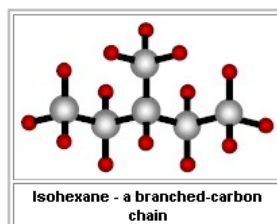
Basic Carbon Chemistry:

- Has 4 valence electrons
- Cannot form ionic bonds
 - Rather, it forms covalent bonds through the sharing of its electrons.
- Has the ability to bond to either itself or four other atoms.
- May form chain, ring & branched structures.

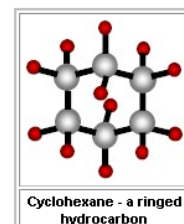
chains:



branched chains:



rings:



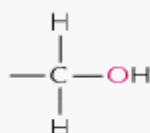
- May form either single bonds (C-C), double bonds (C=C) or triple bonds (C≡C).
- May form either saturated or non saturated molecules
 - **Saturated:** contains the maximum number of Hydrogen atoms possible.
 - **Unsaturated:** due to double/triple carbon bonds, there are less than the maximum possible number of hydrogens.

C-O Compounds:

- Oxygen atoms in carbon-bonded molecules will always have **2 bonds (C=O or C-O-H)** as well as **2 unshared electron pairs**.
- **Functional groups:**

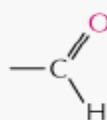
Many biological compounds contain a carbon bonded to an oxygen. For example,

alcohol

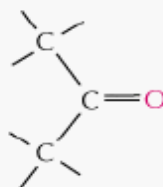


The -OH is called a **hydroxyl** group.

aldehyde

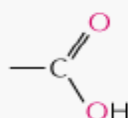


ketone



The C=O is called a **carbonyl** group.

carboxylic acid



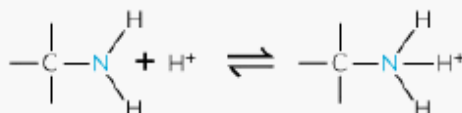
The -COOH is called a **carboxyl** group. In water this loses an H⁺ ion to become -COO⁻.

C-N Compounds:

- **Amines** and **amides** are important C-N compounds.
- **Nitrogen** (in neutral compounds) will always have **3 bonds + 1 unshared electron pair**.

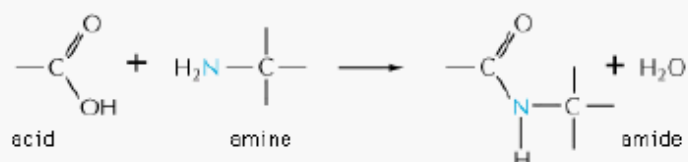
- **Amines:**

Amines in water combine with an H^+ ion to become positively charged.



- **Amides:**

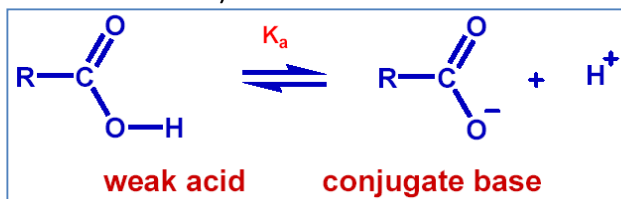
Amides are formed by combining an acid and an amine. Unlike amines, amides are uncharged in water. An example is the peptide bond that joins amino acids in a protein.



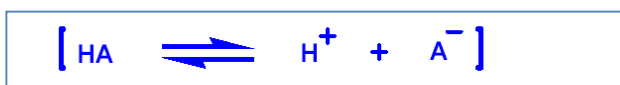
pKa, Amino Acids & Their Ionisation.

Acids: compounds that yield hydrogen ions in a polar solvent (eg. H₂O)

Eg. Carboxylic Acid: (common weak acid)



Also written as:



➤ Note: A weak acid will have an equilibrium favouring the left side.

Weak or Strong?

K_a: The equilibrium constant

- Gives the relative strength of an acid
- Determined by how much of the dissolved compound dissociates into a c.base and a H⁺.
- Is a measure of an acid's propensity to donate H⁺ ions.
- Used to determine whether the acid's functional group will be predominantly protonated/deprotonated in a certain pH.
- Calculated by:

$$K_a = \frac{[\text{RCOO}^-] [\text{H}^+]}{[\text{RCOOH}]} \quad \sim 10^{-3} \text{ to } 10^{-5} \text{ for most simple RCOOH}$$

- The larger the K_a the stronger the acid

pK_a: A more convenient number to remember:

- Calculated by:

$$\text{pK}_a = -\log_{10} K_a \quad \sim 3 \text{ to } 5 \text{ for most simple RCOOH}$$

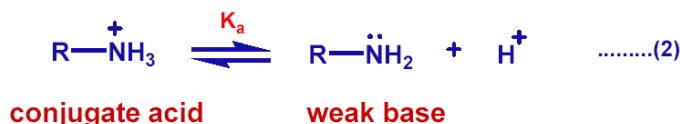
- **The smaller the pK_a the stronger the acid (ie. the weaker the conjugate base) (similar scaling to pH)**
- If the pH of an acid solution corresponds to that acid's pK_a then that acid will be half ionised. (half in protonated form + half in deprotonated form)

Bases: Compounds that accept hydrogen ions in a polar solvent (H₂O)

Eg. Amines R-NH₂ (common weak base)

- Have 2 lone electrons that attract H⁺ ions.

For **weak bases** (most commonly amines RNH₂, general representation B:) it is conventional to quote the pK_a of the conjugate acid.



Also written as:



Weak or Strong?

K_a: The equilibrium constant

- Gives the relative strength of a base
- Determined by how much of the dissociated ions reassociate into the c.acid.
- Is a measure of a base's propensity to accept H⁺ ions.
- Used to determine whether the base's functional group will be predominantly protonated/deprotonated in a certain pH.
- Calculated by:

$$K_a = \frac{[\text{RNH}_2][\text{H}^+]}{[\text{RNH}_3^+]} \quad \sim 10^{-9} \text{ to } 10^{-11} \text{ for most simple RNH}_2$$

- The smaller the K_a the stronger the base.

pK_a: A more convenient number to remember:

- Calculated by:

As before

$$pK_a = -\log_{10} K_a \quad \sim 9 \text{ to } 11 \text{ for most simple RNH}_2$$

- **The larger the pK_a the stronger the base (ie. the weaker the conjugate acid) (similar scaling to pH)**
- If the pH of a base solution corresponds to that base's pK_a then that base will be half ionised. (half in protonated form + half in deprotonated form)

pK_a and pH

Rules of thumb:

- Predicting ionisation states of weak acids and bases at particular pH's, on the basis of their pK_a's.

(using Le Chatelier's Principle of Equilibrium)

-Acids.

- 1) When an acid is placed at a pH that is more acidic than its pK_a the functional group will be predominantly in the protonated form.
- 2) When an acid is placed at a pH that is more basic than its pK_a, the functional group will be predominantly in the deprotonated form.

-Bases.

- 1) When a base is placed at a pH that is more acidic than its pK_a, the functional group will be predominantly in the protonated form.
- 2) When a base is placed at a pH that is more basic than its pK_a, the functional group will be predominantly in the deprotonated form.

(same concept for both acids and bases)

- Remember physiological pH is 7.4

Henderson-Hasselbach Equation:

For the ionisation of a weak acid ($HA \rightleftharpoons H^+ + A^-$):

$$pH = pK_a + \log_{10} ([A^-]/[HA])$$

(For the ionisation of a weak base ($BH^+ \rightleftharpoons B: + H^+$) the corresponding equation is: $pH = pK_a + \log_{10} ([B:]/[BH^+])$)

- Simply sub in the pH & the pK_a and the ratio of protonated to non-protonated species.

Rules of thumb:

- **For Weak acids:**



- If pH > pK_a by 1 unit: 10 deprotonated : 1 protonated
- If pH > pK_a by 2 units: 100 deprotonated : 1 protonated
- If pH > pK_a by 3 units: 1000 deprotonated : 1 protonated

- **For Weak bases:**

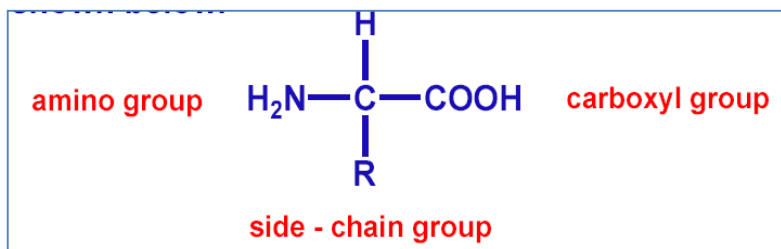


- If pH < pK_a by 1 unit: 10 protonated : 1 deprotonated
- If pH < pK_a by 2 units: 100 protonated : 1 deprotonated
- If pH < pK_a by 3 units: 1000 protonated : 1 deprotonated

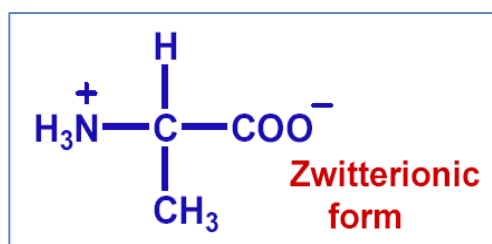
(Buffers: solutions that maintain a near constant pH on addition of a base or an acid)

Amino Acids

- The building blocks of proteins
- Have 2 ionisable groups attached to the central carbon.
 - An acidic carboxyl group –COOH
 - And a basic amino group –NH₂



- Each group has its own pK_a
 - ➔ -COOH pK_a = 2-3
 - ➔ -NH₂ pK_a = 9-10
 - ➔ Therefore at different pHs, one group may be ionised while the other may be protonated and vice versa.
 - When the pH = the average of the 2 pK_as, both groups will be ionised (acid – deprotonated & base – protonated) and the amino acid as a whole is known to be in **zwitterionic form**.



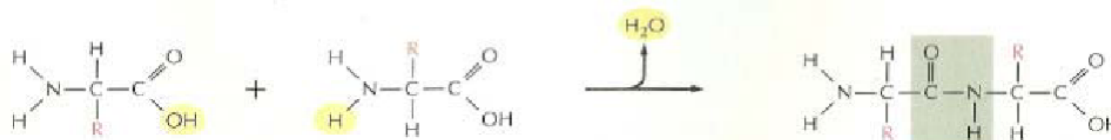
Protein Side-Chains

- Proteins are long **polymers** formed by the linkage of the **carboxyl group (COOH)** of one amino acid to the **amino group (NH₂)** of the next.
 - This forms amide linkages (**peptide**) bonds.
 - H₂O is produced as a by-product

PEPTIDE BONDS

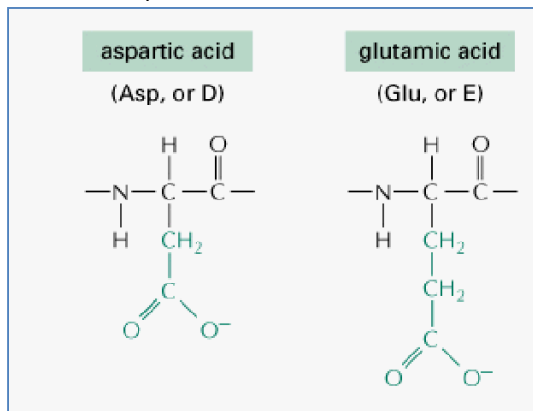
Amino acids are commonly joined together by an amide linkage, called a peptide bond.

The four atoms in each peptide bond (gray box) form a rigid planar unit. There is no rotation around the C–N bond.



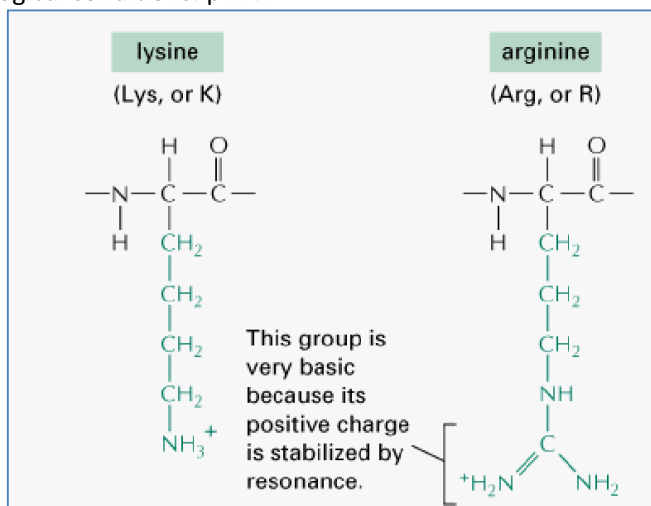
- **Acidic Side Chains:**

- Have pK_a values of 3-5 and are therefore deprotonated (negatively charged) at physiological conditions: pH7.4



- **Basic Side Chains:**

- Have pK_a values of 10ish and are therefore protonated (positively charged) at physiological conditions: pH7.4

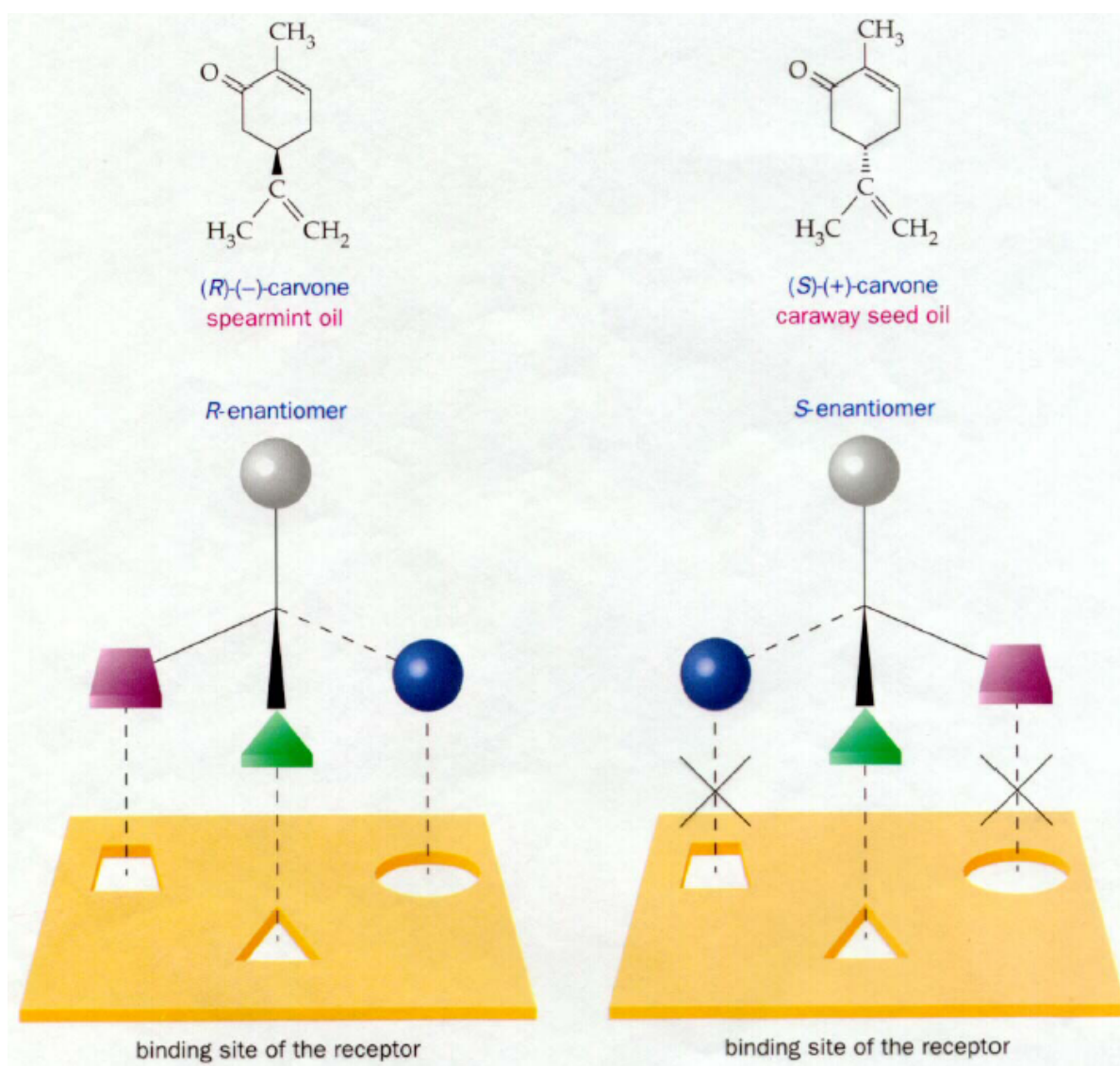


Stereochemistry of Amino Acids:

Chirality:

- The 4 bonds of the central carbon of an amino acid (except glycine) all have different groups.
 - This atom is said to be chiral.
 - Means that that molecule can exist as a pair of **non-superimposable mirror images** called **enantiomers**.
 - Labeled “L” or “D”
 - **Proteins are chiral**
 - Molecular targets of many drugs are **proteins (receptors, enzymes)**
 - The chirality of a drug can profoundly affect its physiological activity.
 - Receptors involved with taste and smell depend on different combinations of “L” and “D” molecules for different tastes.

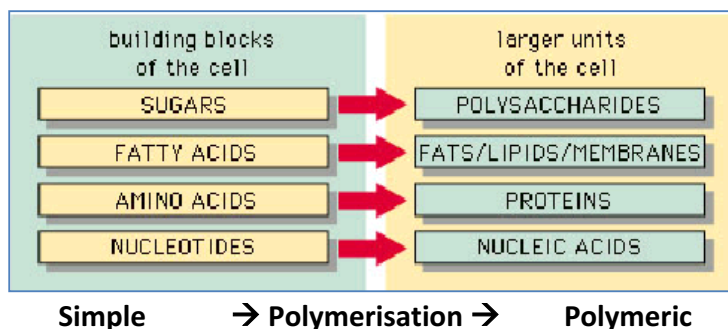
Molecular Recognition:



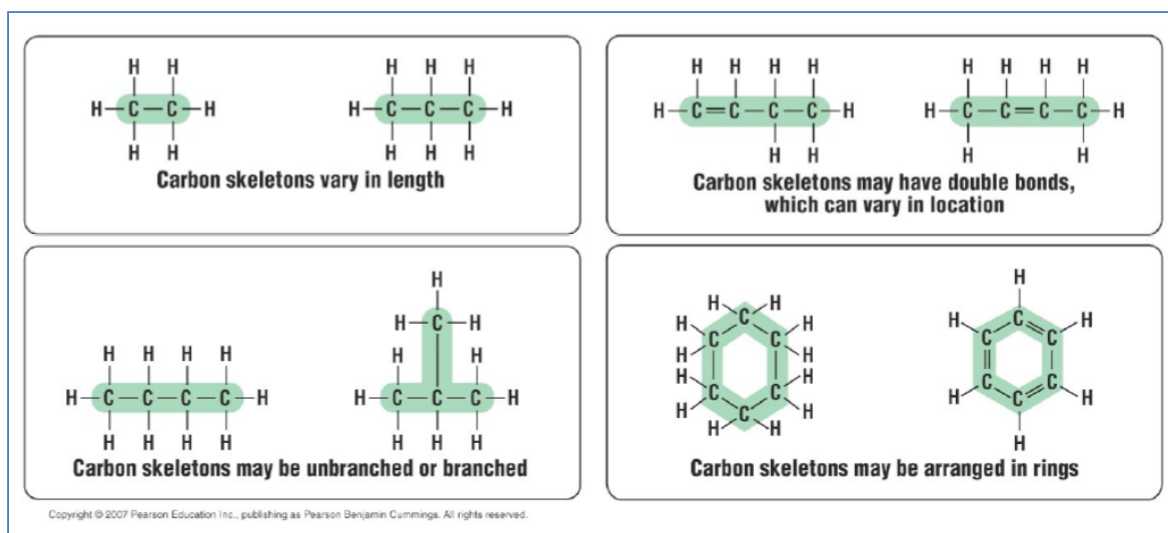
The Molecules of Life Molecular Building Blocks of the Cell:

4 Simple Molecules of Life:

- Sugars
- Fats
- Amino acids
- Nucleotides

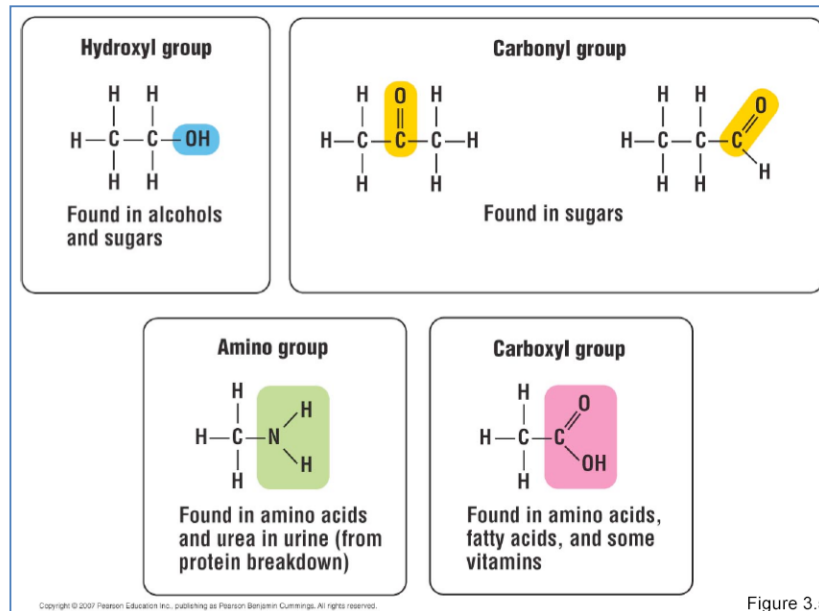


- Are all possible due to the versatility of the carbon atom.
- The simplest organic molecules are **hydrocarbons**:
 - The hydrocarbons of fat molecules provide energy for our bodies.
 - Each organic molecule has a unique shape that defines its function in an organism – molecules of the body recognise each other based on shape.
 - Carbon-based molecules vary greatly in size and shape:



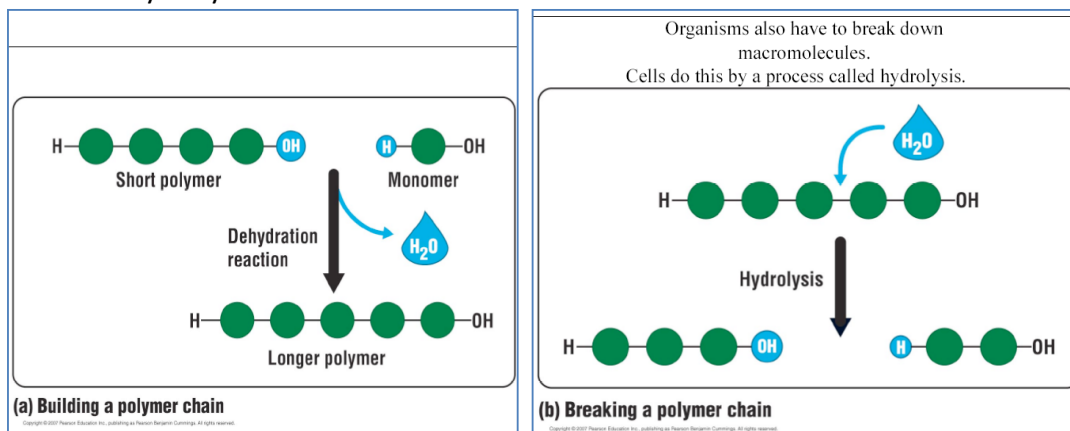
Functional Groups

- The unique properties of an organic compound depend on:
 - The shape of the carbon skeleton
 - The atoms attached to the skeleton
 - Called functional groups:



Biological MACROmolecules:

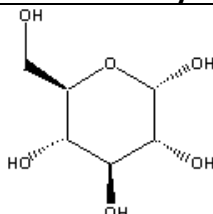
- On a molecular scale, macromolecules are gigantic.
- Eg. DNA, Carbohydrates, Proteins
- Most of them are polymers
 - Made by stringing together many smaller molecules (monomers)
 - Monomers bond (polymerise) by dehydration reactions and break down by hydrolysis:



4 Types of Bio-Macromolecules:

- Carbohydrates
- Lipids
- Proteins
- Nucleic Acids

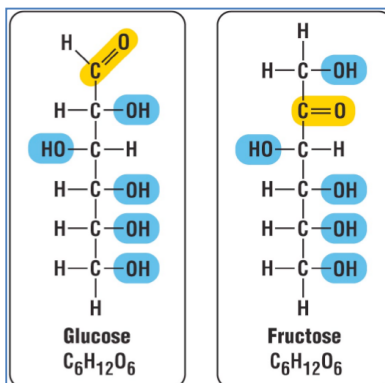
Bio-Macromolecule #1: Carbohydrates (fast energy)



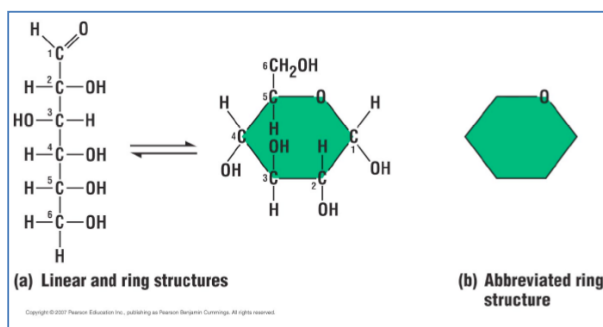
- Biological compounds containing covalently bonded **carbon, hydrogen, and oxygen** (in a 1:2:1 ratio) - are an important **source of food and energy**

Monosaccharides (simple sugars):

- Means: "single" "Sugar-unit"
- A simple sugar (glucose/fructose/galactose/mannose/fuctose) that cannot be broken down into simpler sugars.
- **Glucose & Fructose**
 - Isomers – same formula but different structure.
 - Contain exactly the same amount of energy
 - Glucose: found in sweet drinks
 - Fructose: found in fruit

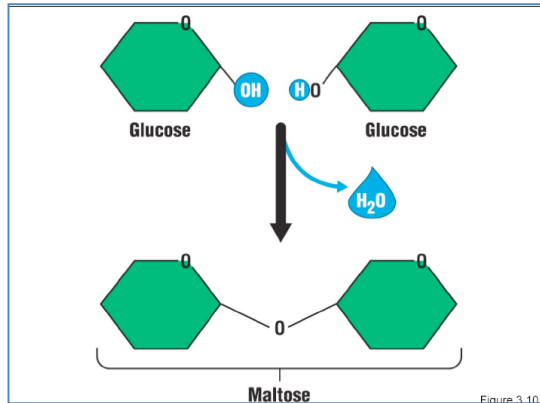


- In aqueous solutions, monosaccharides form rings.
 - Are the main fuel used by cells.



Disaccharides:

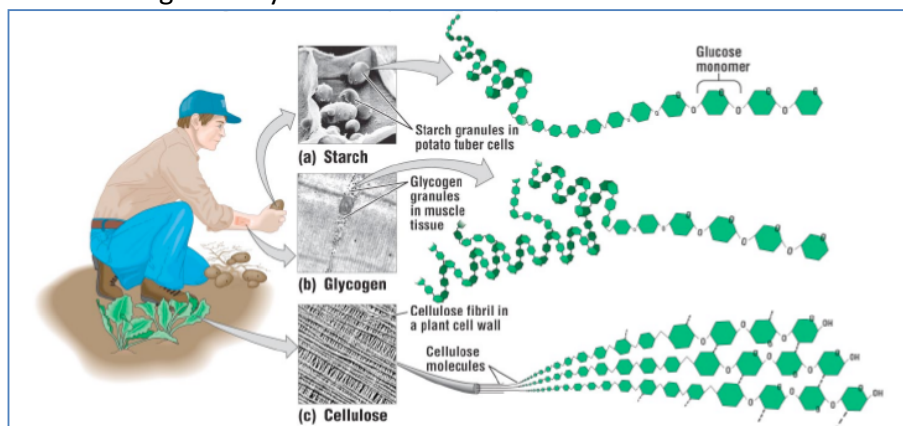
- A **double-sugar**
- A compound consisting of 2 monosaccharides
 - Joined through a dehydration reaction.
 - Eg. **Maltose**: Glucose + Glucose



- Eg. **Lactose**: Glucose + Galactose
- Eg. **Sucrose (table sugar)** : Glucose + Fructose

Polysaccharides:

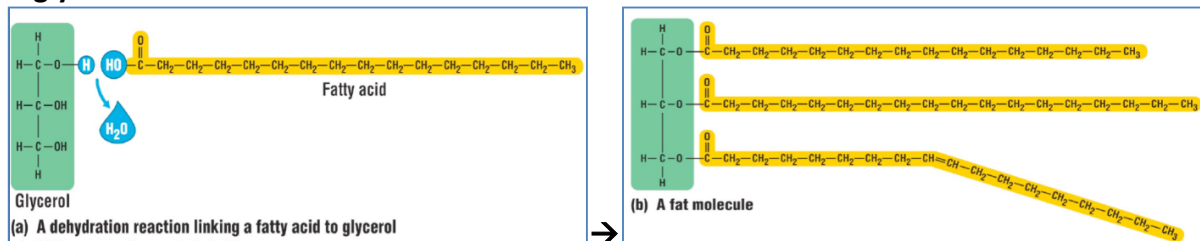
- AKA: **Complex Carbohydrates**
- Long chains of sugar units
- Polymers of monosaccharides
 - Eg. **Starch**
 - Stores energy in plant cells (potatoes/grains)
 - Made of many Glucose monomers.
 - Eg. **Glycogen (animal starch)**
 - Animals store excess sugar as glycogen
 - Made of many Glucose monomers.
 - Contains many branches
 - Eg. **Cellulose**
 - Makes up the structure of plant-cell walls
 - Major component of wood
 - Is a dietary fibre
 - Can only be broken down by grazing animals due to prokaryotes in their digestive system.



Bio-Macromolecule #2: Lipids (Reserve Energy)

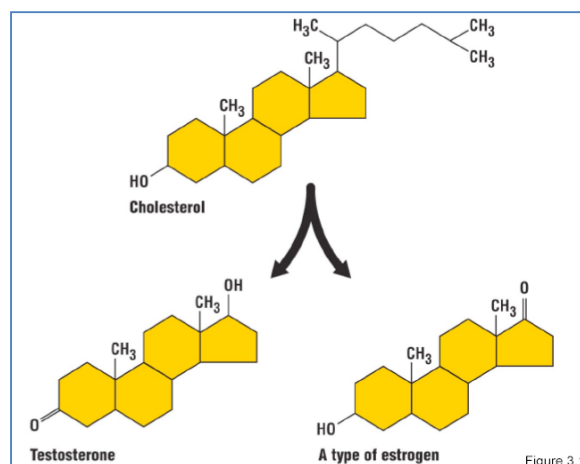
- a biological compound that is not soluble in water (**hydrophobic**)
- Eg. Fats/waxes/oils/sterols/triglycerides/phospholipids.
- **Fats:**
 - energy storage
 - insulation
 - cushioning
 - Are **triglycerides**
 - **Triglycerides:** 3 x fatty acids bonded to a glycerol through dehydration (ester linkage).
 - **Fatty Acid:** A long hydrocarbon chain with a carboxyl group end.
 - May be saturated/unsaturated
 - **Saturated** fatty acids are **straight**
 - Pack tightly together
 - Solid @ RmTp
 - **Unsaturated** fatty acids are **kinked**
 - Pack loosely together
 - Liquid @ RmTp

Triglyceride:



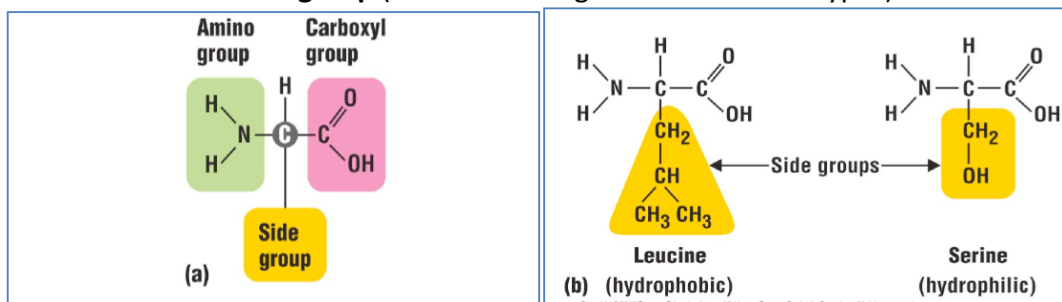
Steroids:

- any of a large group of natural or synthetic fatty substances containing four carbon rings
- cholesterol is the “base steroid” from which your body produces other steroids (sex hormones)

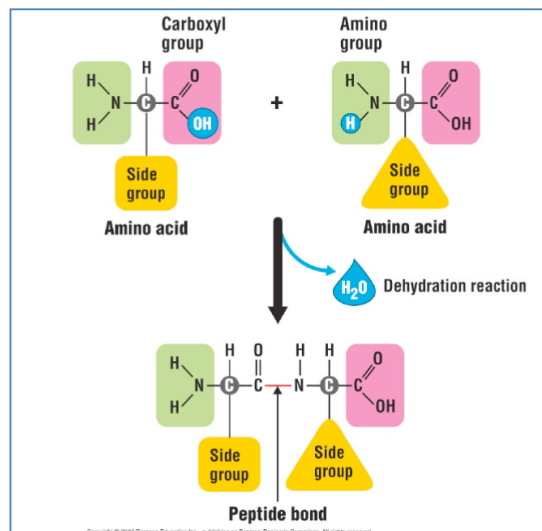


Bio-Macromolecule #3: Proteins

- Proteins are the most complex and functionally diverse molecules of living organisms.
- Proteins compose enzymes, blood cells and muscle tissue just to name a few.
- Proteins are created by RNA during DNA Transcription and Translation.
- Base elements: **C, H, O and N.**
- All proteins are polymers of linked amino acid monomers (via a peptide bond) and are constructed from a common set of **20 kinds of amino acids**
 - Each **amino acid** consists of:
 - **A central carbon** covalently bonded to 4 partners
 - **An amino group**
 - **A carboxyl group**
 - **A side group** (Variable among all 20 amino acid types)



- **Proteins** - Polymers of Amino Acids
 - There are thousands of different kinds of protein (differing by the arrangement of amino acids in the chain)
 - Amino acids join together by dehydration reactions forming peptide bonds:

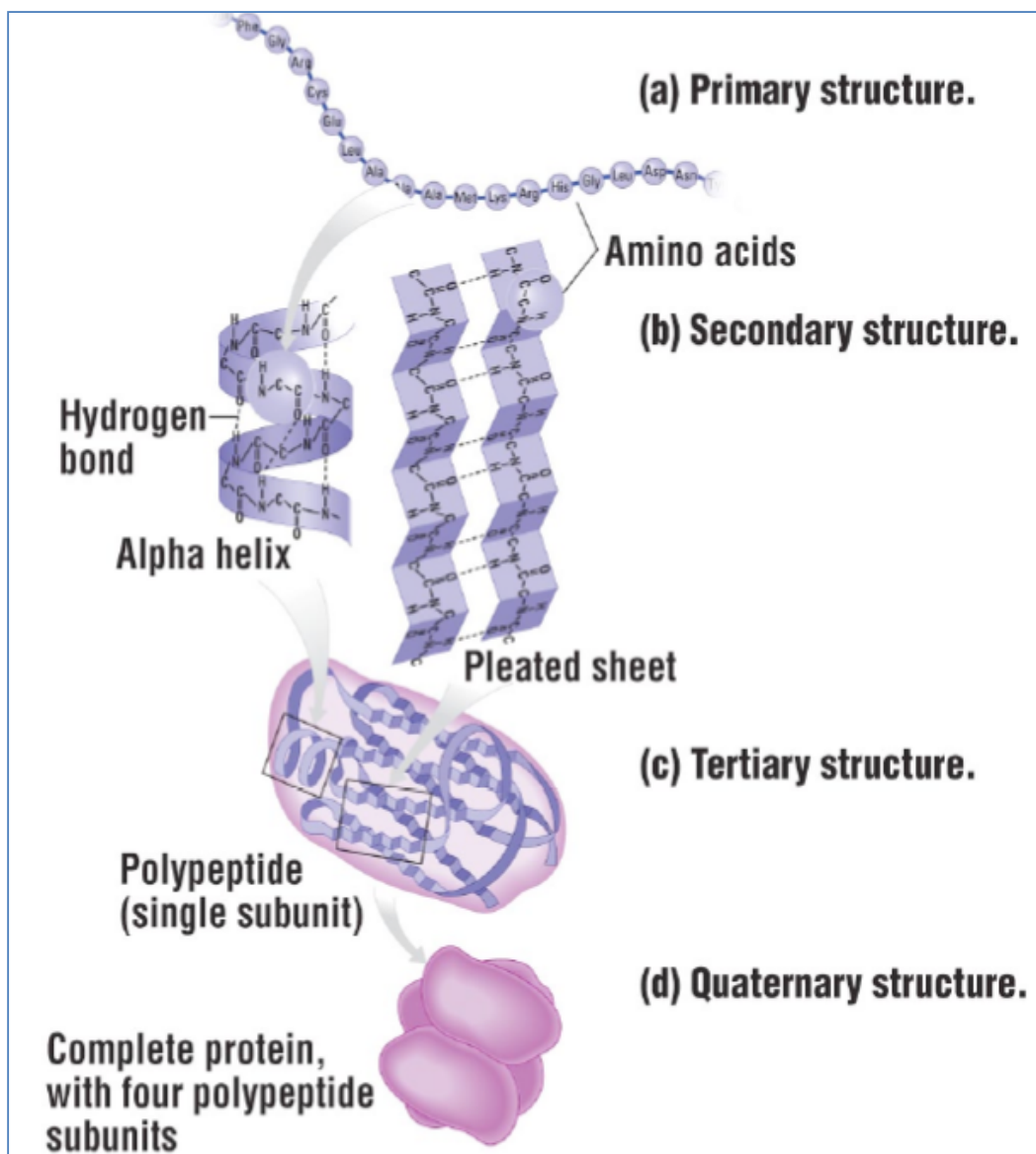


- Proteins are essential to the structure and function of all living cells and viruses.
- Perform most of the tasks the body needs to function
 - Structural Proteins
 - Storage Proteins
 - Contractile Proteins
 - Transport Proteins
 - Defensive Proteins
 - Receptor Proteins
 - Enzymes
 - Hormonal Proteins
 - Sensory Proteins
 - Gene Regulatory Proteins

Protein Shape/Structures:

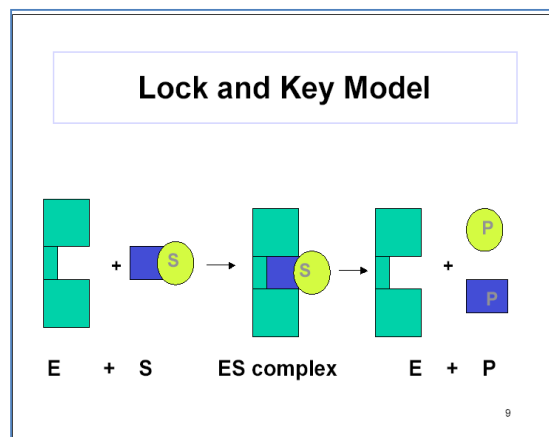
- Divided into 4 categories:
 - **Primary** Protein Structure (multiple peptide bonds = **polypeptide** *chains*)
 - Written L→R from amino end to carboxylic acid end.
 - **Secondary** Protein Structure
 - **Tertiary** Protein Structure
 - **Quaternary** Protein Structure
 - Complete functional protein

NB: A protein's shape is sensitive to the environment and can be denatured by change in temperature and pH.

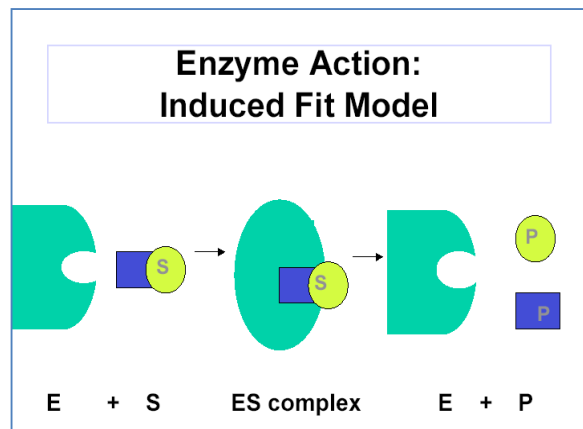


Proteins as Enzymes:

- Catalyse biological reactions
- Almost all enzymes are proteins
- Lower the activation energy of a reaction
- Is useless if denatured
- May contain cofactors (metal ions for vitamins)
- **Names end in “-ase”**
 - Is specific for the chemical that it reacts.
 - Eg. Sucrase – reacts sucrose
 - Eg. Lipase – reacts lipids
 - Describes the function of that enzyme.
 - Eg. Oxidase – catalyses oxidation
 - Eg. Hydrolase – catalyses hydrolysis
 - NOTE: some don't conform: (pepsin, trypsin)
- **Enzyme Action:**
 - **Lock & Key Model:**
 - The active site of the enzyme is the same shape as the substrate that it reacts.



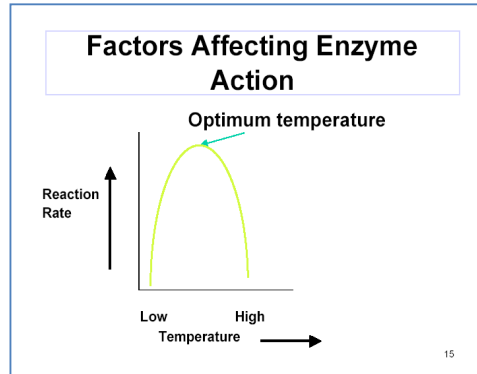
- **Induced Fit Model:**
 - The enzyme and active site adjust shape to bind to the substrate.
 - Therefore is more versatile in terms of range of substrates.



- **Factors Affecting Enzyme Action:**

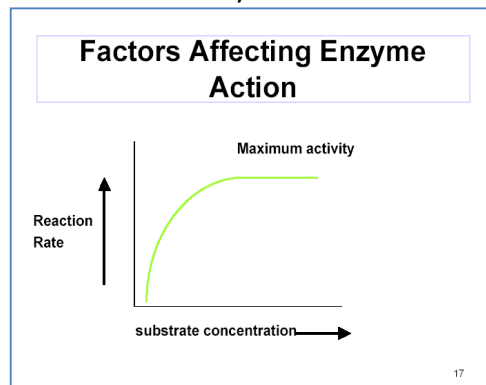
- **Temperature:**

- Little activity at low temp
- Rate increases with temp inc.
- Reach optimum temps. (37°C in humans)
- Activity lost @ high temps due to denaturation.



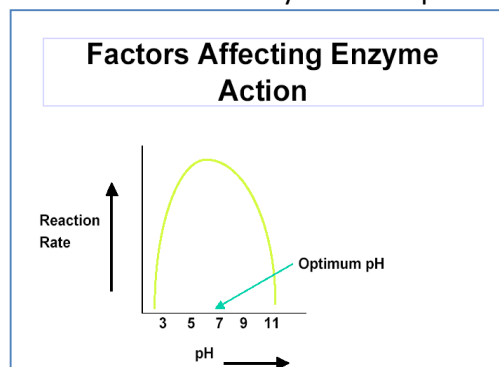
- **Substrate Concentration:**

- Activity increases with increasing substrate concentration.
- Maximum activity reached when concentration of substrate = concentration of enzyme



- **pH:**

- maximum activity at optimum pH (narrow range)
 - R-groups have proper charge
 - Tertiary structure of enzyme is correct.
 - Most lose activity outside optimum range.

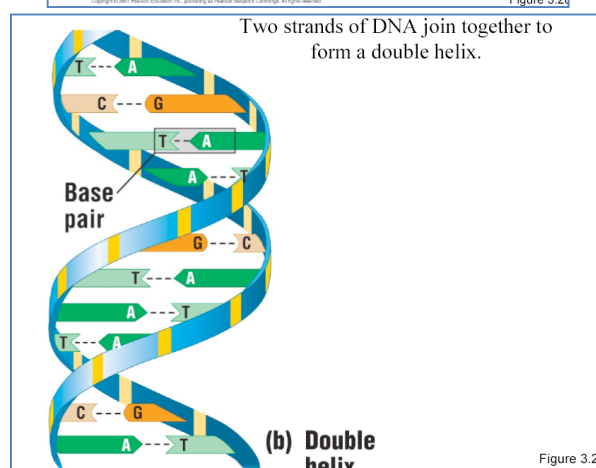
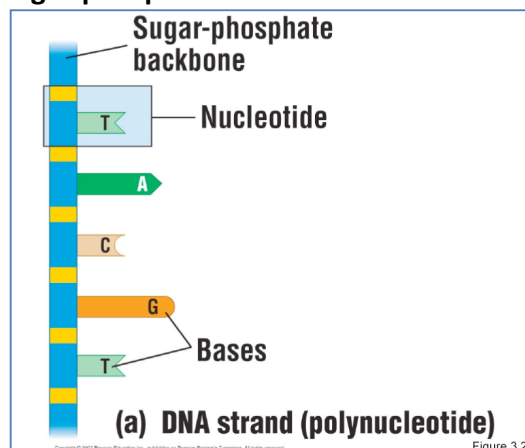


Enzyme Inhibition:

- Change the protein structure of the enzyme
- May be **competitive** or **non-competitive**.
 - **Competitive:**
 - Has a similar structure to substrate
 - Occupies active site
 - Competes with substrate for active site
 - **Non-Competitive:**
 - Not similar in shape to substrate
 - Binds to the enzyme but not the active site.
 - Changes the shape of the enzyme + the active site
 - Substrate cannot fit
 - No reaction occurs.

Bio-Macromolecule #4: Nucleic Acids

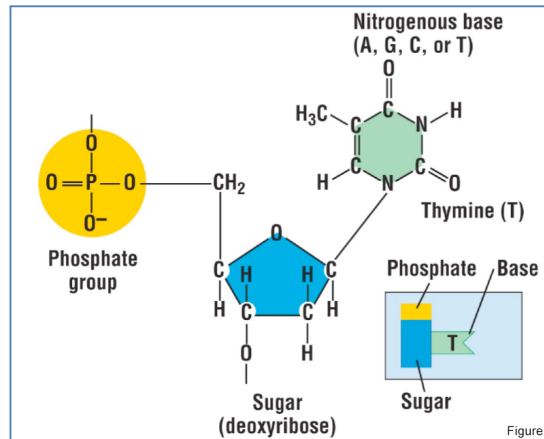
- "Nucleic acid" is the generic name for a family of biopolymers, named for their role in the cell nucleus.
- Provide the directions for building proteins.
- composed of chains of monomeric **nucleotides**.
 - Form chains called **polynucleotides** or just **DNA strands**
 - **Joined by a sugar-phosphate backbone**



- **2 Types Of Nucleic Acids:**

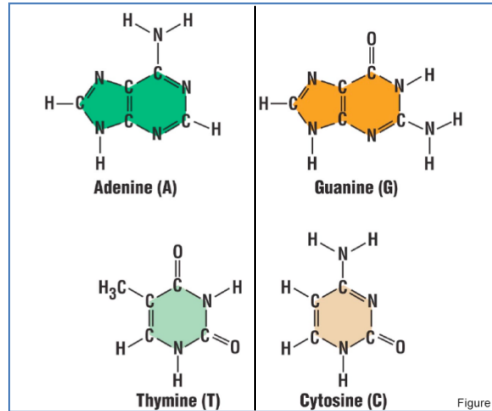
- **DNA:** Deoxyribonucleic Acid

- Contains the genetic instructions for development and function of all living things.
 - needed to construct other components of cells, such as proteins and RNA molecules.



- **BASES:**

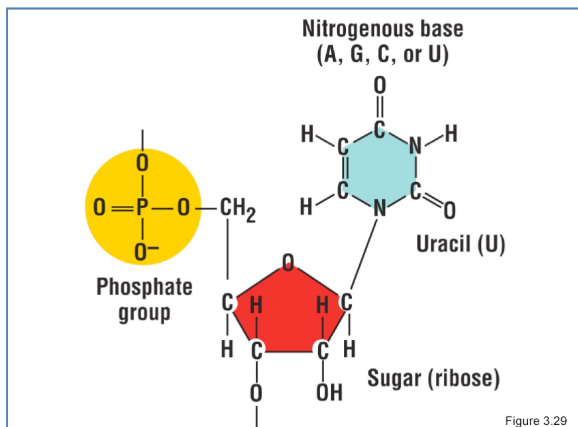
- **Adenine (A)**
 - **Guanine (G)**
 - **Thymine (T)**
 - **Cytosine (C)**



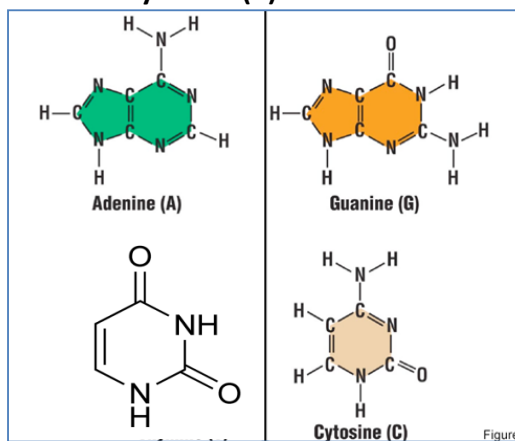
- **Due To Shape:**

- **A only bonds to T**
 - **G only bonds to C**

- **RNA: Ribonucleic Acid**
 - Translates genetic information from DNA into proteins.
 - Acts as a messenger between DNA and the ribosomes (protein synthesis organelles)
 - An essential carrier molecule of amino acids to be used in protein synthesis.
 - Has an **extra OH group**
 - Has the base **Uracil instead of Thymine**



- **BASES:**
 - **Adenine (A)**
 - **Guanine (G)**
 - **Uracil (U)**
 - **Cytosine (C)**

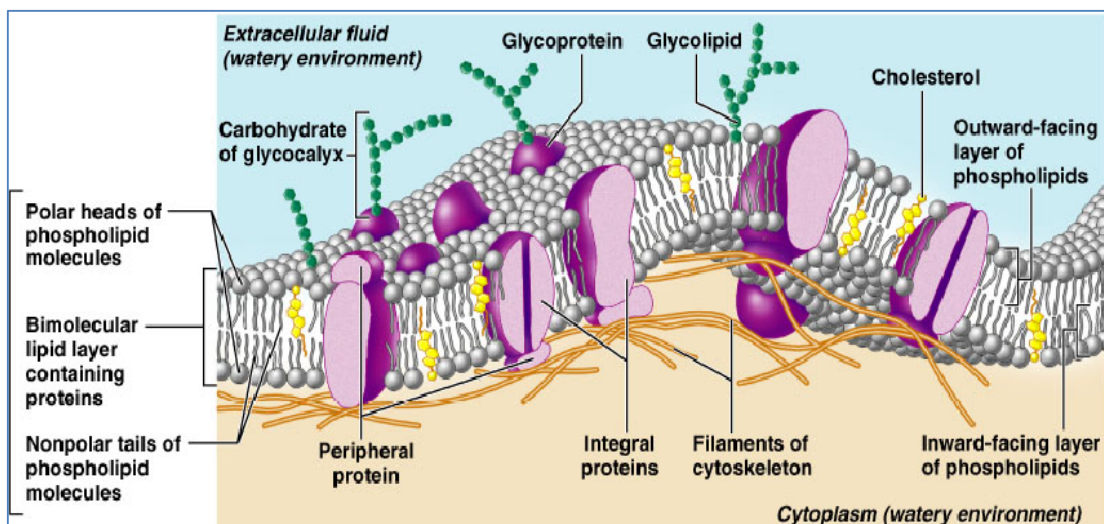


- **Due To Shape:**
 - **A only bonds to U (Uracil)**
 - **G only bonds to C**

Cells Basic Overview Continued:

Structure of a Typical Cell:

- **Plasma membrane**
 - Consists of a bi-lipid layer (diglycerides)
 - Is molten (has properties of both solid and liquid)
 - Contains Cholesterols
 - Contains **proteins**
 - Transportation
 - Catalysis
 - Reception of chemical signals
 - Intercellular joining (2 cells bonding)
 - Cell-Cell Recognition
 - Attachment to extracellular matrix
 - **Membrane Specialisations:**
 - Membrane Junctions (desmosomes/tight/gap)
 - Membrane Projections (microvilli/cilia/flagella)



- **Cytoplasm**
 - Everything inside a cell bar the membrane and the nucleus.
 - Includes all organelles + cytosol
- **Cytosol**
 - The fluid found within the membrane but outside the organelles
 - Largely water with dissolved protein, salts, sugars & other solutes.
- **Inclusions**
 - Chemical substances
 - Glycosomes
 - Glycogen granules
 - Pigment

- **Cytoplasmic Organelles:**

- **Membranous**

- **Nucleus**

- Nuclear envelope, Nucleoli, Chromatin
- Contains the genetic library for nearly all cellular proteins.
- Is the place where mitosis begins

- **Mitochondria**

- Cell power station
- Double Membrane
- Synthesise ATP for energy

- **Endoplasmic reticulum (Rough/Smooth)**

- **Rough:**

- Covered with **ribosomes** (hence rough)
- Synthesis of all proteins secreted from cell + membrane proteins + protein hormones.
- Proteins synthesised by ribosomes are then packaged in the Rough ER for export from the cell.
- Assist in making cellular membranes.

- **Smooth:**

- Not covered with ribosomes (hence smooth)
- Doesn't synthesise proteins.
- Metabolises lipids.
- Synthesises steroid-based hormones (testosterone/oestrogen)
- Detox of drugs/xenobiotic chemicals
- Storage site of calcium ions in skeletal/cardiac muscle.

- **Golgi apparatus**

- The cellular courier
- Modifies, Concentrates and packages proteins and membrane synthesised in the Rough ER for intracellular transport or excretion.
- Packaged proteins/membranes are released from the 'shipping face' in a transport vesicle for either excretion or cellular functions

- **Lysosomes:**

- Membranous sacs **created by the Golgi.**
- Contain concentrated enzymes.
- Inside is acidic for max enzyme function.
- Destroy 'old' cellular material.
- Destroy bacteria/viruses engulfed by white blood cell.

- **Peroxisomes**

- Membranous sacs
- Contain enzymes
- Detoxify harmful xenobiotic substances (alcohol)
- Neutralises highly reactive free radicals (by-products of biochemical processes)

○ Non Membranous Organelles

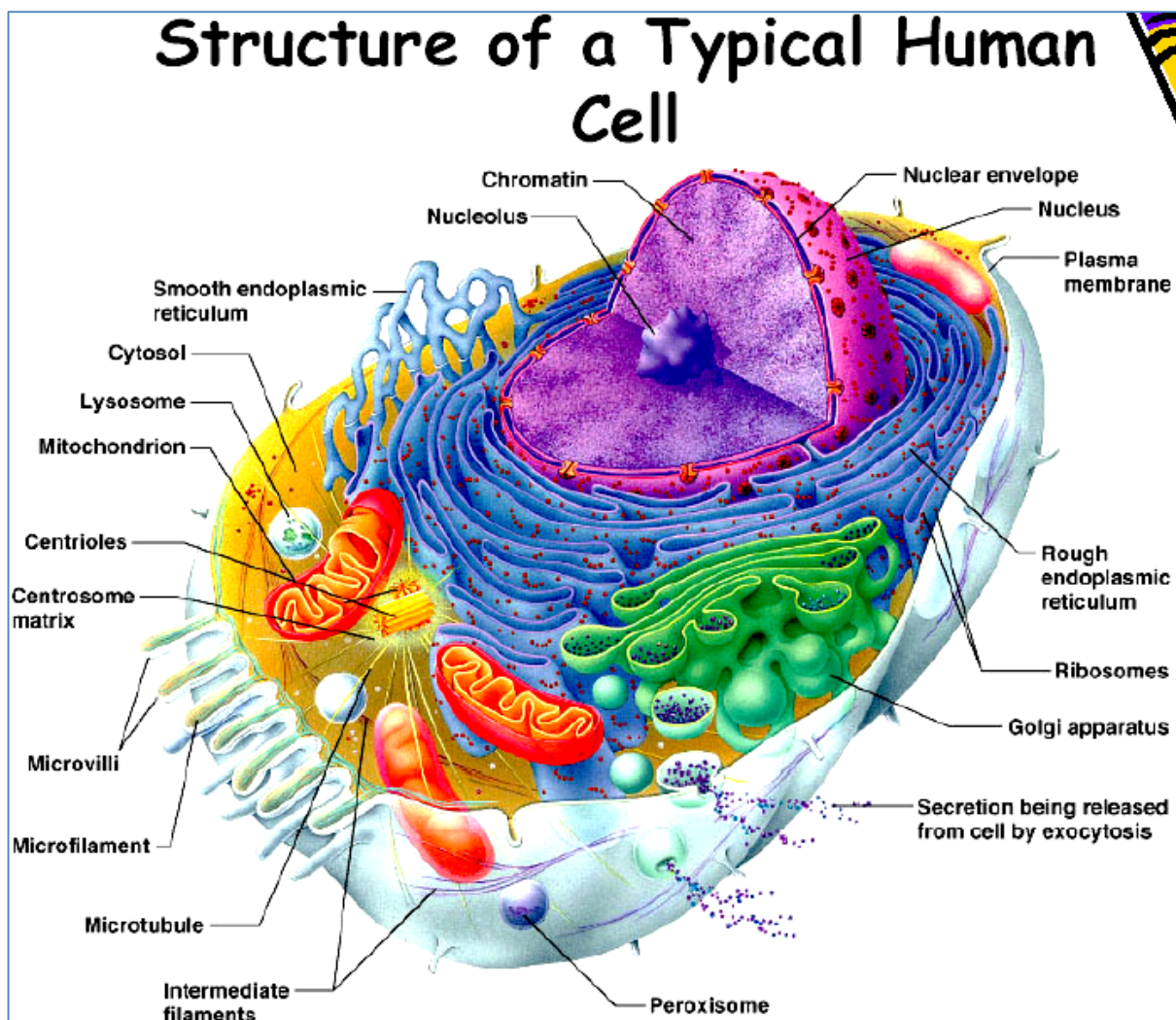
▪ Cytoskeleton

- Elaborate network of large filamentous rod-like proteins
- Provide structural support
- Provide the central mechanism for movement
- Ensures the distribution of organelles throughout cell.

▪ Centrioles

▪ Ribosomes

- Composed of protein & ribosomal RNA (rRNA)
- Are the site of **protein synthesis**
- Found either on the Endoplasmic Reticulum or free in the cytosol.
- ERs with ribosomes are called '**Rough**' ER



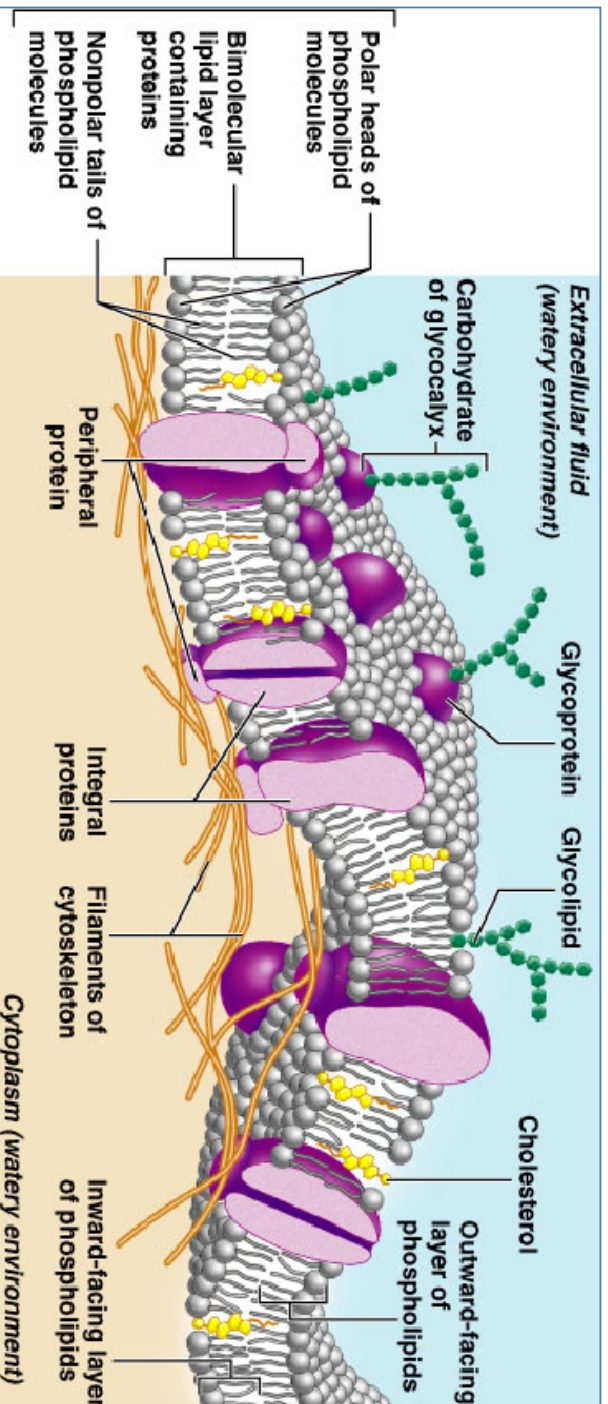
Cell Division:

- Cells reproduce through cell division.
- Replaces everyday wear and tear
- Replaces cells lost in injury.
- **Mitosis**
 - The division of the nucleus of a eukaryotic cell, involving condensation of the DNA into visible chromosomes.
 - Has 5 phases: **IPMAT...C**
 - **Interphase:** The long period of time between cell formation and cell division.
Cell increases in size
DNA is replicated
Centrosome is duplicated.
 - **Prophase:** Replicated chromosomes condense each with 2 sister chromatids.
 - **Prometaphase:** The nuclear envelope breaks down allowing the chromosomes to attach to the spindle microtubules.
 - **Metaphase:** The stage at which chromosomes are firmly attached to the mitotic spindle and align at the cell's equator but have not yet split.
 - **Anaphase:** Where the paired chromatids separate to form pairs of 2 daughter chromosomes & each is pulled slowly toward the spindle pole it is attached to.
 - **Telophase:** Final stage where the 2 sets of separated chromosomes arrive at the spindles. Chromosomes decondense and become enclosed by new nuclear envelopes.
 - **Cytokinesis:** The division of the cytoplasm of the cell into two. (the division of the entire cell into 2 cells)
- **Meiosis**

Cell Membrane & Transport

Membranes:

- Lipid Bilayer of diglycerides (phospholipids) held together by **hydrophobic forces**
 - **Hydrophilic head group (glycerol)**
 - **Hydrophobic fatty acid tails**
 - Some saturated + unsaturated (mpt – determined by saturation level & tail length)
- Imbedded Proteins:
 - **Peripheral:**
 - Associated with the polar head groups
 - Easily removed from the membrane by Δ pH or Δ [salt]
 - **Integral:**
 - Embedded in the membrane
 - Span the width of the membrane
 - Membrane must be destroyed to remove it.
 - Done by adding detergent (small amphipathic molecules)



How Substances Cross Cell Membranes:

- Membrane controls the flow of materials in/out of the cell.
- Either **passive or active processes**:

- **Passive:**

- **Diffusion**

- **Simple Diffusion** – movement of small, uncharged, non-polar and lipid-soluble substances directly through the lipid bilayer. (O₂, CO₂, N, Ethanol, Glycerol, Steroids, fat soluble vitamins)

- **Facilitated Diffusion** – where specific molecules diffuse across membranes, through specific transport proteins. (Carrier/channel)

- **Factors Affecting Rate of Diffusion:**

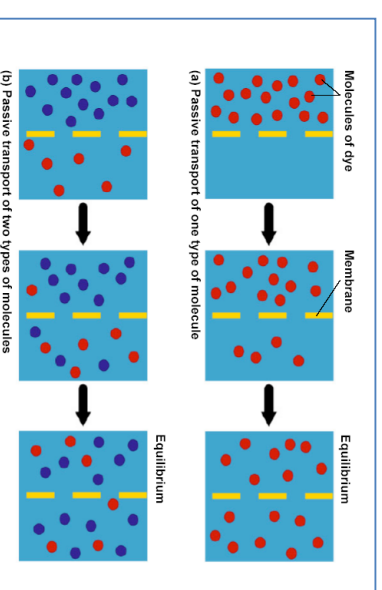
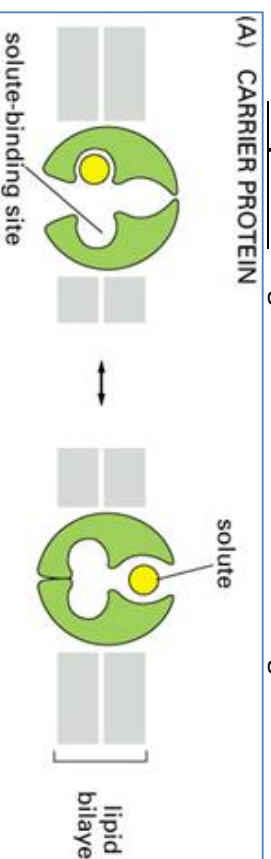
- Concentration gradient
- Molecular size
- Temperature (faster @ higher temps)
- Electric or Pressure gradient

- **Passive Transport Proteins** – facilitate the diffusion of specific chemicals (glucose/amino acids/nucleotides/ions) through the membrane that would otherwise not pass through the bi-lipid layer.

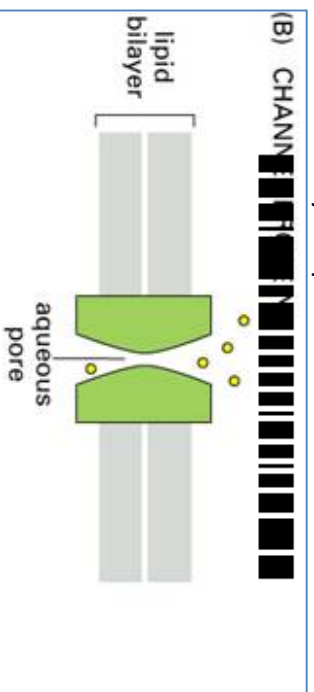
- **2 Types:**

- **#1 Passive Carrier Proteins:**

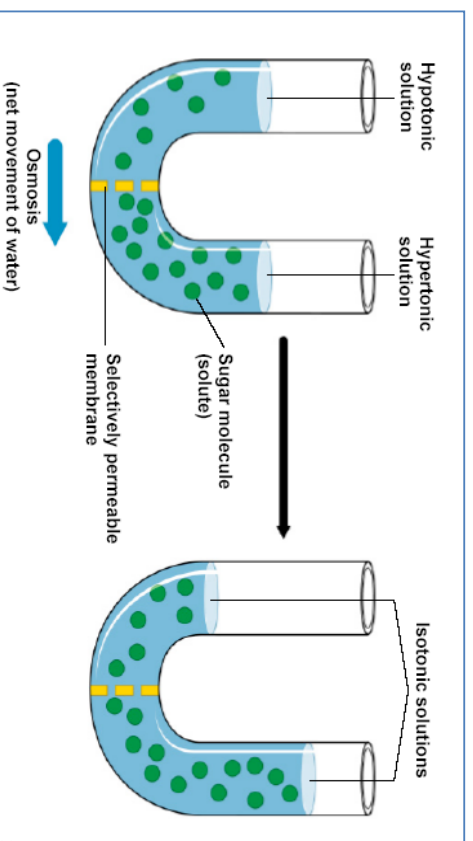
- Discriminates between solutes based on the shape of the protein's **binding site**.
- - then transfers single molecules across the membrane by **changing its conformation**. (similar to a **turnstile**)
- Has a high affinity for its substrate.
- - are therefore very effective at low substrate conc.
- Transfer rate is inhibited by temperature.
- **Uniporters:** single solute → down the conc. gradient.



- #2 Passive Channel Proteins:
 - Discriminates between solutes mainly on **size and electric charge**. (usually transports ions)
 - Act like a **tube** that is **either opened/closed**
 - Has no affinity for its substrate (substrate flow is determined by the concentration gradient of that substrate)
 - Once opened, **ion flow is very rapid**.
 - Not affected by temperature.

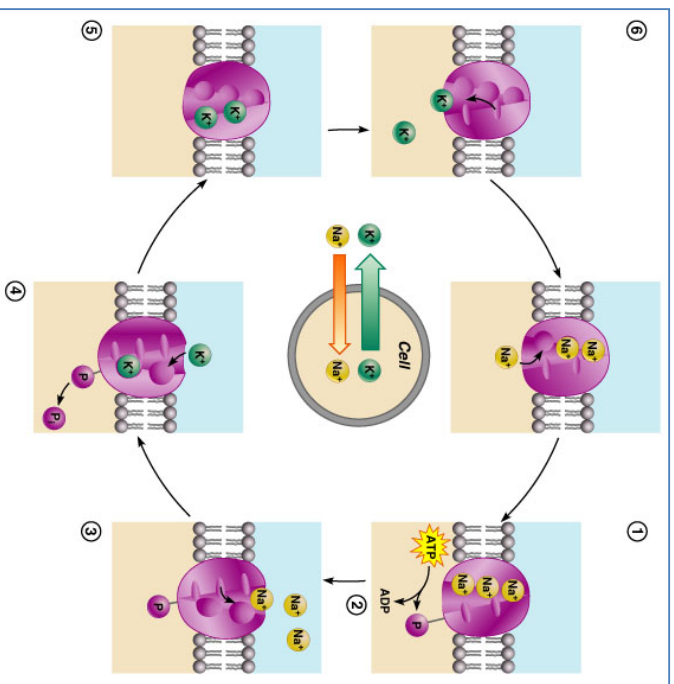


- **Osmosis** – The passive transport of water across a selectively permeable membrane.
 - Survival of the cell is dependent on osmoregulation.
 - **Water will flow from the hypotonic solution to the hypertonic solution through the lipid bilayer to form an isotonic solution.**



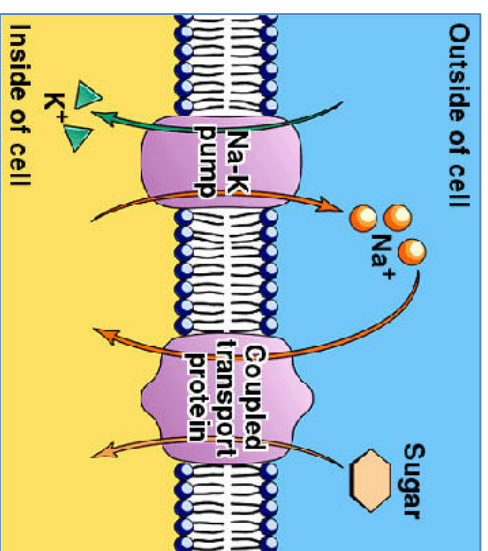
- **Active Processes:**
 - Transports substances against their concentration gradient.
 - Transports substances that would otherwise be too large for channel proteins
- **2 Types: Active Transport & Vesicular Transport**

- **Active Transport (via carrier proteins):** (using energy –ATP- to move molecules across a membrane.)
 - Similar to passive facilitated diffusion in that it requires carrier proteins
 - Active transporters (solute pumps) differ from facilitated diffusion in that they move solutes (mostly ions – Na^+ , K^+ , and Ca^{2+}) uphill against their concentration gradients.
 - In so doing, ATP is expended.
- **2 Classes: Primary & Secondary Active Transport**
 - Distinguished according to their source of energy.
 - **Primary Active Transporters:**
 - Energy comes directly from the hydrolysis of ATP.
 - Solute binds to the active site – then the protein is phosphorylated, causing it to change its shape and release the solute onto the other side of the membrane.
 - **Eg. The Sodium Potassium Pump (The Na^+/K^+ - ATPase Enzyme)**
 - **An Antipporter:** 2 solutes ← opposite directions → both against conc. gradients.

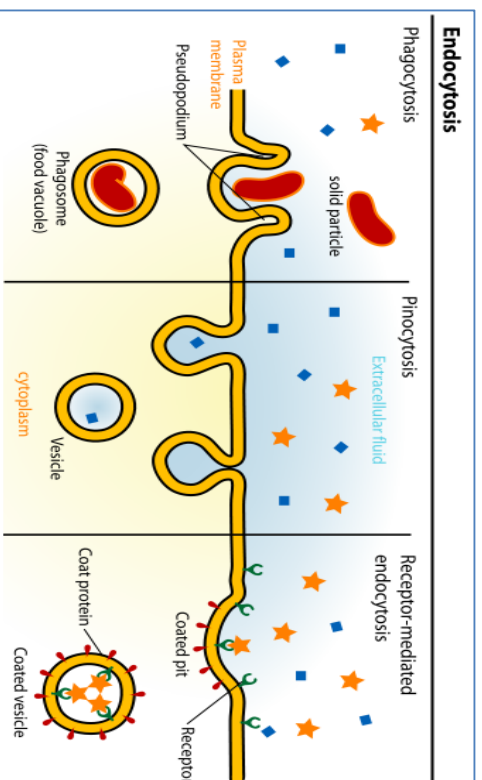
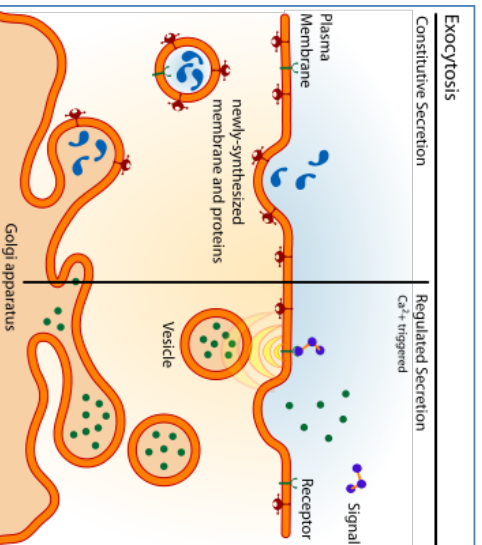


- 1) Cytoplasmic Na^+ binds to the protein, stimulating phosphorylation by ATP.
- 2) Phosphorylation causes protein shape to change.
- 3) Change in shape releases Na^+ to the outside.
- 4) K^+ then binds to the protein, triggering the release of the phosphate group.
- 5) Loss of phosphate restores protein to original shape.
- 6) K^+ ions are then released into the cell.
 - Cycle then repeats.

- **Secondary Active Transporters:**
 - **Symporters:** Using the potential energy of the concentration gradient created by a **primary transporter**, the high conc. solute flows downhill, dragging with it another chemical.
 - **Eg. Na⁺ - Glucose Symporter.**



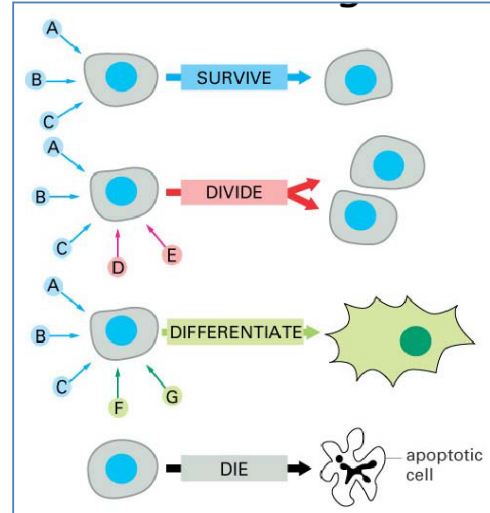
- **Active Transport Via Vesicles:**
 - Transport of **large particles, macromolecules and fluids through cell membranes.**
 - **Exocytosis:** Vesicular transport of substances out of a cell. (secretion)
 - **Endocytosis:** Vesicular transport of substances into a cell.
 - **Phagocytosis:** a large external particle is engulfed and enclosed in a vesicle. (eg. in white blood cells)
 - **Pinocytosis:** external fluid droplet (containing small solutes) is engulfed and enclosed in a vesicle. (absorptive cells – eg. kidney & intestine)
 - **Receptor Mediated:** selective endocytosis – substance binds to membrane receptors & then enclosed in a vesicle.



Chemical Communication: Endocrinology ctd.
Regulation of cell and body function

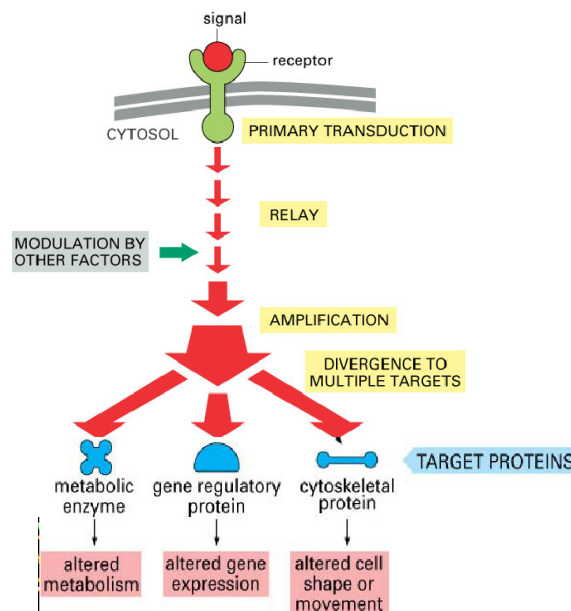
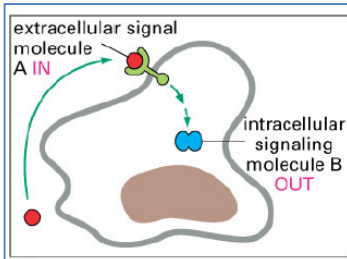
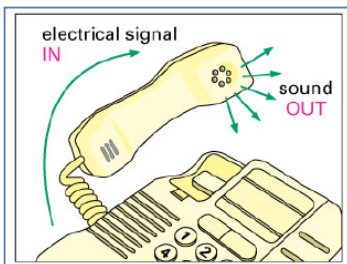
Purpose of intercellular signalling:

- To aid cells in coordinating their functions towards the common good of a **multicellular** organism.
- Cells must interpret the multitude of signals from other cells to help coordinate their functions.
- Effects of coordinated functions include:
 - Movement
 - Growth
 - Reproduction
 - Digestion
 - Metabolism
 - Circulation
 - Respiration
 - Senses
 - Temperature
 - Balance
 - Immune system
 - Differentiation
 - Death (apoptosis)
- NB: different cells may respond to the same signal in different ways.



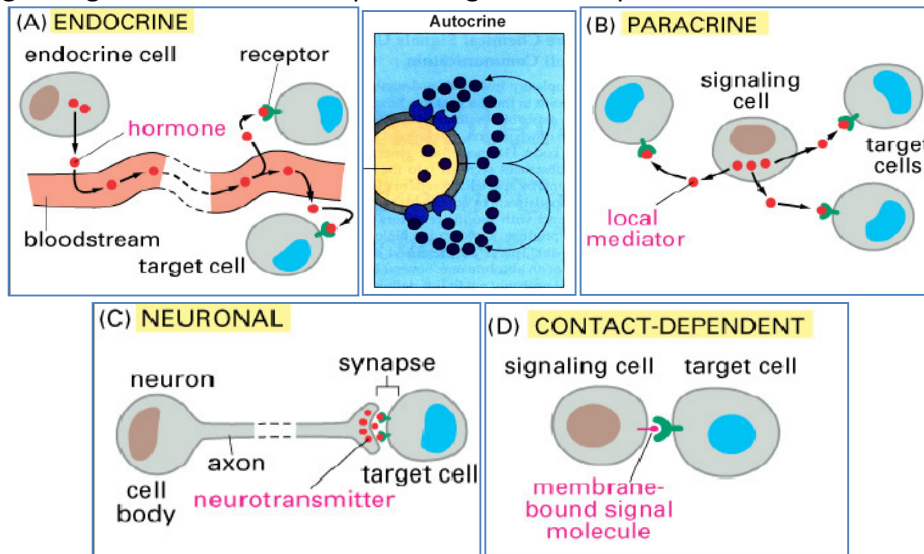
Signal Transduction

- Communication frequently involves converting signals from one form to another.
 - Signalling cell produces a signal molecule. (proteins /peptides /amino acids /nucleotides /steroids /fatty-acid derivatives /gases)
 - Signal molecule is detected by target cell.
 - Receptor protein receives the signal & transduces it to an intracellular signal.
 - Intracellular signal relayed, amplified, & diverged along a signalling 'cascade'
 - Intracellular signals received by target proteins inside cell, altering cell behaviour.



Long or Short Range?

- **Endocrine Signalling:** Some signals are “broadcasted” throughout the entire body via bloodstream.
→ **Hormones** (produced by endocrine cells) [TV]
- **Autocrine:** Signals that affect only cells of the same cell type as the emitting cell. [doctor conference]
- **Paracrine:** Signals (aka local mediators) that act on cells in the vicinity of the emitting cell but on different cell types than the emitting cell. [Lecture]
- **Neuronal:** Specific messages are delivered across long distances to specific target cells. [phone call]
- **Contact dependant:** Does not require secretion of signal molecule. Instead, cells make direct contact through signalling molecules and receptors lodged in their plasma membranes.

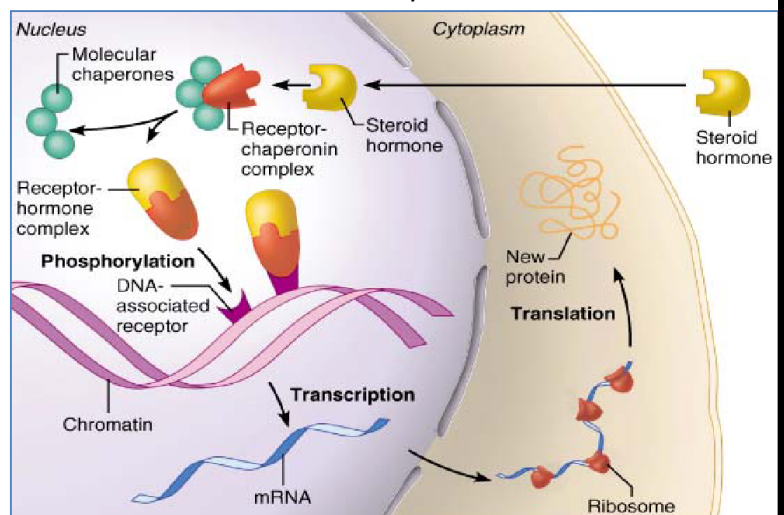


2 Main Receptor Types: (Intracellular & Membrane-bound Receptors)

- Determined by how the hormone receptor binding is relayed to the cytoplasm.
- Mechanism depends on chemical nature of the hormone & the cellular location of receptor.

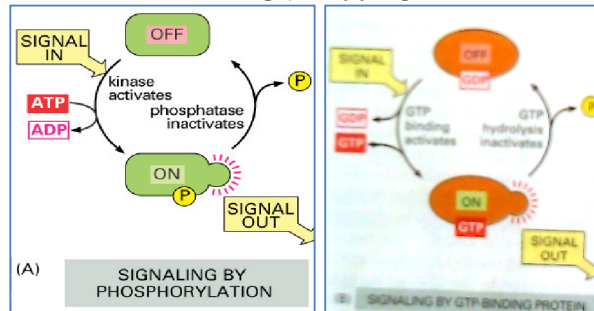
• Intracellular Receptors:

- Lipid-soluble hormones (steroid/thyroid hormones) & even gasses (nitric oxide-blood vessel dilation)
 - Can diffuse straight through the membrane.
 - **Steroid hormones** bind to receptor proteins in the cytosol or the nucleus that regulate gene expression.
 - **Other signal molecules** activate intracellular enzymes.
 - Once bound, the receptor protein undergoes a large conformational change and ‘activates’, allowing it to promote/inhibit transcription of a select set of genes.



- **Plasma-Membrane-Bound-Receptors:**

- Most signal molecules are too large or hydrophilic to cross the plasma membrane of the target cell.
- Therefore bond to transmembrane protein receptors that relay the message (in a new form) into the interior of cell (cytosol)
- Most intracellular signalling proteins act as **molecular switches** activated by either **phosphorylation** OR **GTP-Binding** (swapping a GDP for a GTP)

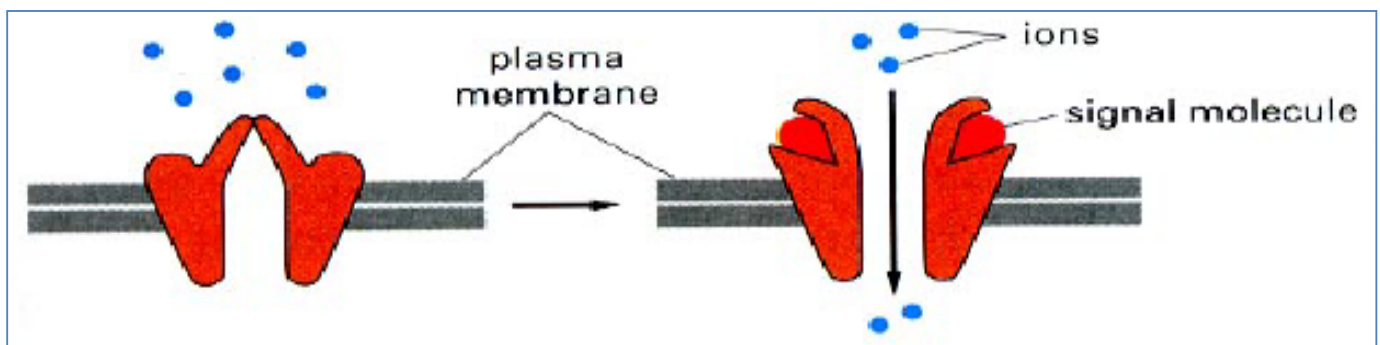


- 3 types differ by the nature of the new intracellular signal generated when extracellular signal binds to them:

- **3 Types:**

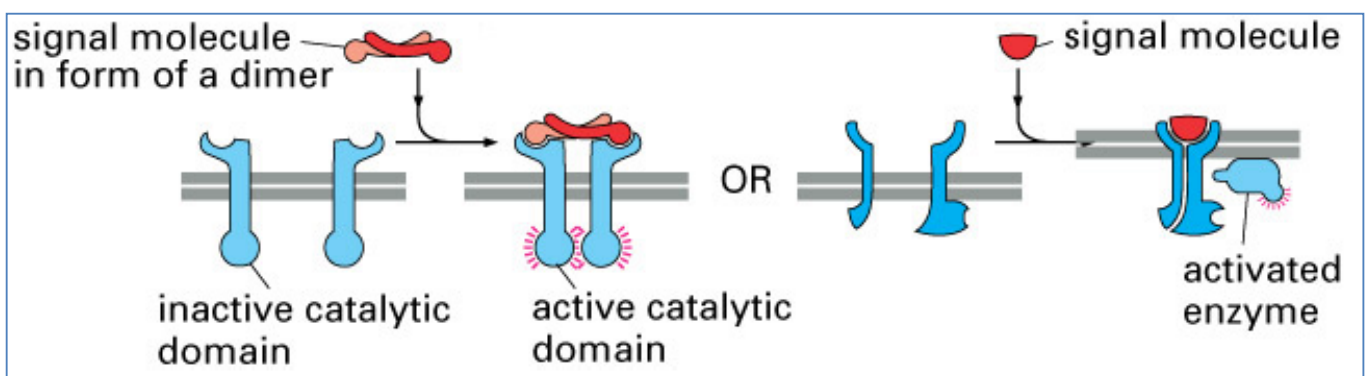
- **Ion-Channel-Linked Receptors**

- Resulting signal is a flow of ions across the membrane – produces an electric current.
 - Signal molecules are often neurotransmitters.



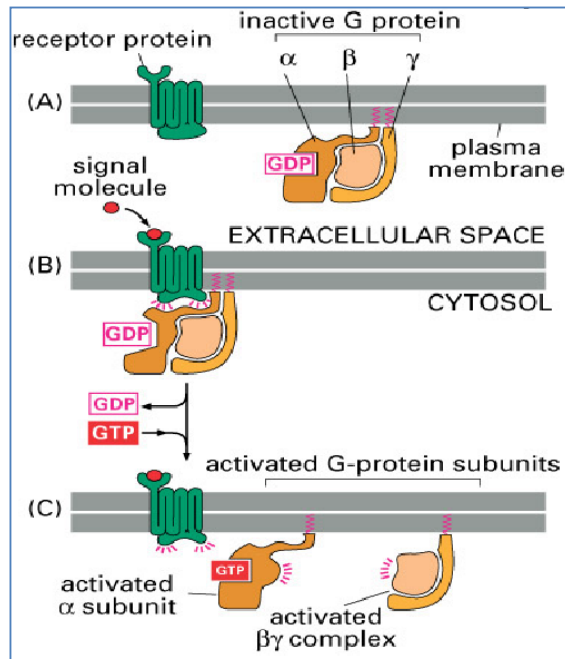
- **Enzyme-Linked Receptors**

- When activated – act as enzymes or are associated with enzymes inside the cell. Switching on this enzymatic activity then initiating a cascade of other effects, including small molecules being released into the cytosol.

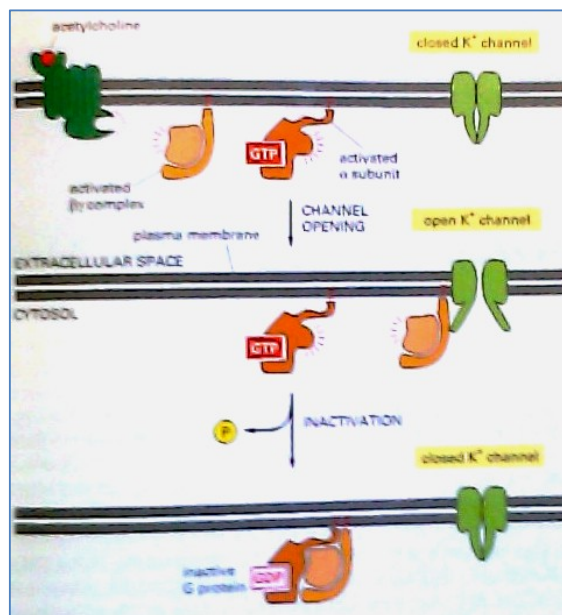


- **G-Protein-Linked Receptors (more common)**

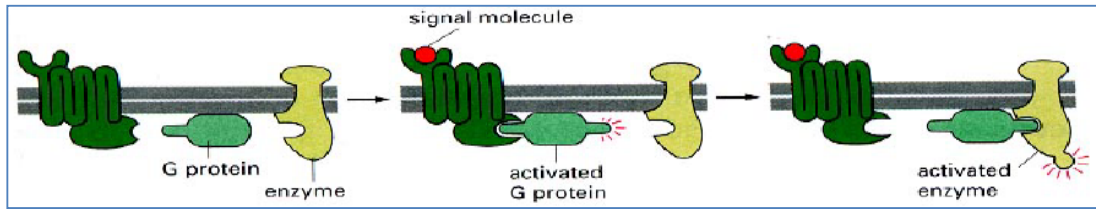
- The largest family of cell-surface receptors.
- Binds to a class of membrane-bound **GTP-Binding-protein (G-Protein)** → becomes activated and released to migrate across the membrane, initiating a cascade of other effects.
- G-Proteins act as molecular switches, transmitting the signal onward for a short period, then switching themselves off by hydrolysing their bound GTP to GDP.



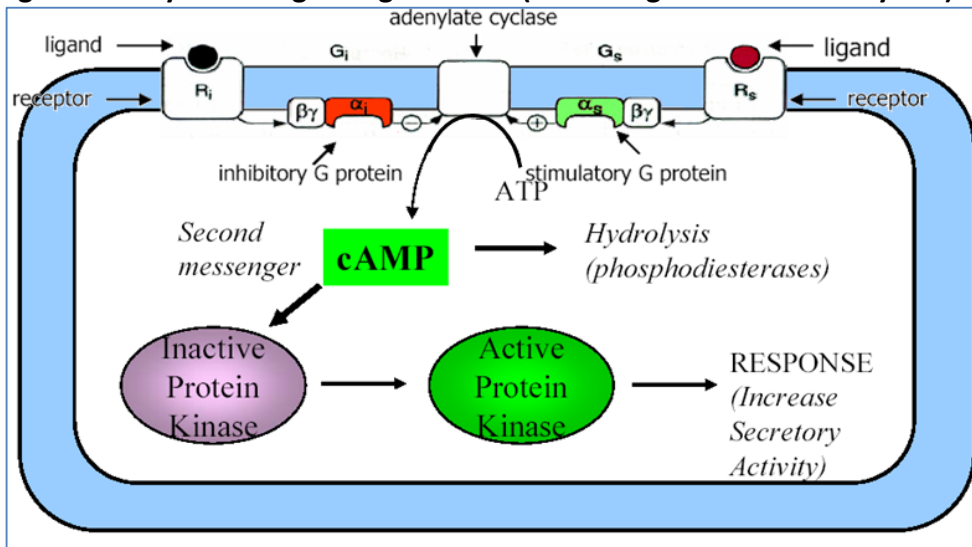
- Some G-Proteins directly regulate ion channels in the plasma membrane.



- Other G-Proteins activate membrane-bound enzymes. Eg. **adenylyl-cyclase** → increases the [second messenger (cyclic-AMP)] → activates an intracellular **signalling protein** (eg. A protein kinase) OR turns on **genes via activated Protein Kinase 'A' (PKA)**.

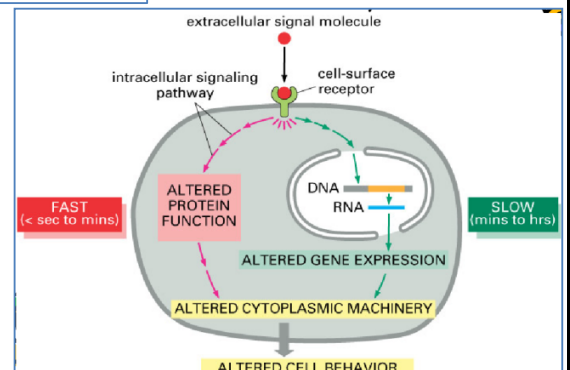
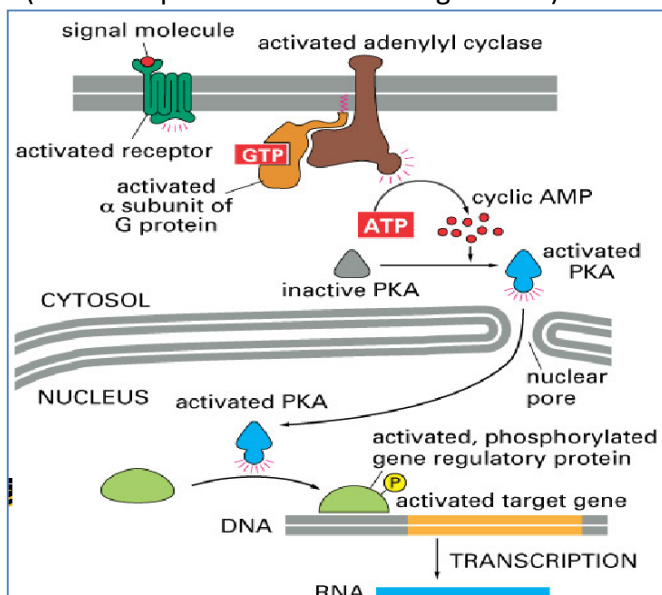


Eg1. cAMP Cytosolic Signalling Cascade: (Activating Intracellular Enzymes)

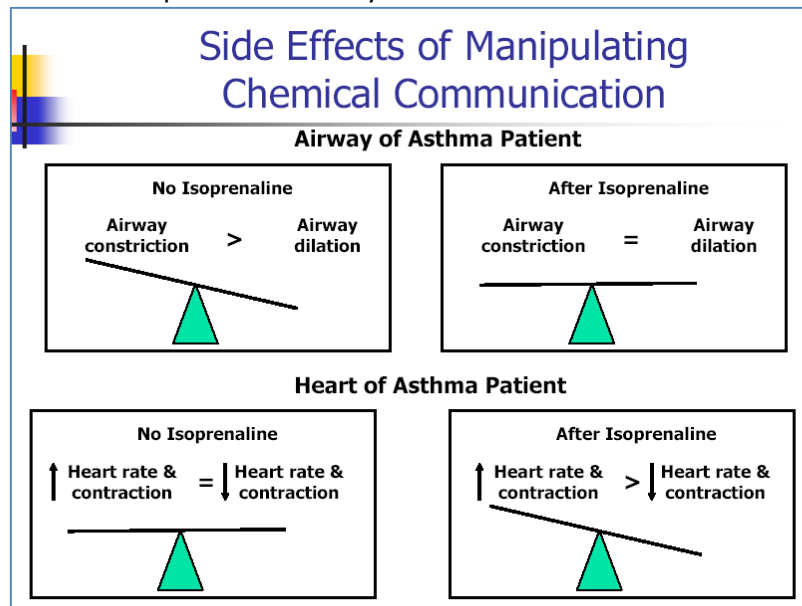


Eg2. cAMP Nucleic Signalling Cascade: (Turning on Genes via activated PKA)

NB. Gene regulatory protein = **CREB Protein**
(cAMP Response Element Binding Protein)



Drug side effects. – A Drug's target receptor on a certain cell may be present on a cell of a different organ, which responds differently to the same chemical stimulus.



Overview

- In multicellular organisms the collective functions of cells must be regulated and coordinated involving complex intercellular communication networks
- Secreted messengers form the best studied process of intercellular communication
- Secreted messengers are a chemically diverse group
- Secreted chemicals must activate a specific receptor
- There are 4 major types/classes of receptors
- Each type of receptor has a different mechanism for converting the secreted signal into a meaningful signal for the cell
- Activation of cell surface receptors results in transduction of the signal into the cell and activation of an intracellular signaling cascade
- Intracellular signaling cascades are complex and diverse but have a number of generic functions
- Intracellular signaling cascades may involve the formation of a secondary messenger such as cAMP
- Cells also have mechanisms for turning off the signaling process

The Cell Cycle & Its Regulation
1e. Cell Division/Reproduction

The Cell Cycle:

- The *cell doctrine*: “where a cell arises there must be a previous cell.”
- For a cell to reproduce, it must duplicate its contents & divide cyclically. **(the cell cycle)**

Fundamental tasks of the cell cycle:

- Copy and pass on genetic info to next generation.
- Produce 2 genetically identical daughter cells
- DNA in each chromosome must be accurately replicated
- Replicated chromosomes must be equally distributed between daughter cells.
- Coordinate growth with division to maintain size & contents.

4 Phases:

➤ **Interphase**

- Cell continues to transcribe genes, synthesize proteins, & grow.

1. **G₁ Phase (gap)**

- Provide additional time for cell to grow & duplicate Cytoplasmic organelles

2. **S Phase (synthesis)**

- DNA Replication
- Restriction/Commitment Point – no turning back.

3. **G₂ Phase (gap)**

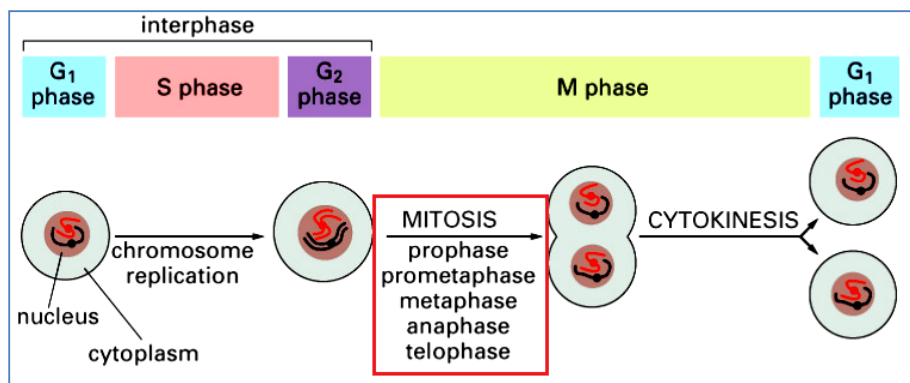
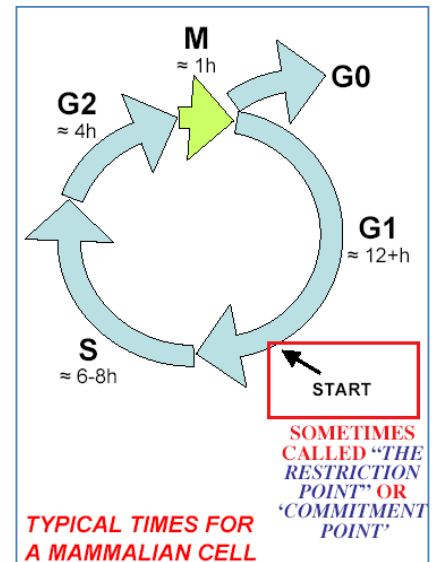
- Provide additional time for cell to grow & duplicate Cytoplasmic organelles
- Replicated chromosomes condense

➤ **Mitosis & Cytokinesis**

4. **M Phase (mitosis & cytokinesis)**

- **Prophase** – nuclear membrane breaks down
- **Prometaphase** – replicated chromosomes are lined up
- **Metaphase** – chromosomes separated into 2 sister chromatids
- **Anaphase** – chromatids arrive at ends of cell, decondense & form separate nuclear membranes
- **Telophase** – Plasma membrane pinches cell into 2.

5. **G₀** = Some cells (neurons) that don't divide, just stop at G₀.

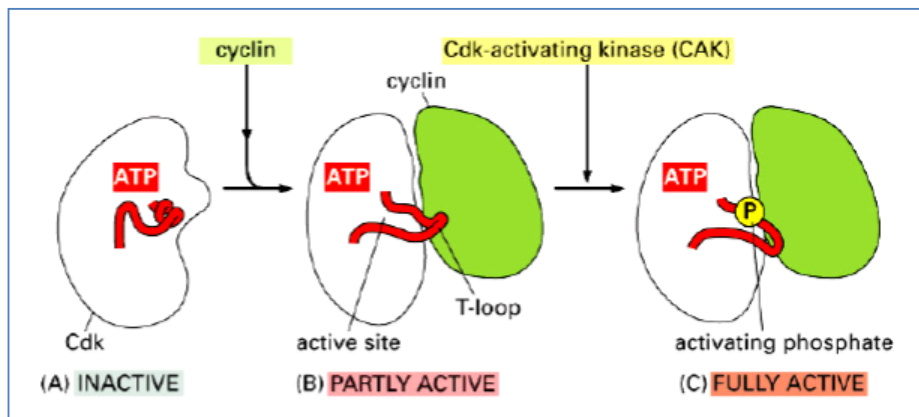


The Cell-Cycle Control System:

- To ensure these tasks are completed, there exists a complex network of **regulatory proteins**, known as the **cell-cycle control system**.
 - o Ordered series of biochemical switches that control the main events of the cycle:
 - DNA replication
 - Segregation of duplicated chromosomes
 - o Responds to various signals from outside & inside the cell
 - o Critical to regulation of cell numbers
 - o Malfunction can lead to cancer. (Abnormal number of chromosomes/Mutated DNA)
- Can stop the cycle using **molecular 'brakes'** at **2 important checkpoints**.

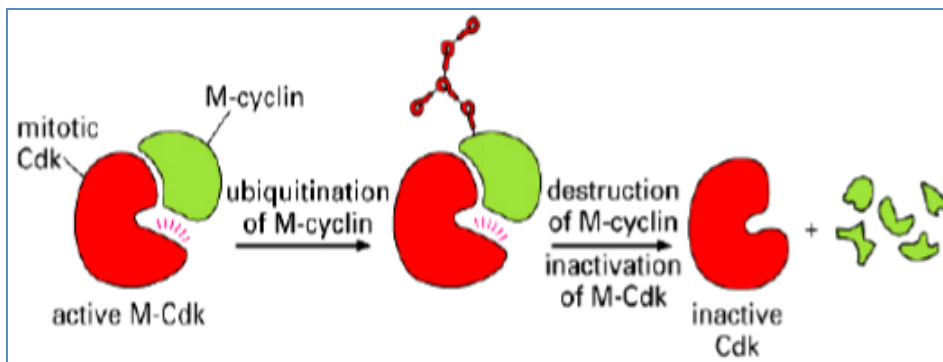
Molecular Brakes of the Cell-Cycle Control System:

- Govern cell-cycle by activating & inactivating proteins that regulate DNA replication, mitosis & cytokinesis.
- Activation via phosphorylation → by **protein kinases** (consume ATP + phosphorylate substrate)
- Deactivation via dephosphorylation → by **protein phosphatases**
- To become fully active, **protein kinases must first** become partially active by **binding to a cyclin**
- **Cyclins** – have no enzymatic activity.
- **Cyclin Dependant Kinases (Cdk's)** – partly activated by cyclin.
 - o **Cyclin + Cyclin Dependant Kinase = Cyclin-Cdk**
- **Cdk-Activating kinase (CAK)** – **phosphorylates** the partly activated **cyclin-Cdk**, **fully activating it**.



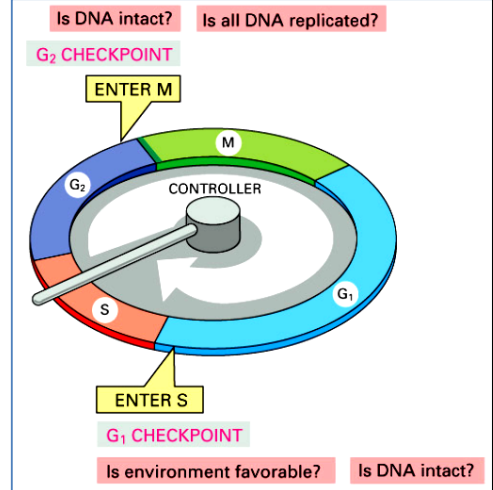
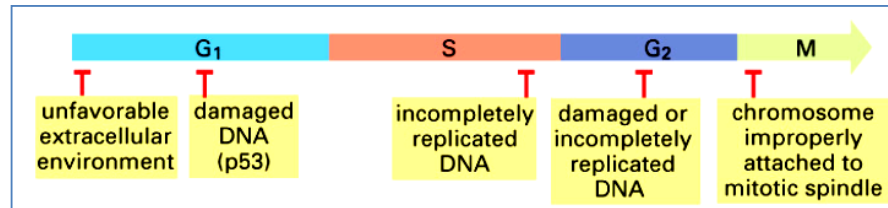
- o **Activation of Cyclin-Cdk complexes** can trigger cell-cycle events. (Entry into S-phase or M-phase.)
 - **'M'-Cyclin + Cdk = M-Cdk** → drives cells into **M-phase**
 - **'S'-Cyclin + Cdk = S-Cdk** → drives cells into **S-phase**

Cdk Inactivation: Once 'M'-Phase is complete, **ubiquitin-dependant proteolysis** destroys cyclins.



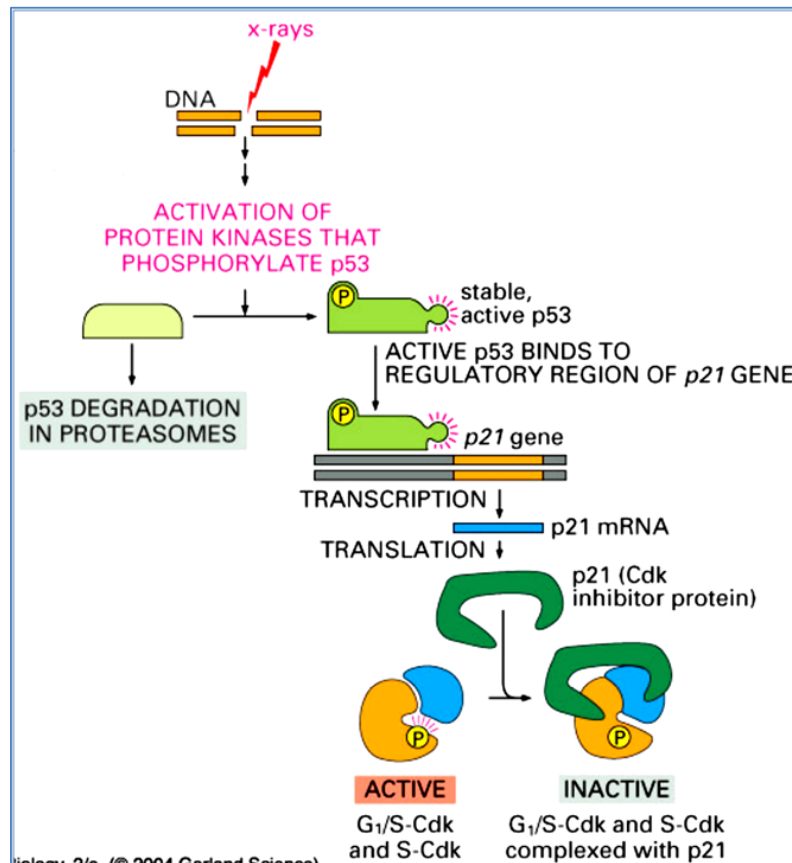
Checkpoints of the Cell-Cycle Control System:

- cell checks that a critical earlier event has occurred
- ensures correct sequence of events
- ensures consistent DNA replication before mitosis
- Loss/misregulation of checkpoints = cancer (uncontrollable cell division)

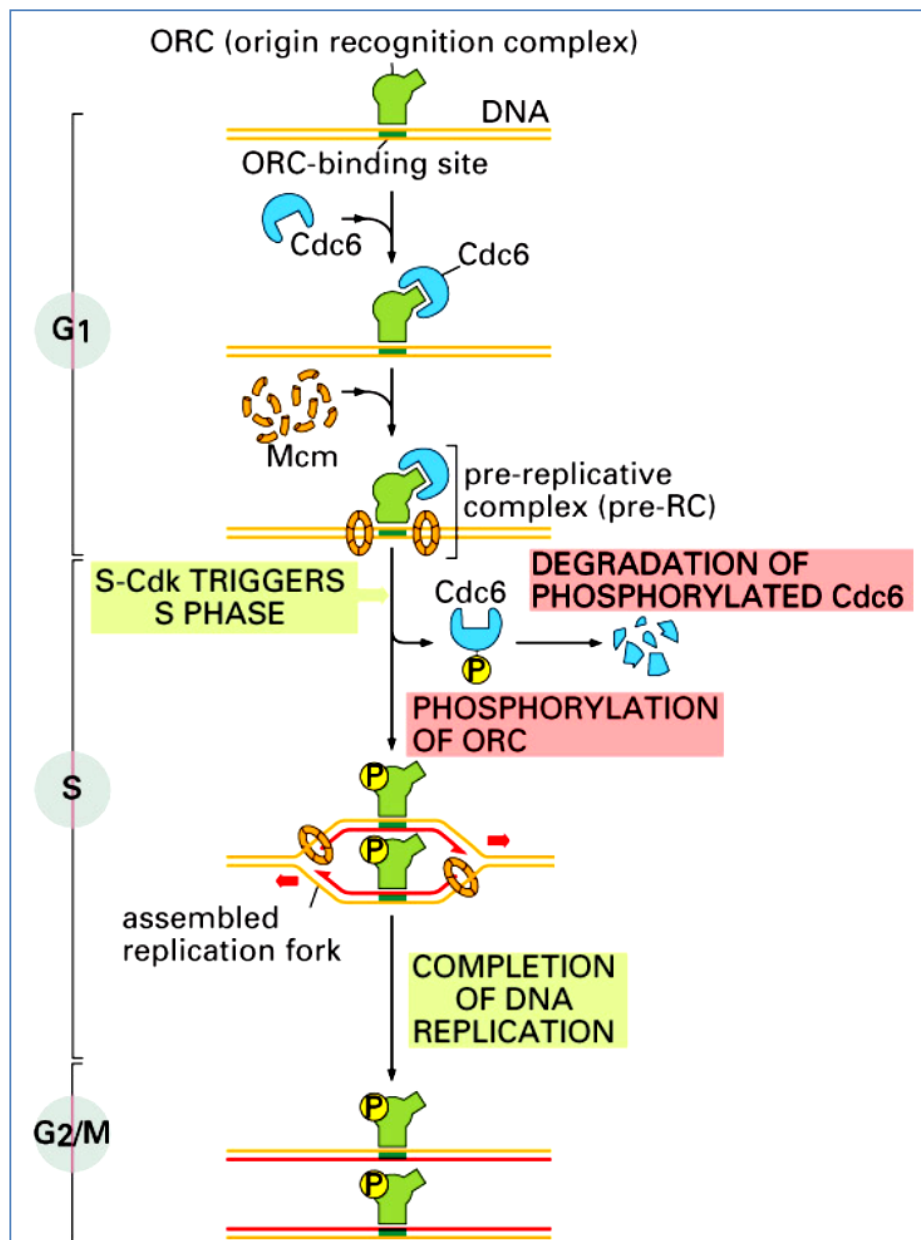


• G₁ Checkpoint: DNA damage prevents S-Phase Entry

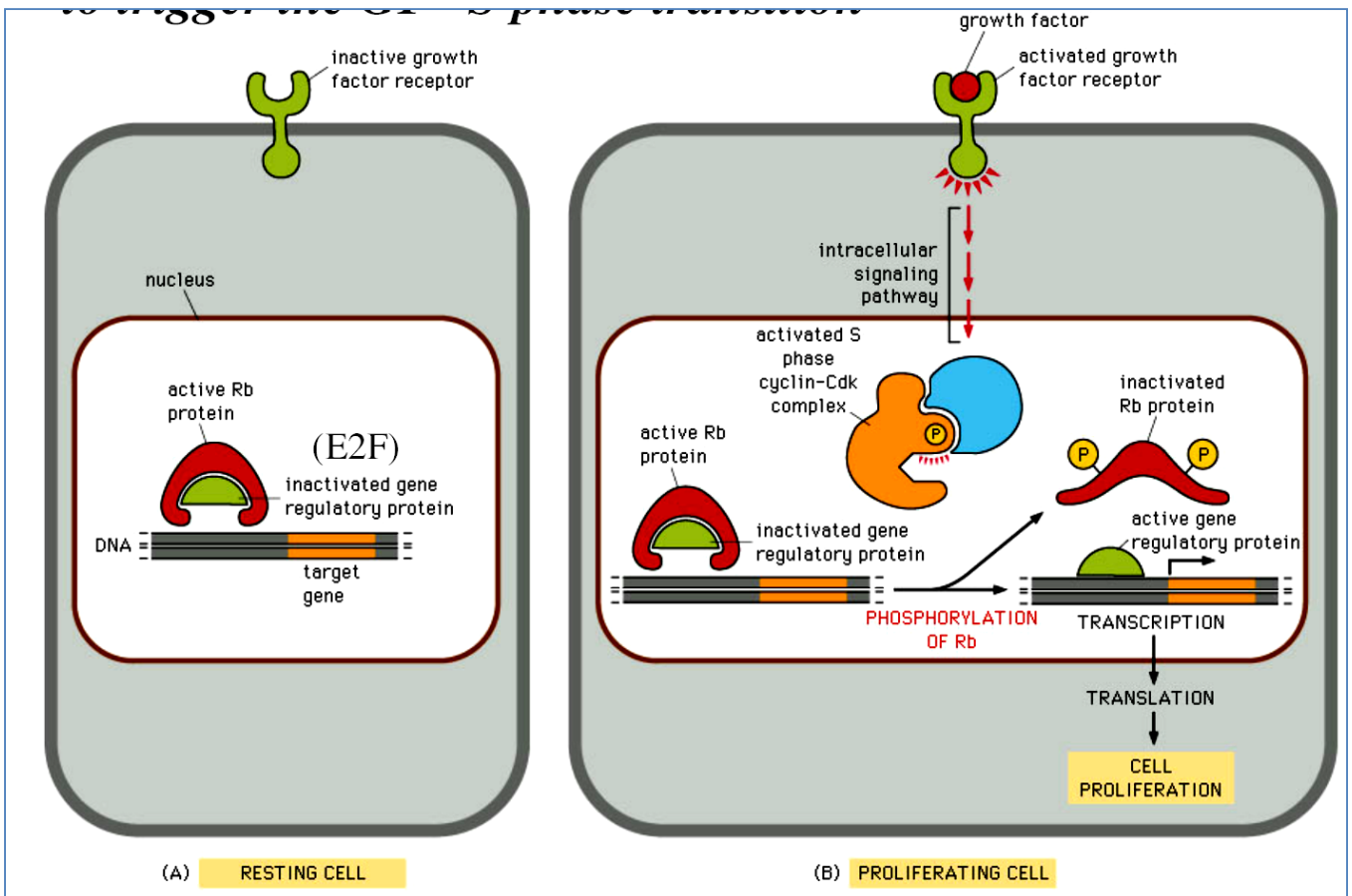
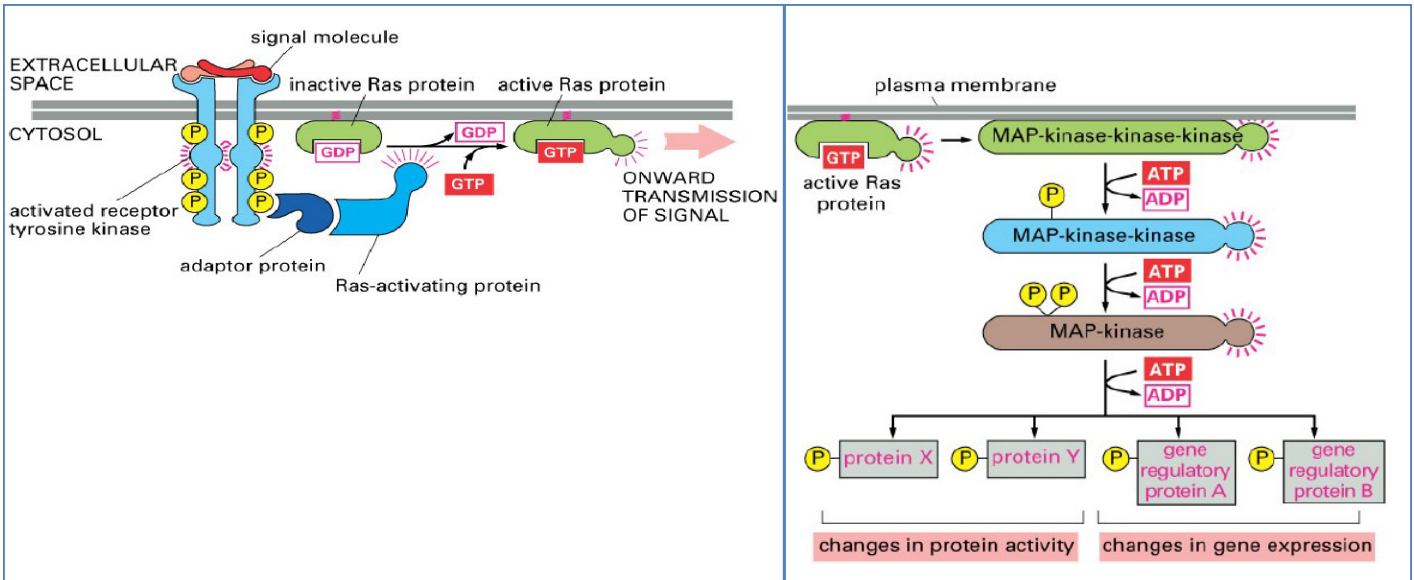
- Ensures **environment is favourable** for cell proliferation.
- Ensures **DNA is intact** before committing it to **replication (S-Phase)**
- **How?:** Damaged DNA causes the transcription & translation of a **Cdk Inhibitor Protein** that inactivates the **S-Cdk**
 - When DNA is damaged, specific kinases are activated and phosphorylate the p53 protein.
 - Activated **p53** stimulates the transcription of the gene for **p21**, a protein that temporarily **inhibits the S-Cdk**.
 - Because S-Cdk is necessary to trigger DNA replication in S-Phase, **inactivation of S-Cdk arrests the cell cycle in G₁ phase**.



- **Cdc6 Prevents DNA Replication** until G₁ checkpoint is satisfied:
S-Cdk then triggers replication by removing Cdc6 via phosphorylation.
 - Initiates DNA replication
 - Helps block rereplication
 - How?
 - Throughout the cell cycle, complexes of proteins - **ORCs (Origin Recognition Complexes)** are associated with the **Origins of Replication (ORI)** on each DNA molecule.
 - In **early G₁**, it acts as a landing pad for regulatory proteins including **Cdc6**
 - The other proteins that bind with ORC & form a **pre-replicative complex**.
 - When **Cdc6** is associated with the ORC it puts a safety switch on DNA replication.
 - Once the **G₁** checkpoint is **satisfied**, active **S-Cdk** then **removes** the **Cdc6** via **phosphorylation**, causing DNA polymerase to commence DNA synthesis.
 - S-Cdk also phosphorylates ORC preventing rereplication after firing.

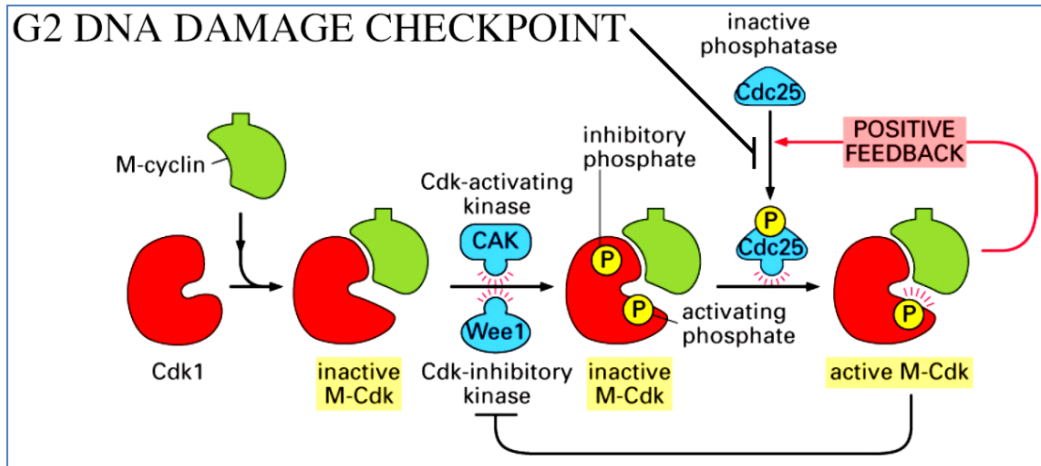


- **Rb-protein prevents transcription** of genes for proteins needed in S-Phase.
- **S-Cdk triggers transcription** by removing Rb-protein via phosphorylation:
 - When G₁ checkpoint is satisfied **AND** external growth-factors are present, an intracellular cascade is initiated:[refer to Wk12 CTL notes]
 - **(enzyme-linked receptor → Ras activated → MAP-Kinase cascade → removes Rb)**
 - Removal of Rb activates gene regulatory proteins – result in protein synthesis.



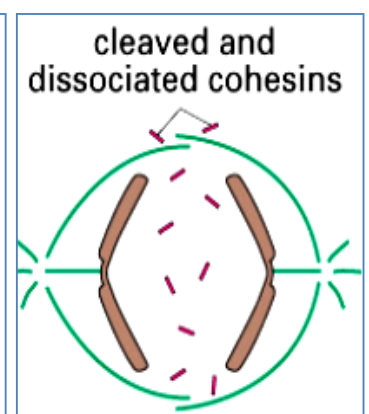
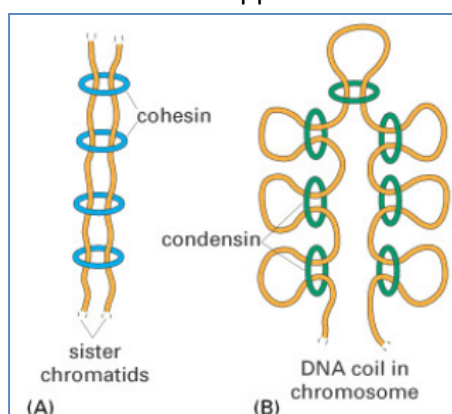
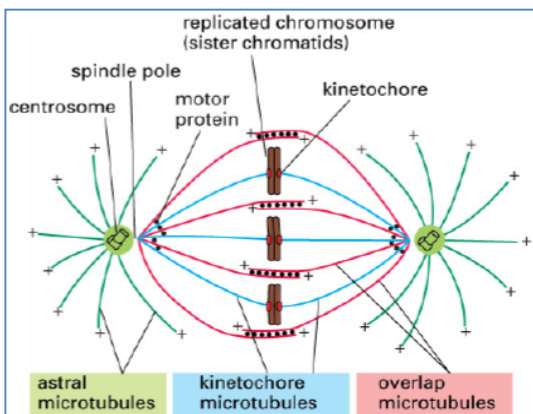
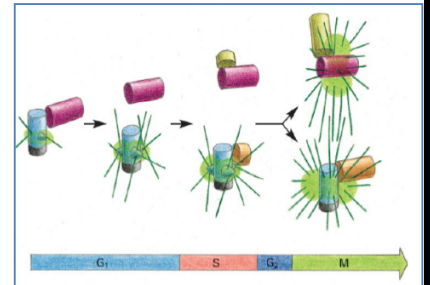
• **G₂ Checkpoint: M-Phase Entry**

- Ensures that cells don't enter **mitosis** until it has completed **DNA replication & repairs**.
- **How?:** M-Cdk is activated by the addition of a phosphor & inhibited by another phosphor.
- If DNA is good, a **Phosphatase Cdc25** removes the **inhibitory phosphor**, instantly activating the M-Cdk.
- If DNA is bad, phosphatase Cdc25 is inactive, & therefore so is M-Cdk.
- **Active M-Cdk** further **activates phosphatase Cdc25** & also **stops the Cdk-inhibitory kinase** from adding the inhibitory phosphor. → → triggers **MITOSIS**



The Centriosome

- **Centrosomes** are needed to **form robust mitotic spindles** to ensure even distribution of genetic material during mitosis.
- Consist of a **pair of Centrioles** (1 mother & 1 daughter)
- Their replication is semi-conservative, but the process is not known.
- Are responsible for the 'pulling apart' of the chromosomes during **anaphase**
 - Sister chromatids are held together by '**cohesin**'.
 - Mitotic **spindles grab** the **chromosomes** on either side at the **kinetichore**.
 - Spindles take up tension.
 - When this 'spindle checkpoint' is satisfied & all chromosomes are bound to spindles, the cohesin is cleaved & chromatids retract to opposite sides of the cell.



Regulation of Cell Fate

Proliferation/Division

- **Regulated process** of cytoplasmic duplication, followed by mitosis.
- Regulated by nutrients, secreted chemical messengers & environmental/local signals.
- Essential in development, growth, maintenance & repair.

Differentiation

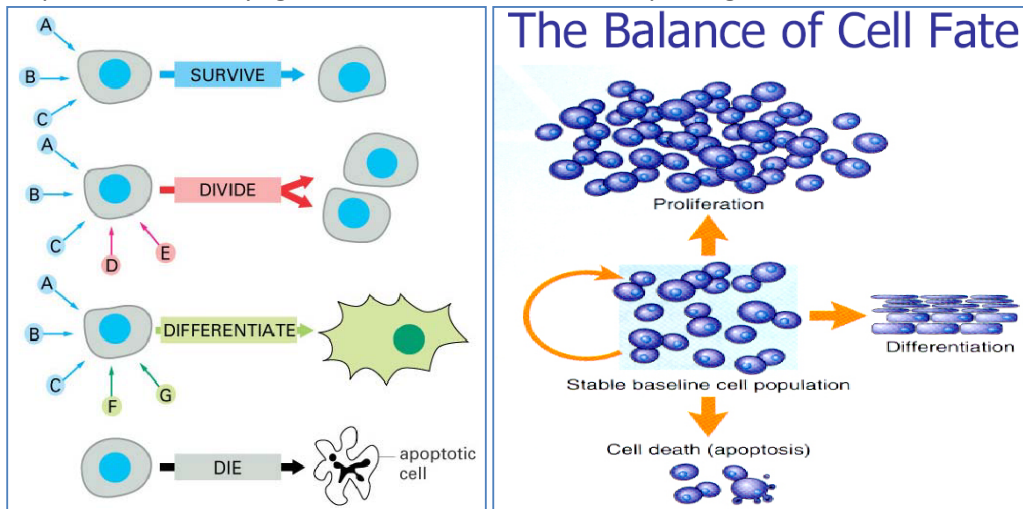
- **Regulated step-wise process** where cells **gain/lose specialised characteristics** (morphological or biochemical)
- Regulated by nutrients, secreted chemical messengers & environmental/local signals.
- Essential in the formation & maintenance of specialised tissues/organs

Terminal Differentiation

- **Regulated process** where cells differentiate but can no longer proliferate.
- Regulated by nutrients, secreted chemical messengers & environmental/local signals.

Apoptosis

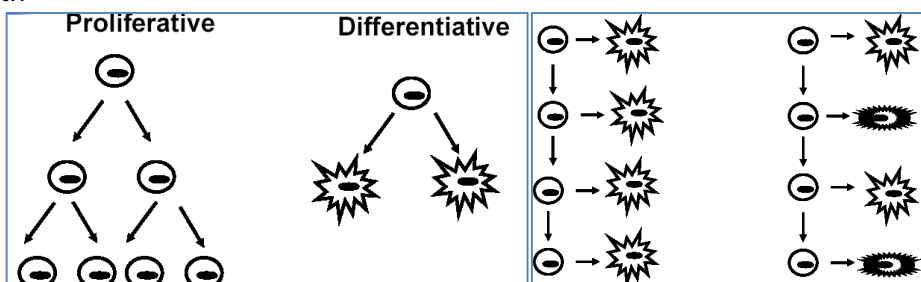
- **Regulated process** where cells die for the benefit of the organism.
- Regulated by nutrients, secreted chemical messengers & environmental/local signals.
- Essential process in embryogenesis, ovulation & mensuration, pathogenesis.



Imbalance of these 4 processes can result in necrosis and/or cancer

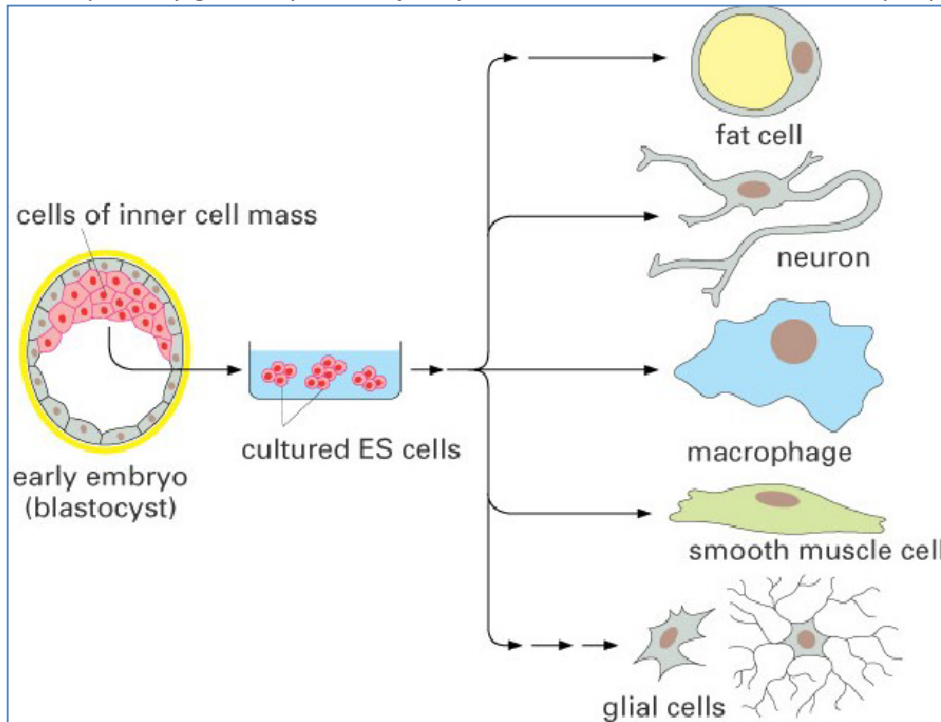
Stem Cells

- Can proliferate
- Can be determined
- Can differentiate into any type of cell.
- **Proliferation**
 - Proliferative - eg. Early embryogenesis
 - Differentiative – eg. Oogenesis (stem cells run out)
 - Both



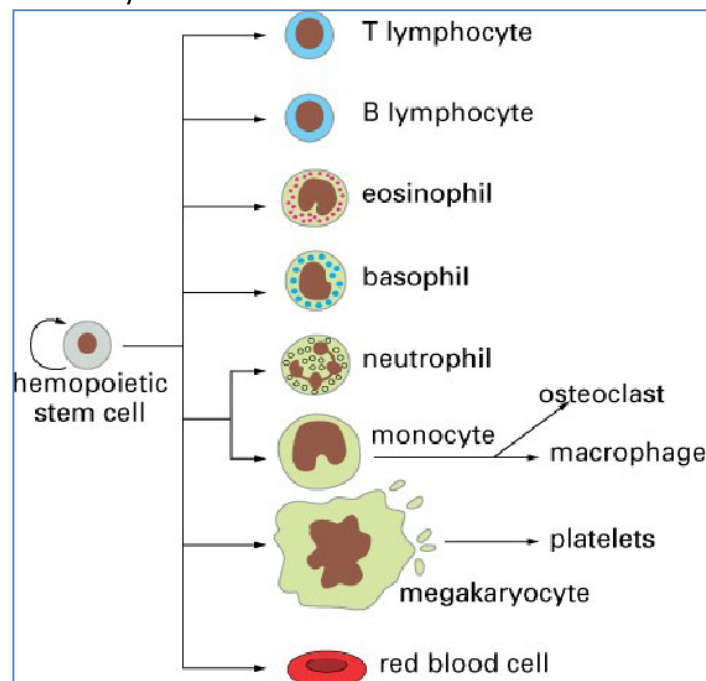
- **Determination**

- Where the cell is preset to a specific phenotype but has not yet differentiated.
- Determined cells are morphologically indistinguishable from stem cells.
- **Eg. Early embryogenesis** – before morulla stage, cells can become any human cell → **totipotent**
- -at the morulla stage, the cells are determined to become either a primary germ layer or trophoblasts; but have not yet differentiated.
- Also the primary germ layers are **pluripotent**=determined, but for multiple possible pathways.



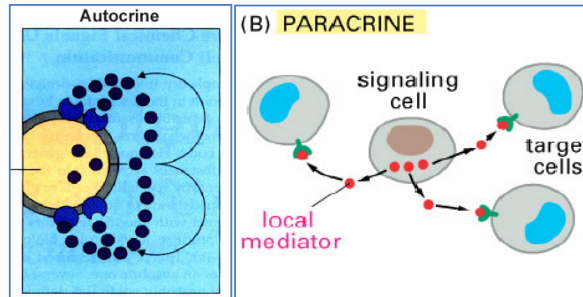
- **Differentiation**

- Once determined, stem cells will differentiate into that cell.
- **Eg. Adult immune system** – **hemopoietic stem cells** in bone marrow can differentiate into any of the immune-system cells.



Regulation of Cell Fate

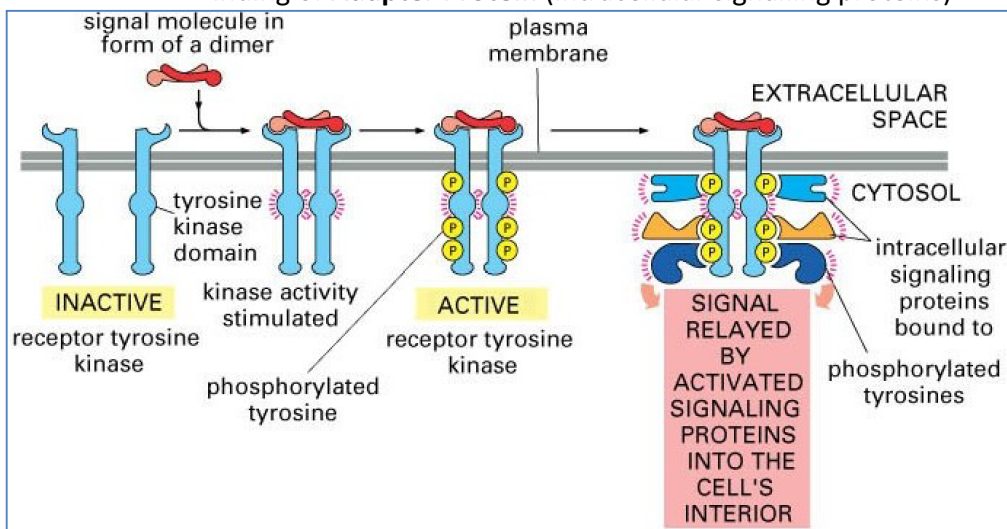
- **Cell Memory**
 - Gene expression is limited (determined) so can't differentiate.
- **Chemical Messengers – “Growth Factors”**
 - **Autocrine or Paracrine**



****note: Mitogens** → Stimulate proliferation only;
Growth Factors → Stimulate proliferation & other constructive processes**

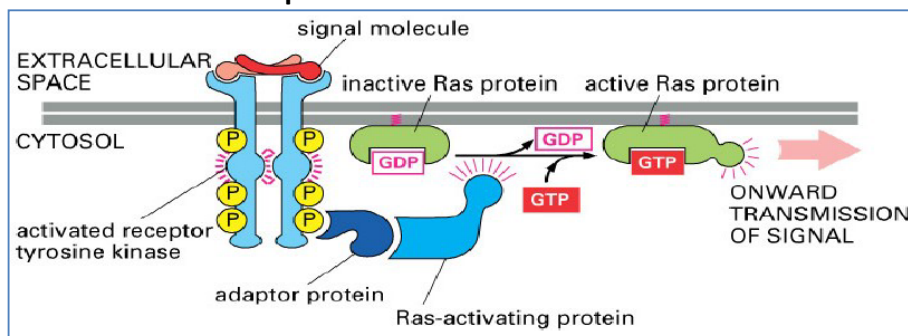
Enzyme-Linked Receptors

- Binding of **growth factor**
- **Dimerisation** of tyrosine kinase receptor
- **Autophosphorylation** of dimer – monomers phosphorylate each other
- Binding of **Adapter Protein** (intracellular signalling proteins)



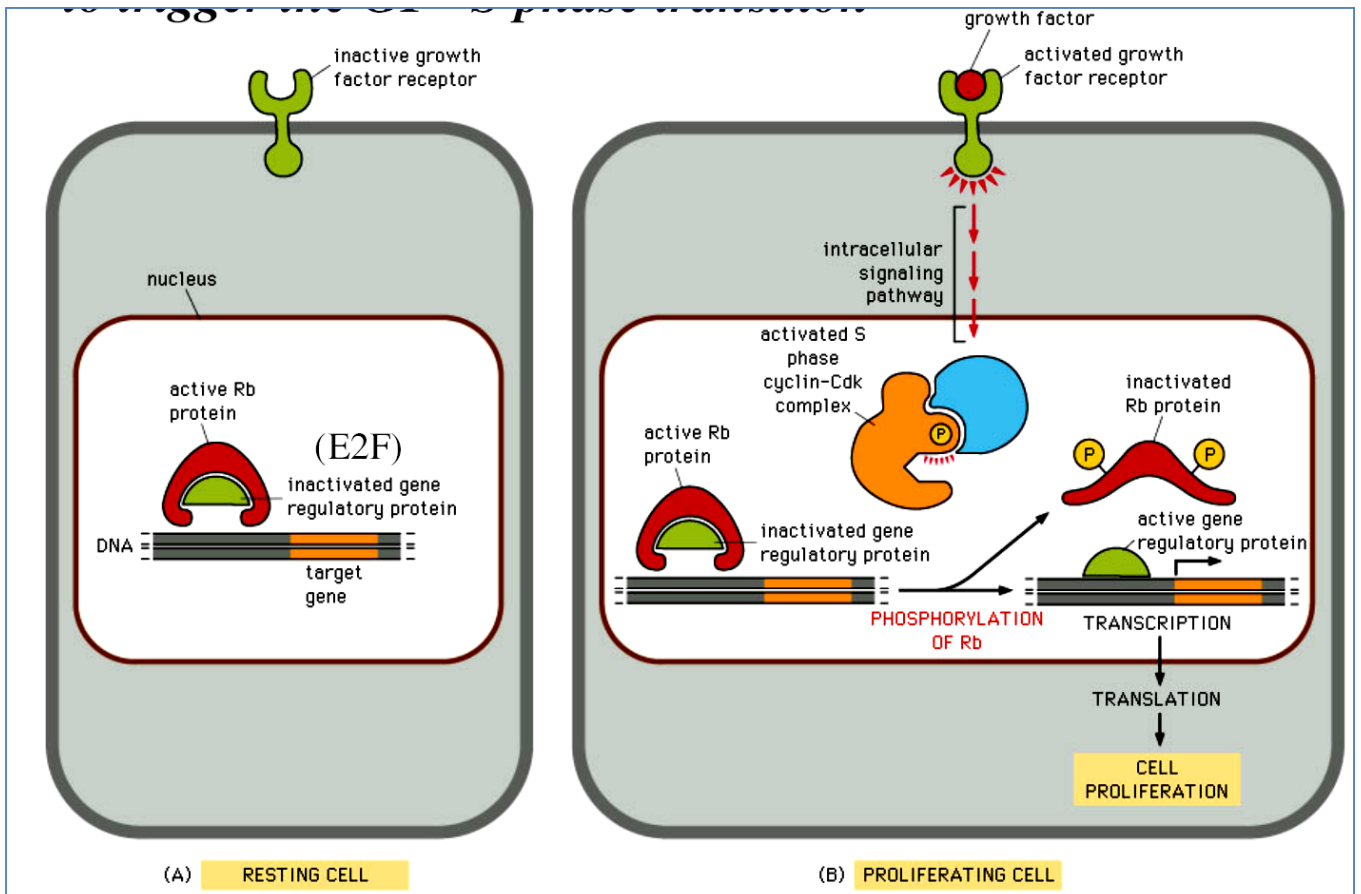
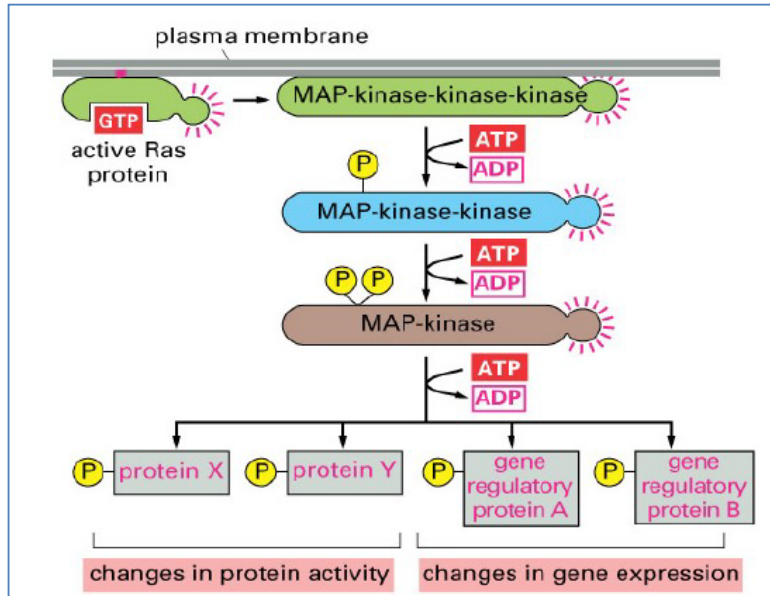
Activation of Ras

- Binding of **Ras-activating protein** to adapter protein
- **Ras loses GDP and binds GTP** → becoming active
- **Active Ras protein** initiates the **MAP-Kinase cascade**



▪ **MAP-Kinase cascade.**

- Active Ras protein **initiates** Mitogen-Activating-Protein-Kinase **cascade**.
- **MAP-Kinase-Kinase-Kinase** phosphorylates **MAP-Kinase-Kinase**
- **MAP-Kinase-Kinase** phosphorylates **MAP-Kinase**
- **MAP-Kinase** **inactivates** gene-inhibitory **Rb-Protein** via phosphorylation
- **Rb-Protein** releases **E2F-Transcription factor**, initiating transcription.
- Transcription of genes results in protein synthesis and proliferation.

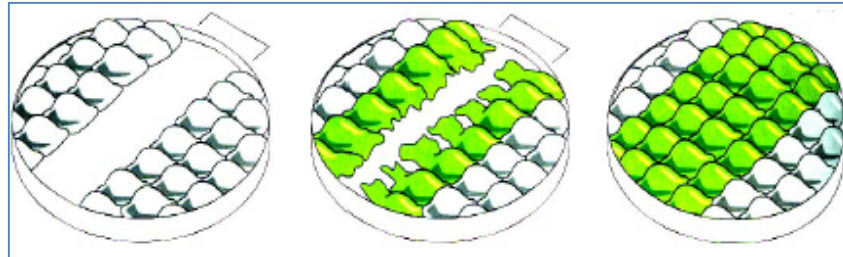


- **Positional Information**

- **Cell/Cell Contact**

- Signalling through gap junctions for gene transcription & proliferation
 - Also **contact inhibition** stops over proliferation.

- Eg. Experiment:

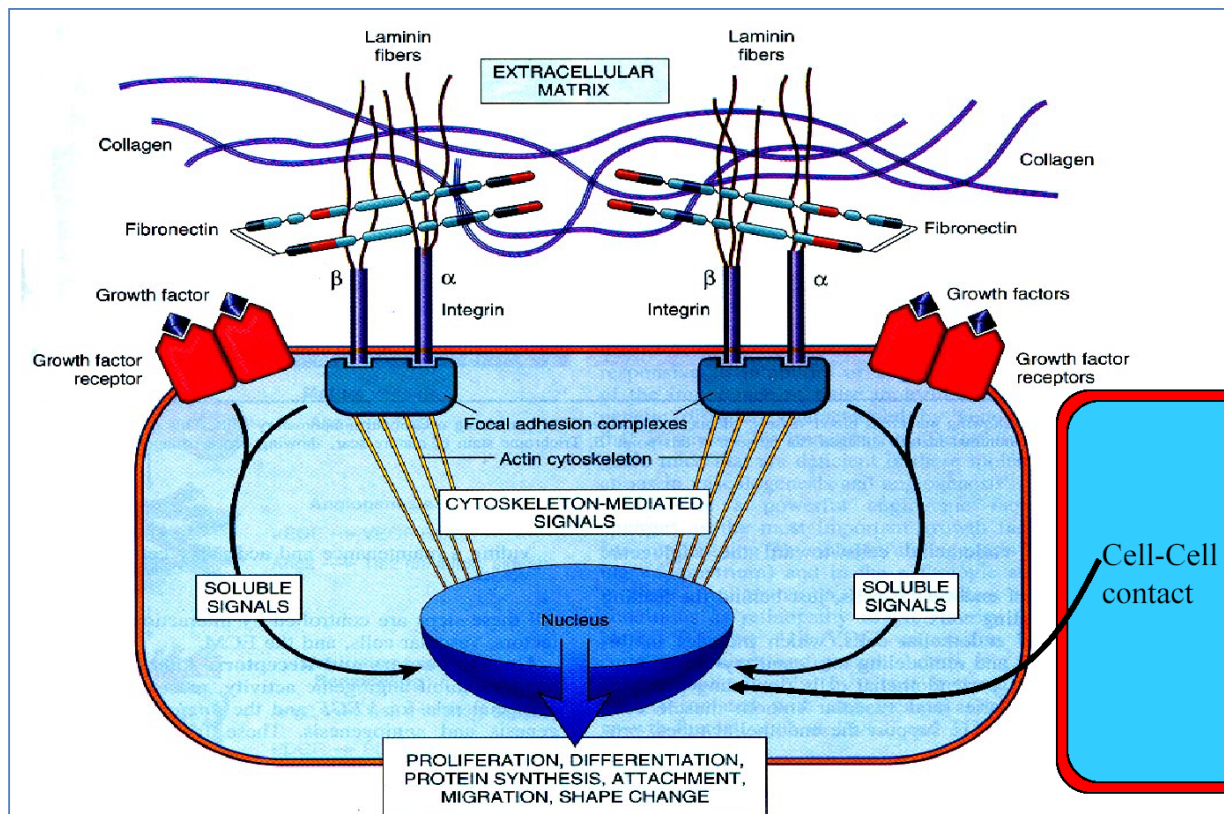
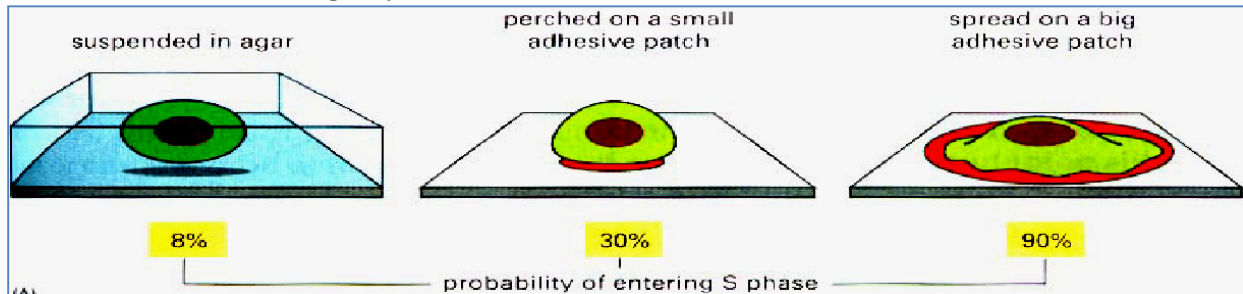


Cells scraped away → Cells grow back → Cells stop dividing once all-round contact is made.

- **Cell-Matrix Contact**

- Fluid, nutrients, waste diffusion medium, fibres guide direction of cell proliferation.
 - **Anchorage dependence** of cell division:

- Eg. Experiment:



Cancer, Cell Death & Cellular Ageing

Growth Characteristics of Normal Cells:

- Subject to **contact inhibition**
- Limited **lifespan**
- **Anchorage dependant**
- **Growth-factor** dependant
- **Able to apoptose.**

Growth Characteristics of Tumour & Cancer Cells:

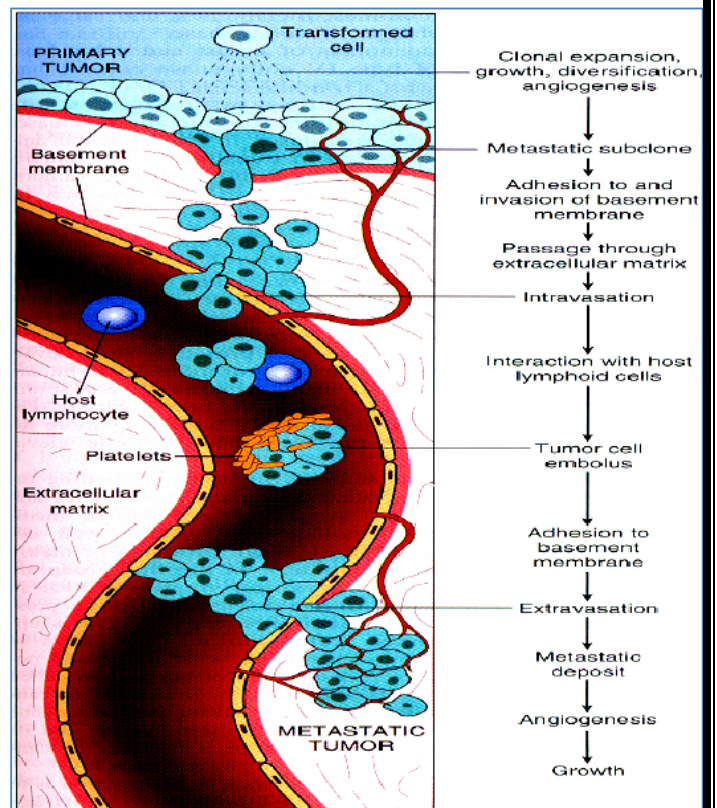
- **Not** subject to **contact inhibition**
- Unlimited **lifespan**
- **Anxhorage Independent**
- **Unresponsive** to **growth-inhibitors**
- **Unable to apoptose.**
- **Differentiate** independently.
 - Differentiated tumours = **teratomas**.
 - May form teeth, hair, bone, nails, toes, brain matter etc.

General Characteristics of BENIGN TUMOUR CELLS:

- **Lower mitotic index** than cancerous tissue.
- **Well-defined capsule**
- **NOT INVASIVE**
- **Well differentiated** – still exhibit characteristics of their normal cells of origin.
- **NOT METASTATIC**

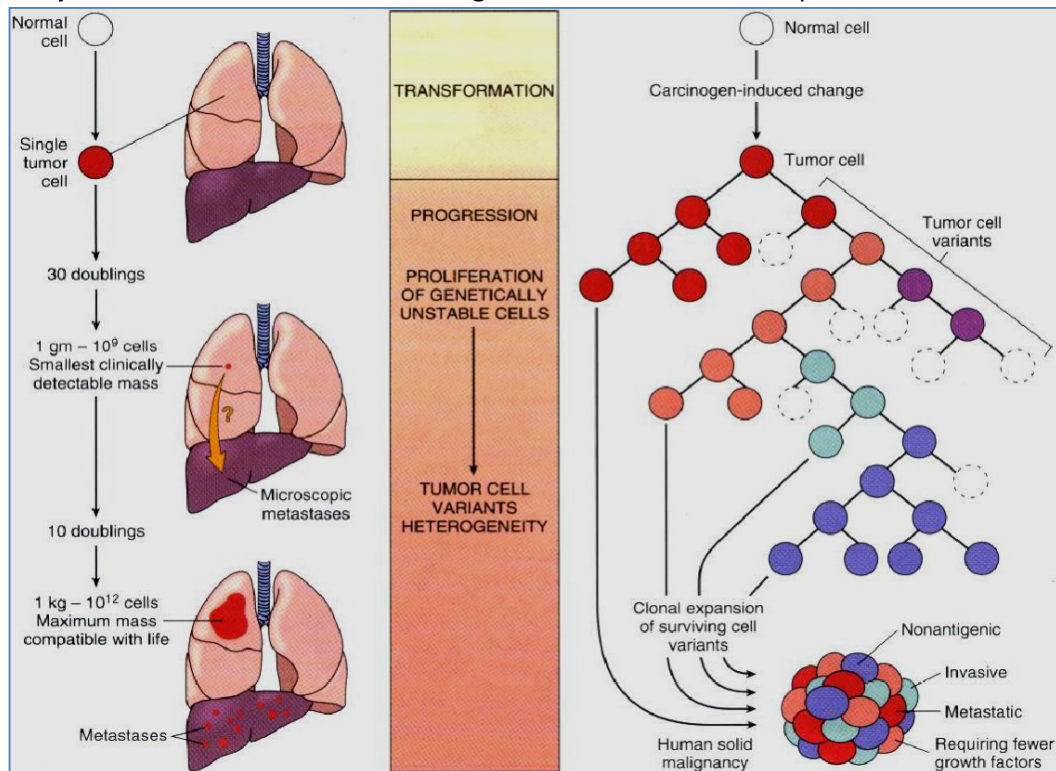
General Characteristics of METASTATIC CANCERS:

- **Abnormally high mitotic rate**
- **Show signs of de-differentiation**
 - have features of **primordial stem-cells**
- **Disordered growth patterns**
 - Grow as a chaotic mass in all directions
- **Can be **Metastatic** (Colonise distant tissues)**
 - Cells can break away from primary tumour & travel through blood/lymph.
 - Establish new tumours (secondaries) called **metastases**.
- **Show gross genetic abnormalities.**
 - Aberration in chromosome number
 - Deletions, translocations in genome
- **Grow in the absence of growth factors.**
- **Are Immortal**
 - Escape cellular ageing (senescence)
 - Many also don't apoptose
- **Malignant phenotype is heritable.**
 - Cancer cells propagate through many mitotic divisions without losing cancerous features.



Cause of Cancer

- Genetic **mutations** that are **non-lethal** to the cell.
- Results from **mutagens**:
 - Chemicals
 - Radiation
 - Carcinogens
 - Free-Radicals
 - Microbes (viruses)
 - Inherited.
- **DNA damage** = dysregulated growth patterns → uncontrolled proliferation.
 - **Damage to regulatory genes**:
 - Results in **loss / gain of function** of:
 - **DNA repair Genes**
 - **Cell Ageing Genes**
 - **Protooncogenes**
 - **Growth-inhibiting (anticancer) Genes**
 - **Apoptosis Genes**
- **Clonal expansion**: cancers arise from a single cell with uncontrolled proliferation.



Defects in DNA Repair Genes:

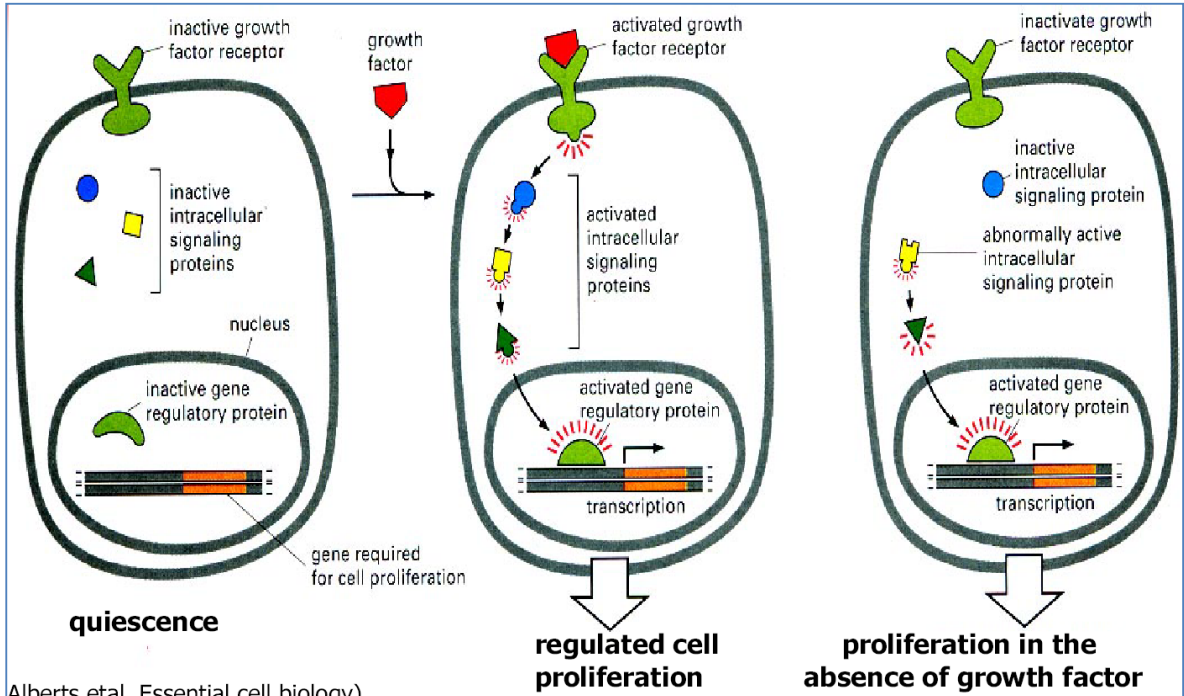
- Genetic mutations happen all the time.
- However, DNA is repaired by the cell.
- Defective DNA repair can lead to uncorrected mutations → cancer

Defects in Cell Ageing Genes:

- Cellular age is determined by the number of divisions.
- When cells age, they enter **senescence**: a terminal non-dividing state.
- Mutations that enable the cell to avoid senescence → cancer.

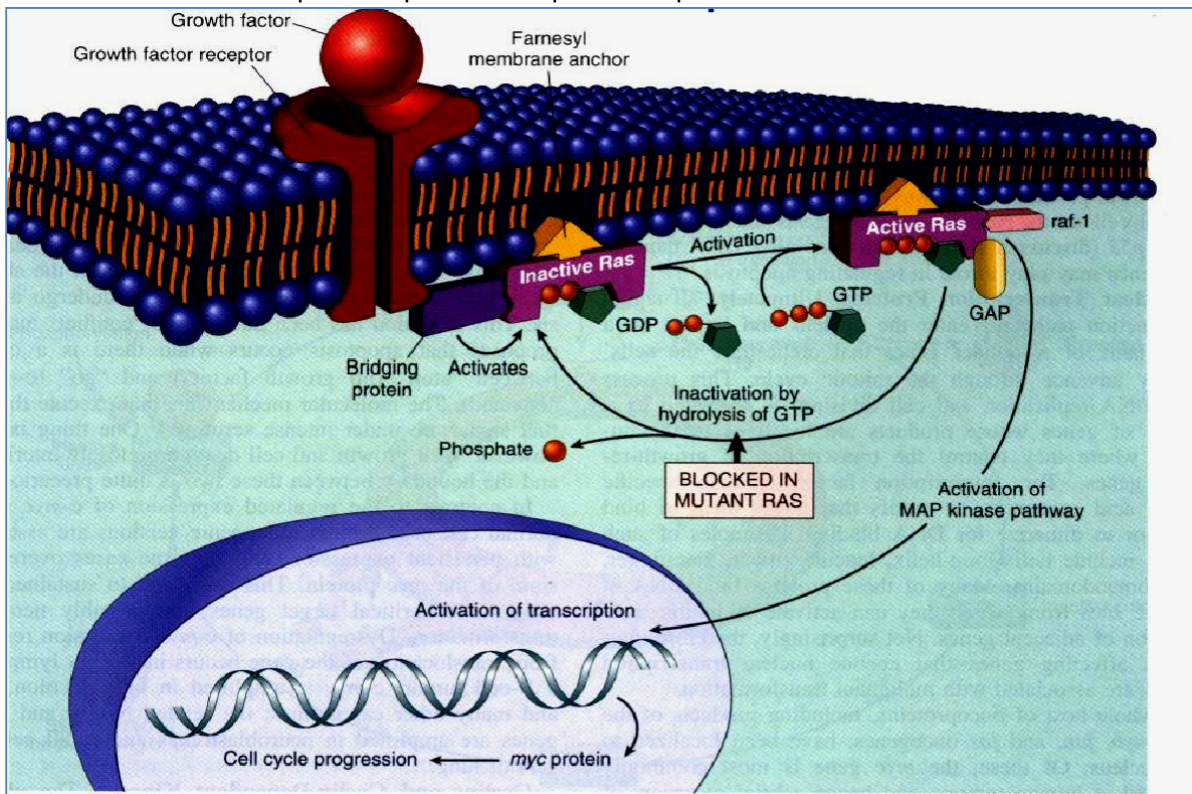
Gain of Function in a Proto-oncogene:

(Proto-oncogene: a normal gene that can become an **oncogene** due to mutations or increased expression. An **oncogene** is a protein encoding gene, which — when deregulated — participates in the onset and development of cancer. Proto-oncogenes code for proteins that help to regulate cell growth and differentiation → such as Ras)



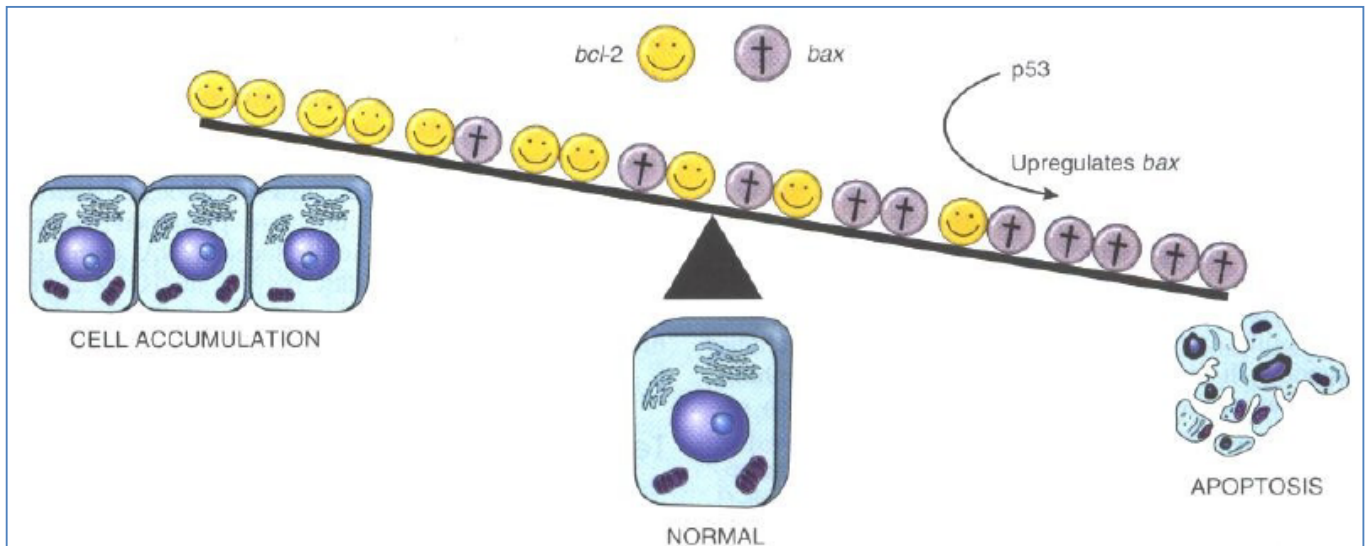
Oncogenic activation of Ras:

- Active Ras protein loses its hydrolysing ability and cannot be turned off.
- Results in over-transcription of proteins required for proliferation.



Abnormal Expression of Apoptosis-Regulating Genes: (Bcl-2)

- Over-expression of anti-apoptotic regulators
- Under-expression of pro-apoptotic regulators (Bax & Bak) → initiates the CASPASE CASCADE
 - Leads to abnormalities in regulation of cell proliferation.



Cell Ageing

- Progressive alterations in structure → loss of functional capacity (senescence) ending in death.

- **On a Cellular Basis:**

- **Changes in Structure & Function:**

- **Decrease in:**

- rate of mitochondrial oxidative phosphorylation
 - nucleic acid synthesis
 - synthesis of proteins (structural/enzymes/receptors/transcription factors)
 - effectiveness of DNA repair mechanisms

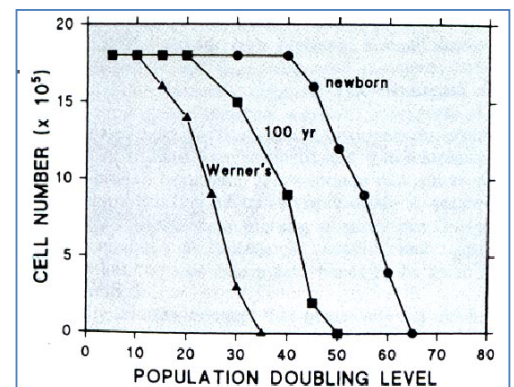
- **Increase in:**

- incorrectly folded proteins
 - irregularly shaped nuclei.

- **Changes in organelle structure & function**

- **Senescence:**

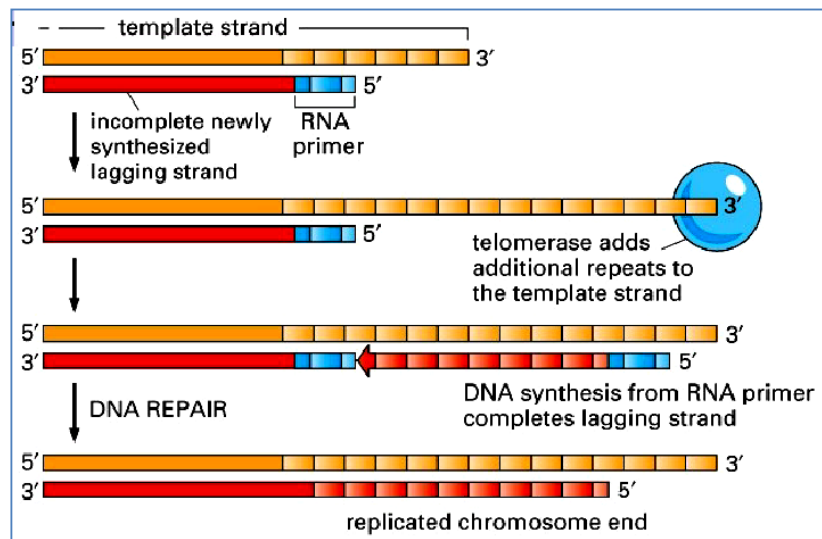
- Irreversible arrest of cell division in G1 phase.
- Non-responsive to mitogens
- Abnormalities in morphology, metabolism & functions
- Increased resistance to apoptosis
- Correlation between # of divisions & senescence.
 - Suggests that # of divisions is limited & decreases with age.



- **Cellular Clocks (the cause of senescence??):**

- **Telomere Replication:**

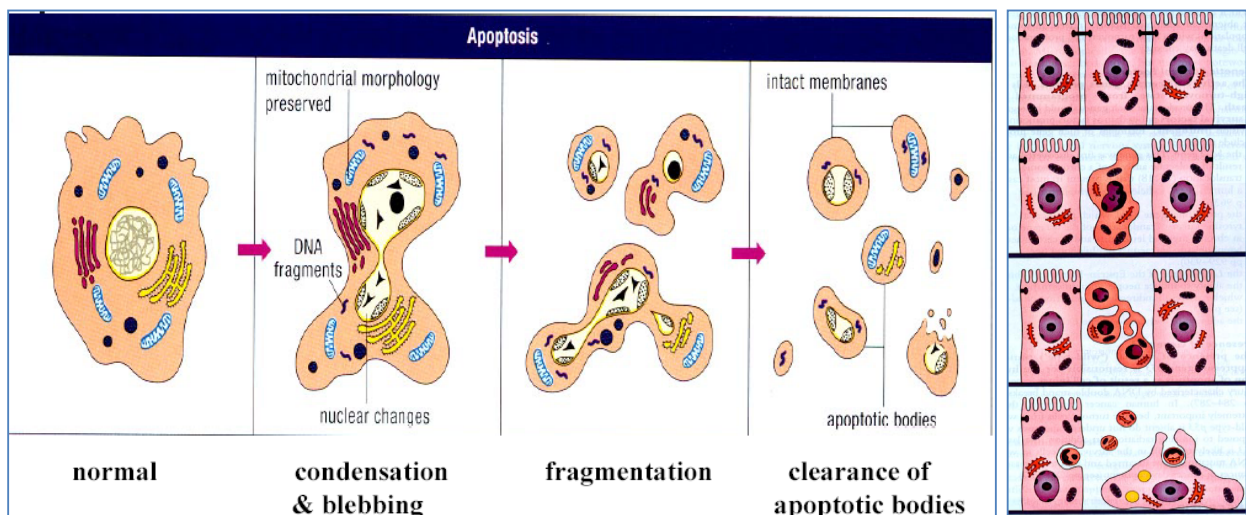
- **Telomere:** *The non-coding end-region of a chromosome-protects the start of the coding sequence from shortening during successive replications.*
 - However, each time DNA replication takes place, the telomere itself gets shorter.
 - **Telomerase** counters this by adding repeats to the template strand, allowing telomere elongation on the new DNA strand.
 - Unfortunately, **telomerase activity decreases with # of cell divisions.**



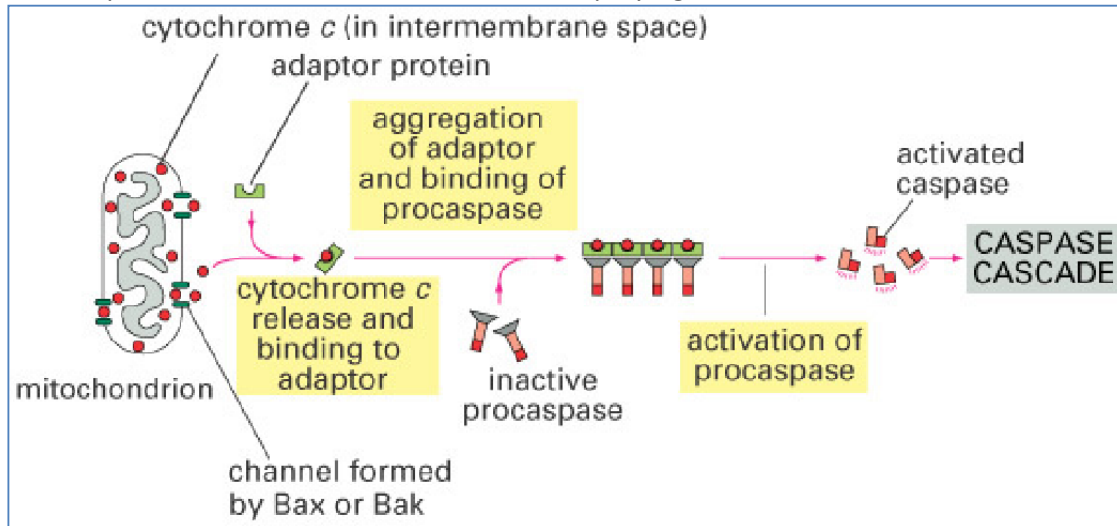
- **Cell Death:**

- **Apoptosis**

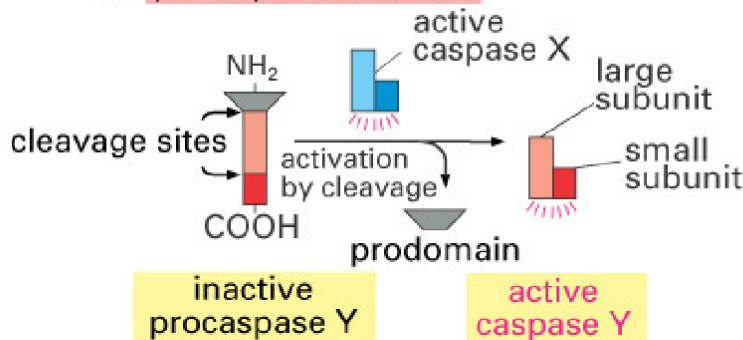
- Cells that undergo apoptosis shrink & condense, dying neatly without damaging neighbours.
 - Normal process
 - Regulated
 - Energy dependent
 - Enzyme dependent (requires gene expression)
 - Ordered disassembly
 - Minimal inflammation
 - Minimal scarring
 - Apoptotic bodies attract phagocytes (eg. Macrophages) and are engulfed/phagocytosed.



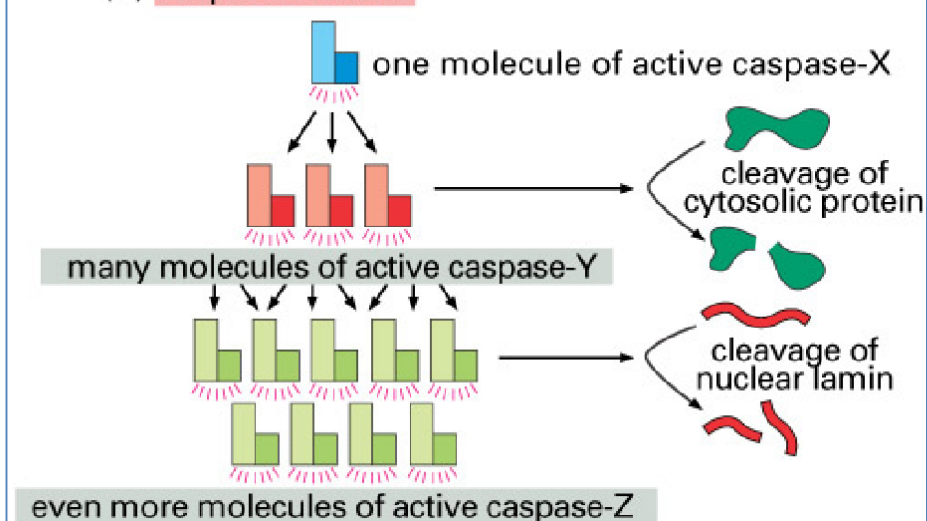
- **Regulated by CASPASES:**
 - Proteolytic enzymes that cut up proteins & nuclear laminin. (nuclear envelope)
- Initially caspases are created as inactive enzymes called **procaspases**.
- The activation of procaspases is regulated by the **Bcl-2** protein family (**Bax & Bak**).
- Bax & Bak increase outer-mito-membrane permeability → releases **cytochrome-C** into cytosol
- **Cytochrome-C** then binds to **adaptor proteins** → **activates procaspases** → **active caspases**
- Active **caspases activate other procaspases** → causes an explosive chain reaction (cascade).
- Caspase cascade → is destructive, self-amplifying, and irreversible.



(A) **procaspase activation**

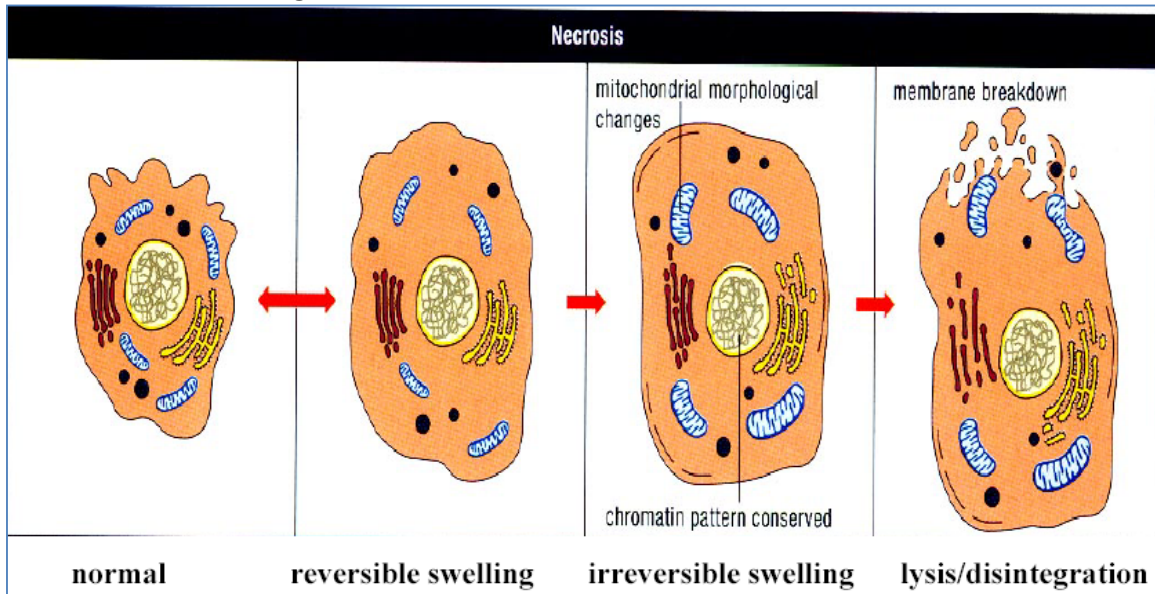


(B) **caspase cascade**



- **Necrosis**

- Cells that die from acute injury typically swell & burst, spilling their contents.
 - Abnormal process (pathophysiological)
 - Unregulated
 - Energy independent
 - Enzyme independent (doesn't require gene expression)
 - Chaotic destruction
 - Activates inflammatory response
 - Results in scarring.



Microbial Diversity

- Some bugs are good (even essential) and some bugs are bad.
- Organisms capable of causing disease are **pathogens**

Normal Flora (commensals)

- Heavily colonise skin – armpit, perineum, interdigital areas
 - Nose and oropharynx
 - GI Tract
 - Uro-genital tract.
- Are normal at certain places where they are not harmful.
 - However when they colonise an area where they shouldn't, they cause disease (nosocomial infection).
 - Known as opportunism.

Pathogenesis

- The biochemical mechanisms whereby microbes (bacteria, fungi, parasites & viruses) causes disease.
- **Virulence**: the propensity of a microbe to cause infection → disease.

Steps to disease:

- I. Entry**
 - Oral
 - Skin
 - Trans-placental
 - Inhalation
 - Inoculation (wound/skin penetration)
 - Sexual
- II. Colonisation**
 - Breach of skin/epithelia/conjunctiva
 - Attachment
- III. Persistence + avoiding host defences.**
 - Beat natural barriers – flushing, mucous + cilia, stomach pH, Lysosomes in saliva, etc.
- IV. Replication**
 - Mucosal (GI tract)/systemic (blood)/nerves (viruses)/cerebrospinal fluid (meningitis)
- V. Dissemination – (Host-Host)**
 - Faecal-oral (diarrhoea), Aerosols (sneezing), Sexual (intercourse)
 - Depends on:
 - Organism size
 - Ability to survive in external environment
- VI. Cause Disease**
 - Can release toxins – either local effects / or systemic
 - Can cause unusual cellular activity
 - Can cause tissue damage

Host-Parasite Interactions:

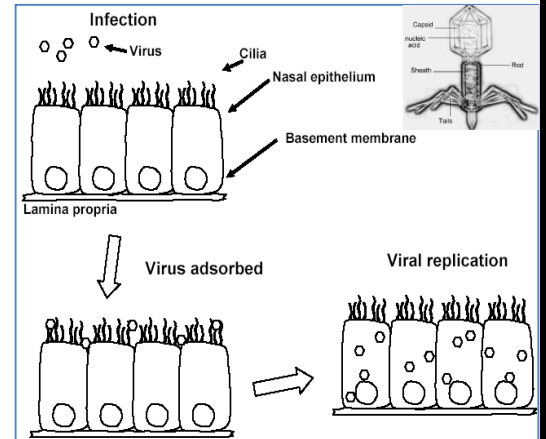
- 1) Colonised, no disease, no illness (asymptomatic)
Eg. Helicobacter – in stomach
- 2) Colonised, disease, no illness (asymptomatic)
Eg. Chlamydia & other genital tract infections.
- 3) Colonised, disease, illness (symptomatic)

The Organisms

• Prokaryotes:

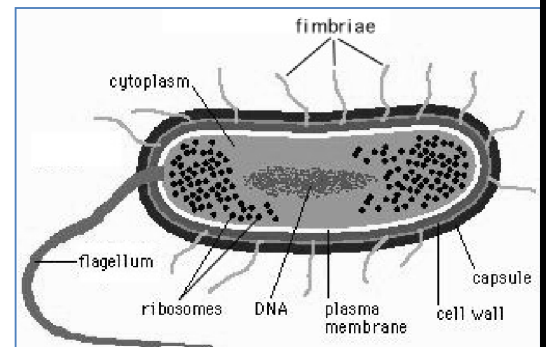
○ Viruses

- Very small
- Nucleic acid inside protein coat (DNA or RNA)(ss or ds)
- Complete parasitic dependency
- Replicates inside cell - but metabolically inert in external environment.
- Need close/direct contact
- Need a moist environment
- Lyses host cells and then infects more.
- Respiratory route / oral / inoculation / sexual transmission.



○ Bacteria

- Larger than viruses
- Visible under light microscope
- Living → replicate by binary fission
- Can be killed
- Intracellular or extracellular
- Motile
- Can produce toxins
- Contain DNA, Ribosomes + Inclusions – no true nucleus
- Resulting disease often more severe.



• Eucaryotes:

○ Protozoa

- Single-Celled **Animals**
- Larger than bacteria – still small enough to live intracellularly.
 - Can also live extracellularly.
- Vectors / faecal-oral route → most infections occur tropically.



○ Helminths

- Multi-celled, often macroscopic organisms.
- Complex body organisation and reproduction (some have sexual dimorphism)
- Difficult for immune system to destroy – too big.
- Cause inflammation
- Are often never eliminated.

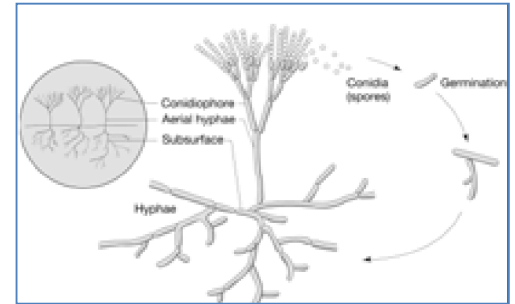


○ **Fungi**

- Thousands of species
- Few are pathogenic to humans
 - 20ish are fatal.
- Resulting Mycoses (disease) either:
 - Superficial
 - Cutaneous
 - Subcutaneous
 - Systemic
 - Opportunistic – seen in compromised hosts

-Depending on site of infection.

- Exist as branched filamentous forms, or yeasts
- Asexual spores (conidia)
- Spores commonly inhaled & cause infection.



Biology:
Epithelial Tissues

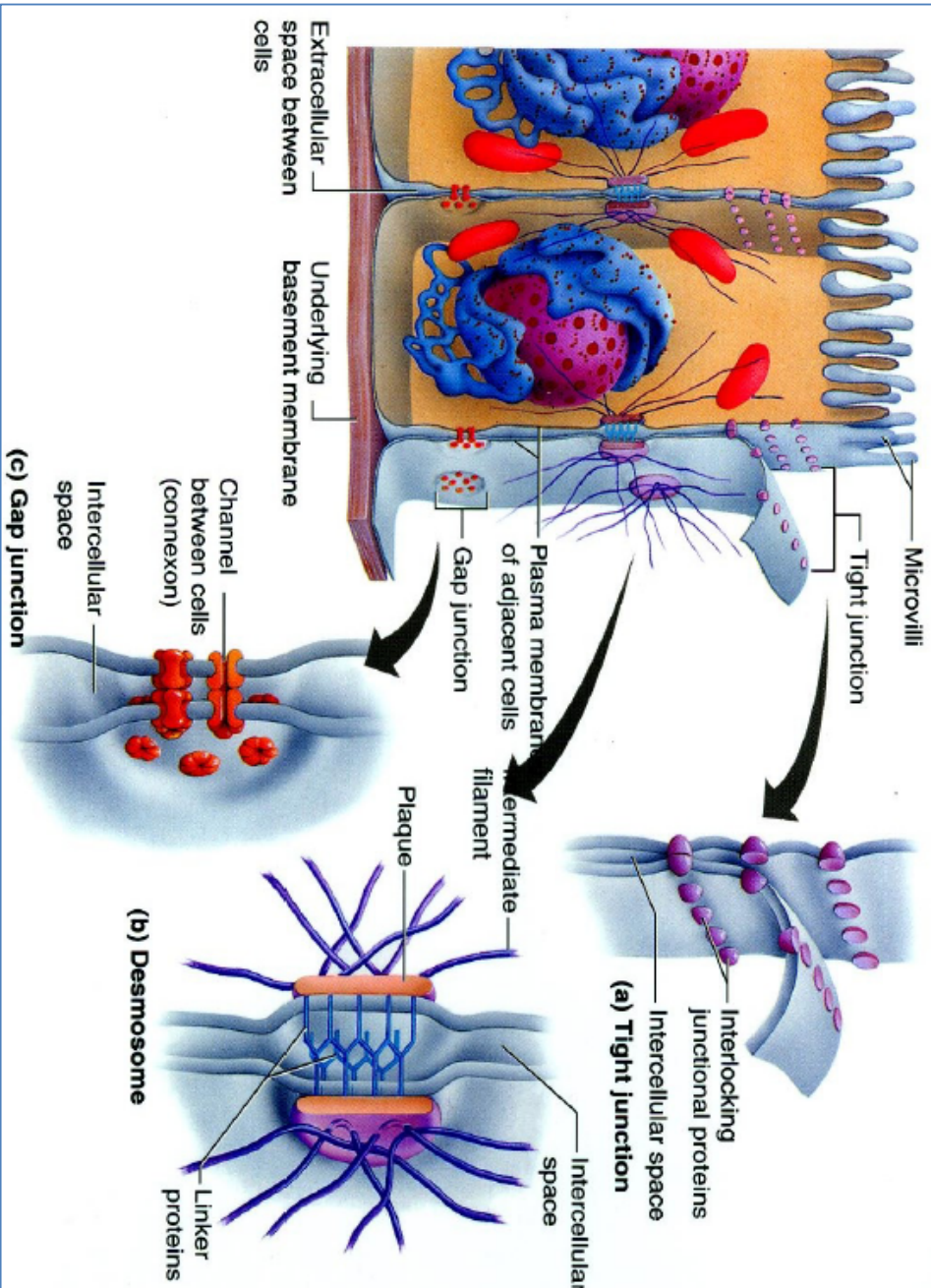
#1. Epithelial Tissues (epithelium):

- One of the 4 basic tissue types (nerve/muscle/connective/epithelial)
- A sheet/sheets of cells that covers a body surface or lines a body cavity.
- Where? : a) **Covering & lining epithelium**
b) **Glandular epithelium**
- Epithelia are avascular, but all epithelia "grow" on an underlying layer of vascular connective tissue.
- Form boundaries between different environments. (interface tissue)
- * Nearly all substances received or given off by the body must pass through an epithelium.
- **General Functions:**
 - Protection
 - Absorption
 - Filtration
 - Excretion
 - Secretion
 - Sensory reception

Characteristics of Epithelium:

- Epithelium differ from other types of cells in that they:
 - o **Exhibit Polarity:** (apical-basal polarity)
 - Have an **apical surface**
 - Surface **exposed to the inside** of the lined cavity.
 - Most have **microvilli** (finger-like extensions of the plasma membrane)
 - Some have **cilia** (arms that propel substances in 1 direction – eg. trachea)
 - o Power & recovery strokes
 - Have a **basal surface**
 - Surface facing connective tissue **on the outside** of the lined cavity.
 - Supported by a **Basement Membrane:**
 - o Lining the basal surface is a thin supporting sheet called the **basal lamina** -determines which molecules can diffuse through the basal membrane.
 - o Below the basal lamina is the **reticular lamina** – fine network of collagen fibres belonging to the underlying connective tissue.

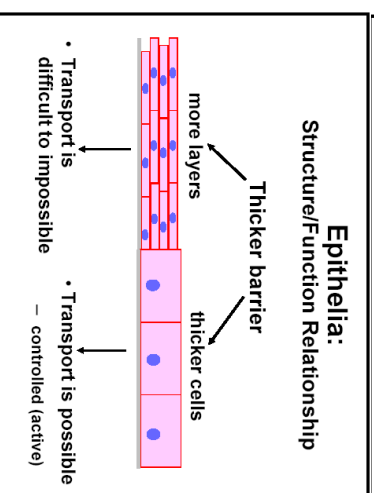
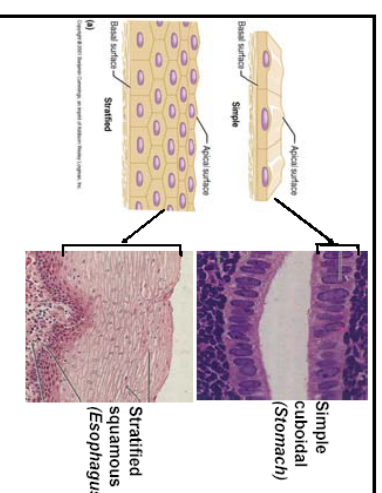
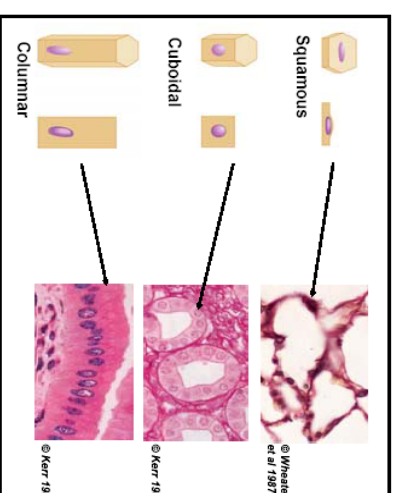
- **Bound by specialised contacts:**
 - Tight junctions – maintain polarity – protect basal side from apical environment.
 - Desmosomes – resist mechanical forces – holds cells together
 - Gap junctions – Allows intercellular transfers & communication.
- **Supported by Connective Tissue:**
 - Provide support
 - Reinforces the epithelial sheet
 - Resists stretching/tearing forces
 - Defines epithelial boundary.



Classification of Epithelia:

- Classed on a combination of the number of cell-layers present and the shape of the cells:

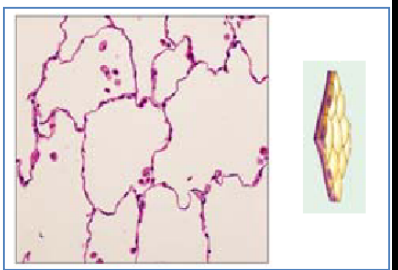
- Shape:
 - Squamous
 - Flat, tile-like. (fried egg)
 - Flat central nucleus
 - Cuboidal
 - Box-like shape
 - Spherical central nucleus
 - Columnar
 - Column/prism shaped
 - Elongated basal nucleus
- Layering:
 - Simple:
 - Single layer.
 - Common in high-secretion/absorption/filtration areas. (requiring a thin epithelial barrier for high diffusion)
 - Not usually for protection.
 - Stratified:
 - Multiple layers.
 - Common in high-abrasion areas for protection (eg. skin/mouth)
 - Named by the shape of the cells in the apical layer.
 - Pseudostratified:
 - Seemingly layered but is still simple (all cells touch the basal lamina)
 - Generally columnar.



Epithelia Combinations + Their Functions/Locations:

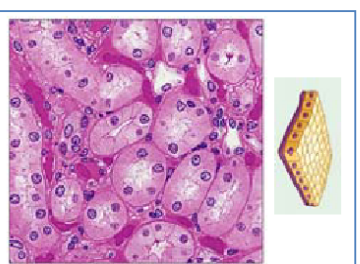
- Simple Squamous:

- Diffusion / Filtration / Friction-reducing lining in lymphatic & cardiovascular systems.
- Present in kidneys, lining of heart, blood vessels, alveoli, lymphatic vessels & serosae.



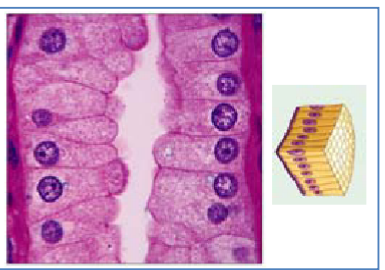
- Simple Cuboidal:

- Secretion / absorption
- Present in kidneys, ducts, secretory portions of small glands, ovary surface.



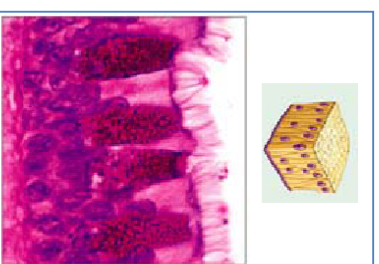
- Simple Columnar:

- Many contain cilia
- Secretion / absorption
- Ciliated:
 - Line small bronchi, uterine tubes, regions of the uterus
- Non-Ciliated:
 - Line the digestive tract and the gallbladder.



- Pseudostratified Columnar:

- Cells with different heights (but all touch basal lamina)
- Nuclei are seen at different levels
- Secretion & propulsion of mucus.
- Ciliated:
 - Trachea
- Non-Ciliated:
 - Sperm-Carrying Ducts

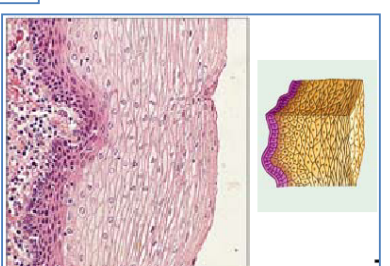
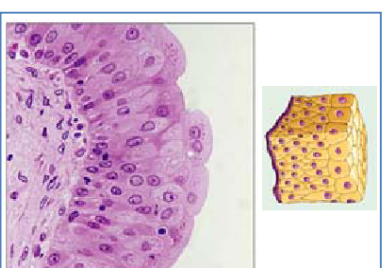


- Stratified Squamous:

- Thick membrane (multiple layers)
- **Protects areas subject to abrasion.**
- External part of **skin's epidermis / oesophagus lining / mouth / vagina**

- Transitional Epithelia:

- Multiple layers
 - **Basal cells = Cuboidal**
 - **Apical cells = Dome shaped**
- **Stretches** to permit expansions / contractions
- Lines the **urinary bladder / ureters / part of urethra**



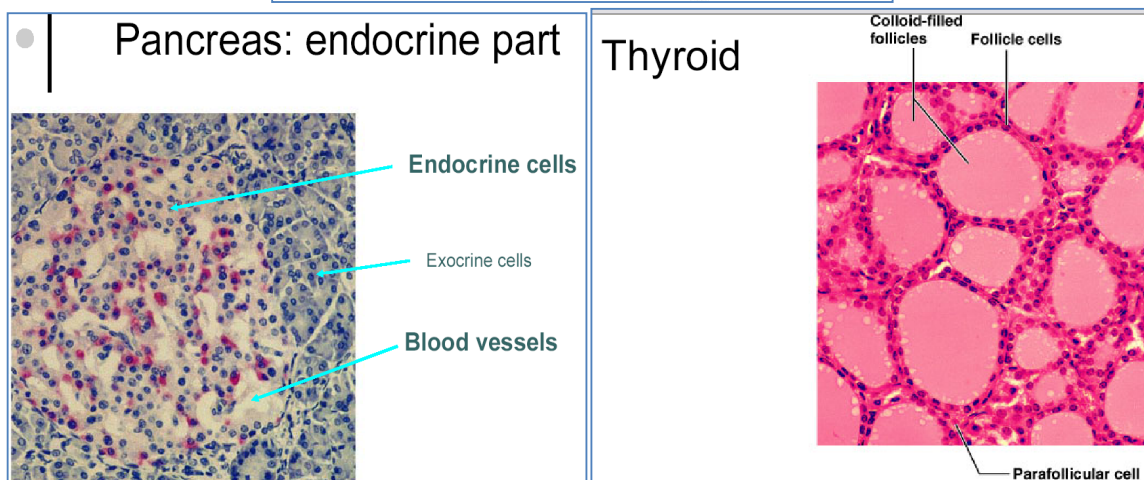
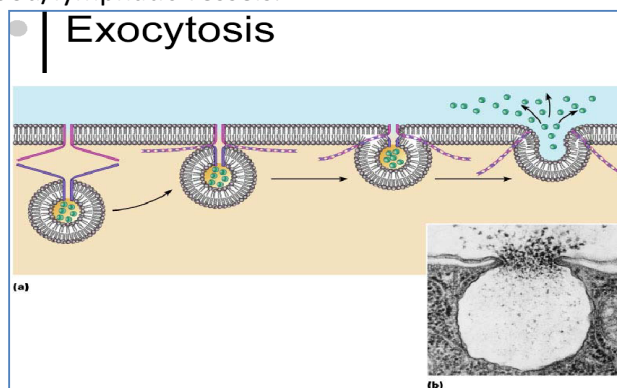
Glandular Epithelia & Epithelial Membranes.

Glandular Epithelia:

- One or more cells that make & secrete an aqueous fluid – usually contains proteins / steroids / lipids.
- Classified by:
 - o Site of product release:
 - Endocrine
 - Exocrine
 - o Number of cells forming the gland:
 - Unicellular – scattered within epithelial sheets – ductless.
 - Multicellular – form by invagination / evagination from an epithelial sheet – have ducts (tube-like connections to epithelial sheets)

Endocrine (diffuse) Glands:

- Ductless glands that produce **mainly hormones**.
 - o Prompts target organs to respond in some way.
- Secretions also include amino acids, proteins, glycoproteins.
- Secrete by exocytosis directly into the extracellular space – hence **diffuse endocrine system**.
- Most are compact Multicellular organs (eg. Thyroid, ovaries, testes, pancreas)
- Situated close to blood/lymphatic vessels.

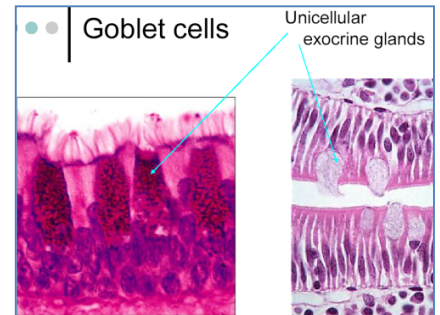


Exocrine Glands:

- More numerous than endocrine glands.
- All secrete products onto body surfaces/into body cavities
- (mucous glands, sweat glands, oil glands, saliva glands, liver, pancreas-exocrine part)

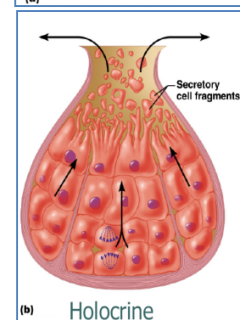
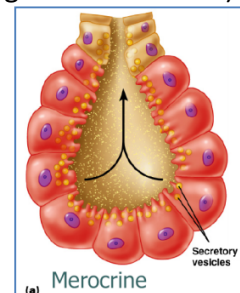
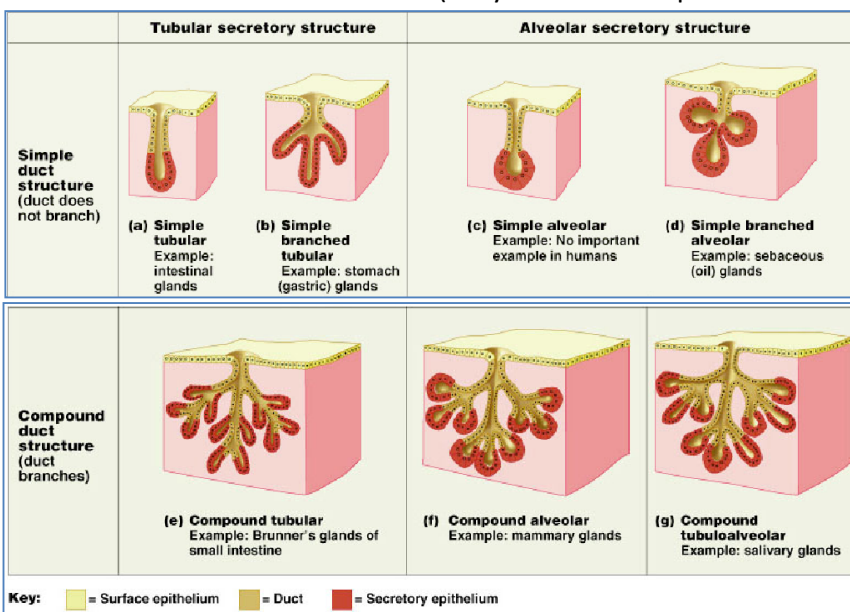
○ **Unicellular**

- Goblet Cells
- Sprinkled among columnar epithelial linings of intestinal & respiratory tracts.
- Secrete mucin directly by exocytosis into lumen.
 - (mucin + water = mucous) slimy coating that protects & lubricates.



○ **Multicellular**

- **2 Parts:**
 - Epithelium-derived duct
 - Secretory unit (acinus) at base of duct – secretory cells
- **Ducted Type Glands: Either -**
 - **Simple** (DUCT is unbranched)
 - **Compound** (DUCT is branched)
- **Structure of secretory units:**
 - **Tubular**
 - **Alveolar**
 - **Tubuloalveolar** – mixture of both types
- **Modes of Secretion:**
 - **Merocrine Glands:**
 - Products secreted by exocytosis (pancreas, sweat, salivary glands)
 - **Holocrine Glands:**
 - Products secreted by the rupture of the apical cells of the gland.
 - Underlying cells replace ruptured cells and repeat process.
 - (Only human example: Sebaceous glands – oil glands of the skin)

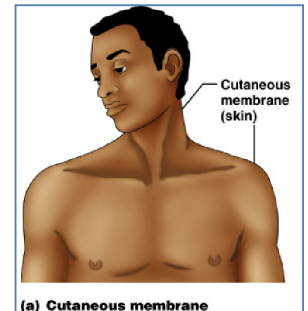


Epithelial Membranes:

- Are “simple organs”
- Continuous multicellular sheets composed of an epithelial layer bound to underlying connective tissue.
 - o Exception: synovial membranes – joint cavities – consist only of connective tissue.

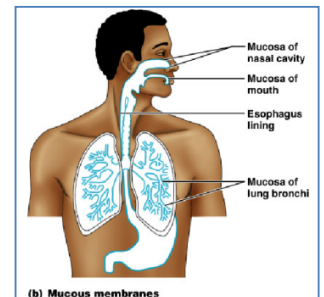
- **Cutaneous:**

- o Keratinized stratified Squamous epithelium attached to a thick layer of dense irregular connective tissue.
- o Is a dry membrane – exposed to the air.



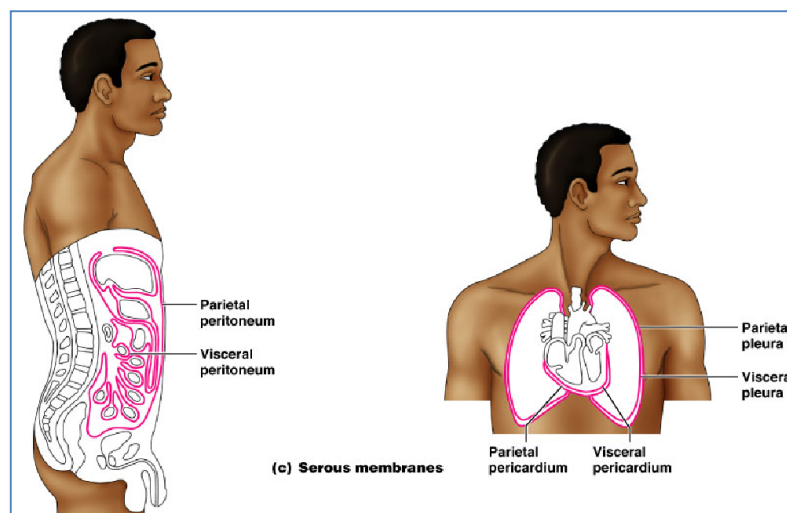
- **Mucous:**

- o Either stratified Squamous or simple columnar epithelial underlain by the lamina propria (loose connective tissue)
- o Is a wet membrane – line body cavities that open to the exterior (digestive, respiratory, urogenitals).
- o Bathed by secretions of copious amounts of mucus (except urinary tract)
- o Adapted for absorption and secretion.



- **Serous:**

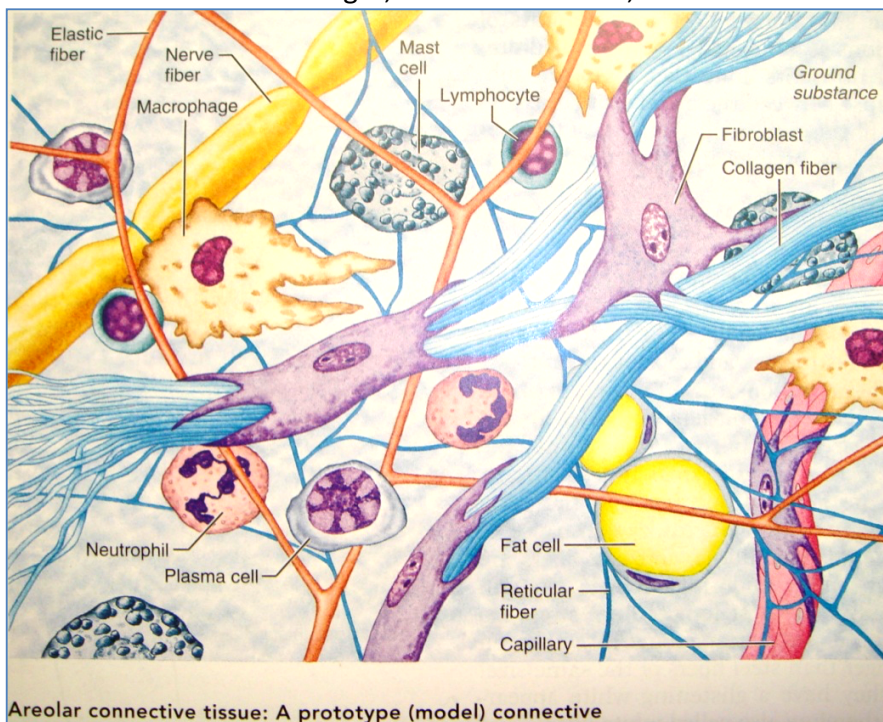
- o Simple Squamous epithelium (a mesothelium) resting on a thin layer of areolar tissue (loose connective tissue)
- o Is a moist membrane – found in closed ventral body cavities.
- o **2 layers:**
 - **Visceral:** Tightly encases organs.
 - **Parietal:** Loosely encases organs.
- o Mesothelial cells create a thin, clear lubricating fluid (Serous Fluid) which fills the gap **between the visceral and parietal** layers.



Connective Tissue

#2. Connective Tissue:

- Found everywhere in the body
- Most abundant primary tissue
- **4 Classes of Connective Tissue:** (see latter pages)
 - Connective tissue proper
 - Cartilage
 - Bone
 - Blood
- **4 Major Functions:**
 - Binding / Support
 - Protection
 - Insulation
 - Transportation (blood)
- **Common Characteristics:**
 - Common Origin
 - All arise from *mesenchyme* (embryonic tissue)
 - Degrees of vascularity
 - Avascular (cartilage)
 - Poorly vascular (dense connective tissue)
 - Rich blood supply.
 - Largely nonliving:
 - Connective tissue is made up largely of non-living extracellular matrix.
 - Some sparse living cells.
 - Can therefore bear weight, withstand tension, trauma & abrasion.



- **Structural Elements:**

○ **Extracellular matrix**

▪ **Ground Substance**

- Unstructured interstitial (tissue) fluid.
- Cell adhesion proteins (laminin & fibronectin) – allows connective tissue cells to attach to matrix elements.
- Proteoglycans – trap water, making it more viscous (varying degrees.)
- Functions as a molecular sieve – nutrients diffuse between blood capillaries and cells.

▪ **Fibres**

• **Collagen Fibres (white fibres)**

- Constructed of the fibrous **protein** “Collagen”
- Found in all connective tissues
- Small cross-linked fibrils bundle together into thick collagen fibres.
- Are extremely tough – high tensile strength

• **Elastic**

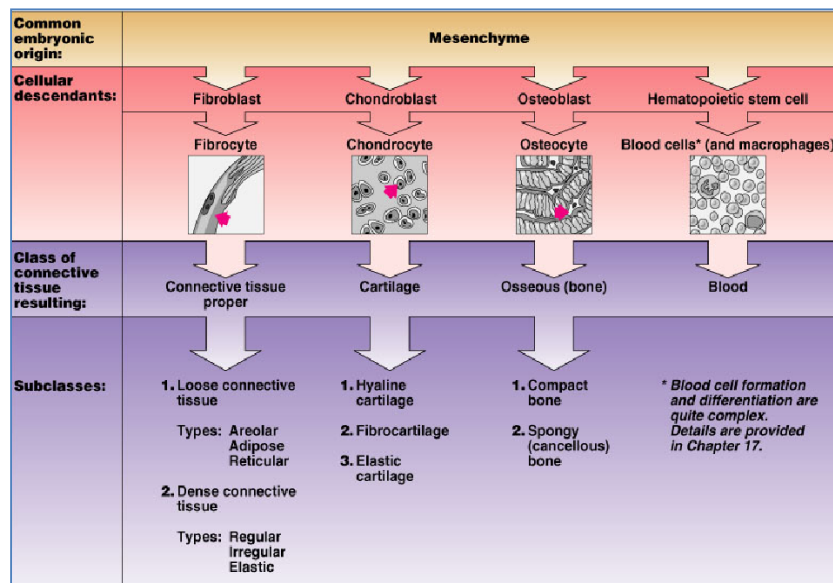
- Long, thin fibres forming branching networks
 - Contain a rubberlike protein, *elastin*.
- Allow for stretch and recoil (skin, lungs, blood-vessels)

• **Reticular**

- Collagenous fibres that form delicate networks
- Surround blood vessels & support soft tissue of organs.
- Particularly common where connective tissues meet other tissue types. (basement membrane of epithelial cells)

○ **Cells**

- Make up connective tissue once matured (blasts = immature, cytes = mature)
- Fibroblasts – Connective tissue proper
- Chondroblasts – Cartilage tissue
- Osteoblast – Bone
- Hematopoietic Stem cells – Blood
- White blood cells, plasma cells, macrophages, mast cells.



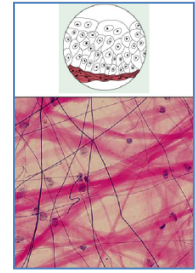
- 4 Classes of Connective Tissue: (see latter pages)

○ 1. Connective tissue proper

▪ Loose Connective Tissue

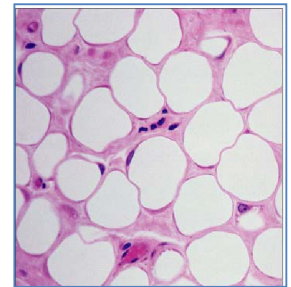
• **Areola**

- Most widely distributed connective tissue in the body
- Loose gel-like matrix
- All 3 connective fibres
- Contains fibroblasts, macrophages, mast cells & white blood cells.



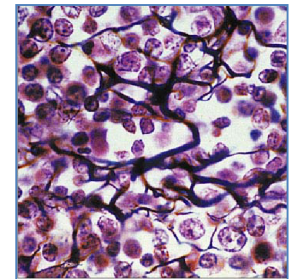
• **Adipose**

- High nutrient-storing ability
- Closely packed adipocytes (fat cells) predominate – 90% of tissue mass.
- Insulates, supports & protects.
- (under skin, around kidneys, breasts)
- Richly vascularised



• **Reticular**

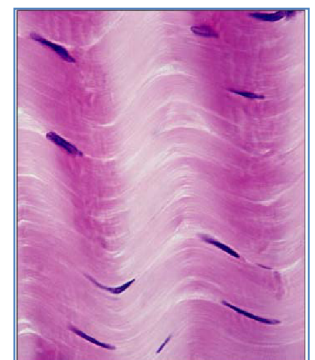
- Reticular fibres only in matrix
- Cells lie on a **reticular fibre** (mattress) **network**
- Function: forms a soft internal skeleton (stroma) that supports other cells (ie. White blood cells, mast cells, & macrophages)
- Found in lymph nodes, bone marrow and the spleen



▪ Dense Connective Tissue (fibrous connective tissues)

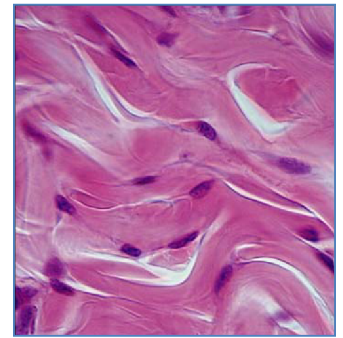
• **Dense Regular**

- **Fibres** form the **predominant** constituent. (**mainly collagen** – few elastic fibres)
- Contains closely packed bundles of **parallel collagen fibres**
 - Collagen fibres are wavy to stretch a little, but once straight, they have no more give.
- Major cell type: **Fibroblasts**
- High tensile strength in a specific direction. Still flexible.
- Poorly vascularised.
- Forms tendons – attach muscles to bones & muscle to muscle.
- Forms Fascia (cling wrap) – fibrous membrane – wraps around muscles, blood vessels & nerves.
- Form ligaments – attach bones to bones @ joints.



- **Dense Irregular**

- Same structural elements as Dense Regular, however the bundles of collagen fibres are much thicker and are arranged irregularly.
- Forms sheets in body areas where multidirectional tension is exerted.
 - Skin (dermis)
- Forms fibrous joint capsules and fibrous coverings surrounding some organs:
 - Kidneys, bones, cartilages, muscles, nerves.



- **2. Cartilage**

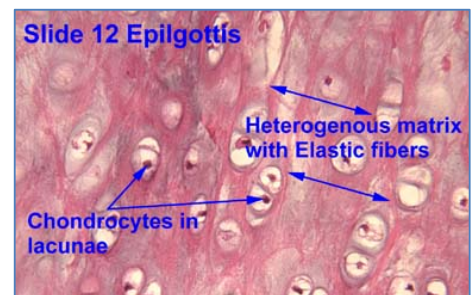
- **Hyaline**

- Amorphous but firm matrix.
- Chondroblasts produce matrix. Chondrocytes = mature cartilage cells.
- Cartilage matrix is approx. 80% water – enables it to rebound after compression.
- Firmly bound collagen fibres (some elastic)
- Has qualities intermediate between dense connective and bone tissue.
- Withstands **tension** and **compression**
- Flexible but rigid.
- Lacks nerve fibres
- Is **avascular**
- Receives nutrients by diffusion from blood vessels in the conn. tissue membrane (perichondrium) surrounding it.
- **Embryonic skeleton, synovial joints, respiratory tubes, nose, sterna-rib joint.**



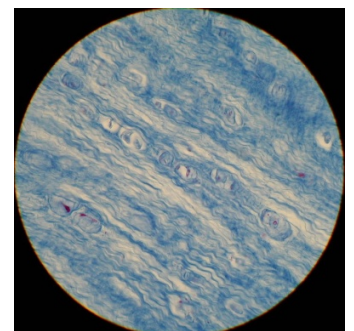
- **Elastic**

- Nearly identical to hyaline cartilage - but has more elastin fibres.
- Found where strength & stretchability are needed.
- **External ear, epiglottis**



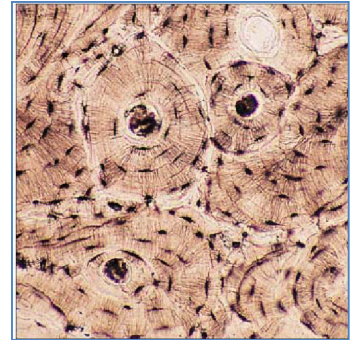
- **Fibrocartilage**

- Perfect structural intermediate between hyaline cartilage and dense regular connective tissue.
- Compressible and resists tension
- Found where strong support and heavy pressure resistance is needed.
 - **Intervertebral discs, knee, etc.**



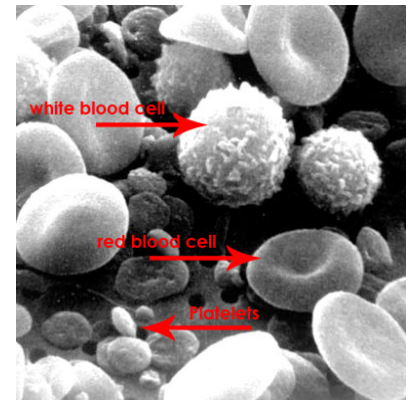
○ **3. Bone (osseous tissue)**

- Similar to that of cartilage but harder and more rigid.
- Highly abundant collagen fibres and inorganic calcium make it very hard and rigid.
- Osteoblasts produce the organic material in the matrix, and bone salts (calcium) deposits between the fibres.
- Mature bone cells have osteocytes.
- Provides cavities for fat/mineral storage & synthesis of blood cells.
- Cross-section – closely packed structural units called osteons
 - Concentric rings of bony matrix surrounding central canals of blood vessels and nerves.
- Well vascularised.



○ **4. Blood**

- Classed as a “connective tissue” because cells develop from mesenchyme and consists of cells surrounded by a nonliving matrix.
- Red (erythrocytes) and white cells in a fluid matrix (plasma)
- Contained within blood vessels
- Transports respiratory gases, nutrients and wastes.



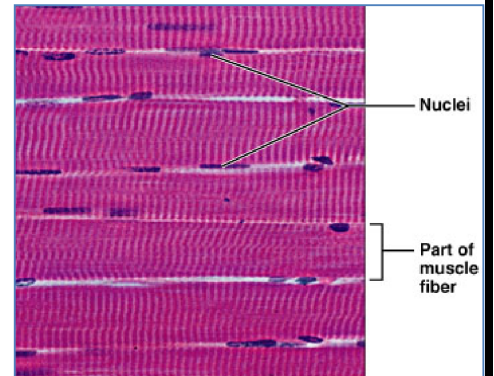
MUSCLE AND NERVOUS TISSUE

Muscle Tissue:

- 3 Types

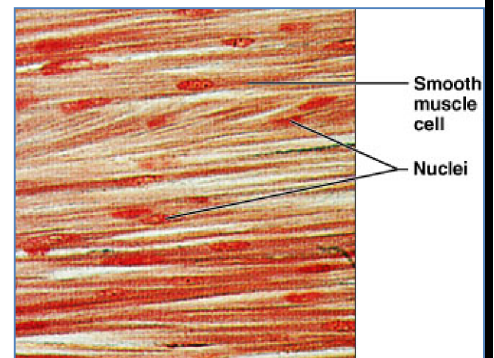
- **Skeletal**

- Attaches to bone for movement (voluntary)
- Long, Cylindrical
- Multinucleated
- Obvious striations → sarcomeres.



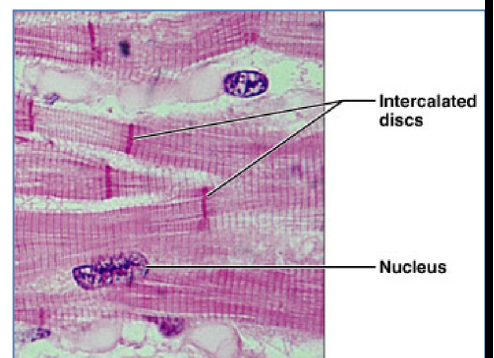
- **Smooth**

- In the walls of visceral organs – eg. GI tract/urinary tract/birth canal
- Spindle-shaped cells
- Central nuclei
- No striations → no sarcomeres
- Cells arranged closely to form sheets (often opposing-laterally perpendicular)
- Usually involuntary – Controlled by the autonomic nervous system



- **Cardiac**

- Makes up the heart.
- Long, **Branched**, Cylindrical
- Striations → sarcomeres
- Usually single-nucleated
- Intercalated discs – cell membranes of 2 adjacent cells bound mechanically (desmosomes), chemically & electrically (gap junctions). Essentially makes the entire heart one single muscle.
- Involuntary – controlled by autonomic nervous system



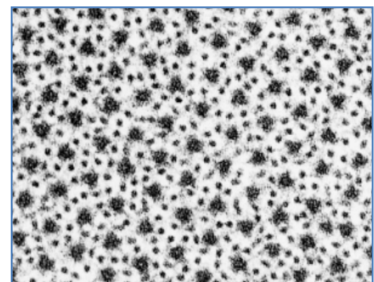
- **Functions:**

- Movement (specialised for contraction)
- Maintains posture
- Stabilises joints
- Generates heat

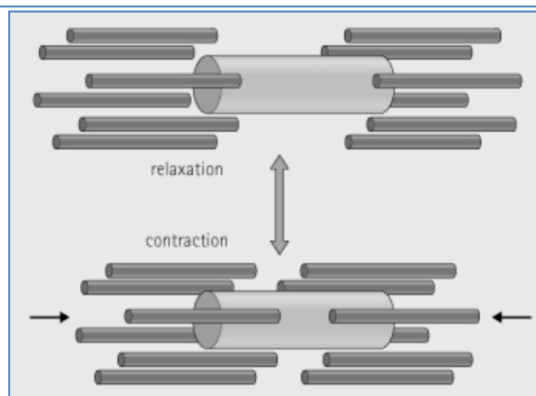
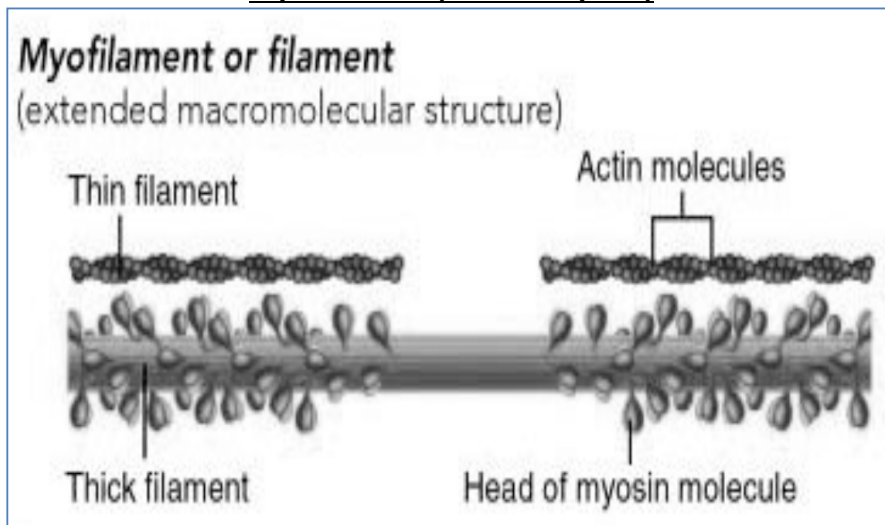
Contractile Stuff:

- **Contractile Proteins Actin & Myosin → Myofilaments:**

- Molecular Level
- Form assemblies within muscle cells that slide over each other resulting in contraction
 - known as **myofilaments** (muscle-filaments) and are of **2 Types**:
 - **Actin**
 - **Thin** Filaments
 - Helical Structure
 - **Myosin**
 - **Thick** Filaments
 - More complex structure → thicker



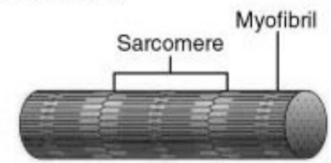
Myofilaments (Actin & Myosin)



- **Contractile Organelles (Myofibrils):**

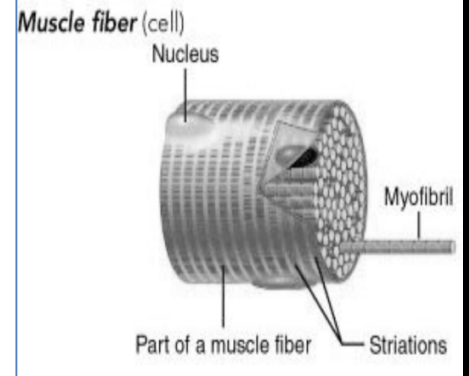
- Sub-Cellular Level
- **Myofibrils:** Bundles of myofilaments.
- Are complex organelles.
- Together form a muscle fibre.
- Have many **contractile units = Sarcomeres**.
 - Cause the **striations** / stripes.
 - Due to thick (dark) & thin (light) myofilaments.
 - Only features in **Cardiac & Skeletal Muscle**.

Myofibril or fibril (complex organelle composed of bundles of myofilaments)



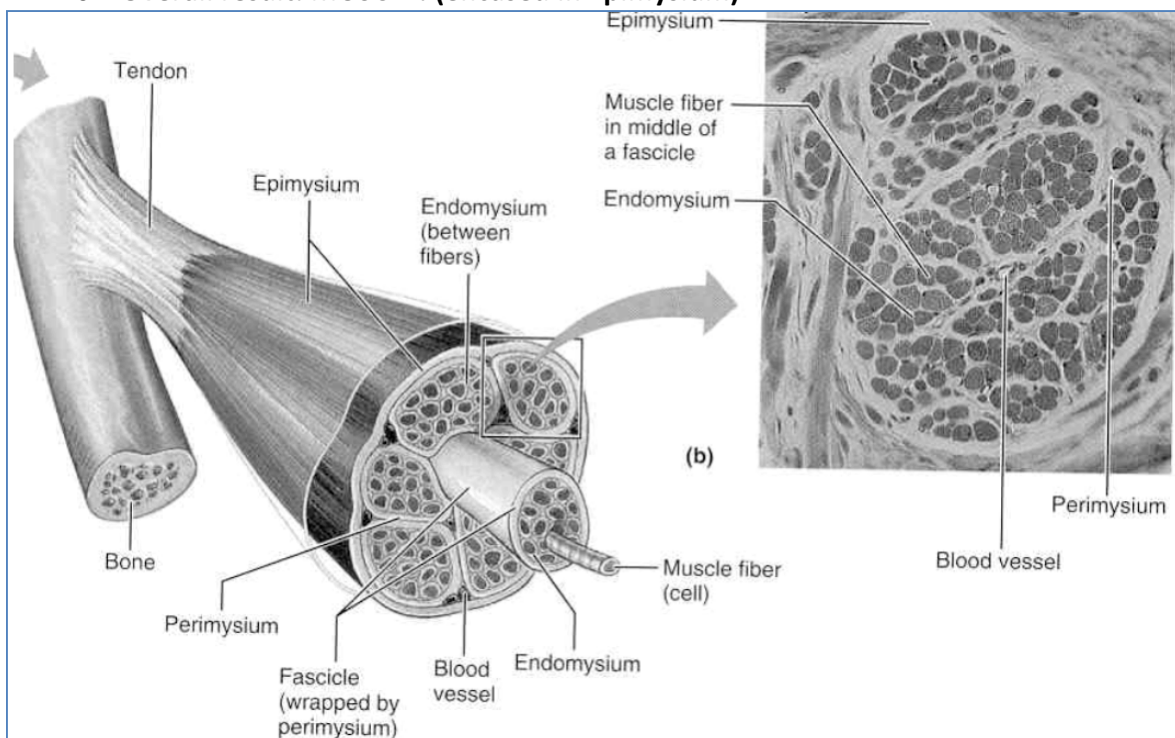
- **Contractile Cells – Muscle Fibres:**

- Cellular level
- Formed by the fusion of myoblasts in embryonic development.
 - Therefore large by fusion
 - **Multinucleated**
 - Packed with **myofibrils** (contractile organelles)
 - **Striated** due to thick and thin actin and myosin.
- Wrapped by Connective Tissue:
 - Endomysium



- **Contractile Tissue – Fascicles:**

- Fine macroscopic level
- Bundles of muscle fibres/cells.
- Wrapped by Connective Tissue:
 - Perimysium
- **Overall result: MUSCLE! (encased in Epimysium)**



Nervous Tissue

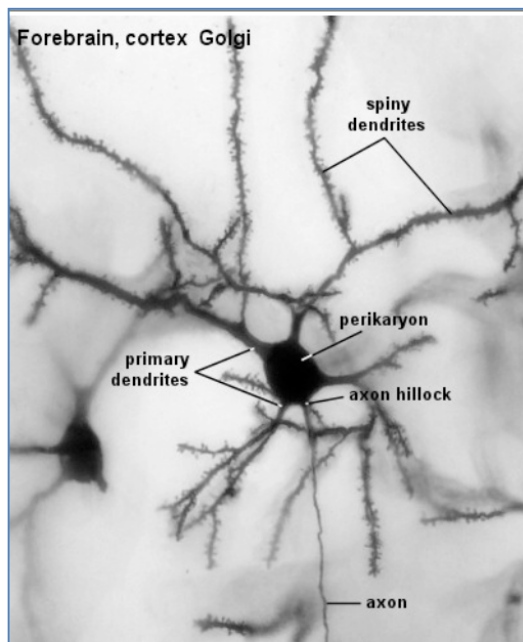
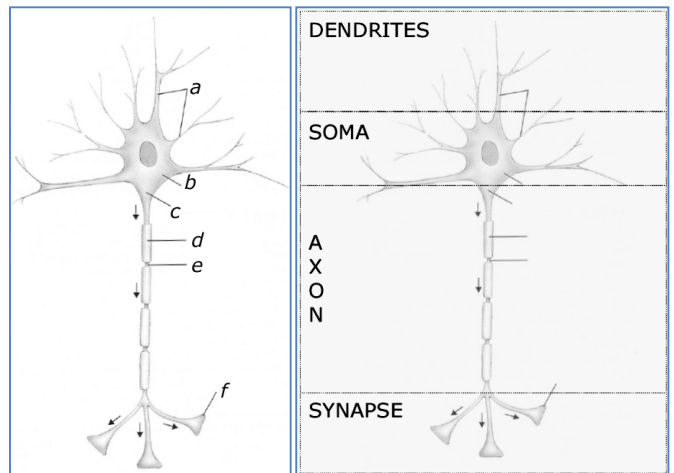
Nervous System:

- **Central Nervous System (CNS)**
 - o Brain & Spinal Chord
 - o Integrating command centre
 - **Peripheral Nervous System (PNS)**
 - o Outside the CNS
 - o Nerves extending to and from the periphery and CNS
-
- Highly cellular cell network
 - Specialised communication cells (**neurons**) of the nervous system.
 - o Communicate via electrical activity (action potential)
 - o Transmit electrical signals from sensory receptors and to effectors (muscles/glands) to control their activity.
 - Branching cells
 - Long neuron "**processes**" – extend from the nucleus-containing cell body

The Neuron:

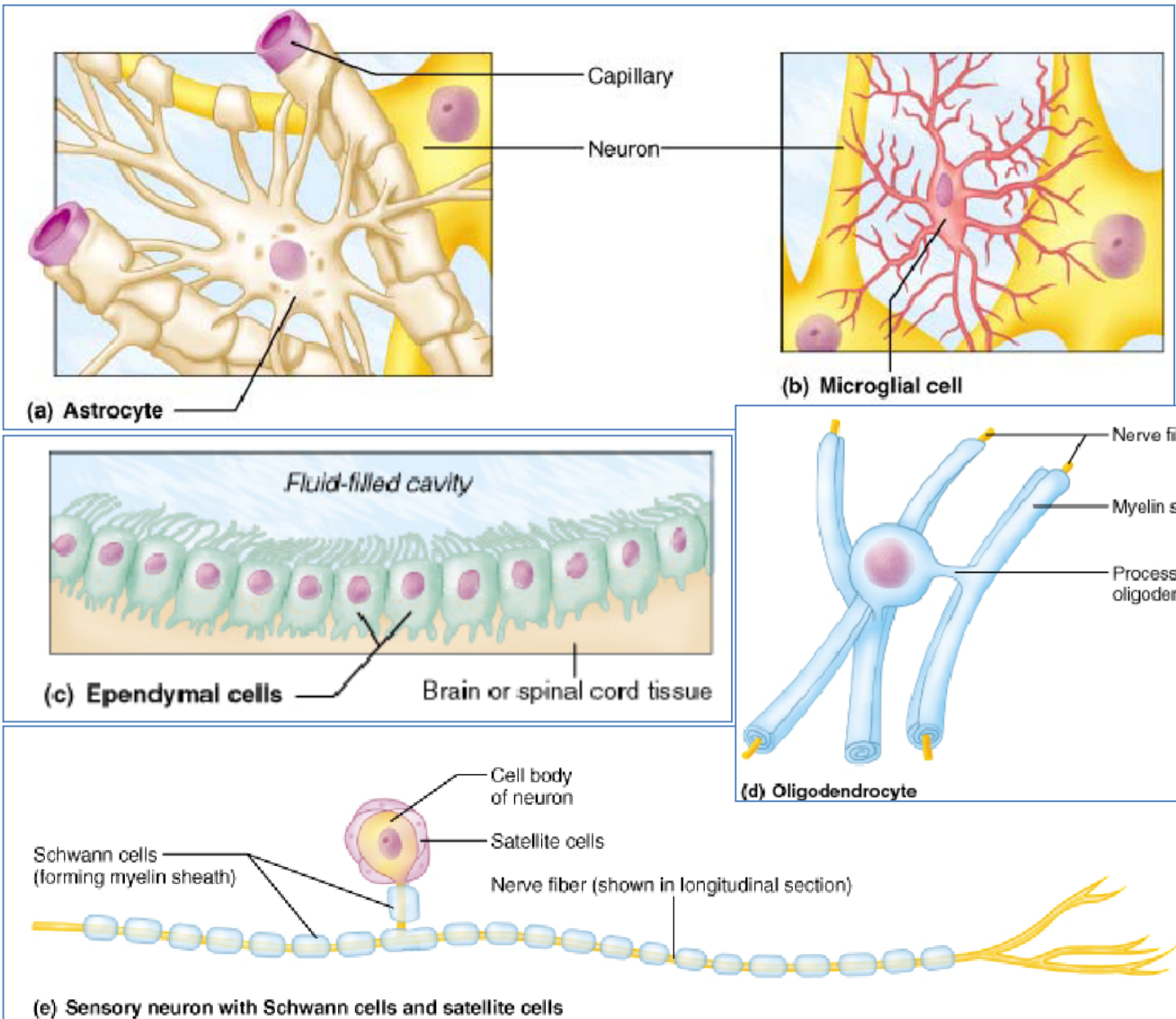
Structural Features:

- a) **Receptive Field: Dendrites**
 - o Stimulated by inputs
- b) **Cell Body: Soma**
 - o Responds to graded inputs
- c) **Efferent Projection: Axon (and axon hillock)**
 - o Conducts nerve impulses to target
 - o Myelinated and unmyelinated
- d) **Efferent Projection: Myelin Sheath**
- e) **Efferent Projection: "Nodes of Ranvier"**
- f) **Output: Synaptic Terminals**

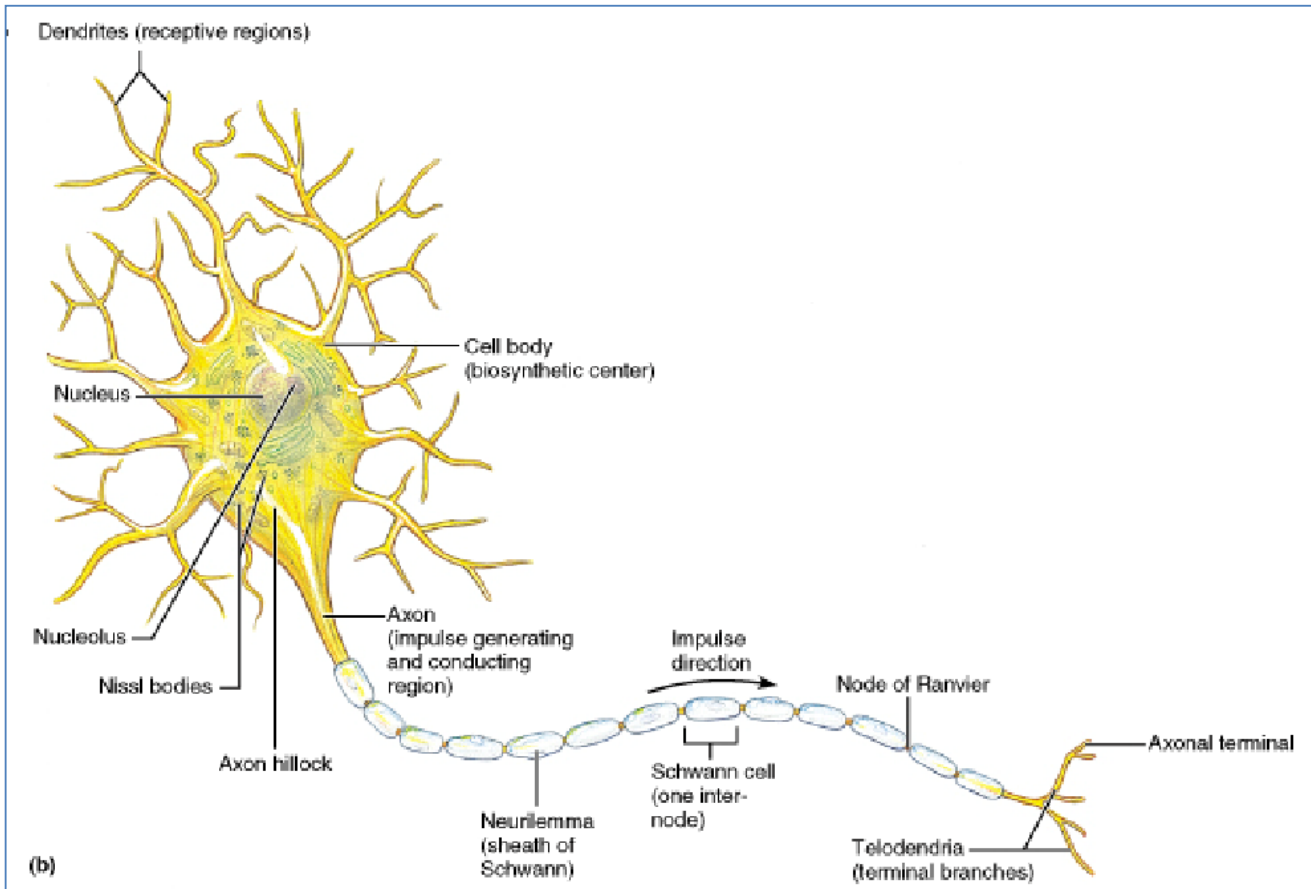


Supporting Cells:

- Numerous support cells within the nervous system
 - More numerous than neurons – but smaller.
- Known as neuroglia (or glia)
 - Structural & mechanical support
 - Roles in maintaining homeostasis
 - Immune response
 - Forming myelination
 - Immune responses via phagocytosis.
- Types of neuroglia:
 - Astrocytes
 - Schwann Cells – Myelin Formation – wrap around axon
 - Oligodendrocytes – Myelin Formation – wrap around axon
 - Microglial cells
 - Ependymal cells
 - Satellite cells



Detailed Diagram of a Neuron

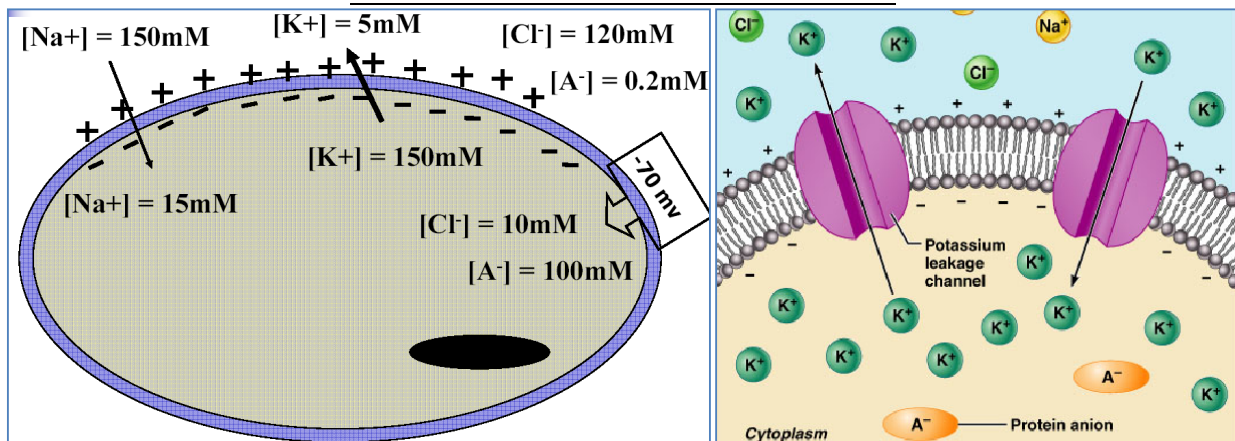


Membrane Potential & Excitable Tissues

Membrane Potential:

- Voltage across membrane
- Cause: unequal distribution of ions (K^+ & Na^+)
- Result of selective/differential permeability of specific plasma membrane proteins. (mainly ion channels)
- Evident in all living cells (ranges between -20 & -200mV)
- In excitable tissues – stimulation causes change in Membrane Potential.
 - Results in activation of the cell.
 - Nervous & Muscle Tissues = Excitable Tissues.
- **Membrane Potential:** Depends on:
 - **Relative permeability** of PM to ions
 - Each ion's **concentration gradient**.
 - **Electrochemical gradient**
- **Resting Membrane Potential:**
 - Stable membrane potential of cells when unstimulated.
 - **For Nerve Cells** – approx -70mV

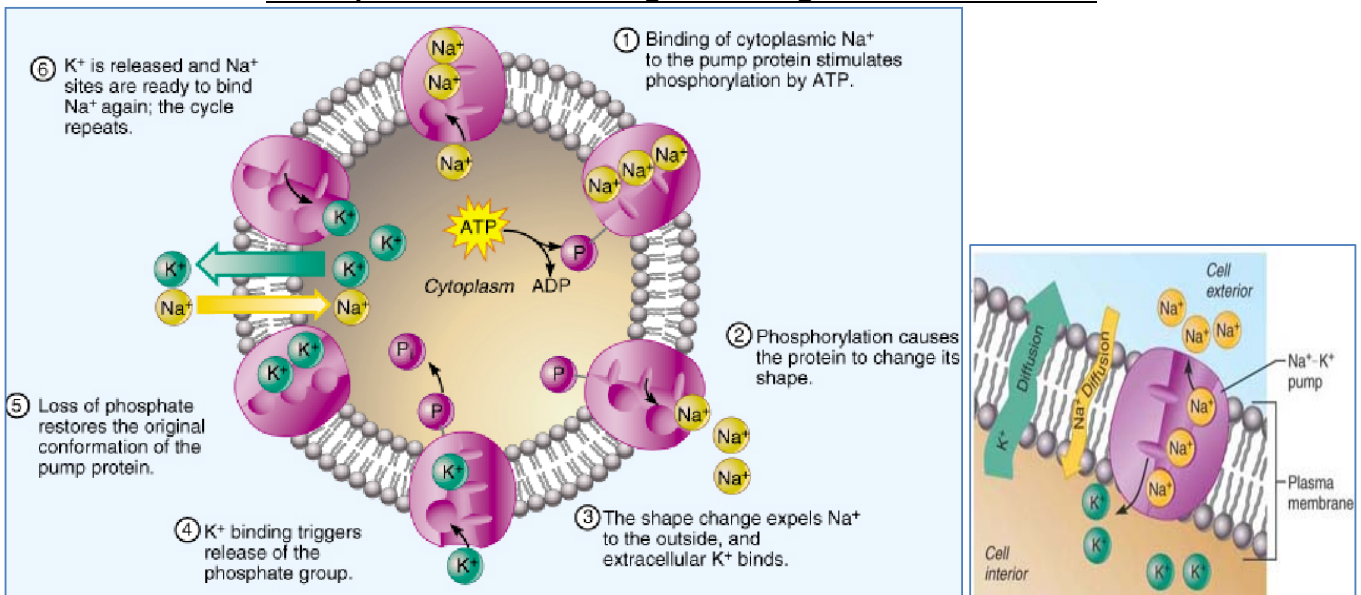
Ion Distribution Across Plasma Membrane



- **K^+** : [greater inside cell]
 - At rest, membrane is **much** more permeable to K^+ than to Na^+ .
 - I.e. K^+ diffuses out of the cell through **leakage channels** down its conc. gradient.
 - Therefore, loss of positive charge from cell makes:
 - Inside the cell negative
 - Outside the cell positive
 - Eventually the negativity of the inner membrane face attracts K^+ back into the cell.
 - Therefore, conc. Gradient drives K^+ out and is equally opposed by electrical gradient. (**equilibrium potential has been reached**)
- **Na^+** : [greater outside cell]
 - Membrane has much lower permeability to Na^+ .
 - Negative inner membrane-face attracts Na^+ into cell, but is opposed by low permeability.
 - Therefore low diffusion of Na^+ into cell.

****Simply: Resting MP is established due to greater diffusion of K^+ out than Na^+ in****

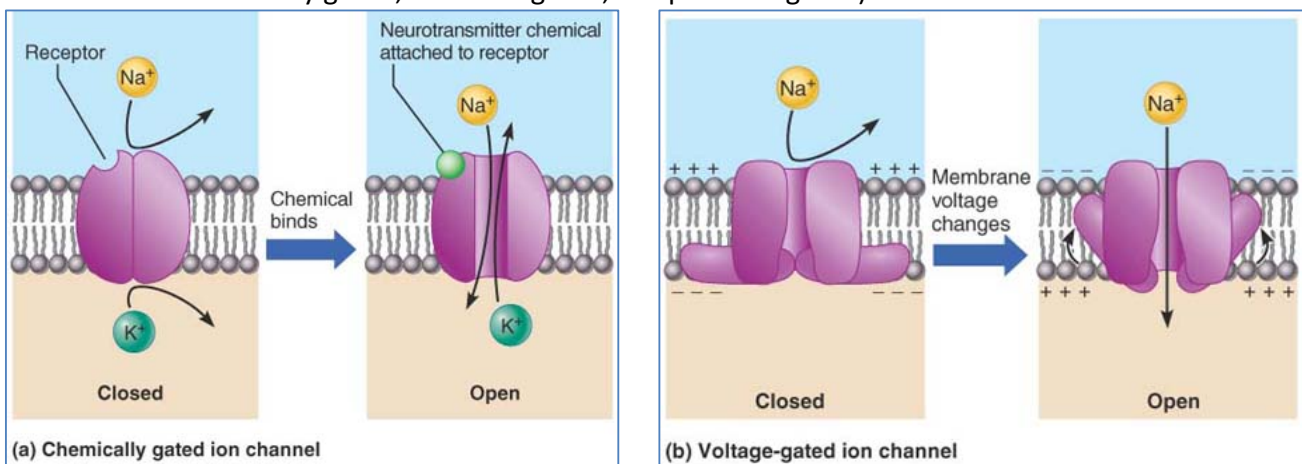
The Na/K ATPase: Maintaining the Resting Membrane Potential.



- Na^+ passively diffuses into cell and K^+ passively diffuses out.
 - Why doesn't the chemical & electrochemical gradients dissipate?
- The **Conc. Gradients** for both Na^+ & K^+ are **maintained** by the **Na/K ATPase**.

Excitable Tissues (Nerves/Muscle)

- In excitable cells, **stimuli** can **alter the permeability** of the membrane to K^+ and/or Na^+ .
 - Via opening/closing **gated ion channels** (**ligand/chemically gated**, **voltage gated**, **mechanically gated**, **vibration gated**, **temperature gated**)



- This changes the membrane potential.
- If the membrane potential is sufficiently altered, an action potential is initiated.
- **Action potential:** an **electrical impulse** generated and conducted along a **nerve's axon** in response to stimuli.

Neuronal Action Potentials:

- **4 Phases:**

1 – Resting Phase:

- Membrane is **much** more permeable to K^+ than to Na^+ .
- Greater diffusion of K out than Na in
- Therefore inside is negative/Outside is positive.
- **Both Na & K voltage gated channels are CLOSED.**

2 – Depolarisation Phase:

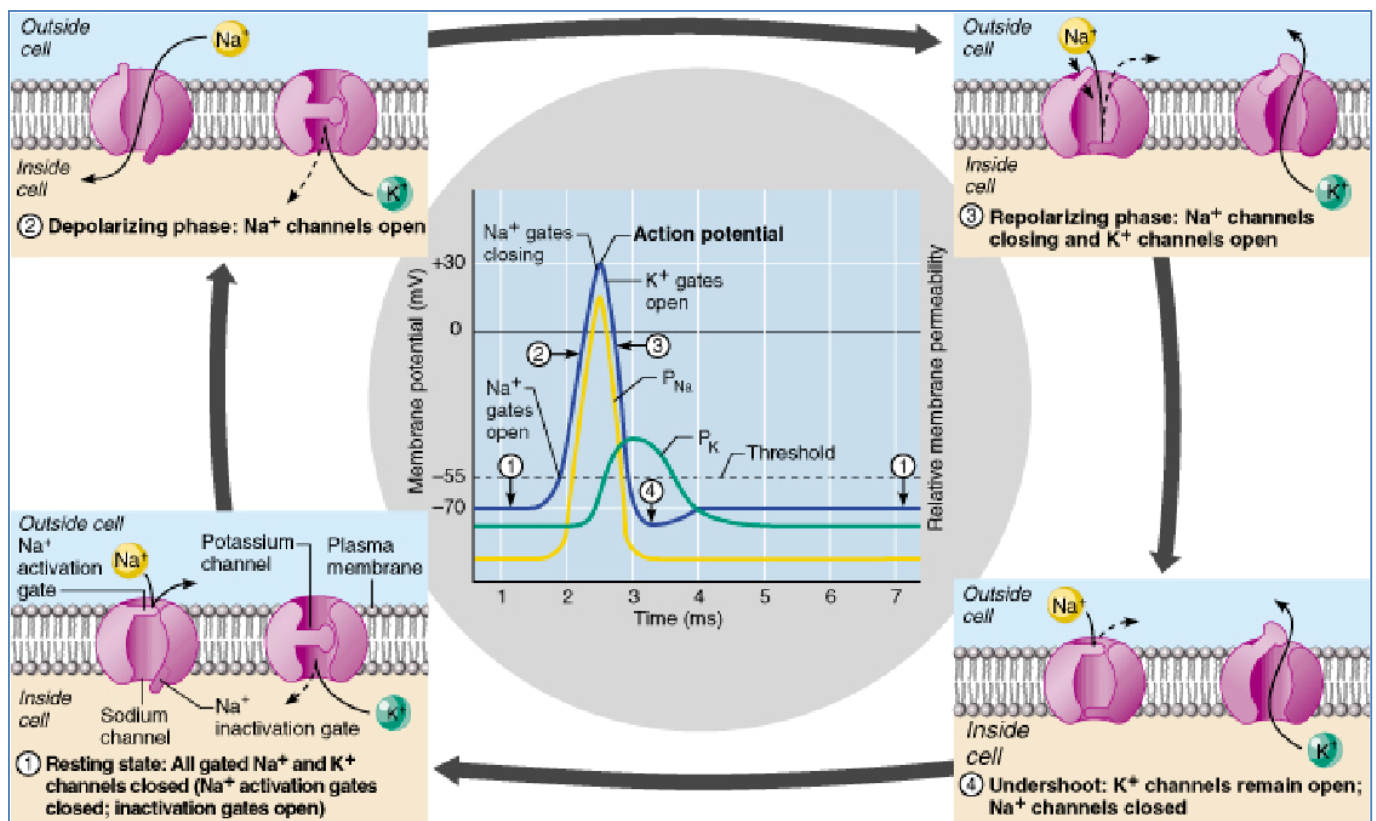
- Mechanical/chemical/vibratory/other stimulus opens some Na^+ channels such that Na^+ flows into the cell.
- Therefore membrane potential becomes less negative (ie. It depolarises)
- If the MP reaches approx. **-55mV (threshold)**, the **voltage gated Na^+ channels open.**
- Na^+ influx increases dramatically – until MP reaches approx. **+30mV** where the voltage-gated Na^+ channels close.

3 – Repolarisation Phase:

- @ approx. +30mV K^+ voltage gated channels open. (perm. of K increases & Na decreases)
- Large outflow of K^+ → membrane potential becomes more negative (repolarises) and returns to -70mV.

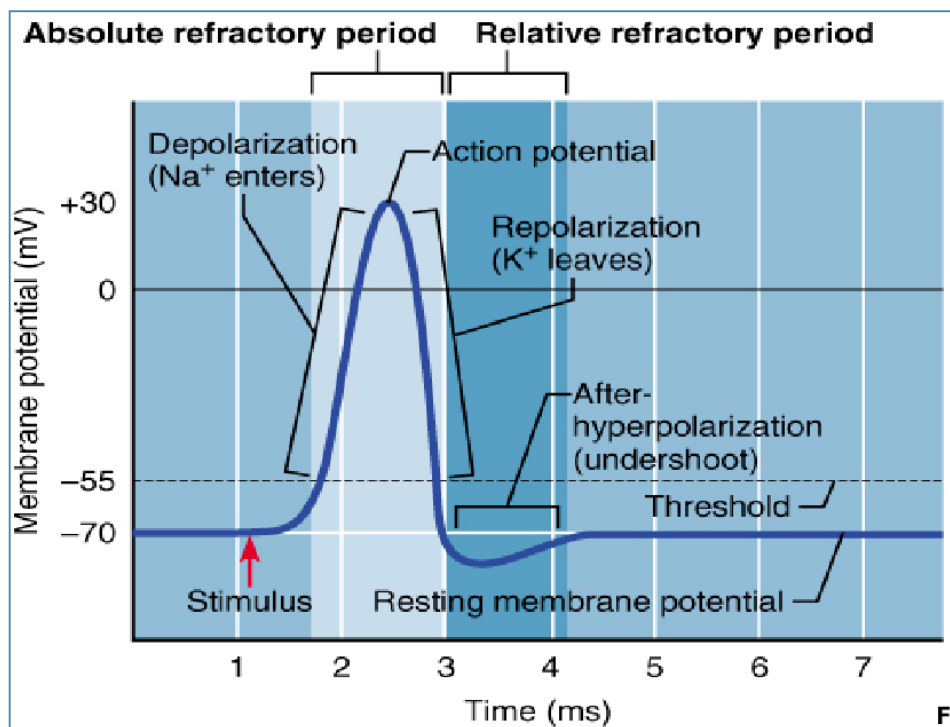
4 – Hyperpolarisation (undershoot) Phase:

- K^+ channels remain open past -70mV and MP becomes more negative than at rest.
- K^+ channels close and Na/K ATPase returns the MP to normal (-70mV)

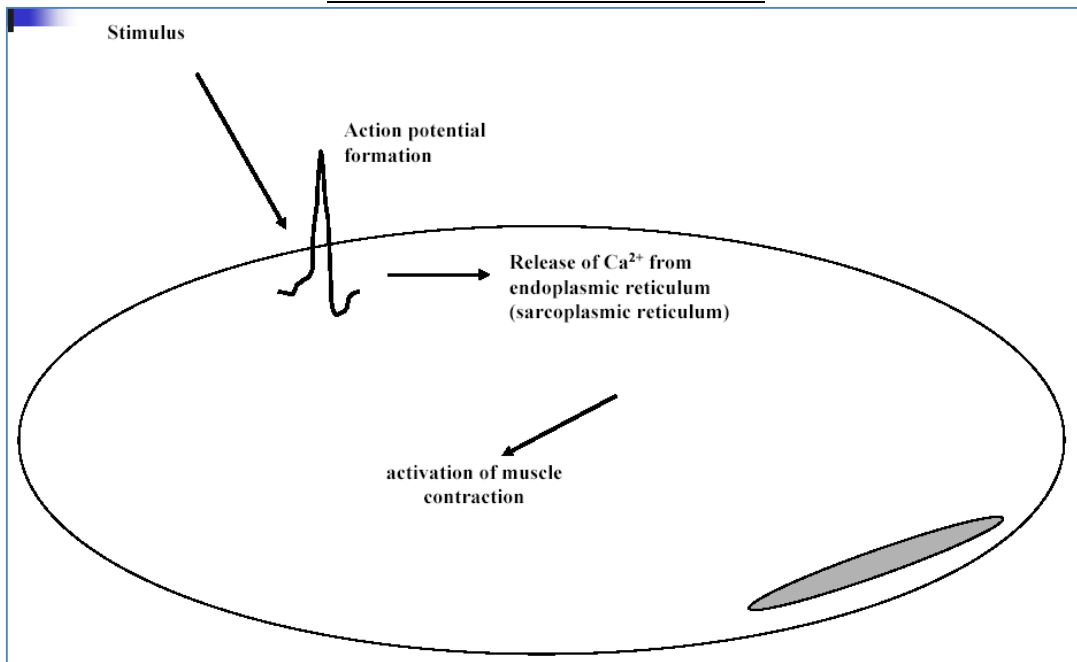


Refractory Periods During the Action Potential:

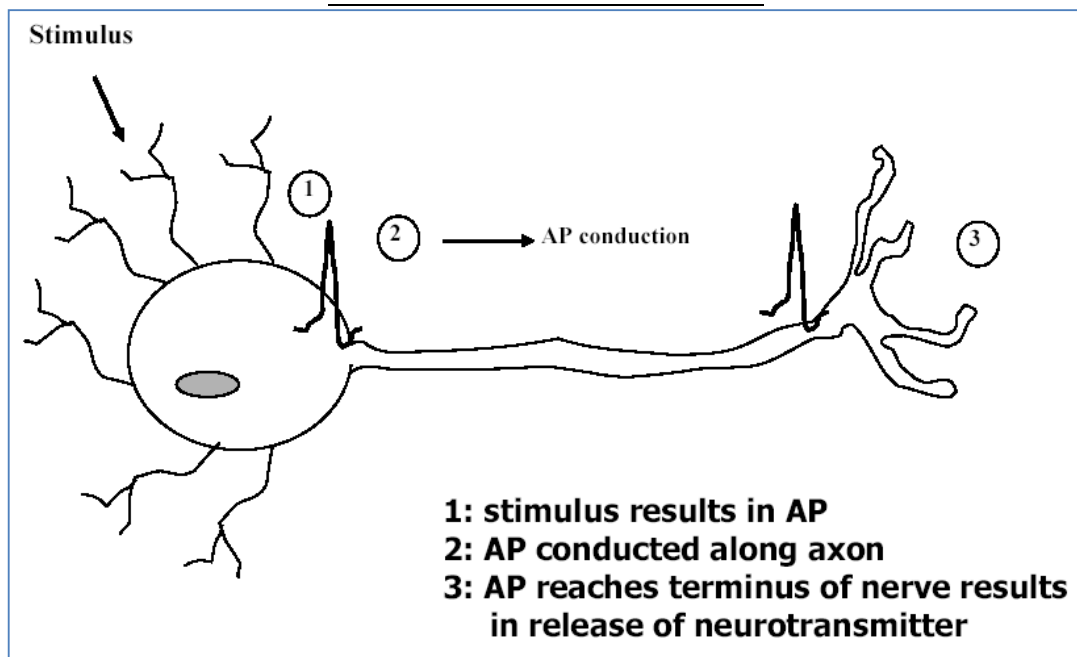
- Basically the total time between a stimulus creating an action potential and the MP returning to rest.
 - Usually 3-4ms
 - Determines how soon a neuron can respond to another stimulus.
- Divided into 2 sub-periods:
 - **Absolute Refractory Period** – no additional stimulus (no matter how large) can initiate a further action potential.
 - Stimulus → Depolarisation
 - Repolarisation
 - **Relative Refractory Period** – If an additional stimulus is to initiate another action potential during this time, it must be larger in order to reach threshold.
 - Hyperpolarisation → Rest.



Role of Action Potential in Muscle



Role of Action Potential in Nerves



The Nervous System: Organisation, Conduction, Neurotransmission & Senses

Functions:

1. **Sensory Input:** Monitor changes occurring inside & outside the body
2. **Integration:** processing and interpretation of sensory info + deciding what to do.
3. **Motor Output:** activation of effector organs in response to stimuli.

Organisation:

- **Central Nervous System (CNS)**

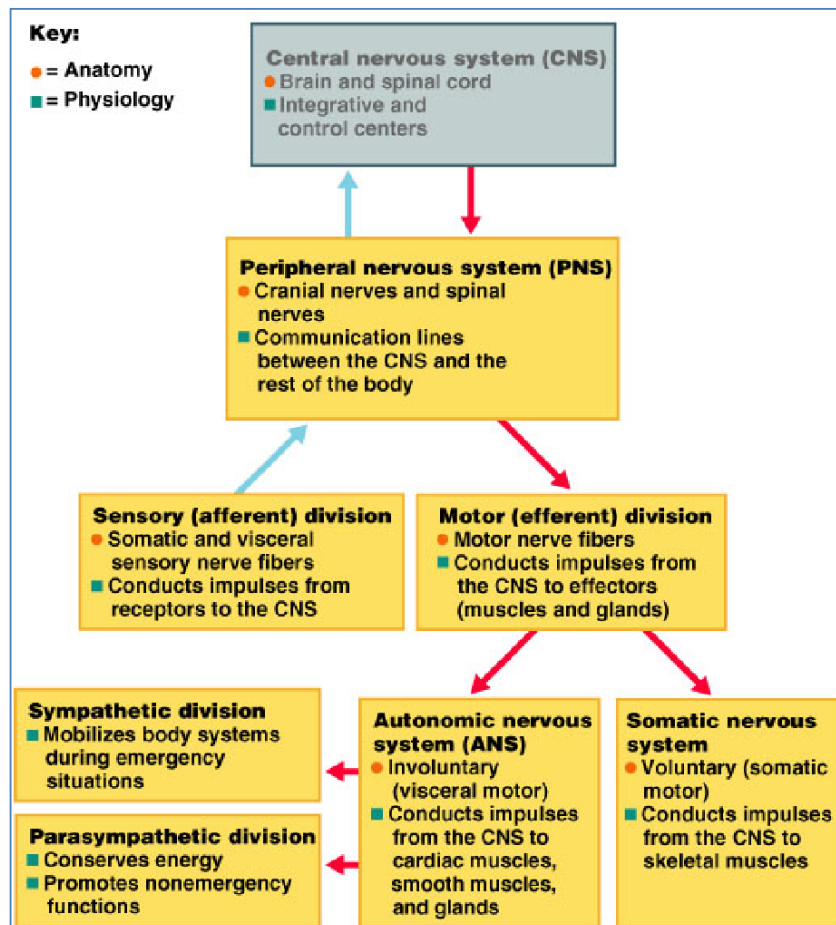
- Brain & Spinal Chord
- Occupies the dorsal body cavity
- Integrating and command centre
- Interprets sensory inputs
- Dictates motor responses.

- **Peripheral Nervous System (PNS)**

Spinal nerves – from spinal chord

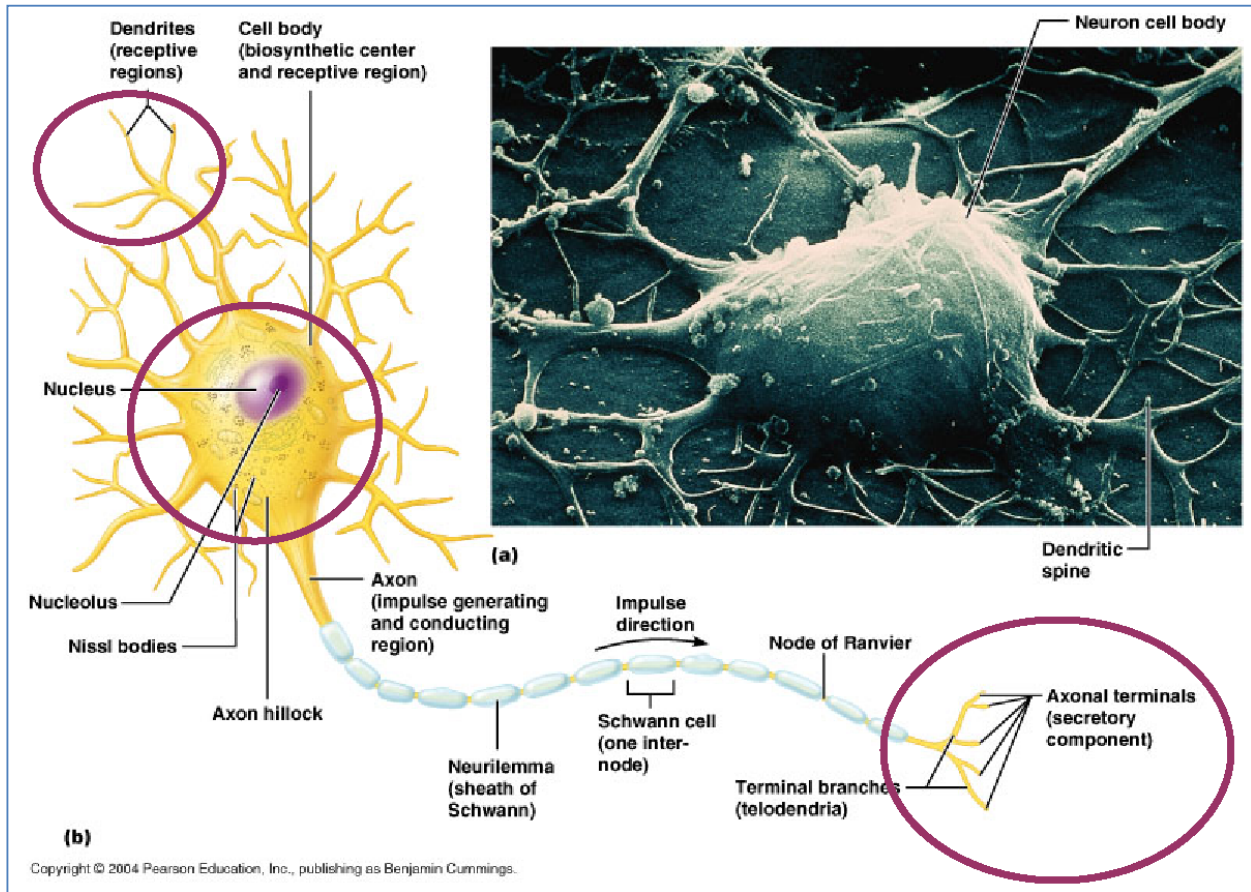
Cranial Nerves – from brain

- **Sensory (afferent – ‘toward’) division** = receives external stimuli.
- **Motor (efferent – ‘away from’) division** = makes things happen
 - **Somatic** (voluntary) nervous system (to skeletal muscles + skin)
 - **Autonomic** (involuntary) nervous system (heart beat, respiration, peristalsis, bladder)



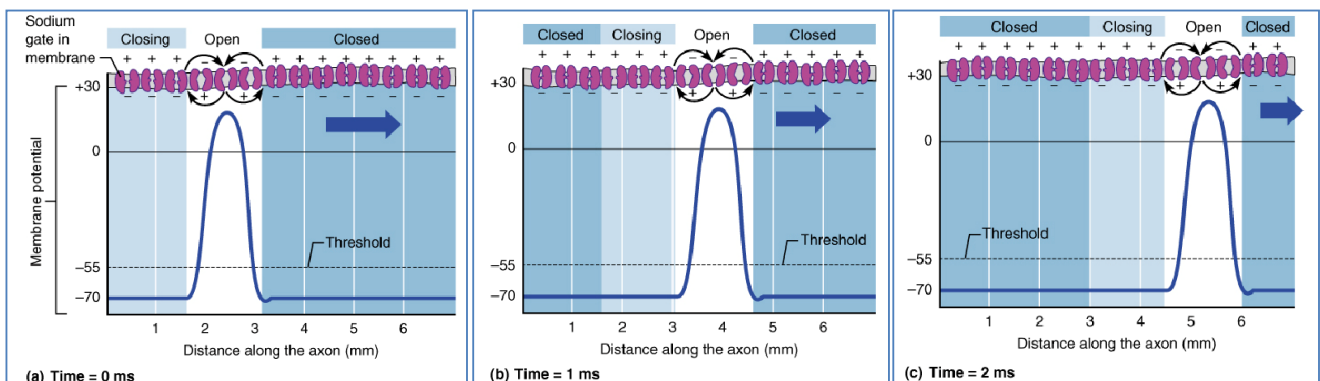
The Neuron: (Nerve Cells)

- The functional unit of the nervous system
- **3 Zones:**
 1. **Receptive zone** - Dendrites
 2. **Receptive and biosynthesis zone** – Cell body
 3. **Secretory Zone** – Axon Terminals (pre-synapse)



Impulses: are conducted along the length of the axon.

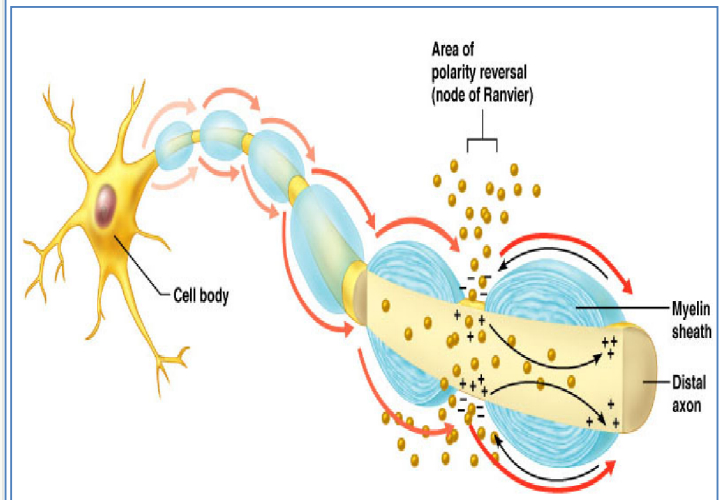
- A wave of action potentials – opening and closing of voltage gated ion channels.
- **Action potential:** an impulse frozen in time.
- Depolarisation, repolarisation and hyperpolarisation of membrane.



- **Speed of impulse:** Dependent upon:

1. Axon Diameter → Larger = Quicker
2. Presence of Myelin (white matter) → Impulse jumps from exposed axon-region to the next instead of having to open & close ion channels across the axon's entire length (which would be slow)

Axons from skin	A α	A β	A δ	C
Axons from muscles	Group I	II	III	IV
Diameter (μm)	13-20	6-12	1-5	0.2-1.5
Speed (m/sec)	80-120	35-75	5-30	0.5-2
Sensory receptors	Proprioceptors of skeletal muscle	Mechanoreceptors of skin	Pain, temperature	Temperature, pain, itch

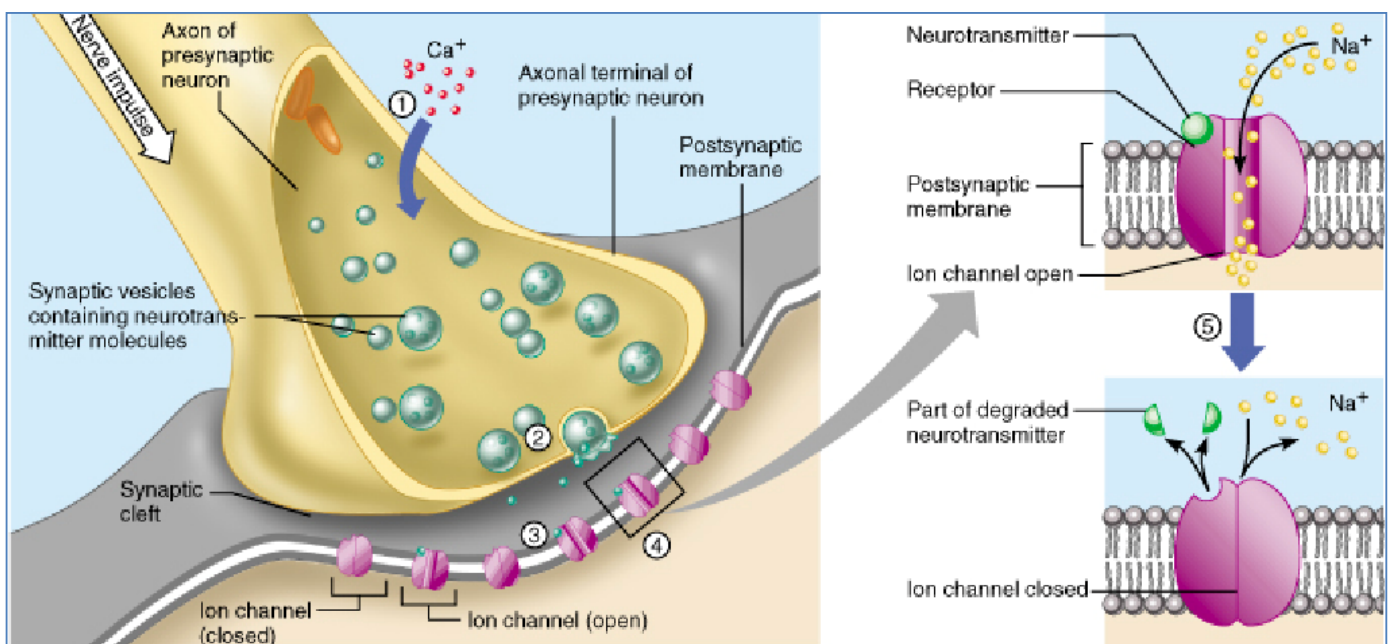


Neurotransmission

- Action potentials are passed from one neuron to another via neurotransmission
- **Synapse** = the site of neurotransmission

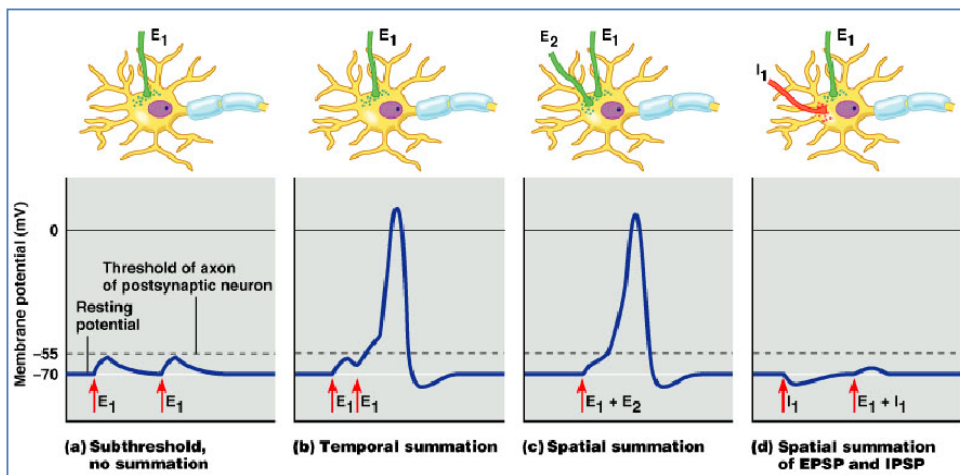
3 components:

- a) Sending Neuron = pre-synaptic neuron
- b) Synaptic cleft = gap between the 2 communicating neurons
- c) Receiving Neuron = post-synaptic neuron

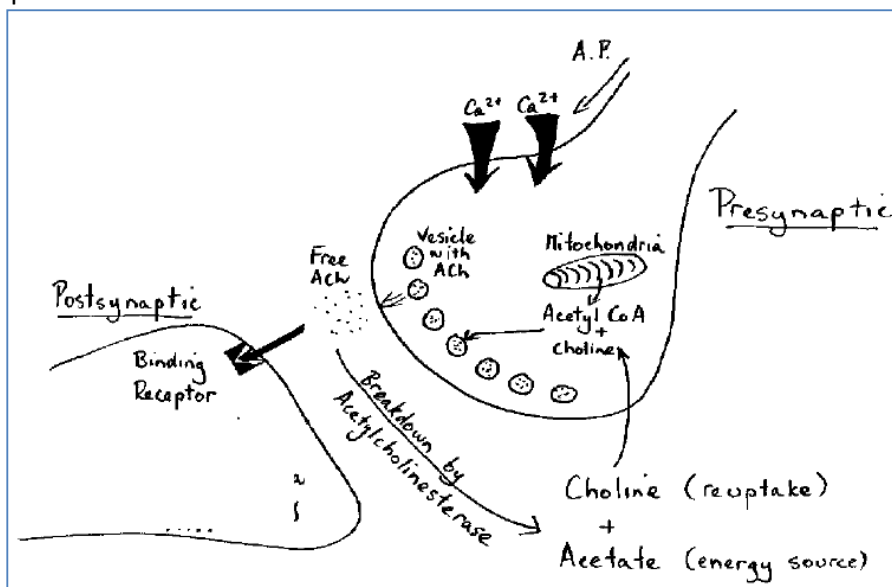


Phases of Neurotransmission:

1. **Action potential** reaches axon terminal, opens voltage-gated Ca^+ channels.
 - **Influx of Ca^+** into axon terminal causes **vesicles** of neurotransmitter to migrate to the axon terminal.
 - '**Neurotransmitter**' released by exocytosis from the sending (**pre-synaptic**) neuron.
 - **Neurotransmitter** (acetylcholine/nor adrenaline/dopamine/glutamate/gaba/etc) diffuses across **synaptic cleft** between 2 neurons.
2. Neurotransmitters bind to **ligand-gated ion channels**, causing change in MP of **post-synaptic neuron** (dendrite) → creating **graded potentials**.
 - Short-lived, localised changes in membrane potential.
 - Current flow decreases in magnitude with distance.
 - The stronger the stimulus, the greater the GP (and further distance)
 - If GP **depolarises** membrane, it is **excitatory**
 - If GP **hyperpolarises** membrane, it is **inhibitory**.



- The **sum** of the GP may cause MP to reach threshold, triggering an action potential on the next neuron.
3. **Neurotransmitter Inactivation** stops continued stimulation of post-synaptic neuron.
 - Neurotransmitter is either broken down by enzymes (eg. ACh-Esterase) or reabsorbed by pre-synaptic terminal.



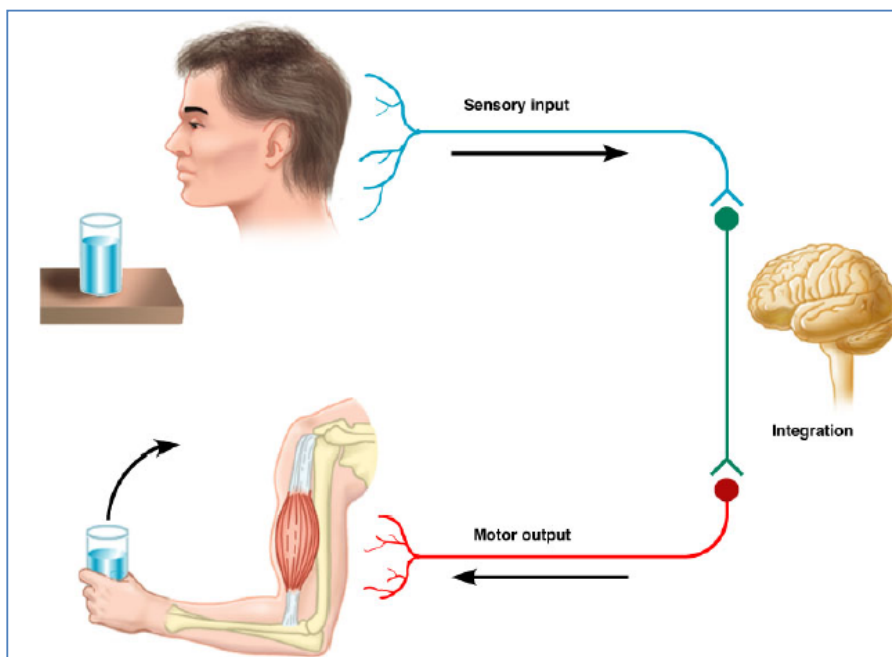
Sensory Receptors:

- A sensory stimulus is a change in a body's environment. (internal/external)
- Nervous system detects stimuli via **specialised nerve endings = sensory receptors**.
- Sensory receptors **convert stimuli to impulses**, which are sent via the **PNS to CNS**.

- Classifying Sensory Receptors:
 - Type of Stimulus:
 - **Mechano:** deformation & mechanical force (touch/pressure/vibration/stretch)
 - **Thermo:** temperature changes
 - **Photo:** light energy
 - **Chemo:** changes in aqueous chemistry of interstitial fluid/smell/taste
 - **Nociceptor:** sense potentially damaging stimuli → pain (heat/cold/pressure/chemicals)
 - Location in Body:
 - **Exteroceptors:** near the body surface – touch/pressure/pain/temperature/ the senses
 - **Interoceptors (visceroceptors):** stimuli within the body [viscera/blood vessels] – (chemical changes/tissue stretch/temperature) → pain/discomfort/hunger/thirst
 - **Proprioceptors:** occur in skeletal muscles/tendons/joints/ligaments/muscle sheaths
 - Structural Complexity:
 - **Simple:** absolute majority – modified dendritic endings of sensory neurons.
 - **Complex:** minority – sense **organs** = collections of cells associated with the “special senses” (vision/hearing/smell/taste)

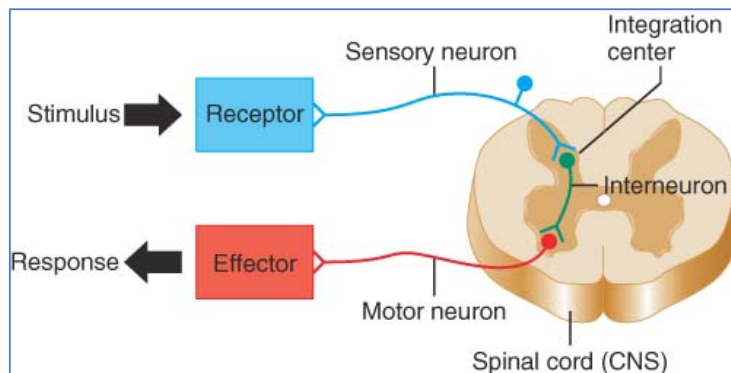
- Once sensory input enters CNS, it travels to the **Thalamus** (sorting station of the brain)
 - Impulses are sorted on the basis of **where they came from** and the **type of sensation**
 - They are then sent to their **relative functional areas** on the **cortex (brain surface)**.
 - Smell/taste/vision/hearing/touch

- **Response:** If a response is required, then a discrete area of the brain will activate it.
 - **Primary motor cortex:** voluntary motor
 - **Language & Speech Centres:** vocalisation
 - **Hypothalamus & Brain Stem:** visceral responses (chest/abdominal – pulse/sweat/B.Pressure)



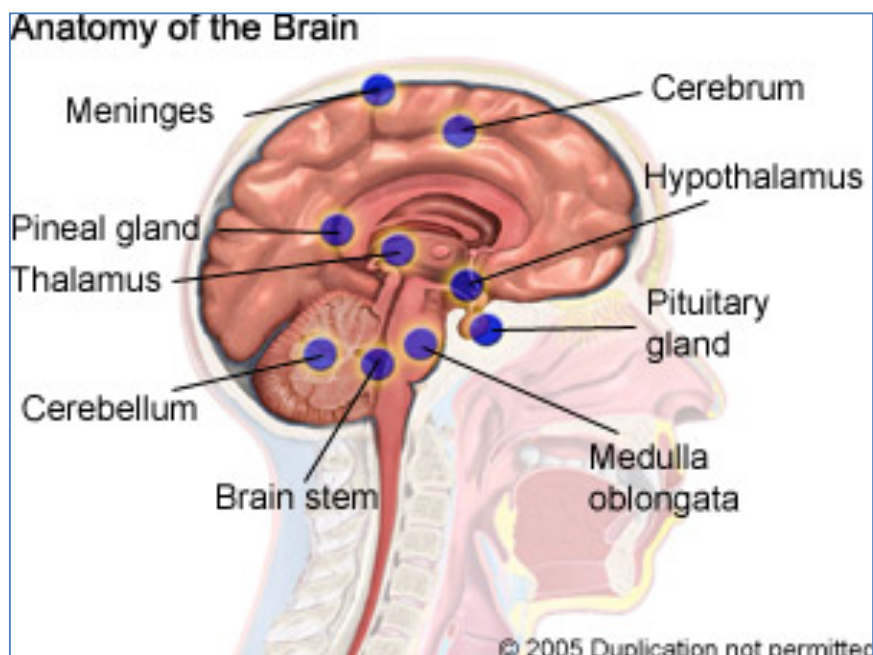
Reflexes:

- Rapid, automatic responses to stimuli.
- Same stimulus always causes the same response.
- Occur over neural pathways called **reflex arcs**.
- **Components of a reflex arc:**
 - Receptor
 - Sensory neuron
 - CNS integration centre
 - Motor neuron
 - Effector



Basic Anatomy of the Brain:

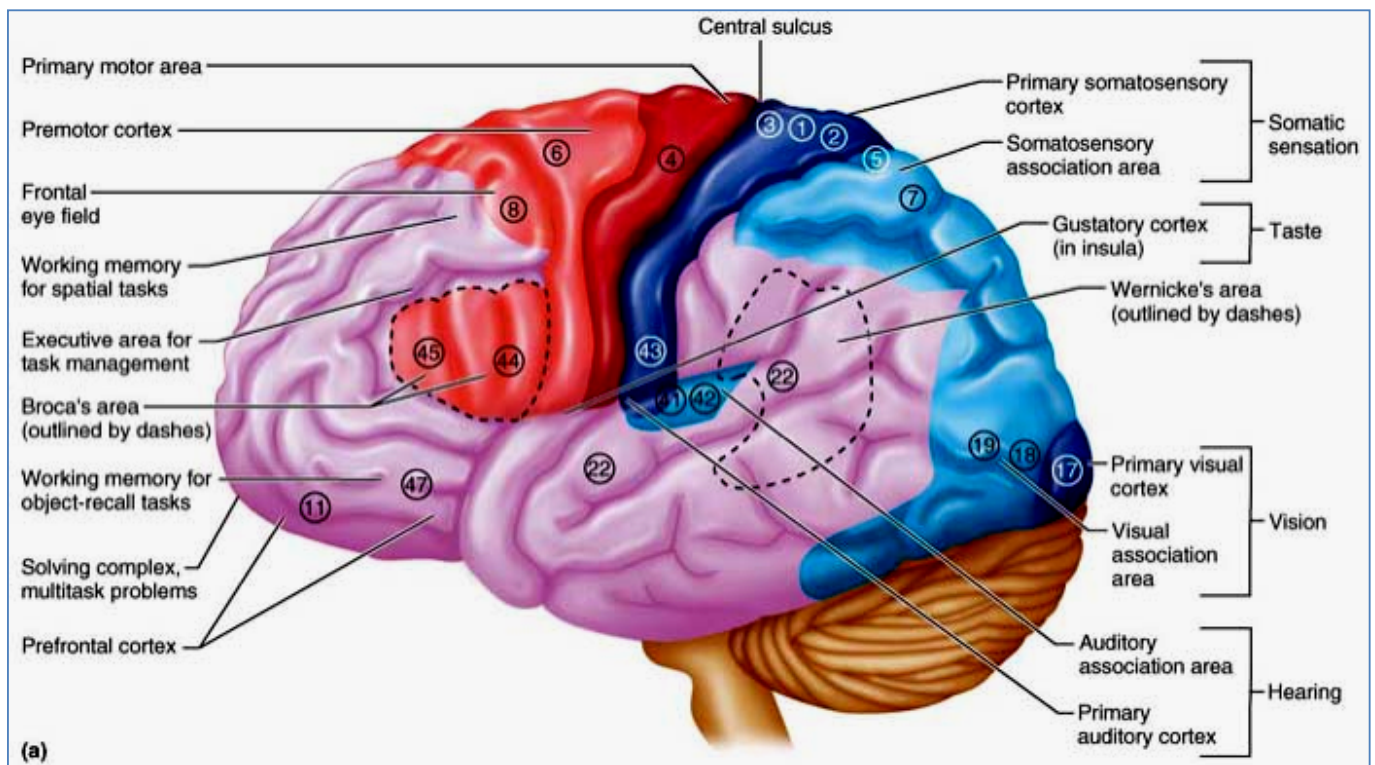
- Cerebrum
- Cerebral cortex
- Brain stem
- Cerebellum
- Thalamus
- Hypothalamus



Functional Sensory Areas of the Brain:

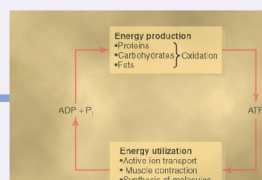
- **Primary visual area** – receives visual information from the retina of the eye.
- **Primary motor area** – controls voluntary skilled movements of our skeletal muscles
- **Pre-motor cortex** – controls learned motor skills (musical instruments/typing/etc)
- **Primary auditory area** – sound energy stimulates hearing receptors and is interpreted as pitch/vol/location.
- **Primary somatosensory area** – receives information from the general (somatic) sensory receptors.
- **Primary gustatory area** – perception of taste stimuli.
- **Primary Olfactory area** – info from smell receptors

Sensory Association Areas – info flows from sensory receptors to a specific primary sensory cortex, then to a specific association area. Association areas give meaning to the received information, store it in memory, relate it to past experiences & decide on plan of action





**Continue Reading For Bonus
Supplementary Study Materials...**



Metabolism of Carbohydrates and Formation of Adenosine Triphosphate

The next few chapters deal with metabolism in the body—that is, the chemical processes that make it possible for the cells to continue living. It is not the purpose of this textbook to present the chemical details of all the various cellular reactions, which lie in the discipline of biochemistry. Instead, these chapters are devoted to (1) a review of the principal chemical processes of the cell and (2) an analysis of their physiological implications, especially the manner in which they fit into the overall body homeostasis.

Release of Energy From Foods and “Free Energy”

Many of the chemical reactions in the cells are aimed at making the energy in foods available to the various physiological systems of the cell. For instance, energy is required for muscle activity, secretion by the glands, maintenance of membrane potentials by the nerve and muscle fibers, synthesis of substances in the cells, absorption of foods from the gastrointestinal tract, and many other functions.

Coupled Reactions. All the energy foods—carbohydrates, fats, and proteins—can be oxidized in the cells, and during this process, large amounts of energy are released. These same foods can also be burned with pure oxygen outside the body in an actual fire, also releasing large amounts of energy; in this case, however, the energy is released suddenly, all in the form of heat. The energy needed by the physiologic processes of the cells is not heat but energy to cause mechanical movement in the case of muscle function, to concentrate solutes in the case of glandular secretion, and to effect other cell functions. To provide this energy, the chemical reactions must be “coupled” with the systems responsible for these physiologic functions. This coupling is accomplished by special cellular enzymes and energy transfer systems, some of which are explained in this and subsequent chapters.

“Free Energy.” The amount of energy liberated by complete oxidation of a food is called the *free energy of oxidation of the food* and is generally represented by the symbol ΔG . Free energy is usually expressed in terms of calories per mole of substance. For instance, the amount of free energy liberated by complete oxidation of 1 mole (180 grams) of glucose is 686,000 calories.

Adenosine Triphosphate Is the “Energy Currency” of the Body

Adenosine triphosphate (ATP) is an essential link between energy-utilizing and energy-producing functions of the body (**Figure 68-1**). For this reason, ATP has been called the energy currency of the body, and it can be gained and spent repeatedly.

Energy derived from the oxidation of carbohydrates, proteins, and fats is used to convert adenosine diphosphate (ADP) to ATP, which is then consumed by the various reactions of the body that are necessary for (1) active transport of molecules across cell membranes; (2) contraction of muscles and performance of mechanical work; (3) various synthetic reactions that create hormones, cell membranes, and many other essential molecules of the body; (4) conduction of nerve impulses; (5) cell division and growth; and (6) many other physiological functions that are necessary to maintain and propagate life.

ATP is a labile chemical compound that is present in all cells. ATP is a combination of adenine, ribose, and three phosphate radicals, as shown in **Figure 68-2**. The last two phosphate radicals are connected with the remainder of the molecule by high-energy bonds, which are indicated by the symbol \sim .

The amount of free energy in each of these high-energy bonds per mole of ATP is about 7300 calories under standard conditions and about 12,000 calories under the usual

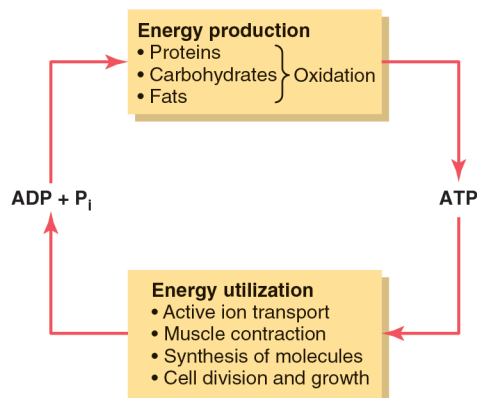


Figure 68-1. Adenosine triphosphate as the central link between energy-producing and energy-utilizing systems of the body. ADP, adenosine diphosphate; P_i , inorganic phosphate.

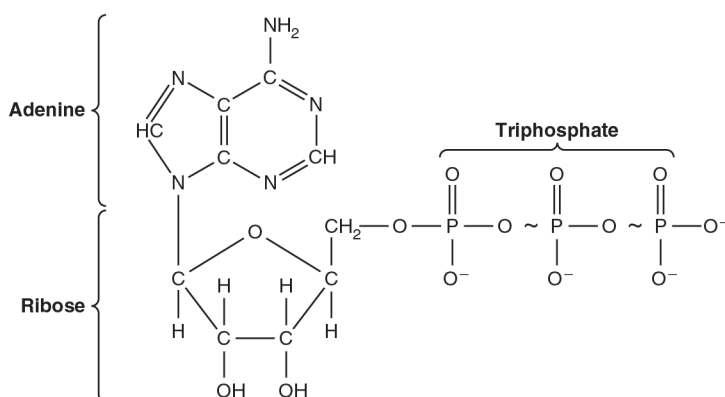
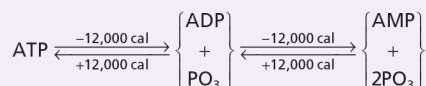


Figure 68-2. Chemical structure of adenosine triphosphate.

conditions of temperature and concentrations of the reactants in the body. Therefore, in the body, removal of each of the last two phosphate radicals liberates about 12,000 calories of energy. After loss of one phosphate radical from ATP, the compound becomes ADP, and after loss of the second phosphate radical, it becomes *adenosine monophosphate* (AMP). The interconversions among ATP, ADP, and AMP are the following:



ATP is present everywhere in the cytoplasm and nucleoplasm of all cells, and essentially all the physiological mechanisms that require energy for operation obtain it directly from ATP (or another similar high-energy compound, guanosine triphosphate). In turn, the food in the cells is gradually oxidized, and the released energy is used to form new ATP, thus always maintaining a supply of this substance. All these energy transfers take place by means of coupled reactions.

The principal purpose of this chapter is to explain how the energy from carbohydrates can be used to form ATP in the cells. Normally, 90 percent or more of all the carbohydrates utilized by the body are for this purpose.

Central Role of Glucose in Carbohydrate Metabolism

As explained in Chapter 66, the final products of carbohydrate digestion in the alimentary tract are almost entirely glucose, fructose, and galactose—with glucose representing, on average, about 80 percent of these products. After absorption from the intestinal tract, much of the fructose and almost all the galactose are rapidly converted into glucose in the liver. Therefore, little fructose and galactose are present in the circulating blood. *Glucose thus becomes the final common pathway for the transport of almost all carbohydrates to the tissue cells.*

In liver cells, appropriate enzymes are available to promote interconversions among the monosaccharides—glucose, fructose, and galactose—as shown in Figure 68-3. Furthermore, the dynamics of the reactions are such that

when the liver releases the monosaccharides back into the blood, the final product is almost entirely glucose. The reason for this is that the liver cells contain large amounts of *glucose phosphatase*. Therefore, glucose-6-phosphate can be degraded to glucose and phosphate, and the glucose can then be transported through the liver cell membrane back into the blood.

Once again, it should be emphasized that usually more than 95 percent of all the monosaccharides that circulate in the blood are the final conversion product, glucose.

Transport of Glucose Through the Cell Membrane

Before glucose can be used by the body's tissue cells, it must be transported through the cell membrane into the cellular cytoplasm. However, glucose *cannot easily diffuse through the pores* of the cell membrane because the maximum molecular weight of particles that can diffuse readily is about 100, and glucose has a molecular weight of 180. Yet glucose does pass to the interior of the cells with a reasonable degree of freedom by the mechanism of *facilitated diffusion*. The principles of this type of transport are discussed in Chapter 4. Basically, they are the following: Penetrating through the lipid matrix of the cell membrane are large numbers of protein *carrier* molecules that can bind with glucose. In this bound form, the glucose can be transported by the carrier from one side of the membrane to the other side and then released. Therefore, if the concentration of glucose is greater on one side of the membrane than on the other side, more glucose will be transported from the high-concentration area to the low-concentration area than in the opposite direction.

The transport of glucose through the membranes of most tissue cells is quite different from that which occurs through the gastrointestinal membrane or through the epithelium of the renal tubules. In both cases, the glucose is transported by the mechanism of *active sodium-glucose co-transport*, in which active transport of sodium provides energy for absorbing glucose *against a concentration difference*. This sodium-glucose co-transport mechanism functions only in certain special epithelial cells that are specifically adapted for active absorption of glucose. At other cell membranes, glucose is transported only from

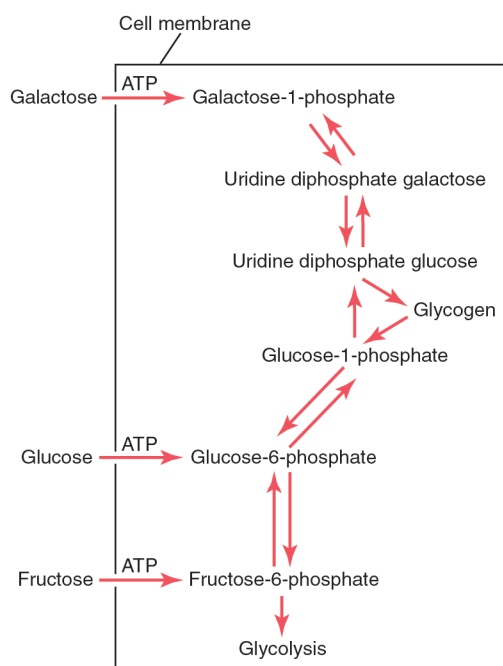


Figure 68-3. Interconversions of the three major monosaccharides—glucose, fructose, and galactose—in liver cells.

higher concentration toward lower concentration by *facilitated diffusion*, made possible by the special binding properties of membrane *glucose carrier protein*. The details of *facilitated diffusion* for cell membrane transport are presented in Chapter 4.

Insulin Increases Facilitated Diffusion of Glucose

The rate of glucose transport, as well as transport of some other monosaccharides, is greatly increased by insulin. When large amounts of insulin are secreted by the pancreas, the rate of glucose transport into most cells increases to 10 or more times the rate of transport when no insulin is secreted. Conversely, the amounts of glucose that can diffuse to the insides of most cells of the body in the absence of insulin, with the exception of liver and brain cells, are far too little to supply the amount of glucose normally required for energy metabolism.

In effect, the rate of carbohydrate utilization by most cells is controlled by the rate of insulin secretion from the pancreas and the sensitivity of the various tissues to insulin's effects on glucose transport. The functions of insulin and its control of carbohydrate metabolism are discussed in detail in Chapter 79.

Phosphorylation of Glucose

Immediately upon entry into the cells, glucose combines with a phosphate radical in accordance with the following reaction:



This phosphorylation is promoted mainly by the enzyme *glucokinase* in the liver and by *hexokinase* in most other

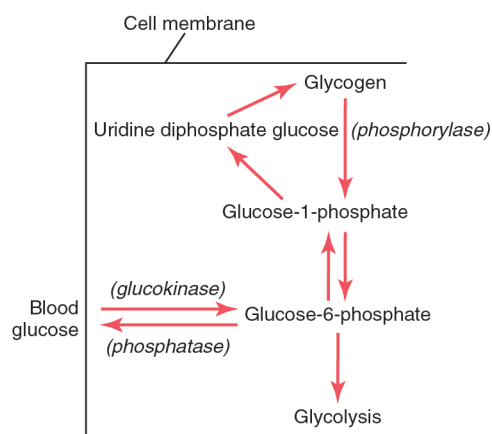


Figure 68-4. Chemical reactions of glycogenesis and glycogenolysis, also showing interconversions between blood glucose and liver glycogen. (The phosphatase required for the release of glucose from the cell is present in liver cells but not in most other cells.)

cells. The phosphorylation of glucose is almost completely irreversible except in liver cells, renal tubular epithelial cells, and intestinal epithelial cells; in these cells, another enzyme, *glucose phosphatase*, is also available, and when activated, it can reverse the reaction. In most tissues of the body, phosphorylation serves to *capture* the glucose in the cell. That is, because of its almost instantaneous binding with phosphate, the glucose will not diffuse back out, except from those special cells, especially liver cells, that have phosphatase.

Glycogen Is Stored in the Liver and Muscle

After absorption into a cell, glucose can be used immediately for release of energy to the cell, or it can be stored in the form of *glycogen*, which is a large polymer of glucose.

All cells of the body are capable of storing at least some glycogen, but certain cells can store large amounts, especially *liver cells*, which can store up to 5 to 8 percent of their weight as glycogen, and *muscle cells*, which can store up to 1 to 3 percent glycogen. The glycogen molecules can be polymerized to almost any molecular weight, with the average molecular weight being 5 million or greater; most of the glycogen precipitates in the form of solid granules.

This conversion of monosaccharides into a high-molecular-weight precipitated compound (glycogen) makes it possible to store large quantities of carbohydrates without significantly altering the osmotic pressure of the intracellular fluids. High concentrations of low-molecular-weight soluble monosaccharides would play havoc with the osmotic relations between intracellular and extracellular fluids.

Glycogenesis—Formation of Glycogen

The chemical reactions for glycogenesis are shown in **Figure 68-4**. In this figure, it can be seen that *glucose-6-phosphate* can become *glucose-1-phosphate*; this substance is converted to *uridine diphosphate glucose*, which is finally converted into glycogen. Several specific enzymes are

required to cause these conversions, and any monosaccharide that can be converted into glucose can enter into the reactions. Certain smaller compounds, including *lactic acid*, *glycerol*, *pyruvic acid*, and some *deaminated amino acids*, can also be converted into glucose or closely allied compounds and then converted into glycogen.

Glycogenolysis—Breakdown of Stored Glycogen

Glycogenolysis means the breakdown of the cell's stored glycogen to re-form glucose in the cells. The glucose can then be used to provide energy. Glycogenolysis does not occur by reversal of the same chemical reactions that form glycogen; instead, each succeeding glucose molecule on each branch of the glycogen polymer is split away by *phosphorylation*, catalyzed by the enzyme *phosphorylase*.

Under resting conditions, the phosphorylase is in an inactive form, and thus glycogen remains stored. When it is necessary to re-form glucose from glycogen, the phosphorylase must first be activated. This activation can be accomplished in several ways, including activation by epinephrine or by glucagon, as described in the next section.

Activation of Phosphorylase by Epinephrine or by Glucagon. Two hormones, *epinephrine* and *glucagon*, can activate phosphorylase and thereby cause rapid glycogenolysis. The initial effect of each of these hormones is to promote the formation of *cyclic AMP* in the cells, which then initiates a cascade of chemical reactions that activates the phosphorylase. This process is discussed in detail in Chapter 79.

Epinephrine is released by the adrenal medullae when the sympathetic nervous system is stimulated. Therefore, one of the functions of the sympathetic nervous system is to increase the availability of glucose for rapid energy metabolism. This function of epinephrine occurs markedly in both liver cells and muscle, thereby contributing (along with other effects of sympathetic stimulation) to preparation of the body for action, as discussed in Chapter 61.

Glucagon is a hormone secreted by the *alpha cells* of the pancreas when the blood glucose concentration falls too low. It stimulates formation of cyclic AMP mainly in the liver cells, which in turn promotes conversion of liver glycogen into glucose and its release into the blood, thereby elevating the blood glucose concentration. The function of glucagon in blood glucose regulation is discussed in Chapter 79.

Release of Energy From Glucose by the Glycolytic Pathway

Because complete oxidation of 1 gram-mole of glucose releases 686,000 calories of energy and only 12,000 calories of energy are required to form 1 gram-mole of ATP, energy would be wasted if glucose were decomposed all at once into water and carbon dioxide while forming only a single ATP molecule. Fortunately, cells of the body contain special enzymes that cause the glucose molecule to split a little at a time in many successive steps, so that its energy is released in small packets to form one molecule of ATP at a time, thus forming a total of 38 moles of ATP for each mole of glucose metabolized by the cells.

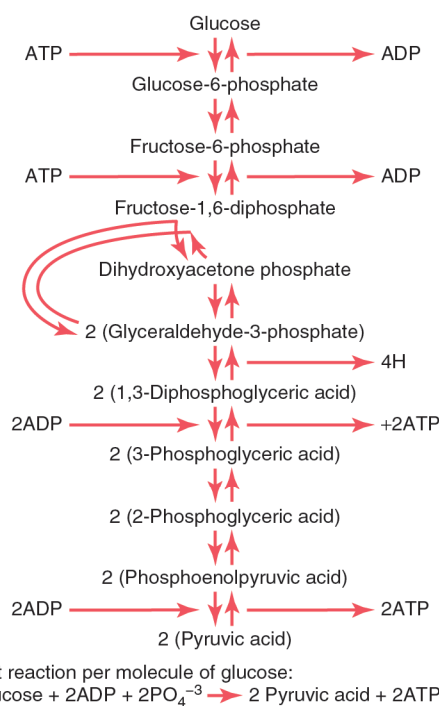


Figure 68-5. Sequence of chemical reactions responsible for glycolysis.

In the next sections we describe the basic principles of the processes by which the glucose molecule is progressively dissected and its energy released to form ATP.

Glycolysis—Splitting Glucose to Form Pyruvic Acid

By far the most important means of releasing energy from the glucose molecule is initiated by *glycolysis*. The end products of glycolysis are then oxidized to provide energy. Glycolysis means splitting of the glucose molecule to form *two molecules of pyruvic acid*.

Glycolysis occurs by 10 successive chemical reactions, shown in **Figure 68-5**. Each step is catalyzed by at least one specific protein enzyme. Note that glucose is first converted into fructose-1,6-diphosphate and then split into two three-carbon-atom molecules, glyceraldehyde-3-phosphate, each of which is then converted through five additional steps into pyruvic acid.

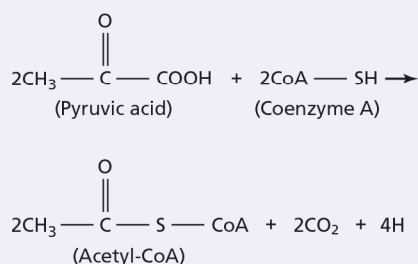
Formation of ATP During Glycolysis. Despite the many chemical reactions in the glycolytic series, only a small portion of the free energy in the glucose molecule is released at most steps. However, between the 1,3-diphosphoglyceric acid and the 3-phosphoglyceric acid stages, and again between the phosphoenolpyruvic acid and the pyruvic acid stages, the packets of energy released are greater than 12,000 calories per mole, the amount required to form ATP, and the reactions are coupled in such a way that ATP is formed. Thus, a total of 4 moles of ATP are formed for each mole of fructose-1,6-diphosphate that is split into pyruvic acid.

Yet, 2 moles of ATP are required to phosphorylate the original glucose to form fructose-1,6-diphosphate before

glycolysis could begin. Therefore, *the net gain in ATP molecules by the entire glycolytic process is only 2 moles for each mole of glucose utilized.* This amounts to 24,000 calories of energy that becomes transferred to ATP, but during glycolysis, a total of 56,000 calories of energy were lost from the original glucose, giving an overall *efficiency* for ATP formation of only 43 percent. The remaining 57 percent of the energy is lost in the form of heat.

Conversion of Pyruvic Acid to Acetyl Coenzyme A

The next stage in the degradation of glucose is a two-step conversion of the two pyruvic acid molecules from **Figure 67-5** into two molecules of *acetyl coenzyme A* (acetyl-CoA), in accordance with the following reaction:



Two carbon dioxide molecules and four hydrogen atoms are released from this reaction, while the remaining portions of the two pyruvic acid molecules combine with coenzyme A, a derivative of the vitamin pantothenic acid, to form two molecules of acetyl-CoA. In this conversion, no ATP is formed, but up to six molecules of ATP are formed when the four released hydrogen atoms are later oxidized, as discussed later.

Citric Acid Cycle (Krebs Cycle)

The next stage in the degradation of the glucose molecule is called the *citric acid cycle* (also called the *tricarboxylic acid cycle* or the *Krebs cycle* in honor of Hans Krebs for his discovery of this cycle). The citric acid cycle is a sequence of chemical reactions in which the acetyl portion of acetyl-CoA is degraded to carbon dioxide and hydrogen atoms. These reactions all occur in the *matrix of mitochondria*. The released hydrogen atoms add to the number of these atoms that will subsequently be oxidized (as discussed later), releasing tremendous amounts of energy to form ATP.

Figure 68-6 shows the different stages of the chemical reactions in the citric acid cycle. The substances to the left are added during the chemical reactions, and the products of the chemical reactions are shown to the right. Note at the top of the column that the cycle begins with *oxaloacetic acid*, and at the bottom of the chain of reactions, *oxaloacetic acid* is formed again. Thus, the cycle can continue repeatedly.

In the initial stage of the citric acid cycle, *acetyl-CoA* combines with *oxaloacetic acid* to form *citric acid*. The coenzyme A portion of the acetyl-CoA is released and can be used repeatedly for the formation of still more quantities of acetyl-CoA from pyruvic acid. The acetyl portion, however, becomes an integral part of the citric acid molecule. During the successive stages of the citric acid cycle,

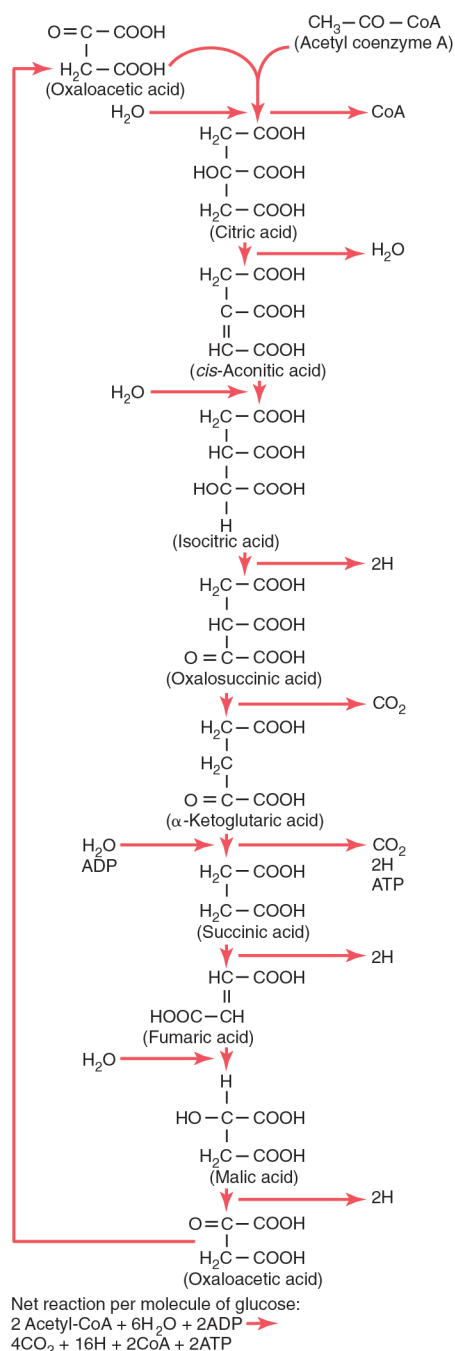


Figure 68-6. Chemical reactions of the citric acid cycle, showing the release of carbon dioxide and a number of hydrogen atoms during the cycle.

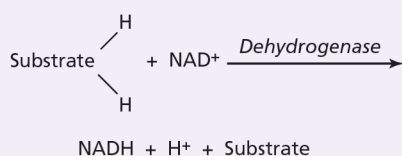
several molecules of water are added, as shown on the left in **Figure 68-6**, and *carbon dioxide* and *hydrogen atoms* are released at other stages in the cycle, as shown on the right in the figure.

The net results of the entire citric acid cycle are provided in the explanation at the bottom of **Figure 68-6**,

demonstrating that for each molecule of glucose originally metabolized, two acetyl-CoA molecules enter into the citric acid cycle, along with six molecules of water. These molecules are then degraded into 4 carbon dioxide molecules, 16 hydrogen atoms, and 2 molecules of coenzyme A. Two molecules of ATP are formed, as follows.

Formation of ATP in the Citric Acid Cycle. The citric acid cycle itself does not cause a great amount of energy to be released; a molecule of ATP is formed in only one of the chemical reactions—during the change from α -ketoglutaric acid to succinic acid. Thus, for each molecule of glucose metabolized, two acetyl-CoA molecules pass through the citric acid cycle, each forming a molecule of ATP, or a total of two molecules of ATP formed.

Function of Dehydrogenases and Nicotinamide Adenine Dinucleotide in Causing Release of Hydrogen Atoms in the Citric Acid Cycle. As already noted at several points in this discussion, hydrogen atoms are released during different chemical reactions of the citric acid cycle—4 hydrogen atoms during glycolysis, 4 during formation of acetyl-CoA from pyruvic acid, and 16 in the citric acid cycle; thus a total of 24 hydrogen atoms are released for each original molecule of glucose. However, the hydrogen atoms are not simply turned loose in the intracellular fluid. Instead, they are released in packets of two, and in each instance, the release is catalyzed by a specific protein enzyme called a *dehydrogenase*. Twenty of the 24 hydrogen atoms immediately combine with nicotinamide adenine dinucleotide (NAD^+), a derivative of the vitamin niacin, in accordance with the following reaction:



This reaction will not occur without intermediation of the specific dehydrogenase or without the availability of NAD^+ to act as a hydrogen carrier. Both the free hydrogen ion and the hydrogen bound with NAD^+ subsequently enter into multiple oxidative chemical reactions that form large quantities of ATP, as discussed later.

The remaining four hydrogen atoms released during the breakdown of glucose—the four released during the citric acid cycle between the succinic and fumaric acid stages—combine with a specific dehydrogenase but are not subsequently released to NAD^+ . Instead, they pass directly from the dehydrogenase into the oxidative process.

Function of Decarboxylases in Causing Release of Carbon Dioxide. Referring again to the chemical reactions of the citric acid cycle, as well as to those for the formation of acetyl-CoA from pyruvic acid, we find that there are three stages in which carbon dioxide is released. To cause the release of carbon dioxide, other specific protein enzymes, called *decarboxylases*, split the carbon dioxide away from the substrate. The carbon dioxide is then dissolved in the body fluids and transported to the lungs, where it is expired from the body (see Chapter 41).

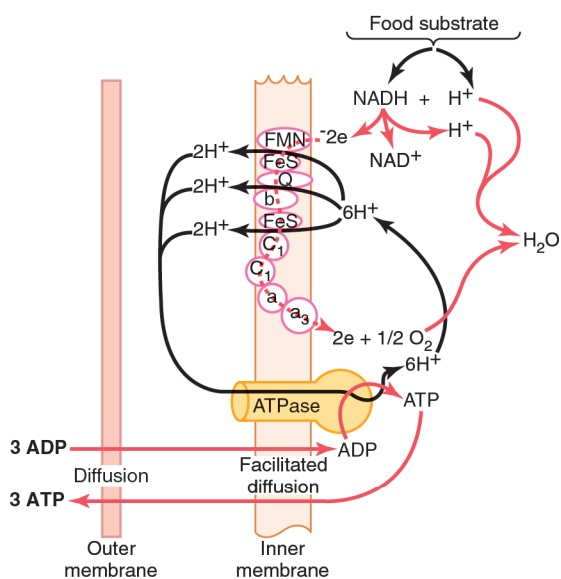


Figure 68-7. Mitochondrial chemiosmotic mechanism of oxidative phosphorylation for forming large quantities of ATP. This figure shows the relationship of the oxidative and phosphorylation steps at the outer and inner membranes of the mitochondrion. FeS, iron sulfide protein; FMN, flavin mononucleotide; Q, ubiquinone.

Formation of Large Quantities of ATP by Oxidation of Hydrogen—The Process of Oxidative Phosphorylation

Despite all the complexities of (1) glycolysis, (2) the citric acid cycle, (3) dehydrogenation, and (4) decarboxylation, pitifully small amounts of ATP are formed during all these processes—only two ATP molecules in the glycolysis scheme and another two in the citric acid cycle for each molecule of glucose metabolized. Instead, almost 90 percent of the total ATP created through glucose metabolism is formed during subsequent oxidation of the hydrogen atoms that were released at early stages of glucose degradation. Indeed, the principal function of all these earlier stages is to make the hydrogen of the glucose molecule available in forms that can be oxidized.

Oxidation of hydrogen is accomplished, as illustrated in **Figure 68-7**, by a series of enzymatically catalyzed reactions *in the mitochondria*. These reactions (1) split each hydrogen atom into a hydrogen ion and an electron and (2) use the electrons eventually to combine dissolved oxygen of the fluids with water molecules to form hydroxyl ions. Then the hydrogen and hydroxyl ions combine with each other to form water. During this sequence of oxidative reactions, tremendous quantities of energy are released to form ATP. Formation of ATP in this manner is called *oxidative phosphorylation*, which occurs entirely in the mitochondria by a highly specialized process called the *chemiosmotic mechanism*.

Chemiosmotic Mechanism of the Mitochondria to Form ATP

Ionization of Hydrogen, the Electron Transport Chain, and Formation of Water. The first step in oxidative phosphorylation in the mitochondria is to ionize the hydrogen atoms that have been removed from the food substrates. As described earlier, these hydrogen atoms are removed in pairs: one immediately becomes a hydrogen ion, H^+ ; the other combines with NAD^+ to form reduced nicotinamide adenine dinucleotide (NADH). The upper portion of **Figure 68-7** shows the subsequent fate of the NADH and H^+ . The initial effect is to release the other hydrogen atom from the NADH to form another hydrogen ion, H^+ ; this process also reconstitutes NAD^+ that will be reused repeatedly.

The electrons that are removed from the hydrogen atoms to cause the hydrogen ionization immediately enter an *electron transport chain of electron acceptors* that are an integral part of the inner membrane (the shelf membrane) of the mitochondrion. The electron acceptors can be reversibly reduced or oxidized by accepting or giving up electrons. The important members of this electron transport chain include *flavoprotein* (flavin mononucleotide), several *iron sulfide proteins*, *ubiquinone*, and *cytochromes B, C1, C, A, and A3*. Each electron is shuttled from one of these acceptors to the next until it finally reaches cytochrome A3, which is called *cytochrome oxidase* because it is capable of giving up two electrons and thus reducing elemental oxygen to form ionic oxygen, which then combines with hydrogen ions to form water.

Thus, **Figure 68-7** shows the transport of electrons through the electron chain and then their ultimate use by cytochrome oxidase to cause the formation of water molecules. During the transport of these electrons through the electron transport chain, energy is released that is used to cause the synthesis of ATP, as follows.

Pumping of Hydrogen Ions Into the Outer Chamber of the Mitochondrion, Caused by the Electron Transport Chain. As the electrons pass through the electron transport chain, large amounts of energy are released. This energy is used to pump hydrogen ions from the inner matrix of the mitochondrion (to the right in **Figure 68-7**) into the outer chamber between the inner and outer mitochondrial membranes (to the left). This process creates a high concentration of positively charged hydrogen ions in this chamber; it also creates a strong negative electrical potential in the inner matrix.

Formation of ATP. The next step in oxidative phosphorylation is to convert ADP into ATP. This conversion occurs in conjunction with a large protein molecule that protrudes all the way through the inner mitochondrial membrane and projects with a knoblike head into the inner mitochondrial matrix. This molecule is an ATPase, the physical nature of which is shown in **Figure 68-7**. It is called *ATP synthetase*.

The high concentration of positively charged hydrogen ions in the outer chamber and the large electrical potential difference across the inner membrane cause the hydrogen ions to flow into the inner mitochondrial matrix *through the substance of the ATPase molecule*. In doing so, energy

derived from this hydrogen ion flow is used by ATPase to convert ADP into ATP by combining ADP with a free ionic phosphate radical (P_i), thus adding another high-energy phosphate bond to the molecule.

The final step in the process is transfer of ATP from the inside of the mitochondrion back to the cell cytoplasm. This step occurs by facilitated diffusion outward through the inner membrane and then by simple diffusion through the permeable outer mitochondrial membrane. In turn, ADP is continually transferred in the other direction for continual conversion into ATP. *For each two electrons that pass through the entire electron transport chain (representing the ionization of two hydrogen atoms), up to three ATP molecules are synthesized.*

Summary of ATP Formation During the Breakdown of Glucose

We can now determine the total number of ATP molecules that, under optimal conditions, can be formed by the energy from one molecule of glucose.

1. During glycolysis, four molecules of ATP are formed and two are expended to cause the initial phosphorylation of glucose to get the process going, giving a net gain of *two molecules of ATP*.
2. During each revolution of the citric acid cycle, one molecule of ATP is formed. However, because each glucose molecule splits into two pyruvic acid molecules, there are two revolutions of the cycle for each molecule of glucose metabolized, giving a net production of *two more molecules of ATP*.
3. During the entire schema of glucose breakdown, a total of 24 hydrogen atoms are released during glycolysis and during the citric acid cycle. Twenty of these atoms are oxidized in conjunction with the chemiosmotic mechanism shown in **Figure 68-7**, with the release of three ATP molecules per two atoms of hydrogen metabolized. This process gives an additional *30 ATP molecules*.
4. The remaining four hydrogen atoms are released by their dehydrogenase into the chemiosmotic oxidative schema in the mitochondrion beyond the first stage of **Figure 68-7**. Two ATP molecules are usually released for every two hydrogen atoms oxidized, thus giving a total of *four more ATP molecules*.

Now, adding all the ATP molecules formed, we find a maximum of *38 ATP molecules* formed for each molecule of glucose degraded to carbon dioxide and water. Thus, 456,000 calories of energy can be stored in the form of ATP, whereas 686,000 calories are released during the complete oxidation of each gram-molecule of glucose. This outcome represents an overall maximum *efficiency* of energy transfer of 66 percent. The remaining 34 percent of the energy becomes heat and, therefore, cannot be used by the cells to perform specific functions.

Effect of ATP and ADP Cell Concentrations in Controlling Glycolysis and Glucose Oxidation

Continual release of energy from glucose when the cells do not need energy would be an extremely wasteful process.

Instead, glycolysis and the subsequent oxidation of hydrogen atoms are continually controlled in accordance with the need of the cells for ATP. This control is accomplished by multiple feedback control mechanisms within the chemical schemata. Among the more important of these mechanisms are the effects of cell concentrations of both ADP and ATP in controlling the rates of chemical reactions in the energy metabolism sequence.

One important way in which ATP helps control energy metabolism is to inhibit the enzyme *phosphofructokinase*. Because this enzyme promotes the formation of fructose-1,6-diphosphate, one of the initial steps in the glycolytic series of reactions, the net effect of excess cellular ATP is to slow or even stop glycolysis, which in turn stops most carbohydrate metabolism. Conversely, ADP (and AMP as well) causes the opposite change in this enzyme, greatly increasing its activity. Whenever ATP is used by the tissues for energizing a major fraction of almost all intracellular chemical reactions, this action reduces the ATP inhibition of the enzyme phosphofructokinase and at the same time increases its activity as a result of the excess ADP formed. Thus, the glycolytic process is set in motion, and the total cellular store of ATP is replenished.

Another control linkage is the *citrate ion* formed in the citric acid cycle. An excess of this ion also *strongly inhibits phosphofructokinase*, thus preventing the glycolytic process from getting ahead of the citric acid cycle's ability to use the pyruvic acid formed during glycolysis.

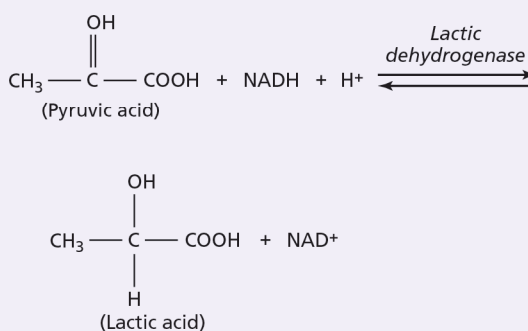
A third way by which the ATP-ADP-AMP system controls carbohydrate metabolism, as well as controlling energy release from fats and proteins, is the following: Referring to the various chemical reactions for energy release, we see that if all the ADP in the cell has already been converted into ATP, additional ATP simply cannot be formed. As a result, the entire sequence involved in the use of foodstuffs—glucose, fats, and proteins—to form ATP is stopped. Then, when ATP is used by the cell to energize the different physiological functions in the cell, the newly formed ADP and AMP turn on the energy processes again, and ADP and AMP are almost instantly returned to the ATP state. In this way, essentially a full store of ATP is automatically maintained, except during extreme cellular activity, such as very strenuous exercise.

Anaerobic Release of Energy— Anaerobic Glycolysis

Occasionally, oxygen becomes either unavailable or insufficient, so oxidative phosphorylation cannot take place. Yet even under these conditions, a small amount of energy can still be released to the cells by the glycolysis stage of carbohydrate degradation, because the chemical reactions for the breakdown of glucose to pyruvic acid do not require oxygen.

This process is extremely wasteful of glucose because only 24,000 calories of energy are used to form ATP for each molecule of glucose metabolized, which represents only a little over 3 percent of the total energy in the glucose molecule. Nevertheless, this release of glycolytic energy to the cells, which is called *anaerobic energy*, can be a lifesaving measure for up to a few minutes when oxygen becomes unavailable.

Formation of Lactic Acid During Anaerobic Glycolysis Allows Release of Extra Anaerobic Energy. The *law of mass action* states that as the end products of a chemical reaction build up in a reacting medium, the rate of the reaction decreases, approaching zero. The two end products of the glycolytic reactions (see [Figure 68-5](#)) are (1) pyruvic acid and (2) hydrogen atoms combined with NAD^+ to form NADH and H^+ . The buildup of either or both of these substances would stop the glycolytic process and prevent further formation of ATP. When their quantities begin to be excessive, these two end products react with each other to form lactic acid, in accordance with the following equation:



Thus, under anaerobic conditions, the major portion of the pyruvic acid is converted into lactic acid, which diffuses readily out of the cells into the extracellular fluids and even into the intracellular fluids of other less active cells. Therefore, lactic acid represents a type of "sinkhole" into which the glycolytic end products can disappear, thus allowing glycolysis to proceed far longer than would otherwise be possible. Indeed, glycolysis could proceed for only a few seconds without this conversion. Instead, it can proceed for several minutes, supplying the body with considerable extra quantities of ATP, even in the absence of respiratory oxygen.

Reconversion of Lactic Acid to Pyruvic Acid When Oxygen Becomes Available Again. When a person begins to breathe oxygen again after a period of anaerobic metabolism, the lactic acid is rapidly reconverted to pyruvic acid and NADH plus H^+ . Large portions of these substances are immediately oxidized to form large quantities of ATP. This excess ATP then causes as much as three fourths of the remaining excess pyruvic acid to be converted back into glucose.

Thus, the large amount of lactic acid that forms during anaerobic glycolysis is not lost from the body because, when oxygen is available again, the lactic acid can be either reconverted to glucose or used directly for energy. By far the greatest portion of this reconversion occurs in the liver, but a small amount can also occur in other tissues.

Use of Lactic Acid by the Heart for Energy. Heart muscle is especially capable of converting lactic acid to pyruvic acid and then using the pyruvic acid for energy. This process occurs to a great extent during heavy exercise, when large amounts of lactic acid are released into the blood from the skeletal muscles and consumed as an extra energy source by the heart.

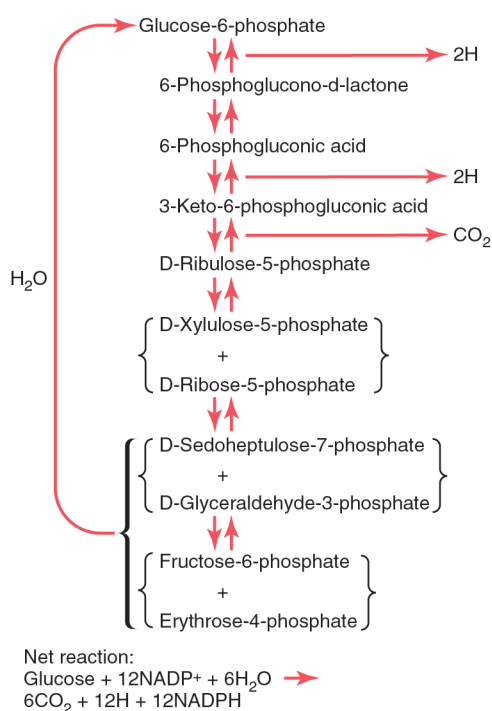


Figure 68-8. Pentose phosphate pathway for glucose metabolism.

Release of Energy From Glucose by the Pentose Phosphate Pathway

In almost all the body's muscles, essentially all the carbohydrates utilized for energy are degraded to pyruvic acid by glycolysis and then oxidized. However, this glycolytic scheme is not the only means by which glucose can be degraded and used to provide energy. A second important mechanism for the breakdown and oxidation of glucose is called the *pentose phosphate pathway* (or *phosphogluconate pathway*), which is responsible for *as much as 30 percent of the glucose breakdown in the liver and even more than this in fat cells*.

This pathway is especially important because it can provide energy independently of all the enzymes of the citric acid cycle and therefore is an alternative pathway for energy metabolism when certain enzymatic abnormalities occur in cells. It has a special capacity for providing energy to multiple cellular synthetic processes.

Release of Carbon Dioxide and Hydrogen by the Pentose Phosphate Pathway. Figure 68-8 shows most of the basic chemical reactions in the pentose phosphate pathway. It demonstrates that glucose, during several stages of conversion, can release one molecule of carbon dioxide and four atoms of hydrogen, with the resultant formation of a five-carbon sugar, D-ribulose. This substance can change progressively into several other five-, four-, seven-, and three-carbon sugars. Finally, various combinations of these sugars can resynthesize glucose. However, *only five molecules of glucose are resynthesized for every six molecules of glucose that initially enter into the reactions*. That is, the pentose phosphate pathway is a cyclical process in

which one molecule of glucose is metabolized for each revolution of the cycle. Thus, by repeating the cycle again and again, all the glucose can eventually be converted into carbon dioxide and hydrogen, and the hydrogen can enter the oxidative phosphorylation pathway to form ATP; more often, however, it is used for the synthesis of fat or other substances, as follows.

Use of Hydrogen to Synthesize Fat; the Function of Nicotinamide Adenine Dinucleotide Phosphate. The hydrogen released during the pentose phosphate cycle does not combine with NAD^+ as in the glycolytic pathway but combines with nicotinamide adenine dinucleotide phosphate (NADP^+), which is almost identical to NAD^+ except for an extra phosphate radical, P. This difference is extremely significant because only hydrogen bound with NADP^+ in the form of NADPH can be used for the synthesis of fats from carbohydrates (as discussed in Chapter 69) and for the synthesis of some other substances.

When the glycolytic pathway for using glucose becomes slowed because of cellular inactivity, the pentose phosphate pathway remains operative (mainly in the liver) to break down any excess glucose that continues to be transported into the cells, and NADPH becomes abundant to help convert acetyl-CoA, also derived from glucose, into long fatty acid chains. This is another way in which energy in the glucose molecule is used other than for the formation of ATP—in this instance, *for the formation and storage of fat in the body*.

Glucose Conversion to Glycogen or Fat

When glucose is not immediately required for energy, the extra glucose that continually enters the cells is either stored as glycogen or converted into fat. Glucose is preferentially stored as glycogen until the cells have stored as much glycogen as they can—an amount sufficient to supply the energy needs of the body for only 12 to 24 hours.

When the glycogen-storing cells (primarily liver and muscle cells) approach saturation with glycogen, the additional glucose is converted into fat in liver and fat cells and is stored as fat in the fat cells. Other steps in the chemistry of this conversion are discussed in Chapter 69.

Formation of Carbohydrates From Proteins and Fats—Gluconeogenesis

When the body's stores of carbohydrates decrease below normal, moderate quantities of glucose can be formed from *amino acids* and the *glycerol* portion of fat. This process is called *gluconeogenesis*.

Gluconeogenesis is especially important in preventing an excessive reduction in the blood glucose concentration during fasting. Glucose is the primary substrate for energy in tissues such as the brain and the red blood cells, and adequate amounts of glucose must be present in the blood for several hours between meals. The liver plays a key role in maintaining blood glucose levels during fasting by converting its stored glycogen to glucose (glycogenolysis) and by synthesizing glucose, mainly from lactate and amino acids (gluconeogenesis). Approximately 25 percent of the liver's glucose production during fasting is from gluconeogenesis, helping to provide a steady supply of glucose to the

brain. During prolonged fasting, the kidneys also synthesize considerable amounts of glucose from amino acids and other precursors.

About 60 percent of the amino acids in the body proteins can be converted easily into carbohydrates; the remaining 40 percent have chemical configurations that make this conversion difficult or impossible. Each amino acid is converted into glucose by a slightly different chemical process. For instance, alanine can be converted directly into pyruvic acid simply by deamination; the pyruvic acid is then converted into glucose or stored glycogen. Several of the more complicated amino acids can be converted into different sugars that contain three-, four-, five-, or seven-carbon atoms. They can then enter the phosphogluconate pathway and eventually form glucose. Thus, by means of deamination plus several simple interconversions, many of the amino acids can become glucose. Similar interconversions can change glycerol into glucose or glycogen.

Regulation of Gluconeogenesis

Diminished carbohydrates in the cells and decreased blood sugar are the basic stimuli that increase the rate of gluconeogenesis. Diminished carbohydrates can directly reverse many of the glycolytic and phosphogluconate reactions, thus allowing the conversion of deaminated amino acids and glycerol into carbohydrates. In addition, the hormone *cortisol* is especially important in this regulation, as described in the following section.

Effect of Corticotropin and Glucocorticoids on Gluconeogenesis. When normal quantities of carbohydrates are not available to the cells, the adenohypophysis, for reasons not completely understood, secretes increased quantities of the hormone *corticotropin*. This secretion stimulates the adrenal cortex to produce large quantities of *glucocorticoid hormones*, especially *cortisol*. In turn, cortisol mobilizes proteins from essentially all cells of the body, making these proteins available in the form of amino acids in the body fluids. A high proportion of these amino acids immediately become deaminated in the liver and provide ideal substrates for conversion into glucose. Thus, one of the most important means by which gluconeogenesis is promoted is through the release of glucocorticoids from the adrenal cortex.

Blood Glucose

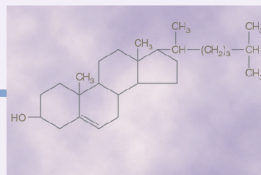
The normal blood glucose concentration in a person who has not eaten a meal within the past 3 to 4 hours is

about 90 mg/dl. After a meal containing large amounts of carbohydrates, this level seldom rises above 140 mg/dl unless the person has diabetes mellitus, which is discussed in Chapter 79.

The regulation of blood glucose concentration is intimately related to the pancreatic hormones insulin and glucagon; this subject is discussed in detail in Chapter 79 in relation to the functions of these hormones.

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Lipid Metabolism

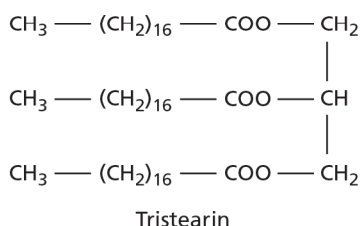
Several chemical compounds in food and in the body are classified as *lipids*. Lipids include (1) *neutral fat*, also known as *triglycerides*; (2) *phospholipids*; (3) *cholesterol*; and (4) a few others of less importance. Chemically, the basic lipid moiety of triglycerides and phospholipids is *fatty acids*, which are long-chain hydrocarbon organic acids. A typical fatty acid, palmitic acid, is the following: $\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$.

Although cholesterol does not contain fatty acid, its sterol nucleus is synthesized from portions of fatty acid molecules, thus giving it many of the physical and chemical properties of other lipids.

The triglycerides are used in the body mainly to provide energy for the different metabolic processes, a function they share almost equally with carbohydrates. However, some lipids, especially cholesterol, phospholipids, and small amounts of triglycerides, are used to form the membranes of all cells of the body and to perform other cellular functions.

BASIC CHEMICAL STRUCTURE OF TRIGLYCERIDES (NEUTRAL FAT)

Because most of this chapter deals with the utilization of triglycerides for energy, the following typical structure of the triglyceride molecule should be understood.



Note that three long-chain fatty acid molecules are bound with one molecule of glycerol. The three fatty acids most commonly present in the triglycerides of the human body are (1) *stearic acid* (shown in the tristearin example), which has an 18-carbon chain and is fully saturated with hydrogen atoms; (2) *oleic acid*, which also has an 18-carbon chain but has one double bond in the middle of the chain; and (3) *palmitic acid*, which has 16 carbon atoms and is fully saturated.

TRANSPORT OF LIPIDS IN THE BODY FLUIDS

TRANSPORT OF TRIGLYCERIDES AND OTHER LIPIDS FROM THE GASTROINTESTINAL TRACT BY LYMPH—THE CHYLOMICRONS

As explained in Chapter 66, almost all the fats in the diet, with the principal exception of a few short-chain fatty acids, are absorbed from the intestines into the intestinal lymph. During digestion, most triglycerides are split into monoglycerides and fatty acids. Then, while passing through the intestinal epithelial cells, the monoglycerides and fatty acids are resynthesized into new molecules of triglycerides that enter the lymph as minute, dispersed droplets called *chylomicrons* (Figure 69-1), whose diameters are between 0.08 and 0.6 micron. A small amount of *apoprotein B* is adsorbed to the outer surfaces of the chylomicrons. The remainder of the protein molecules project into the surrounding water and thereby increase the suspension stability of the chylomicrons in the lymph fluid and prevent their adherence to the lymphatic vessel walls.

Most of the cholesterol and phospholipids absorbed from the gastrointestinal tract enter the chylomicrons. Thus, although the chylomicrons are composed principally of triglycerides, they also contain about 9 percent phospholipids, 3 percent cholesterol, and 1 percent apoprotein B. The chylomicrons are then transported upward through the thoracic duct and emptied into the circulating venous blood at the juncture of the jugular and subclavian veins.

REMOVAL OF THE CHYLOMICRONS FROM THE BLOOD

About 1 hour after a meal that contains large quantities of fat, the chylomicron concentration in the plasma may rise to 1 to 2 percent of the total plasma, and because of the large size of the chylomicrons, the plasma appears turbid and sometimes yellow. However, the chylomicrons have a half-life of less than 1 hour, so the plasma becomes clear again within a few hours. The fat of the chylomicrons is removed mainly in the following way.

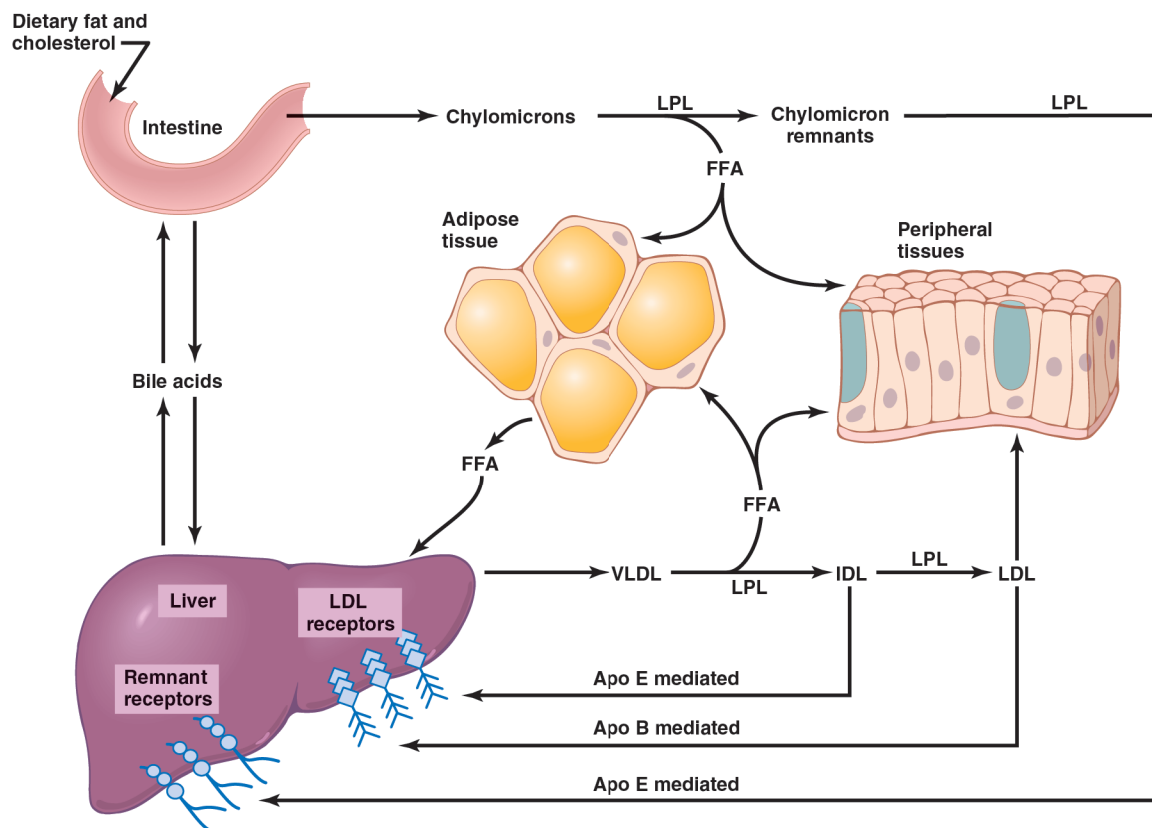


Figure 69-1. Summary of major pathways for metabolism of chylomicrons synthesized in the intestine and very low density lipoprotein (VLDL) synthesized in the liver. Apo B, apolipoprotein B; Apo E, apolipoprotein E; FFA, free fatty acids; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase.

Chylomicron Triglycerides Are Hydrolyzed by Lipoprotein Lipase, and Fat Is Stored in Adipose Tissue.

Most of the chylomicrons are removed from the circulating blood as they pass through the capillaries of various tissues, especially adipose tissue, skeletal muscle, and heart. These tissues synthesize the enzyme *lipoprotein lipase*, which is transported to the surface of capillary endothelial cells, where it hydrolyzes the triglycerides of chylomicrons as they come in contact with the endothelial wall, thus releasing fatty acids and glycerol (see [Figure 69-1](#)).

The fatty acids released from the chylomicrons, being highly miscible with the membranes of the cells, diffuse into the fat cells of the adipose tissue and muscle cells. Once inside these cells, the fatty acids can be used for fuel or again synthesized into triglycerides, with new glycerol being supplied by the metabolic processes of the storage cells, as discussed later in the chapter. The lipase also causes hydrolysis of phospholipids, which also releases fatty acids to be stored in the cells in the same way.

After the triglycerides are removed from the chylomicrons, the cholesterol-enriched *chylomicron remnants* are rapidly cleared from the plasma. The chylomicron

remnants bind to receptors on endothelial cells in the liver sinusoids. *Apolipoprotein-E* on the surface of the chylomicron remnants and secreted by liver cells also plays an important role in initiating clearance of these plasma lipoproteins.

“Free Fatty Acids” Are Transported in the Blood in Combination With Albumin

When fat that has been stored in the adipose tissue is to be used elsewhere in the body to provide energy, it must first be transported from the adipose tissue to the other tissue. It is transported mainly in the form of *free fatty acids*. This transport is achieved by hydrolysis of the triglycerides back into fatty acids and glycerol.

At least two classes of stimuli play important roles in promoting this hydrolysis. First, when the amount of glucose available to the fat cell is inadequate, one of the glucose breakdown products, α -*glycerophosphate*, is also available in insufficient quantities. Because this substance is required to maintain the glycerol portion of triglycerides, the result is hydrolysis of triglycerides. Second, a *hormone-sensitive cellular lipase* can be activated by several hormones from the endocrine glands, and this also promotes

rapid hydrolysis of triglycerides. This topic is discussed later in the chapter.

Upon leaving fat cells, fatty acids ionize strongly in the plasma and the ionic portion combines immediately with albumin molecules of the plasma proteins. Fatty acids bound in this manner are called *free fatty acids* or *non-esterified fatty acids*, to distinguish them from other fatty acids in the plasma that exist in the form of (1) esters of glycerol, (2) cholesterol, or (3) other substances.

The concentration of free fatty acids in the plasma under resting conditions is about 15 mg/dl, which is a total of only 0.45 gram of fatty acids in the entire circulatory system. Even this small amount accounts for almost all the transport of fatty acids from one part of the body to another for the following reasons:

1. Despite the minute amount of free fatty acid in the blood, its rate of “turnover” is extremely rapid: *half the plasma fatty acid is replaced by new fatty acid every 2 to 3 minutes*. One can calculate that at this rate, almost all the normal energy requirements of the body can be provided by the oxidation of transported free fatty acids, without using any carbohydrates or proteins for energy.
2. Conditions that increase the rate of utilization of fat for cellular energy also increase the free fatty acid concentration in the blood; in fact, the concentration sometimes increases fivefold to eightfold. Such a large increase occurs especially in cases of *starvation* and in *diabetes mellitus*; in both these conditions, the person derives little or no metabolic energy from carbohydrates.

Under normal conditions, only about 3 molecules of fatty acid combine with each molecule of albumin, but as many as 30 fatty acid molecules can combine with a single albumin molecule when the need for fatty acid transport is extreme. This shows how variable the rate of lipid transport can be under different physiological conditions.

Lipoproteins—Their Special Function in Transporting Cholesterol and Phospholipids

In the postabsorptive state, after all the chylomicrons have been removed from the blood, more than 95 percent of all the lipids in the plasma are in the form of *lipoprotein*. These lipids are small particles—much smaller than chylomicrons, but qualitatively similar in composition—containing *triglycerides*, *cholesterol*, *phospholipids*, and *protein*. The total concentration of lipoproteins in the plasma averages about 700 milligrams per 100 milliliters of plasma—that is, 700 mg/dl—and can be broken down into the following individual lipoprotein constituents:

	mg/dl of Plasma
Cholesterol	180
Phospholipids	160
Triglycerides	160
Protein	200

Types of Lipoproteins. Aside from the chylomicrons, which are very large lipoproteins, there are four major

types of lipoproteins, classified by their densities as measured in the ultracentrifuge: (1) *very low density lipoproteins (VLDLs)*, which contain high concentrations of triglycerides and moderate concentrations of both cholesterol and phospholipids; (2) *intermediate-density lipoproteins (IDLs)*, which are VLDLs from which a share of the triglycerides has been removed, so the concentrations of cholesterol and phospholipids are increased; (3) *low-density lipoproteins (LDLs)*, which are derived from IDLs by the removal of almost all the triglycerides, leaving an especially high concentration of cholesterol and a moderately high concentration of phospholipids; and (4) *high-density lipoproteins (HDLs)*, which contain a high concentration of protein (about 50 percent) but much smaller concentrations of cholesterol and phospholipids.

Formation and Function of Lipoproteins. Almost all the lipoproteins are formed in the liver, which is also where most of the plasma cholesterol, phospholipids, and triglycerides are synthesized. In addition, small quantities of HDLs are synthesized in the intestinal epithelium during the absorption of fatty acids from the intestines.

The primary function of the lipoproteins is to transport their lipid components in the blood. The VLDLs transport triglycerides synthesized in the liver mainly to the adipose tissue, whereas the other lipoproteins are especially important in the different stages of phospholipid and cholesterol transport from the liver to the peripheral tissues or from the periphery back to the liver. Later in the chapter, we discuss in more detail special problems of cholesterol transport in relation to the disease *atherosclerosis*, which is associated with the development of fatty lesions on the insides of arterial walls.

Fat Deposits

Adipose Tissue

Large quantities of fat are stored in two major tissues of the body, the *adipose tissue* and the *liver*. The adipose tissue is usually called *fat deposits*, or simply tissue fat.

A major function of adipose tissue is storage of triglycerides until they are needed to provide energy elsewhere in the body. Additional functions are to provide *heat insulation* for the body, as discussed in Chapter 74, and *secretion of hormones*, such as *leptin* and *adiponectin*, which affect multiple body functions, including appetite and energy expenditure, as discussed in Chapter 72.

Fat Cells (Adipocytes) Store Triglycerides. The fat cells (adipocytes) of adipose tissue are modified fibroblasts that store almost pure triglycerides in quantities as great as 80 to 95 percent of the entire cell volume. Triglycerides inside the fat cells are generally in a liquid form. When the tissues are exposed to prolonged cold, the fatty acid chains of the cell triglycerides, over a period of weeks, become either shorter or more unsaturated to decrease their melting point, thereby always allowing the fat to remain in a liquid state. This characteristic is particularly important because only liquid fat can be hydrolyzed and transported from the cells.

Fat cells can synthesize very small amounts of fatty acids and triglycerides from carbohydrates; this function

transported, as is also true for free fatty acid transport. The rapid transport of both these substances results from their high solubility in the membranes of the target cells, which allows almost instantaneous diffusion into the cells.

Ketosis in Starvation, Diabetes, and Other Diseases.

The concentrations of acetoacetic acid, β -hydroxybutyric acid, and acetone occasionally rise to levels many times normal in the blood and interstitial fluids; this condition is called *ketosis* because acetoacetic acid is a keto acid. The three compounds are called *ketone bodies*. Ketosis occurs especially as a consequence of starvation, in persons with diabetes mellitus, and sometimes even when a person's diet is composed almost entirely of fat. In all these states, essentially no carbohydrates are metabolized—in starvation and with a high-fat diet because carbohydrates are not available, and in diabetes because insulin is not available to cause glucose transport into the cells.

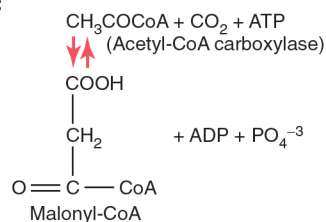
When carbohydrates are not used for energy, almost all the energy of the body must come from metabolism of fats. We shall see later in the chapter that the unavailability of carbohydrates automatically increases the rate of removal of fatty acids from adipose tissues. In addition, several hormonal factors—such as increased secretion of glucocorticoids by the adrenal cortex, increased secretion of glucagon by the pancreas, and decreased secretion of insulin by the pancreas—further enhance the removal of fatty acids from the fat tissues. As a result, large quantities of fatty acids become available (1) to the peripheral tissue cells to be used for energy and (2) to the liver cells, where much of the fatty acid is converted to ketone bodies.

The ketone bodies pour out of the liver to be carried to the cells. For several reasons, the cells are limited in the amount of ketone bodies that can be oxidized. The most important reason for this limitation is that one of the products of carbohydrate metabolism is the *oxaloacetate* that is required to bind with acetyl-CoA before it can be processed in the citric acid cycle. Therefore, deficiency of oxaloacetate derived from carbohydrates limits the entry of acetyl-CoA into the citric acid cycle, and when a simultaneous outpouring of large quantities of acetoacetic acid and other ketone bodies from the liver occurs, the blood concentrations of acetoacetic acid and β -hydroxybutyric acid sometimes rise to as high as 20 times normal, thus leading to extreme acidosis, as explained in Chapter 31.

The acetone that is formed during ketosis is a volatile substance, some of which is blown off in small quantities in the expired air of the lungs, thus giving the breath an acetone smell that is frequently used as a diagnostic criterion of ketosis.

Adaptation to a High-Fat Diet. When changing slowly from a carbohydrate diet to a diet almost completely consisting of fat, a person's body adapts to use far more acetoacetic acid than usual, and in this instance, ketosis normally does not occur. For instance, in the Inuit (Eskimos), who sometimes live mainly on a fat diet, ketosis does not develop. Undoubtedly, several factors, none of which is clear, enhance the rate of acetoacetic acid metabolism by the cells. After a few weeks, even the brain cells, which normally derive almost all their energy from glucose, can derive 50 to 75 percent of their energy from fats.

Step 1:



Step 2:

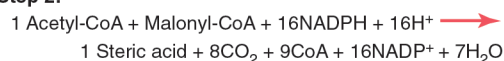


Figure 69-3. Synthesis of fatty acids.

Synthesis of Triglycerides From Carbohydrates

Whenever a greater quantity of carbohydrates enters the body than can be used immediately for energy or can be stored in the form of glycogen, the excess is rapidly converted into triglycerides and stored in this form in the adipose tissue.

In humans, most triglyceride synthesis occurs in the liver, but minute quantities are also synthesized in the adipose tissue. The triglycerides formed in the liver are transported mainly in VLDLs to the adipose tissue, where they are stored.

Conversion of Acetyl-CoA Into Fatty Acids. The first step in the synthesis of triglycerides is conversion of carbohydrates into acetyl-CoA. As explained in Chapter 68, this conversion occurs during the normal degradation of glucose by the glycolytic system. Because fatty acids are actually large polymers of acetic acid, it is easy to understand how acetyl-CoA can be converted into fatty acids. However, the synthesis of fatty acids from acetyl-CoA is not achieved by simply reversing the oxidative degradation described earlier. Instead, this occurs by the two-step process shown in Figure 69-3, using *malonyl-CoA* and reduced nicotinamide adenine dinucleotide phosphate (NADPH) as the principal intermediates in the polymerization process.

Combination of Fatty Acids With α -Glycerophosphate to Form Triglycerides

Once the synthesized fatty acid chains have grown to contain 14 to 18 carbon atoms, they bind with glycerol to form triglycerides. The enzymes that cause this conversion are highly specific for fatty acids, with chain lengths of 14 carbon atoms or greater, a factor that controls the physical quality of the triglycerides stored in the body.

As shown in Figure 69-4, the glycerol portion of triglycerides is furnished by α -glycerophosphate, which is another product derived from the glycolytic scheme of glucose degradation. This mechanism is discussed in Chapter 68.

Efficiency of Carbohydrate Conversion Into Fat. During triglyceride synthesis, only about 15 percent of the original energy in the glucose is lost in the form of heat; the remaining 85 percent is transferred to the stored triglycerides.

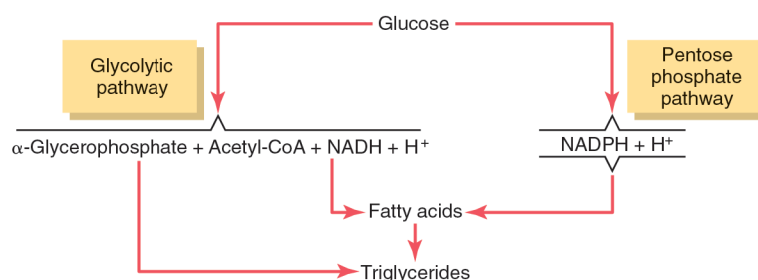


Figure 69-4. Overall schema for synthesis of triglycerides from glucose.

Importance of Fat Synthesis and Storage. Fat synthesis from carbohydrates is especially important for two reasons:

1. The ability of the different cells of the body to store carbohydrates in the form of glycogen is generally slight; a maximum of only a few hundred grams of glycogen can be stored in the liver, the skeletal muscles, and all other tissues of the body put together. In contrast, many kilograms of fat can be stored in adipose tissue. Therefore, fat synthesis provides a means by which the energy of excess ingested carbohydrates (and proteins) can be stored for later use. Indeed, the average person has almost 150 times as much energy stored in the form of fat as stored in the form of carbohydrate.
2. Each gram of fat contains almost two and a half times the calories of energy contained by each gram of glycogen. Therefore, for a given weight gain, a person can store several times as much energy in the form of fat as in the form of carbohydrate, which is exceedingly important when an animal must be highly motile to survive.

Failure to Synthesize Fats From Carbohydrates in the Absence of Insulin. When insufficient insulin is available, as occurs in persons with serious cases of diabetes mellitus, fats are poorly synthesized, if at all, for the following reasons: First, when insulin is not available, glucose does not enter the fat and liver cells satisfactorily, so little of the acetyl-CoA and NADPH needed for fat synthesis can be derived from glucose. Second, lack of glucose in the fat cells greatly reduces the availability of α -glycerophosphate, which also makes it difficult for the tissues to form triglycerides.

Synthesis of Triglycerides From Proteins

Many amino acids can be converted into acetyl-CoA, as discussed in Chapter 70. The acetyl-CoA can then be synthesized into triglycerides. Therefore, when people have more proteins in their diets than their tissues can use as proteins, a large share of the excess is stored as fat.

Regulation of Energy Release From Triglycerides

Carbohydrates Are Preferred Over Fats for Energy When Excess Carbohydrates Are Available. When excess quantities of carbohydrates are available in the body, carbohydrates are used preferentially over triglycerides for energy. Several reasons exist for this “fat-sparing” effect of carbohydrates. First, fats in adipose tissue cells are present in

two forms: stored triglycerides and small quantities of free fatty acids. They are in constant equilibrium with each other. When excess quantities of α -glycerophosphate are present (which occurs when excess carbohydrates are available), the excess α -glycerophosphate binds the free fatty acids in the form of stored triglycerides. As a result, the equilibrium between free fatty acids and triglycerides shifts toward the stored triglycerides; consequently, only minute quantities of fatty acids are available to be used for energy. Because α -glycerophosphate is an important product of glucose metabolism, the availability of large amounts of glucose automatically inhibits the use of fatty acids for energy.

Second, when carbohydrates are available in excess, fatty acids are synthesized more rapidly than they are degraded. This effect is caused partially by the large quantities of acetyl-CoA formed from the carbohydrates and by the low concentration of free fatty acids in the adipose tissue, thus creating conditions appropriate for the conversion of acetyl-CoA into fatty acids.

An even more important effect that promotes the conversion of carbohydrates to fats is the following: The first step, which is the rate-limiting step, in the synthesis of fatty acids is carboxylation of acetyl-CoA to form malonyl-CoA. The rate of this reaction is controlled primarily by the enzyme *acetyl-CoA carboxylase*, the activity of which is accelerated in the presence of intermediates of the citric acid cycle. When excess carbohydrates are being used, these intermediates increase, automatically causing increased synthesis of fatty acids.

Thus, an excess of carbohydrates in the diet not only acts as a fat-sparer but also increases fat stores. In fact, all the excess carbohydrates not used for energy or stored in the small glycogen deposits of the body are converted to fat for storage.

Acceleration of Fat Utilization for Energy in the Absence of Carbohydrates. All the fat-sparing effects of carbohydrates are lost and actually reversed when carbohydrates are not available. The equilibrium shifts in the opposite direction, and fat is mobilized from adipose cells and used for energy in place of carbohydrates.

Also important are several hormonal changes that take place to promote rapid fatty acid mobilization from adipose tissue. Among the most important of these hormonal changes is a marked decrease in pancreatic secretion of insulin caused by the absence of carbohydrates. This decrease not only reduces the rate of glucose utilization by the tissues but also decreases fat storage, which further

shifts the equilibrium in favor of fat metabolism in place of carbohydrates.

Hormonal Regulation of Fat Utilization. At least seven of the hormones secreted by the endocrine glands have significant effects on fat utilization. Some important hormonal effects on fat metabolism—in addition to *lack of insulin*, discussed in the previous paragraph—are noted here.

Probably the most dramatic increase that occurs in fat utilization is that observed during heavy exercise. This increase results almost entirely from release of *epinephrine* and *norepinephrine* by the adrenal medullae during exercise, as a result of sympathetic stimulation. These two hormones directly activate *hormone-sensitive triglyceride lipase*, which is present in abundance in the fat cells, and this activation causes rapid breakdown of triglycerides and mobilization of fatty acids. Sometimes the free fatty acid concentration in the blood of an exercising person rises as much as eightfold, and the use of these fatty acids by the muscles for energy is correspondingly increased. Other types of stress that activate the sympathetic nervous system can also increase fatty acid mobilization and utilization in a similar manner.

Stress also causes large quantities of *corticotropin* to be released by the anterior pituitary gland, which causes the adrenal cortex to secrete extra quantities of *glucocorticoids*. Both corticotropin and glucocorticoids activate either the same hormone-sensitive triglyceride lipase as that activated by epinephrine and norepinephrine or a similar lipase. When corticotropin and glucocorticoids are secreted in excessive amounts for long periods, as occurs in the endocrine condition called *Cushing's syndrome*, fats are frequently mobilized to such a great extent that ketosis results. Corticotropin and glucocorticoids are then said to have a *ketogenic effect*. *Growth hormone* has an effect similar to but weaker than that of corticotropin and glucocorticoids in activating hormone-sensitive lipase. Therefore, growth hormone can also have a mild ketogenic effect.

Thyroid hormone causes rapid mobilization of fat, which is believed to result indirectly from an increased overall rate of energy metabolism in all cells of the body under the influence of this hormone. The resulting reduction in acetyl-CoA and other intermediates of both fat and carbohydrate metabolism in the cells is a stimulus to fat mobilization.

The effects of the different hormones on metabolism are discussed further in the chapters dealing with each hormone.

Obesity—Excess Deposition of Fat

Obesity is discussed in Chapter 72 in relation to dietary balances, but briefly, it is caused by the ingestion of greater amounts of food than can be used by the body for energy. The excess food, whether fats, carbohydrates, or proteins, is then stored almost entirely as fat in the adipose tissue, to be used later for energy.

Several strains of rodents have been found in which *hereditary obesity* occurs. In at least one of these strains, the obesity is caused by ineffective mobilization of fat from the adipose tissue by tissue lipase, while synthesis and storage of fat continue normally. Such a one-way process

causes progressive enhancement of the fat stores, resulting in severe obesity. Multiple genetic factors that influence brain feeding centers or pathways that control energy expenditure or that alter energy storage can also cause hereditary obesity in humans. However, monogenic (single gene) causes of human obesity are rare, as discussed in Chapter 72.

Phospholipids and Cholesterol

Phospholipids

The major types of body phospholipids are *lecithins*, *cephalins*, and *sphingomyelin*; their typical chemical formulas are shown in **Figure 69-5**. Phospholipids always contain one or more fatty acid molecules and one phosphoric acid radical, and they usually contain a nitrogenous base. Although the chemical structures of phospholipids are somewhat variant, their physical properties are similar because they are all lipid soluble, transported in lipoproteins, and used throughout the body for various structural purposes, such as in cell membranes and intracellular membranes.

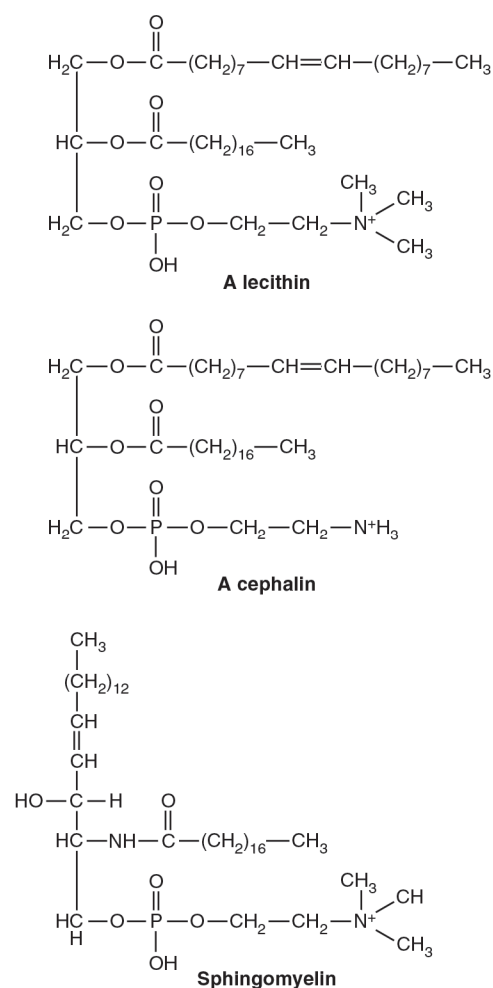


Figure 69-5. Typical phospholipids.

Formation of Phospholipids. Phospholipids are synthesized in essentially all cells of the body, although certain cells have a special ability to form great quantities of them. Probably 90 percent are formed in liver cells; substantial quantities are also formed by the intestinal epithelial cells during lipid absorption from the gut.

The rate of phospholipid formation is governed to some extent by the usual factors that control the overall rate of fat metabolism because, when triglycerides are deposited in the liver, the rate of phospholipid formation increases. Also, certain specific chemical substances are needed for the formation of some phospholipids. For instance, *choline*, either obtained in the diet or synthesized in the body, is necessary for the formation of lecithin, because choline is the nitrogenous base of the lecithin molecule. In addition, *inositol* is necessary for the formation of some cephalins.

Specific Uses of Phospholipids. Phospholipids have several functions, including the following:

1. Phospholipids are an important constituent of lipoproteins in the blood and are essential for the formation and function of most of these lipoproteins; in the absence of phospholipids, serious abnormalities of transport of cholesterol and other lipids can occur.
2. Thromboplastin, which is necessary to initiate the clotting process, is composed mainly of one of the cephalins.
3. Large quantities of sphingomyelin are present in the nervous system; this substance acts as an electrical insulator in the myelin sheath around nerve fibers.
4. Phospholipids are donors of phosphate radicals when these radicals are necessary for different chemical reactions in the tissues.
5. Perhaps the most important of all the functions of phospholipids is participation in the formation of structural elements—mainly membranes—in cells throughout the body, as discussed in the next section of this chapter in connection with a similar function for cholesterol.

Cholesterol

Cholesterol, the formula of which is shown in **Figure 69-6**, is present in the normal diet, and it can be absorbed slowly from the gastrointestinal tract into the intestinal lymph. It is highly fat soluble but only slightly soluble in water. It is specifically capable of forming esters with fatty acids. Indeed, about 70 percent of the cholesterol in the lipoproteins of the plasma is in the form of cholesterol esters.

Formation of Cholesterol. Besides the cholesterol absorbed each day from the gastrointestinal tract, which is called *exogenous cholesterol*, an even greater quantity is formed in the cells of the body, called *endogenous*

cholesterol. Essentially all the endogenous cholesterol that circulates in the lipoproteins of the plasma is formed by the liver, but all other cells of the body form at least some cholesterol, which is consistent with the fact that many of the membranous structures of all cells are partially composed of this substance.

The basic structure of cholesterol is a sterol nucleus, which is synthesized entirely from multiple molecules of acetyl-CoA. In turn, the sterol nucleus can be modified by various side chains to form (1) cholesterol; (2) cholic acid, which is the basis of the bile acids formed in the liver; and (3) many important steroid hormones secreted by the adrenal cortex, the ovaries, and the testes (these hormones are discussed in later chapters).

Factors That Affect Plasma Cholesterol Concentration—Feedback Control of Body Cholesterol. Among the important factors that affect plasma cholesterol concentration are the following:

1. An increase in the *amount of cholesterol ingested each day* may increase the plasma concentration slightly. However, when cholesterol is ingested, the rising concentration of cholesterol inhibits the most essential enzyme for endogenous synthesis of cholesterol, 3-hydroxy-3-methylglutaryl CoA reductase, thus providing an intrinsic feedback control system to prevent an excessive increase in plasma cholesterol concentration. As a result, plasma cholesterol concentration *usually* is not changed upward or downward more than ± 15 percent by altering the amount of cholesterol in the diet, although the response of individuals differs markedly.
2. A diet *high in saturated fat* increases blood cholesterol concentration 15 to 25 percent, especially when this diet is associated with excess weight gain and obesity. This increase in blood cholesterol results from increased fat deposition in the liver, which then provides increased quantities of acetyl-CoA in the liver cells for the production of cholesterol. Therefore, to decrease the blood cholesterol concentration, maintaining a diet low in saturated fat and a normal body weight is even more important than maintaining a diet low in cholesterol.
3. Ingestion of fat containing highly *unsaturated fatty acids* usually depresses the blood cholesterol concentration a slight to moderate amount. The mechanism of this effect is unknown, despite the fact that this observation is the basis of much present-day dietary strategy.
4. *Lack of insulin* or *thyroid hormone* increases the blood cholesterol concentration, whereas excess thyroid hormone decreases the concentration. These effects are probably caused mainly by changes in the degree of activation of specific enzymes responsible for the metabolism of lipid substances.
5. *Genetic disorders* of cholesterol metabolism may greatly increase plasma cholesterol levels. For example, mutations of the *LDL receptor* gene prevent the liver from adequately removing the cholesterol-rich LDLs from the plasma. As discussed later, this phenomenon causes the liver to produce excessive amounts of cholesterol. Mutations of the gene that

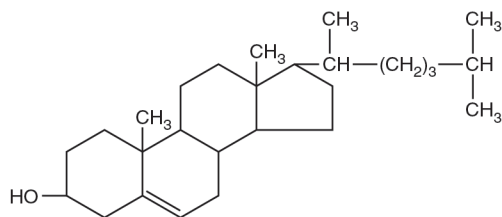


Figure 69-6. Cholesterol.

encodes *apolipoprotein B*, the part of the LDL that binds to the receptor, also cause excessive cholesterol production by the liver.

Specific Uses of Cholesterol in the Body. By far the most abundant non-membranous use of cholesterol in the body is to form cholic acid in the liver. As much as 80 percent of cholesterol is converted into cholic acid. As explained in Chapter 71, cholic acid is conjugated with other substances to form bile salts, which promote digestion and absorption of fats.

A small quantity of cholesterol is used by (1) the adrenal glands to form *adrenocortical hormones*, (2) the ovaries to form *progesterone* and *estrogen*, and (3) the testes to form *testosterone*. These glands can also synthesize their own sterols and then form hormones from them, as discussed in the chapters on endocrinology.

A large amount of cholesterol is precipitated in the corneum of the skin. This cholesterol, along with other lipids, makes the skin highly resistant to the absorption of water-soluble substances and to the action of many chemical agents because cholesterol and the other skin lipids are highly inert to acids and to many solvents that might otherwise easily penetrate the body. Also, these lipid substances help prevent water evaporation from the skin; without this protection, the amount of evaporation can be 5 to 10 liters per day (as occurs in patients with burns who have lost their skin) instead of the usual 300 to 400 milliliters.

Cellular Structural Functions of Phospholipids and Cholesterol—Especially for Membranes

The previously mentioned uses of phospholipids and cholesterol are of only minor importance in comparison with their function of forming specialized structures, mainly membranes, in all cells of the body. In Chapter 2, it was pointed out that large quantities of phospholipids and cholesterol are present in both the cell membrane and the membranes of the internal organelles of all cells. It is also known that the *ratio* of membrane cholesterol to phospholipids is especially important in determining the fluidity of cell membranes.

For membranes to be formed, substances that are not soluble in water must be available. In general, the only substances in the body that are not soluble in water (besides the inorganic substances of bone) are the lipids and some proteins. Thus, the physical integrity of cells everywhere in the body is based mainly on phospholipids, cholesterol, and certain insoluble proteins. The polar charges on the phospholipids also reduce the interfacial tension between the cell membranes and the surrounding fluids.

Another fact that indicates the importance of phospholipids and cholesterol for the formation of structural elements of the cells is the slow turnover rates of these substances in most non-hepatic tissues—turnover rates measured in months or years. For instance, their function in brain cells to provide memory processes is related mainly to their indestructible physical properties.

Atherosclerosis

Atherosclerosis is a disease of the large and intermediate-sized arteries in which fatty lesions called *atheromatous*

plaques develop on the inside surfaces of the arterial walls. *Arteriosclerosis*, in contrast, is a general term that refers to thickened and stiffened blood vessels of all sizes.

One abnormality that can be measured very early in blood vessels that later become atherosclerotic is *damage to the vascular endothelium*. This damage, in turn, increases the expression of adhesion molecules on endothelial cells and decreases their ability to release nitric oxide and other substances that help prevent adhesion of macromolecules, platelets, and monocytes to the endothelium. After damage to the vascular endothelium occurs, circulating monocytes and lipids (mostly LDLs) begin to accumulate at the site of injury (**Figure 69-7A**). The monocytes cross the endothelium, enter the *intima* of the vessel wall, and differentiate to become *macrophages*, which then ingest and oxidize the accumulated lipoproteins, giving the macrophages a foamlike appearance. These *macrophage foam cells* then aggregate on the blood vessel and form a visible *fatty streak*.

With time, the fatty streaks grow larger and coalesce, and the surrounding fibrous and smooth muscle tissues proliferate to form larger and larger plaques (see **Figure 69-7B**). Also, the macrophages release substances that cause *inflammation* and further proliferation of smooth muscle and fibrous tissue on the inside surfaces of the arterial wall. The lipid deposits plus the cellular proliferation can become so large that the plaque bulges into the lumen of the artery and greatly reduces blood flow, sometimes completely occluding the vessel. Even without occlusion, the fibroblasts of the plaque eventually deposit extensive amounts of dense connective tissue; *sclerosis* (fibrosis) becomes so great that the arteries become stiff. Still later, calcium salts often precipitate with the cholesterol and other lipids of the plaques, leading to bony-hard calcifications that can make the arteries rigid tubes. Both of these later stages of the disease are called “hardening of the arteries.”

Atherosclerotic arteries lose most of their distensibility, and because of the degenerative areas in their walls, they are easily ruptured. Also, where the plaques protrude into the flowing blood, their rough surfaces can cause blood clots to develop, with resultant thrombus or embolus formation (see Chapter 37), leading to a sudden blockage of all blood flow in the artery.

Almost half of all deaths in the United States and Europe are due to vascular disease. About two thirds of these deaths are caused by thrombosis of one or more coronary arteries. The remaining one third are caused by thrombosis or hemorrhage of vessels in other organs of the body, especially the brain (causing strokes), but also the kidneys, liver, gastrointestinal tract, limbs, and so forth.

Roles of Cholesterol and Lipoproteins in Atherosclerosis

Increased Low-Density Lipoproteins. An important factor in causing atherosclerosis is a high blood plasma concentration of cholesterol in the form of LDLs. The plasma concentration of these high-cholesterol LDLs is increased by several factors, especially by eating highly saturated fat in the daily diet, obesity, and physical inactivity. To a much lesser extent, eating excess cholesterol may also raise plasma levels of LDLs.

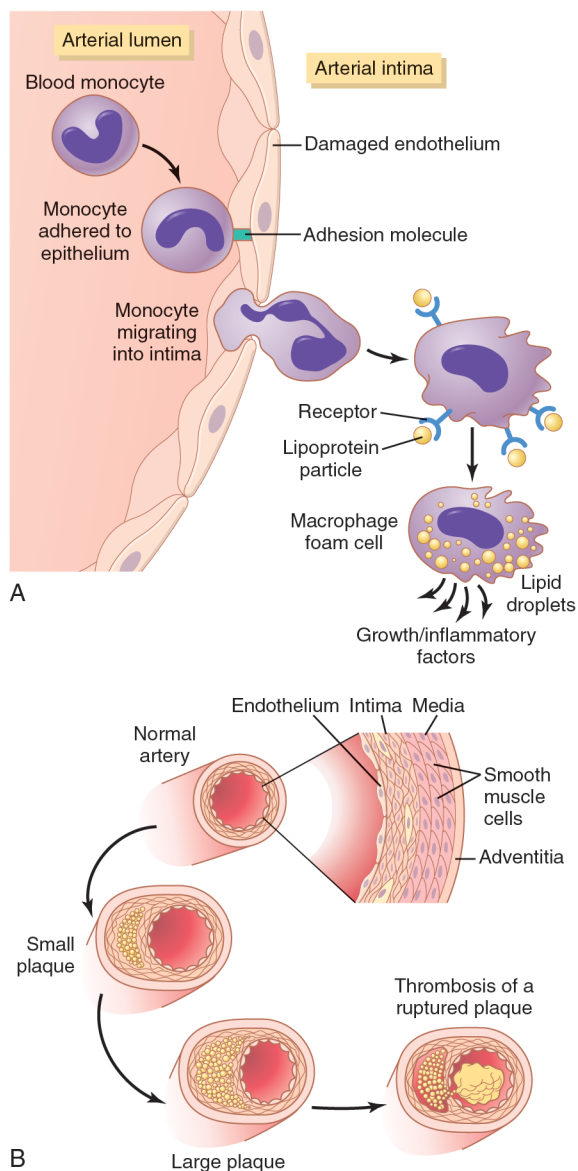


Figure 69-7. Development of atherosclerotic plaque. **A**, Attachment of a monocyte to an adhesion molecule on a damaged endothelial cell of an artery. The monocyte then migrates through the endothelium into the intimal layer of the arterial wall and is transformed into a macrophage. The macrophage then ingests and oxidizes lipoprotein molecules, becoming a macrophage foam cell. The foam cells release substances that cause inflammation and growth of the intimal layer. **B**, Additional accumulation of macrophages and growth of the intima cause the plaque to grow larger and accumulate lipids. Eventually, the plaque may occlude the vessel or rupture, causing the blood in the artery to coagulate and form a thrombus. (Modified from Libby P: *Inflammation in atherosclerosis*. *Nature* 420:868, 2002.)

Familial Hypercholesterolemia. Familial hypercholesterolemia is a disease in which the person inherits defective genes for the formation of LDL receptors on the membrane surfaces of the body's cells. In the absence of these receptors, the liver cannot absorb either IDL or LDL. Without this absorption, the cholesterol machinery of the liver cells goes on a rampage, producing new cholesterol; it is no longer responsive to the feedback inhibition of too much plasma cholesterol. As a result, the number of VLDLs released by the liver into the plasma increases immensely.

Patients with full-blown familial hypercholesterolemia may have blood cholesterol concentrations of 600 to 1000 mg/dl, levels that are four to six times normal. If untreated, many of these people die before age 30 years because of myocardial infarction or other sequelae of atherosclerotic blockage of blood vessels throughout the body.

Heterozygous familial hypercholesterolemia is relatively common and occurs in about 1 in 500 people. The more severe form of this disorder caused by homozygous mutations is much rarer, occurring in only about one of every million births on average.

Role of High-Density Lipoproteins in Preventing Atherosclerosis. Much less is known about the function of HDLs compared with that of LDLs. It is believed that HDLs can actually absorb cholesterol crystals that are beginning to be deposited in arterial walls. Animal experiments also suggest that HDL may have other actions that protect against atherosclerosis, such as inhibition of oxidative stress and prevention of inflammation in blood vessels. Whether or not these mechanisms are true, epidemiological studies indicate that when a person has a high ratio of high-density to low-density lipoproteins, the likelihood of developing atherosclerosis is greatly reduced. Yet, clinical studies with drugs that increase HDL levels have failed to demonstrate decreased risk for cardiovascular disease. These discrepant results indicate the need for additional research on the basic mechanisms by which HDL may influence atherosclerosis.

Other Major Risk Factors for Atherosclerosis

In some people with perfectly normal levels of cholesterol and lipoproteins, atherosclerosis still develops. Some of the factors that are known to predispose to atherosclerosis are (1) *physical inactivity* and *obesity*, (2) *diabetes mellitus*, (3) *hypertension*, (4) *hyperlipidemia*, and (5) *cigarette smoking*.

Hypertension, for example, increases the risk for atherosclerotic coronary artery disease by at least twofold. Likewise, a person with diabetes mellitus has, on average, more than a twofold increased risk of developing coronary artery disease. When hypertension and diabetes mellitus occur together, the risk for coronary artery disease is increased by more than eightfold. When hypertension, diabetes mellitus, and hyperlipidemia are all present, the risk for atherosclerotic coronary artery disease is increased almost 20-fold, suggesting that these factors interact in a synergistic manner to increase the risk of developing atherosclerosis. In many overweight and obese patients, these three risk factors do occur together, greatly increasing their risk for atherosclerosis, which in turn may lead to heart attack, stroke, and kidney disease.

In early and middle adulthood, men are more likely to develop atherosclerosis than are women of comparable age, suggesting that male sex hormones might be atherogenic or, conversely, that female sex hormones might be protective.

Some of these factors cause atherosclerosis by increasing the concentration of LDLs in the plasma. Others, such as hypertension, lead to atherosclerosis by causing damage to the vascular endothelium and other changes in the vascular tissues that predispose to cholesterol deposition.

To add to the complexity of atherosclerosis, experimental studies suggest that *excess blood levels of iron* can lead to atherosclerosis, perhaps by forming free radicals in the blood that damage the vessel walls. About one quarter of all people have a special type of LDL called lipoprotein(a), containing an additional protein, *apolipoprotein(a)*, that almost doubles the incidence of atherosclerosis. The precise mechanisms of these atherogenic effects have yet to be discovered.

Prevention of Atherosclerosis

The most important measures to protect against the development of atherosclerosis and its progression to serious vascular disease are (1) maintaining a healthy weight, being physically active, and eating a diet that contains mainly unsaturated fat with a low cholesterol content; (2) preventing hypertension by maintaining a healthy diet and being physically active, or effectively controlling blood pressure with antihypertensive drugs if hypertension does develop; (3) effectively controlling blood glucose with insulin treatment or other drugs if diabetes develops; and (4) avoiding cigarette smoking.

Several types of drugs that lower plasma lipids and cholesterol have proved to be valuable in preventing atherosclerosis. Most of the cholesterol formed in the liver is converted into bile acids and secreted in this form into the duodenum; then, more than 90 percent of these same bile acids is reabsorbed in the terminal ileum and used over and over again in the bile. Therefore, any agent that combines with the bile acids in the gastrointestinal tract and prevents their reabsorption into the circulation can decrease the total bile acid pool in the circulating blood. As a result, far more of the liver cholesterol is converted into new bile acids. Thus, simply eating *oat bran*, which binds bile acids and is a constituent of many breakfast cereals, increases the proportion of liver cholesterol that forms new bile acids rather than forming new LDLs and atherogenic plaques. *Resin agents* can also be used to bind bile acids in the gut and increase their fecal excretion, thereby reducing cholesterol synthesis by the liver.

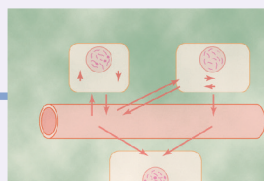
Another group of drugs called *statins* competitively inhibits *hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase*, a rate-limiting enzyme in the synthesis of cholesterol. This inhibition decreases cholesterol synthesis and increases LDL receptors in the liver, usually causing a 25 to 50 percent reduction in plasma levels of LDLs. The statins may also have other beneficial effects that help prevent

atherosclerosis, such as attenuating vascular inflammation. These drugs are now widely used to treat patients who have increased plasma cholesterol levels.

In general, studies show that for each 1 mg/dl decrease in LDL cholesterol in the plasma, there is about a 2 percent decrease in mortality from atherosclerotic heart disease. Therefore, appropriate preventive measures are valuable in decreasing heart attacks.

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Protein Metabolism

About three quarters of the body solids are proteins. These proteins include structural proteins, enzymes, nucleoproteins, proteins that transport oxygen, proteins of the muscle that cause muscle contraction, and many other types that perform specific intracellular and extracellular functions throughout the body.

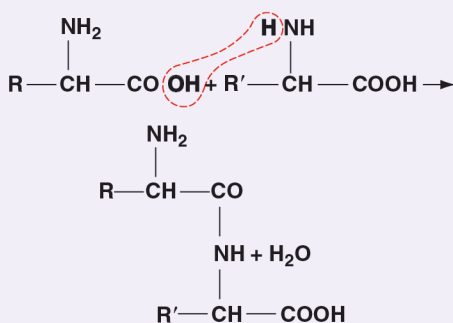
The basic chemical properties that explain the diverse functions of proteins are so extensive that they constitute a major portion of the entire discipline of biochemistry. For this reason, the current discussion is confined to a few specific aspects of protein metabolism that are important as background for other discussions in this text.

Basic Properties of Proteins

Amino Acids Are the Principal Constituents of Proteins

The principal constituents of proteins are amino acids. Twenty of these amino acids are present in the body proteins in significant quantities. **Figure 70-1**, which shows the chemical formulas of these 20 amino acids, demonstrates that they all have two features in common: each amino acid has an acidic group ($-\text{COOH}$) and a nitrogen atom attached to the molecule, usually represented by the amino group ($-\text{NH}_2$).

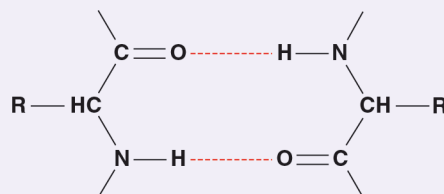
Peptide Linkages and Peptide Chains. The amino acids of proteins are aggregated into long chains by means of *peptide linkages*. The chemical nature of this linkage is demonstrated by the following reaction:



Note in this reaction that the nitrogen of the amino radical of one amino acid bonds with the carbon of the carboxyl radical of the other amino acid. A hydrogen ion is

released from the amino radical, and a hydroxyl ion is released from the carboxyl radical; these two ions combine to form a molecule of water. After the peptide linkage has been formed, an amino radical and a carboxyl radical are still at opposite ends of the new, longer molecule. Each of these radicals is capable of combining with additional amino acids to form a *peptide chain*. Some complicated protein molecules have many thousands of amino acids combined by peptide linkages, and even the smallest protein molecule usually has more than 20 amino acids combined by peptide linkages. The average is about 400 amino acids.

Other Linkages in Protein Molecules. Some protein molecules are composed of several peptide chains rather than a single chain, and these chains are bound to one another by other linkages, often by *hydrogen bonding* between the CO and NH radicals of the peptides, as follows:



Many peptide chains are coiled or folded, and the successive coils or folds are held in a tight spiral or in other shapes by similar hydrogen bonding and other forces.

Transport and Storage of Amino Acids

Blood Amino Acids

The normal concentration of amino acids in the blood is between 35 and 65 mg/dl, which is an average of about 2 mg/dl for each of the 20 amino acids, although some are present in far greater amounts than are others. Because the amino acids are relatively strong acids, they exist in the blood principally in the ionized state, as a result of the removal of one hydrogen atom from the NH_2 radical. They actually account for 2 to 3 milliequivalents of the negative ions in the blood. The precise distribution of the different amino acids in the blood depends to some extent on the types of proteins eaten, but the concentrations of at least some individual amino acids are regulated by selective synthesis in the different cells.

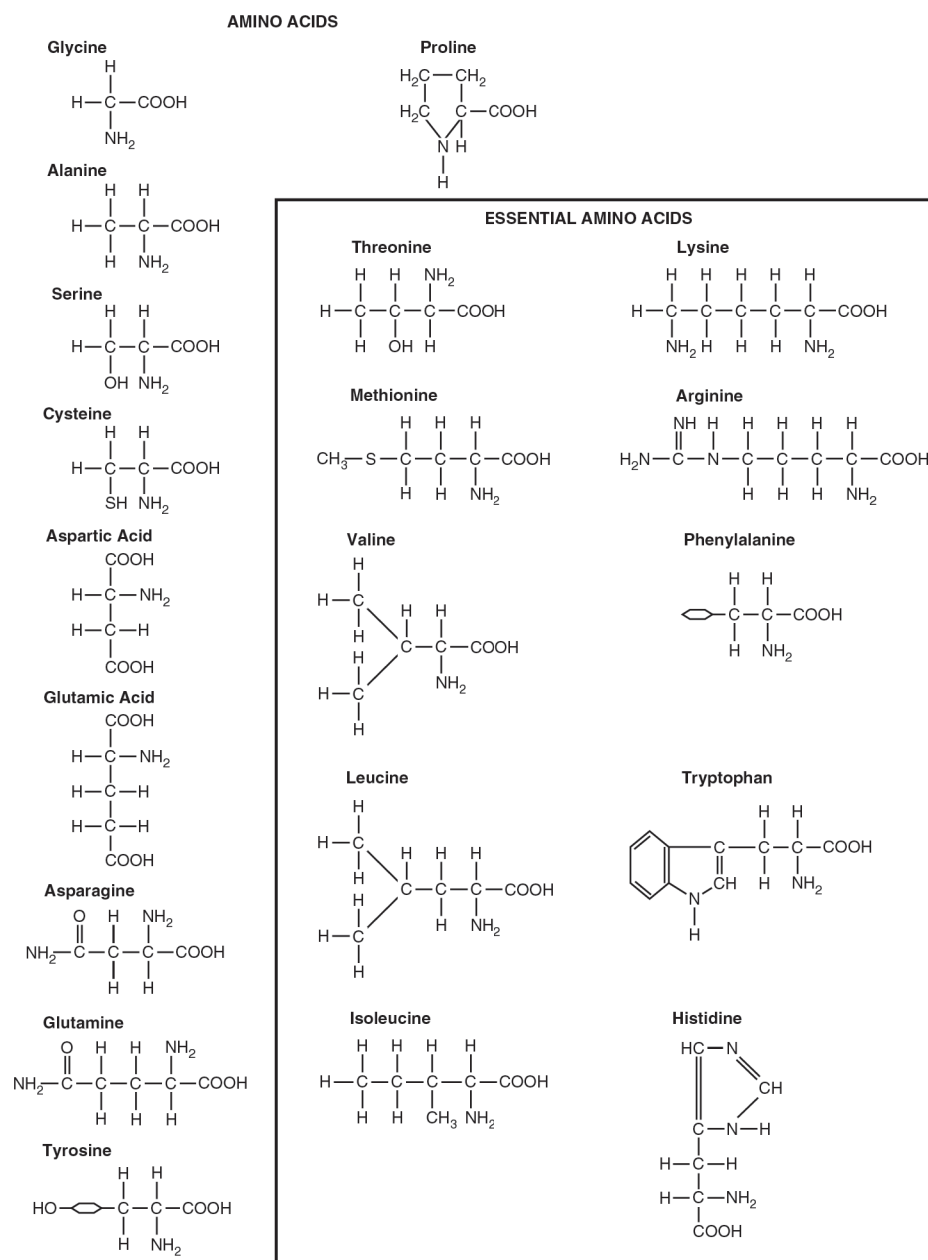


Figure 70-1. Amino acids. The 10 *essential* amino acids cannot be synthesized in sufficient quantities in the body; these amino acids must be obtained, already formed, from food.

Fate of Amino Acids Absorbed From the Gastrointestinal Tract.

The products of protein digestion and absorption in the gastrointestinal tract are almost entirely amino acids; only rarely are polypeptides or whole protein molecules absorbed from the digestive tract into the blood. Soon after a meal, the amino acid concentration in a person's blood rises, but the increase is usually only a few milligrams per deciliter, for two reasons: First, protein digestion and absorption are usually extended over 2 to 3 hours, which allows only small quantities of amino acids to be absorbed

at a time. Second, after entering the blood, the additional amino acids are absorbed within 5 to 10 minutes by cells throughout the body, especially by the liver. Therefore, large concentrations of amino acids almost never accumulate in the blood and tissue fluids. Nevertheless, the turn-over rate of the amino acids is so rapid that many grams of proteins can be carried from one part of the body to another in the form of amino acids each hour.

Active Transport of Amino Acids Into the Cells. The molecules of all the amino acids are much too large to

diffuse readily through the pores of the cell membranes. Therefore, significant quantities of amino acids can move either inward or outward through the membranes only by facilitated transport or active transport using carrier mechanisms. The nature of some of the carrier mechanisms is not completely understood, but a few are discussed in Chapter 4.

Renal Threshold for Amino Acids. In the kidneys, the different amino acids can be reabsorbed through the proximal tubular epithelium by *secondary active transport*, which removes them from the glomerular filtrate and returns them to the blood as they filter into the renal tubules through the glomerular membranes. However, as is true of other active transport mechanisms in the renal tubules, there is an upper limit to the rate at which each type of amino acid can be transported. For this reason, when the concentration of a particular type of amino acid becomes too high in the plasma and glomerular filtrate, the excess that cannot be actively reabsorbed is lost into the urine.

Storage of Amino Acids as Proteins in the Cells

After entry into tissue cells, amino acids combine with one another by peptide linkages, under the direction of the cell's messenger RNA and ribosomal system, to form cellular proteins. Therefore, the concentration of free amino acids inside most cells usually remains low, and storage of large quantities of free amino acids does not occur in the cells; instead, they are stored mainly in the form of actual proteins. However, many of these intracellular proteins can be rapidly decomposed again into amino acids under the influence of intracellular lysosomal digestive enzymes. These amino acids can then be transported back out of the cell into the blood. Special exceptions to this reversal process are the proteins in the chromosomes of the nucleus and the structural proteins such as collagen and muscle contractile proteins. These proteins do not participate significantly in this reverse digestion and transport back out of the cells.

Some tissues of the body participate in the storage of amino acids to a greater extent than do others. For instance, the liver, which is a large organ and has special systems for processing amino acids, can store large quantities of rapidly exchangeable proteins, which is also true of the kidneys and the intestinal mucosa to a lesser extent.

Release of Amino Acids From the Cells as a Means of Regulating Plasma Amino Acid Concentration. Whenever plasma amino acid concentrations fall below normal levels, the required amino acids are transported out of the cells to replenish their supply in the plasma. In this way, the plasma concentration of each type of amino acid is maintained at a reasonably constant value. Later, it is noted that some of the hormones secreted by the endocrine glands are able to alter the balance between tissue proteins and circulating amino acids. For instance, growth hormone and insulin increase the formation of tissue proteins, whereas adrenocortical glucocorticoid hormones increase the concentration of plasma amino acids.

Reversible Equilibrium Between the Proteins in Different Parts of the Body. Because cellular proteins in the liver (and, to a much less extent, in other tissues) can

be synthesized rapidly from plasma amino acids, and because many of these proteins can be degraded and returned to the plasma almost as rapidly, constant interchange and equilibrium occurs between the plasma amino acids and labile proteins in virtually all cells of the body. For instance, if a particular tissue requires proteins, it can synthesize new proteins from the amino acids of the blood; in turn, the blood amino acids are replenished by degradation of proteins from other cells of the body, especially from the liver cells. These effects are particularly noticeable in relation to protein synthesis in cancer cells. Cancer cells are often prolific users of amino acids; therefore, the proteins of the other cells can become markedly depleted.

Upper Limit for the Storage of Proteins. Each particular type of cell has an upper limit with regard to the amount of proteins it can store. After all the cells have reached their limits, the excess amino acids still in the circulation are degraded into other products and used for energy, as discussed subsequently, or they are converted to fat or glycogen and stored in these forms.

Functional Roles of the Plasma Proteins

The major types of protein present in the plasma are *albumin*, *globulin*, and *fibrinogen*.

A major function of *albumin* is to provide *colloid osmotic pressure* in the plasma, which prevents plasma loss from the capillaries, as discussed in Chapter 16.

The *globulins* perform several *enzymatic functions* in the plasma, but equally important, they are principally responsible for both the natural and acquired *immunity* of the body against invading organisms, as discussed in Chapter 35.

Fibrinogen polymerizes into long fibrin threads during blood coagulation, thereby *forming blood clots* that help repair leaks in the circulatory system, as discussed in Chapter 37.

Formation of the Plasma Proteins. Essentially all the albumin and fibrinogen of the plasma proteins, as well as 50 to 80 percent of the globulins, are formed in the liver. The remaining globulins, which are formed almost entirely in the lymphoid tissues, are mainly the gamma globulins that constitute the antibodies used in the immune system.

The rate of plasma protein formation by the liver can be extremely high—as much as 30 g/day. Certain disease conditions cause rapid loss of plasma proteins; for example, severe burns that denude large surface areas of the skin can cause the loss of several liters of plasma through the denuded areas each day. The rapid production of plasma proteins by the liver is valuable in preventing death in such states. Occasionally, a person with severe renal disease loses as much as 20 grams of plasma protein in the urine each day for months, and this plasma protein is continually replaced mainly by liver production of the required proteins.

In persons with *cirrhosis of the liver*, large amounts of fibrous tissue develop among the liver parenchymal cells, causing a reduction in their ability to synthesize plasma proteins. As discussed in Chapter 25, this phenomenon leads to decreased plasma colloid osmotic pressure, which causes generalized edema.

Plasma Proteins as a Source of Amino Acids for the Tissues. When the tissues become depleted of proteins, the plasma proteins can act as a source of rapid replacement. Indeed, whole plasma proteins can be imbibed in toto by tissue macrophages through the process of pinocytosis; once in these cells, they are split into amino acids that are transported back into the blood and used throughout the body to build cellular proteins wherever they are needed. In this way, the plasma proteins function as a labile protein storage medium and represent a readily available source of amino acids whenever a particular tissue requires them.

Reversible Equilibrium Between the Plasma Proteins and the Tissue Proteins. As shown in **Figure 70-2**, a constant state of equilibrium exists among the plasma proteins, the amino acids of the plasma, and the tissue proteins. On the basis of radioactive tracer studies, it has been estimated that normally about 400 grams of body protein are synthesized and degraded each day as part of the continual state of flux of amino acids, which demonstrates the general principle of reversible exchange of amino acids among the different proteins of the body. Even during starvation or severe debilitating diseases, the ratio of total tissue proteins to total plasma proteins in the body remains relatively constant at about 33:1.

Because of this reversible equilibrium between plasma proteins and the other proteins of the body, one of the most effective therapies for severe, acute whole-body protein deficiency is intravenous transfusion of plasma protein. Within a few days, or sometimes within hours, the amino

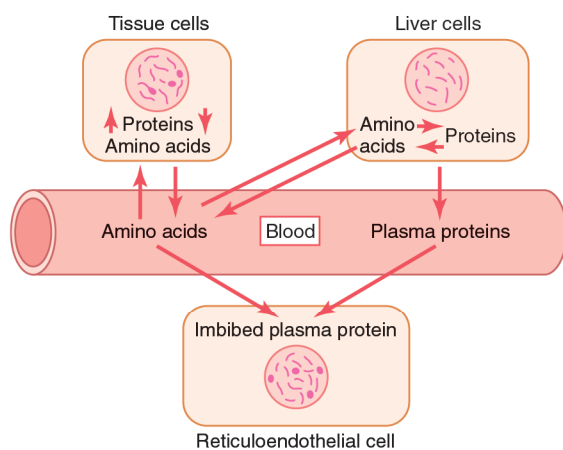
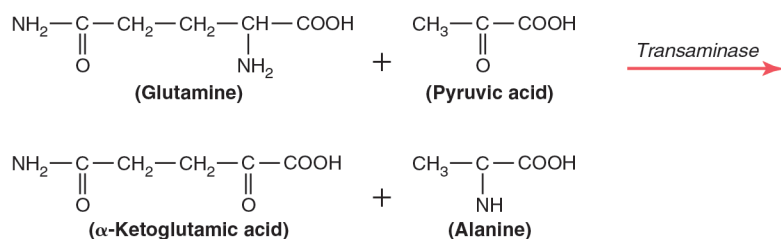


Figure 70-2. Reversible equilibrium among the tissue proteins, plasma proteins, and plasma amino acids.



acids of the administered protein are distributed throughout the cells of the body to form new proteins as needed.

Essential and Nonessential Amino Acids. Ten of the amino acids normally present in animal proteins can be synthesized in the cells, whereas the other 10 either cannot be synthesized or are synthesized in quantities too small to supply the body's needs. This second group of amino acids that cannot be synthesized is called the *essential amino acids*. Use of the word "essential" does not mean that the other 10 "nonessential" amino acids are not required for the formation of proteins but only that the others are *not essential in the diet* because they can be synthesized in the body.

Synthesis of the nonessential amino acids depends mainly on the formation of appropriate α -keto acids, which are the precursors of the respective amino acids. For instance, *pyruvic acid*, which is formed in large quantities during the glycolytic breakdown of glucose, is the keto acid precursor of the amino acid *alanine*. Then, by the process of *transamination*, an amino radical is transferred to the α -keto acid, and the keto oxygen is transferred to the donor of the amino radical. This reaction is shown in **Figure 70-3**. Note that the amino radical is transferred to the pyruvic acid from another chemical that is closely allied to the amino acids—*glutamine*. Glutamine is present in the tissues in large quantities, and one of its principal functions is to serve as an amino radical storehouse. In addition, amino radicals can be transferred from *asparagine*, *glutamic acid*, and *aspartic acid*.

Transamination is promoted by several enzymes, among which are the *aminotransferases*, which are derivatives of pyridoxine, one of the B vitamins (B_6). Without this vitamin, the amino acids are poorly synthesized and protein formation cannot proceed normally.

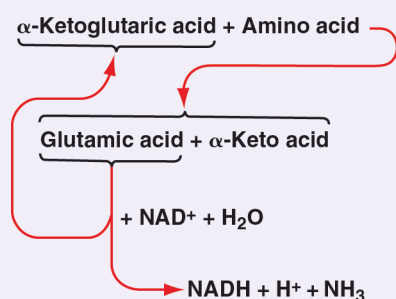
Use of Proteins for Energy

Once the cells are filled to their limits with stored protein, any additional amino acids in the body fluids are degraded and used for energy or are stored mainly as fat or secondarily as glycogen. This degradation occurs almost entirely in the liver, and it begins with *deamination*, which is explained in the following section.

Deamination—the Removal of Amino Groups From Amino Acids. Deamination occurs mainly by *transamination*, which means transfer of the amino group to some acceptor substance. This process is the reverse of transamination, which was explained earlier in relation to the synthesis of amino acids.

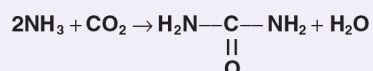
The greatest amount of deamination occurs according to the following transamination schema:

Figure 70-3. Synthesis of alanine from pyruvic acid by transamination.



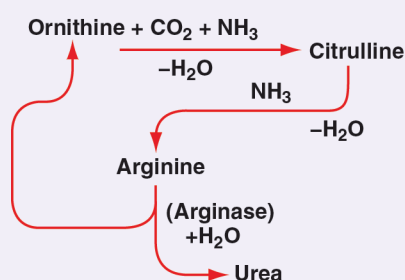
Note from this schema that the amino group from the amino acid is transferred to α -ketoglutaric acid, which then becomes glutamic acid. The glutamic acid can then transfer the amino group to other substances or release it in the form of ammonia (NH_3). In the process of losing the amino group, the glutamic acid once again becomes α -ketoglutaric acid, so the cycle can be repeated again and again. To initiate this process, the excess amino acids in the cells, especially in the liver, induce activation of large quantities of *aminotransferases*, the enzymes responsible for initiating most deamination.

Urea Formation by the Liver. The ammonia released during deamination of amino acids is removed from the blood almost entirely by conversion into urea. Two molecules of ammonia and one molecule of carbon dioxide combine in the following net reaction:



Essentially all urea formed in the human body is synthesized in the liver. In the absence of the liver or in persons with serious liver disease, ammonia accumulates in the blood. This accumulation of ammonia is extremely toxic, especially to the brain, and can lead to a state called *hepatic coma*.

The stages in the formation of urea are essentially the following:



After its formation, the urea diffuses from the liver cells into the body fluids and is excreted by the kidneys.

Oxidation of Deaminated Amino Acids. Once amino acids have been deaminated, the resulting keto acids can, in most instances, be oxidized to release energy for metabolic purposes. This oxidation usually involves two successive processes: (1) The keto acid is changed into an appropriate chemical substance that can enter the citric

acid cycle, and (2) this substance is degraded by the cycle and used for energy in the same manner that acetyl coenzyme A (acetyl-CoA) derived from carbohydrate and lipid metabolism is used, as explained in Chapters 68 and 69. In general, the amount of adenosine triphosphate formed for each gram of protein that is oxidized is slightly less than that formed for each gram of glucose that is oxidized.

Gluconeogenesis and Ketogenesis. Certain deaminated amino acids are similar to the substrates normally used by the cells, mainly the liver cells, to synthesize glucose or fatty acids. For instance, deaminated alanine is pyruvic acid, which can be converted into either glucose or glycogen. Alternatively, it can be converted into acetyl-CoA, which can then be polymerized into fatty acids. Also, two molecules of acetyl-CoA can condense to form acetoacetic acid, which is one of the ketone bodies, as explained in Chapter 69.

The conversion of amino acids into glucose or glycogen is called *gluconeogenesis*, and the conversion of amino acids into keto acids or fatty acids is called *ketogenesis*. Of the 20 deaminated amino acids, 18 have chemical structures that allow them to be converted into glucose, and 19 of them can be converted into fatty acids.

Obligatory Degradation of Proteins

When a person eats no proteins, a certain proportion of body proteins is degraded into amino acids and then deaminated and oxidized. This process involves 20 to 30 grams of protein each day, which is called the *obligatory loss* of proteins. Therefore, to prevent net loss of protein from the body, the average person must ingest a minimum of 20 to 30 grams of protein each day, although this amount depends on multiple factors, including muscle mass, activity, and age; to be on the safe side, a minimum of 60 to 75 grams is usually recommended.

The ratios of the different amino acids in the dietary protein must be about the same as the ratios in the body tissues if the entire dietary protein is to be fully usable to form new proteins in the tissues. If one particular type of essential amino acid is low in concentration, the others become unusable because cells synthesize either whole proteins or none at all, as explained in Chapter 3 in relation to protein synthesis. The unusable amino acids are deaminated and oxidized. A protein that has a ratio of amino acids different from that of the average body protein is called a *partial protein* or an *incomplete protein*, and such a protein is less valuable for nutrition than is a *complete protein*.

Effect of Starvation on Protein Degradation. Except for the 20 to 30 grams of obligatory protein degradation each day, the body uses almost entirely carbohydrates or fats for energy, as long as they are available. However, after several weeks of starvation, when the quantities of stored carbohydrates and fats begin to run out, the amino acids of the blood are rapidly deaminated and oxidized for energy. From this point on, the proteins of the tissues degrade rapidly—as much as 125 grams daily—and, as a result, cellular functions deteriorate precipitously. Because carbohydrate and fat utilization for energy normally occurs in preference to protein utilization, carbohydrates and fats are called *protein spacers*.

Hormonal Regulation of Protein Metabolism

Growth Hormone Increases the Synthesis of Cellular Proteins. Growth hormone causes the tissue proteins to increase. The precise mechanism by which this increase occurs is not known, but it is believed to result mainly from increased transport of amino acids through the cell membranes, acceleration of the DNA and RNA transcription and translation processes for protein synthesis, and decreased oxidation of tissue proteins.

Insulin Is Necessary for Protein Synthesis. Total lack of insulin reduces protein synthesis to almost zero. Insulin accelerates the transport of some amino acids into cells, which could be the stimulus for protein synthesis. Also, insulin reduces protein degradation and increases the availability of glucose to the cells, so the need for amino acids for energy is correspondingly reduced.

Glucocorticoids Increase Breakdown of Most Tissue Proteins. The glucocorticoids secreted by the adrenal cortex *decrease* the quantity of protein in *most* tissues while increasing the amino acid concentration in the plasma, as well as increasing *liver proteins and plasma proteins*. It is believed that the glucocorticoids act by increasing the rate of breakdown of extrahepatic proteins, thereby making increased quantities of amino acids available in the body fluids. This allows the liver to synthesize increased quantities of hepatic cellular proteins and plasma proteins.

Testosterone Increases Protein Deposition in Tissues. Testosterone, the male sex hormone, causes increased deposition of protein in tissues throughout the body, especially the contractile proteins of the muscles (a 30 to 50 percent increase). The mechanism of this effect is unknown, but it is definitely different from the effect of growth hormone, in the following way: Growth hormone causes tissues to continue growing almost indefinitely, whereas testosterone causes the muscles and, to a much lesser extent, some other protein tissues to enlarge for only several months. Once the muscles and other protein tissues have reached a maximum, despite continued administration of testosterone, further protein deposition ceases.

Estrogen. Estrogen, the principal female sex hormone, also causes some deposition of protein, but the effect of estrogen is much less compared with that of testosterone.

Thyroxine Increases Metabolism of Cells. Thyroxine indirectly affects protein metabolism by increasing metabolism of the cells. If insufficient carbohydrates and fats are available for energy, thyroxine causes rapid degradation of proteins and uses them for energy. Conversely, if adequate quantities of carbohydrates and fats are available and excess amino acids are also available in the extracellular fluid, thyroxine can actually increase the rate of protein synthesis. In growing animals or human beings, deficiency of thyroxine causes growth to be greatly inhibited because of lack of protein synthesis. In essence, it is believed that thyroxine has little specific effect on protein metabolism but does have an important general effect by increasing the rates of both normal anabolic and normal catabolic protein reactions.

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