# IASM Notes

## Semester I

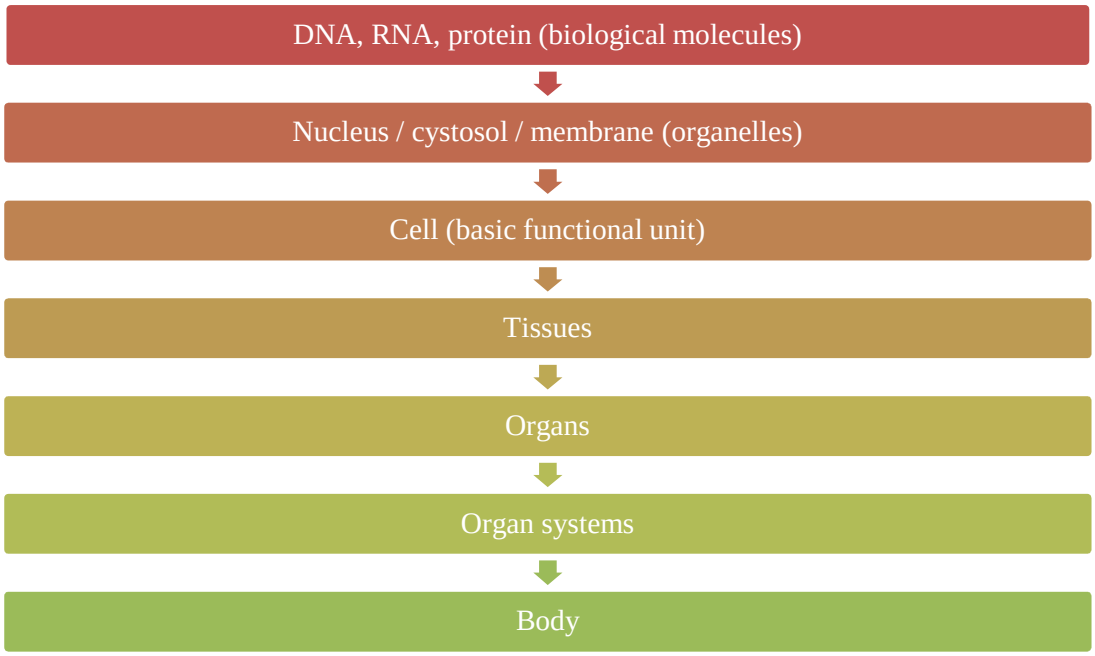
(Adapted from lecture notes)

# Content

# L1 Organization and Homeostasis of Body Functions

## A. Hierarchical Organization of Body

- Body consists of $10^{14}$ cells organized into organs




- Organ systems include nervous, endocrine, immune, CVS, respiratory, urogenital, musculoskeletal, digestive and reproductive working together

| System | Some organs/tissues within system | Function |
|---|---|---|
| Endocrine | Hypothalamus, pituitary gland, adrenal gland, thyroid gland, parathyroid glands, thymus, pancreas | Provide communication between cells of the body through the release of hormones into the bloodstream |
| Nervous | Brain, spinal cord, peripheral nerves | Provide communication between cells of the body through electrical signals and the release of neurotransmitters into small gaps between certain cells |
| Musculoskeletal | Skeletal muscle, bones, tendons, ligaments | Support the body; allow voluntary movement of the body; allow facial expressions |
| Cardiovascular | Heart, blood vessels, blood | Transport molecules throughout the body in the bloodstream |
| Respiratory | Lungs, pharynx, trachea, bronchi | Bring oxygen into the body and eliminate carbon dioxide from the body |
| Urinary | Kidneys, ureters, bladder, urethra | Filter the blood to regulate acidity, blood volume, and ion concentrations; eliminate wastes |
| Gastrointestinal | Mouth, esophagus, stomach, small intestine, large intestine, liver, pancreas, gallbladder | Break down food and absorb it into the body |
| Reproductive | Gonads, reproductive tracts and glands | Generate offspring |
| Immune | White blood cells, thymus, lymph nodes, spleen, tonsils, adenoids | Defend the body against pathogens and abnormal cells |
| Integumentary | Skin | Protect the body from the external environment |

- Cells communicate via electrochemical signals:
  - **Endocrine** via blood
  - **Paracrine** for short-distanced
  - **Autocrine** for itself
  - **Neural** for electrical signal via neurons to excitable cells

# B. Homeostasis

- Definition: maintenance of constant conditions in internal environment (i.e. extracellular fluid)
- Each cell benefit from homeostasis and in turn contributes towards it

# 1. Body Fluids and Electrolytes

## a. Classification and Composition

- Total body fluid: ~60% of body weight, ~42L in 70kg body
- Distribution:

| | | | | |
|---|---|---|---|---|
| Intracellular | | Within cell | 2/3 | 28L |
| Extracellular | Intravascular | Blood plasma | 1/4 x 1/3 | 3-3.5L |
| | interstitial | In tissue | 3/4 x 1/3 | 10.5-11L |

- Predominant cation in interstitial fluid: $Na^+$
- ~90% of $K^+$ is intracellular
- No protein in interstitial fluid while plasma contains proteins (eg albumin)
- Total body stores of $Na^+ = K^+ = 3000$mmol

**Some Important Constituents and Physical Characteristics of the Extracellular Fluid, and the Normal Range of Control**

| | Normal Value | Normal Range | Units |
|---|---|---|---|
| Oxygen | 90 | 80 - 100 | mm Hg |
| Carbon dioxide | 40 | 35 - 45 | mm Hg |
| Sodium ion | 142 | 138 - 146 | mmol/L |
| Potassium ion | 4.2 | 3.8 - 5.0 | mmol/L |
| Calcium ion | 1.2 | 1.0 - 1.4 | mmol/L |
| Chloride ion | 108 | 103 - 112 | mmol/L |
| Bicarbonate ion | 28 | 24 - 32 | mmol/L |
| Glucose | 85 | 75 - 95 | mg/dl |
| Body temperature | 98.4 (37.0) | 98 - 98.8 (37.0) | °F (°C) |
| Acid-base | 7.4 | 7.3 - 7.5 | pH |

## b. Osmolality and Osmolarity

- **Osmolality** (osmole, Osm/kg): amount of solute per unit <u>weight</u> of solvent
- **Osmolarity** (Osm/L): amount of solute per unit <u>volume</u> of solvent
- Plasma osmolarity ≈ <u>2</u> $[Na^+]$ + 2 $[K^+]$ + [urea] + [glc]

*$[Na^+]$, $[K^+]$ x 2 to account for anions associated with the cations

- Osmolarity slightly > osmolality (because volume < weight due to solvent present) and their difference is called 'osmolar gap' (OG)

# 2. Maintenance of Homeostasis

- A combination of **negative feedback** and **positive feedback**

## a. Negative Feedback

- Direction of correction opposite to error → promote stability
- Eg. Thermoregulation
- Efficiency = $\frac{\text{correction}}{\text{error}}$ > -1

## b. Positive Feedback

- Direction of correction same as deviation → reinforce change
- Eg 1. Ferguson reflex in labour: pressure on internal end of cervix → posterior pituitary gland secretes more oxytocin → uterine contraction → more pressure
- Eg 2. Blood clotting
- Eg 3. Pre-ovulatory LH surge: FSH ↑ → follicle develops → E↑ → FSH ↑ LH↑ → FSH increases LH receptors, LH increases E secretion → FSH↑ LH↑ E↑, follicle grows rapidly

# L2 Genes are Made of DNA

## A. Discovery

- Avery's experiment:

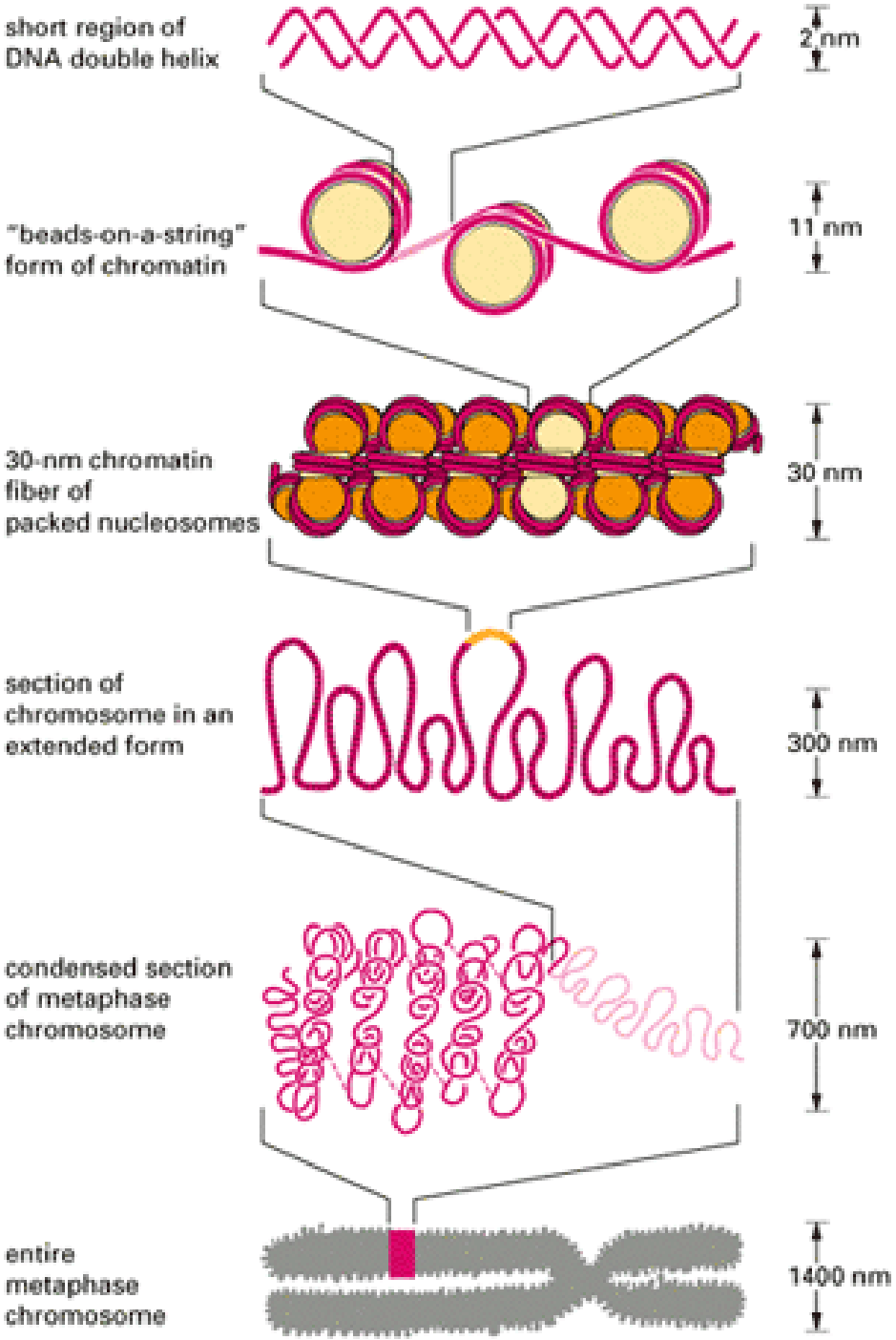
1) Two strains of *Pneumococcus* exist: S (Smooth) with sugar coat and R (Rough) without. **S can kill but R cannot.**
2) Heated S strain does not kill but can make R strain kill. Killing characteristics can be passed on to next generation → genetic material transferred.
3) After isolation procedures, he discovered that only DNA part of inactivated S can make R kill → DNA is genetic material

## B. DNA as Genetic Material

- In eukaryotic cells, bacteria and virus
- Some viruses stores genetic material in RNA (eg RSV) and use reverse transcription to produce DNA to manipulate cell machinery
- Composed of 3 parts: **deoxyribose**, **phosphate**, **base**
- 3' and 5' C in deoxyribose joined with phosphate (replication from 5' end to 3' end)
- In double helix shape (discovered by Watson and Crick)

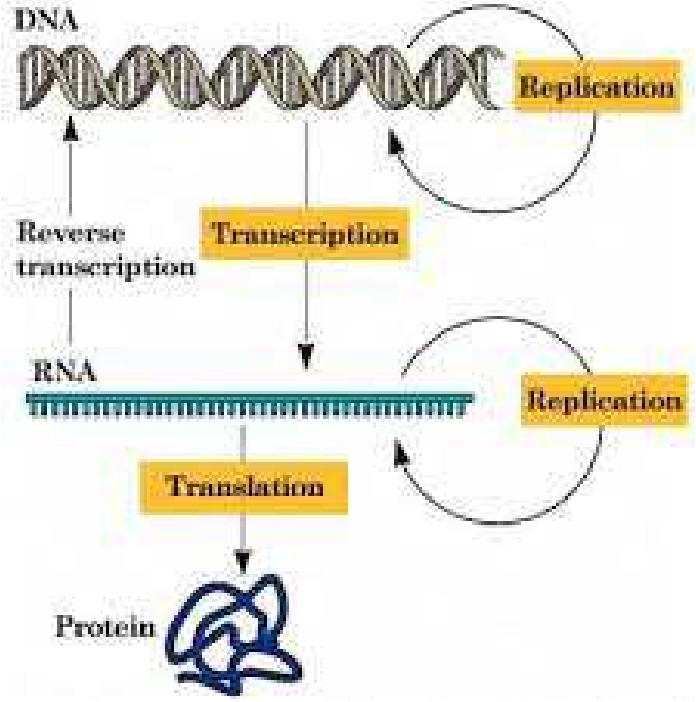
# C. DNA packing

1) DNA strand + 8 histone protein → 1 **nucleosome** (10nm fibre, euchromatin)
2) 6 nucleosome attached by 6 H1 histone protein → 30nm fibre (solenoid, heterochromatin)
3) Loops of 30nm fibre on scaffold protein
4) Condensation into chromosome



# L3 From DNA to Protein

## A. Central Dogma of Molecular Biology

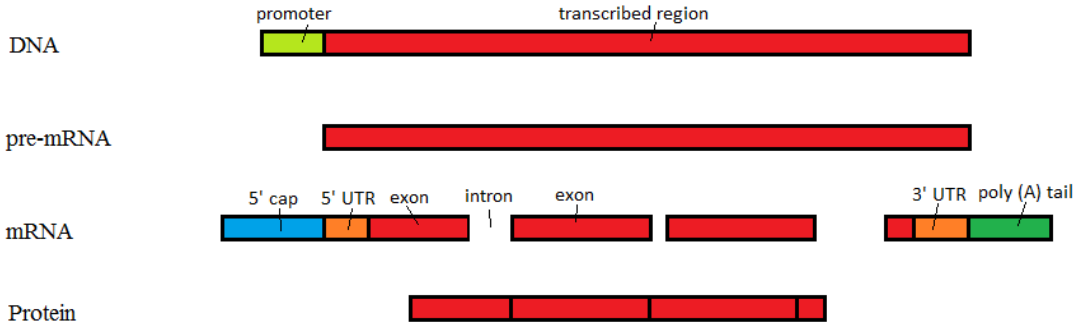



## B. Transcription

- DNA and RNA differs in 2' carbon of ribose (w/ or w/o O between C and H)
- **Transcription unit**: (promoter) + (transcribed region)

1) Promoter on template strand recognized by **transcription factors** (protein) → guide RNA polymerase to attach to gene;
2) Free ribonucleotide binds to template strand and RNA polymerase catalyze formation of **mRNA precursor** (or pre-mRNA);
3) 5' cap and 3' poly(A) tail are added and introns are cleaved (to form circular DNA) by spliceosomes
4) Cap and tail joins together to form a ring structure (to ensure completeness of transcription) and exits nuclear envelope for translation

*Fx of 5' cap and 3' poly(A) tail are to prevent degradation by enzymes



# C. Translation

- tRNA brings amino acid to mRNA at ribosome
- Peptide linkage is formed between adjacent amino acids
- A polypeptide is thus formed according to genetic coding in DNA

# D. Control of Gene Expression

- Need: Different proteins have to be expressed in different cells at different stages for different purposes
- Controlled through:
  - DNA: replication, rearrangement (eg memory WBCs)
  - RNA: transcription, modification, degradation
  - Protein: translation, modification, degradation

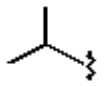
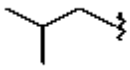
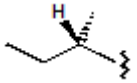
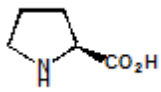
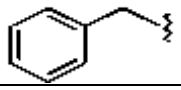
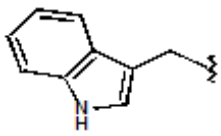
# E. Detection of Gene Expression

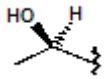
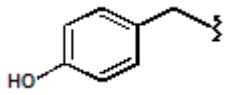
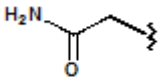
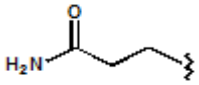
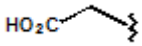
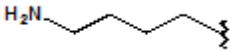
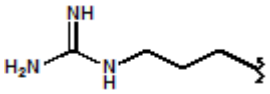
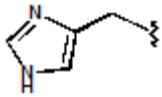
- DNA: Southern blot
- RNA: Northern blot, cDNA microarray (coupling DNA sequences in array with fluorescent material)
- Protein: Western blot

# L4 From Amino Acids to Protein Structure

## A. Amino Acids

- Can be found in two forms:
  - Powder (solid form): without charge
  - Aqueous form: as **zwitterion** (doubly charged)
- Natural occurring amino acids are all *L*-amino acids
- List of 20 common amino acids:

| 1. Non-polar (9) | | |
|---|---|---|
| Glycine | Gly, G |  |
| Alanine | Ala, A |  |
| Valine | Val, V |  |
| Leucine | Leu, L |  |
| Isoleucine | Ile, I |  |
| Proline | Pro, P |  |
| Phenylalanine | Phe, F |  |
| Methionine | Met, M |  |
| Tryptophan | Trp, W |  |

| | | |
|---|---|---|
| 2. Polar (6) | | |
| Serine | Ser, S |  |
| Threonine | Thr, T |  |
| Tyrosine | Tyr, Y |  |
| Cysteine | Cys, C |  |
| Asparagine | Asn, N |  |
| Glutamine | Gln, Q |  |
| 3. Negatively charged (2) | | |
| Aspartic Acid | Asp, D |  |
| Glutamic Acid | Glu, E |  |
| 4. Positively charged (3) | | |
| Lysine | Lys, K |  |
| Arginine | Arg, R |  |
| Histidine | His, H |  |

- Things to note:
  - Hydrophobic a.a. are typically used in hydrophobic protein core while hydrophilic a.a. tends to be found on surface of protein
  - Proline: $\alpha$-amino group secondary → exceptional conformation rigidity
  - Cysteine can be used in disulphide bridges (esp in oxidative conditions in ECF)
  - Charged a.a. are critical in catalysis and other protein functions
  - Aromatic a.a. have unique absorption wavelength at 280nm → can be used to measure protein conc. directly
- Amino acid sequence named from *N*-terminus to *C*-terminus (by convention)
- CO-NH act as rigid coplanar unit → equivalent to a single bond (virtual bond)
- Consecutive peptide links act as rigid coplanar units pivoting around $\alpha$-C atoms
- F, V, T, W, I, M, L , K, H are the 9 essential amino acids

# B. Protein Structure

- Four levels of protein structure:
  - Primary: by amino acid sequence
  - Secondary: local conformation (eg α-helix and β-sheets) by H-bond
  - Tertiary: 3D organization of domains (substructures that can fold independently) by disulphide bonds, H-bonds etc.
  - Quaternary: complex of polypeptide chains
- Extracellular proteins are frequently stabilized by covalent cross-linkages including disulphide bonds between Cys (extracellular conditions are usually oxidative → removal of H from SH group in Cys)

# L5 From Protein Structure to Protein Function

## A. Protein Functioning

- Protein can bind to other molecules
- **Ligand**: a molecule that bind reversibly via non-covalent forces
  - **Binding site**: site where ligand binds
  - Reversibility of binding enables interactions to be transient
- **Prosthetic group**: a molecule/group that is permanently bound to a protein by covalent forces

## B. Fibrous Proteins

### 1. Collagen

- Commonly found in connective tissues
- Collagen is a right-handed **triple helix** of three left-handed α-helices
- Structure stabilized by inter-chain H-bonds and a sheath of ordered water molecules of solvation
- Contains high level of hydroxyproline

*Vit. C required in forming hydroxyproline from proline → important in maintaining c. t.

### 2. Hair Keratin

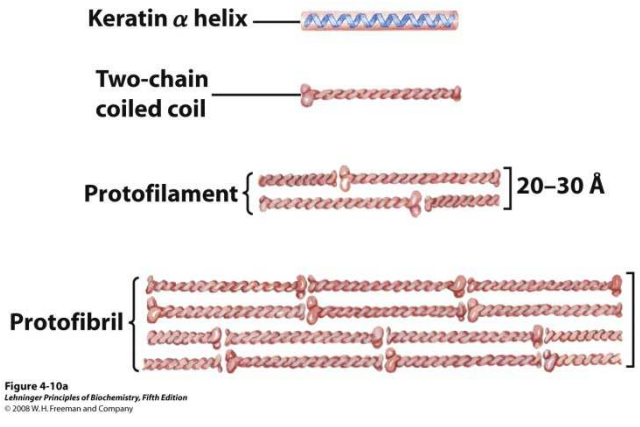



Figure 4-10a
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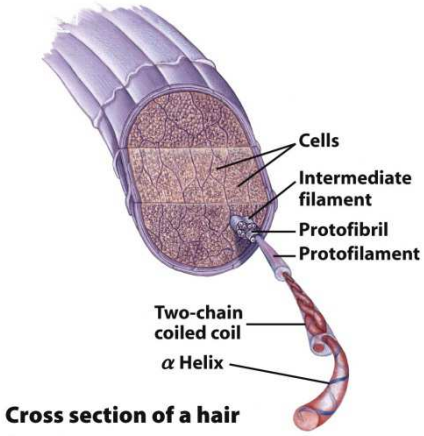


Figure 4-10b
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# C. Hemoglobin and Myoglobin

- **Hemoglobin (Hb)**: specialized protein in RBC that transports oxygen in blood
  - Tetrameric ($\alpha_2\beta_2$) with four heme groups
- **Myoglobin**: specialized protein in muscle that facilitates oxygen diffusion
  - Monomeric with one heme group
- **Heme**: prosthetic group permanently bound to myoglobin and haemoglobin etc.
  - Porphyrin ring surrounding $Fe^{2+}$
  - Gives red colour of blood (most proteins have no colour)
  - $Fe^{2+}$ bound to protein with histidine on one side and oxygen on the other

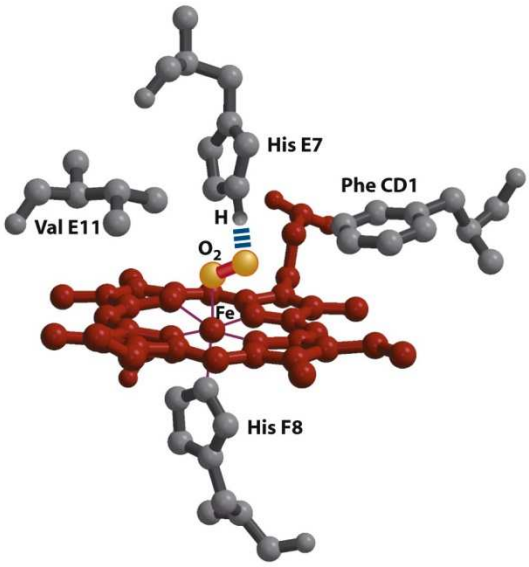


**Figure 5-5c**
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# 1. Spectroscopic Detection of $O_2$ binding to Hb

- Heme group is a strong **chromophore** (part of molecule that provides colour) that absorbs both in UV and visible range
- $Fe^{2+}$ without $O_2$ has an intense Soret band at 429 nm (blue)
- $O_2$ binding alters electronic properties of heme, shifting position of Soret band to 414 nm (purplish blue)
- Binding of $O_2$ can be monitored by UV-Vis spectrophotometry
- Deoxyhaemoglobin appears purplish while oxyhaemoglobin is red

# 2. Cooperativity of Hb to $O_2$ binding

- Hb can exist in two states: tense (T) and relaxed (R)
- **R has higher $O_2$ affinity than T**
- Deoxyhaemoglobin subunits are more stable in T state
- $O_2$ binding triggers a **T→R conformational change** (by breaking of ion pairs between α1-β2 interface)
- As there is four subunits (i.e. 4 binding sites), binding of $O_2$ at first subunit will facilitate binding at the other 3

- Refer to graph on right:
  - θ: degree of filling of haemoglobin by $O_2$
  - As $pO_2$ ↑, Hb transits from low-affinity to high-affinity state
    → sigmoid (cooperative) binding curve
- Also note **Hill plot** (graph showing cooperativity of protein)
  - $n_H$: **Hill coefficient** showing degree of cooperativity
  - ↑Hill coefficient →↑cooperativity
- Phenomenon known as **cooperativity**: affinity of ligand varies with number of binding
  - Positive cooperativity ($n_H > 1$): first binding event increases affinity at remaining sites
  - Negative cooperativity ($n_H < 1$): first binding event reduces affinity at remaining sites

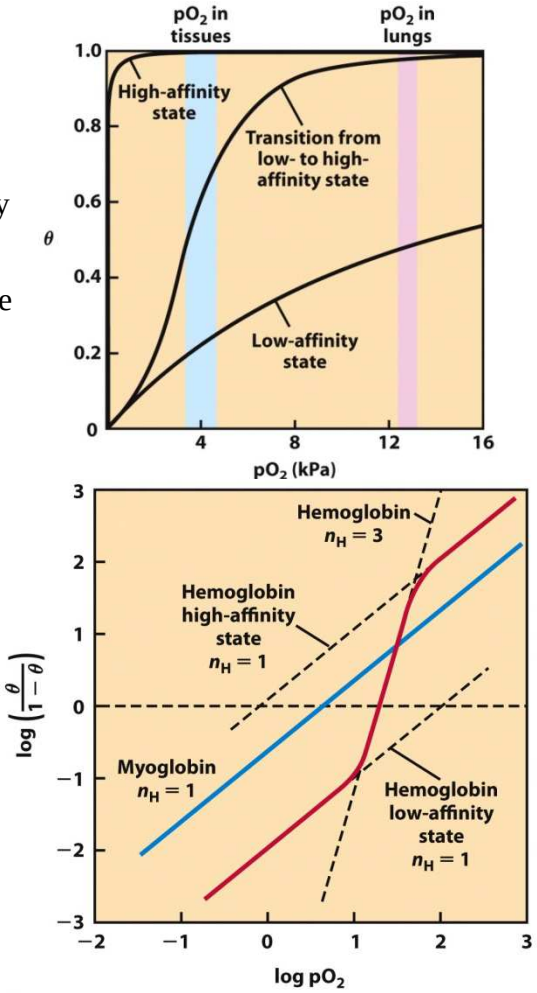

Figure 5-14
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- Significance:
  - In high $pO_2$ (lungs, 13kPa), $O_2$ binds stronger to Hb → can pick up $O_2$
  - In low $pO_2$ (tissues, 4kPa), $O_2$ binds weaker to Hb → can release $O_2$ effectively
  - If no cooperativity (i.e. in myoglobin), $O_2$ won't be released at tissues

# 3. Cooperative Binding of CO

- CO has similar size and shape as $O_2$ → can fit to the same binding site ($O_2$ binds at an angle but not for CO)
- CO binds >20k times better than $O_2$ because CO has a filled lone electron pair that can be donated to vacant d-orbitals on $Fe^{2+}$
- Protein pocket decreases affinity for CO but still ~250x better than $O_2$
- Toxicity originated from competitive effect and **increase in cooperativity**
  - Shifts oxygen dissociation curve leftwards → stronger $O_2$ affinity at tissue $pO_2$ levels ($O_2$ affinity of remaining 3 sites if COHb even higher than $O_2Hb$)→ extra $O_2$ retained at tissue → hypoxia (even when $pO_2$ at normal)
  - Even worse than being anemic
- CO poisoning accounts for > 1/2 yearly deaths from poisoning worldwide

*15% COHb: headaches; 25%: nausea, dizziness; 50% COHb: coma, death

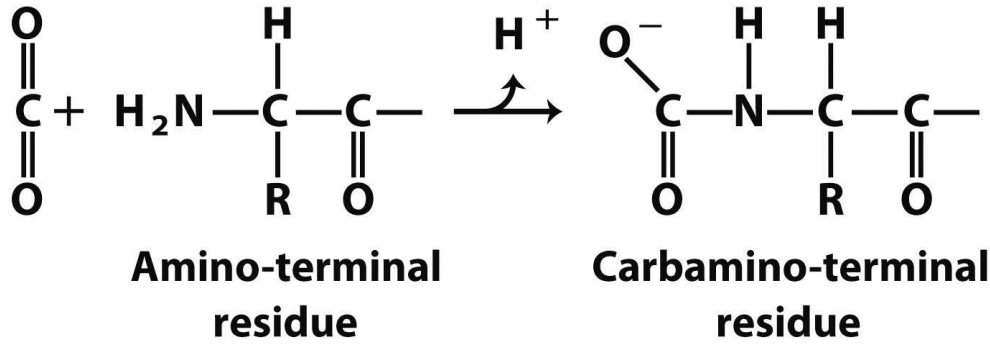
# 4. Effect of pH on $O_2$-Hb binding

- Affinity for $O_2$ depends on pH: pH↑ → affinity ↑
- i.e. $O_2$ dissociation curve shifted **leftwards** at higher pH
- Protonation of amino acid residues stabilize Hb in T state
- Note blood in lungs has higher pH (because of lower $CO_2$ content) → pH difference increase $O_2$ transfer efficiency
- Phenomenon known as **Bohr effect**

*Hb binds protons to several a.a., thus actually carrying 40% of total $H^+$ from tissues

# 5. Haemoglobin and $CO_2$ Export

- Some $CO_2$ exported as dissolved bicarbonate in blood
- Some $CO_2$ exported in form of a **carbamate** on amino terminal residues of hemoglobin
- Note that formation of a carbamate yields a proton which can bind to hemoglobin and promote $O_2$ dissociation




Unnumbered 5 p166
*Lehninger Principles of Biochemistry, Fifth Edition*


# 6. Fetal Variant of Hemoglobin

- Adult Hb has $\alpha_2\beta_2$ structure
- Fetal Hb (HbF) has $\alpha_2\gamma_2$ structure (because one of subunits is transcribed/translated from a different gee)
- HbF binds to $O_2$ more tightly than adult Hb → fetal blood in placenta can take $O_2$ from maternal blood

# D. Importance of Protein Structure to Medicine

# 1. Sickle Cell Anaemia

- Gln at position 6 in β chain of Hb is mutated to Val → deoxygenated Hb stick to each other → sickle shaped RBCs
- Heterozygotes have evolutionary advantage in malaria endemic areas (as lower RBC half-life confers resistance to malaria parasites, which spend part of life cycle in RBCs)
- Homozygotes develop sickle cell anemia

## 2. Drug Target in Avian Influenza

- Viral NS1 protein binds to CPSF30 protein
- Blocking such interaction provides target for antiviral drug development

## 3. G6PD Deficiency

- G6P dehydrogenase (G6PD) variants also confers resistance to malaria
- Also result in susceptibility to acute hemolytic anemia (AHA)

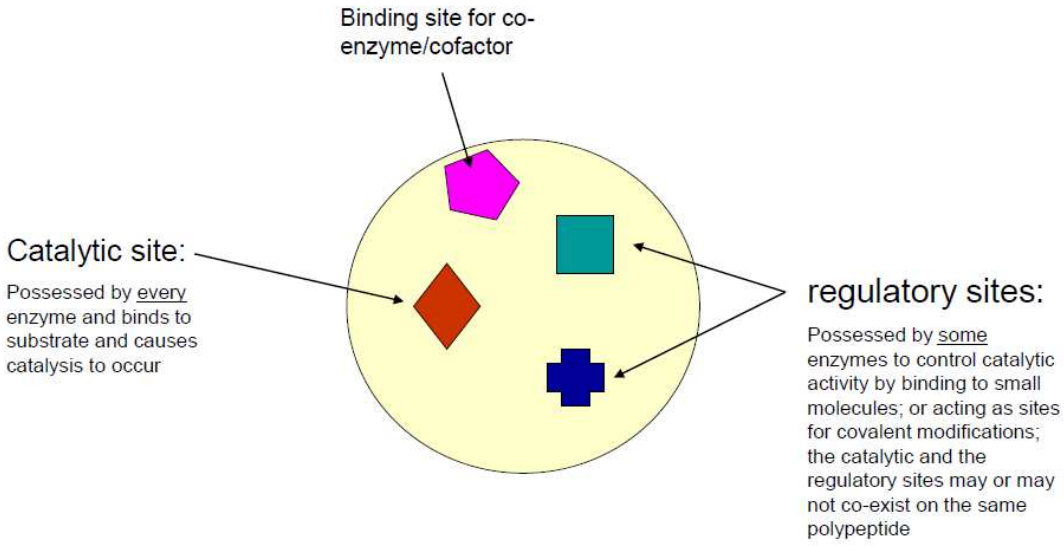
## 4. Prion Diseases

- Misfolding/aggregation of endogenous protein is cause of prion and Alzheimer's disease
- When entering body, prions induces normal body protein to fold into faulty prion form → exponential growth in prion number
- Prion will then aggregate to form fibril structure → prion disease

# L6 Enzymes are Powerful and Specific Catalysts

## A. Properties of Enzymes

- **Enzymes**: proteins that are able to accelerate (catalyse) a metabolic reaction
- Need for enzymes in body:
  - Low concentration of metabolites in cells → low reaction rate
  - More or less fixed pH in cells → protein will not denature
  - Constant body temperature → protein will not denature
  - High energy barrier of metabolic reaction → low reaction rate
  - Need for metabolic regulation (change metabolic rate according to environment)
- Catalytic action of an enzyme is specific
- Enzymes are sensitive to pH and temperature (because thermal vibration may destroy protein structure of enzyme)
- Generic features of enzyme:




- **Monomeric** enzyme has only one polypeptide unit and binds only one substrate molecule
- **Oligomeric** enzyme has more than one polypeptide unit and binds several substrate molecules (more common than 1 polypeptide having multiple catalytic sites)

# 1. Co-enzymes and co-factors

- Enzymes often require co-enzymes or co-factors to work
- Apoenzyme (inactive) + co-enzyme/co-factor → holoenzyme (active)
- **Co-enzymes** are organic in nature (eg. Vit. B, FAD, heme)
- **Co-factors** are inorganic in nature, usually metal ions (eg. Fe, Cu, Mo)
- **Prosthetic group**: a co-enzyme or co-factor that is very tightly bound (or covalently bound) to an enzyme

# 2. Reaction Model for Enzyme-catalyzed Reaction

- Enzyme + substrate → E/S complex → E/C complex → enzyme + products
- Rate = $\frac{[S]V_{max}}{k_m+[S]}$ where $k_m$ is the Michaelis constant (i.e. [S] at which V = $\frac{1}{2}V_{max}$)
- Result is a hyperbolic curve

## a. Cooperative Reaction Model for Enzyme-catalyzed Reaction

- Enzyme + n(substrate) → enzyme/n(substrate) complex
- Each binding increase affinity for the next substrate
- Product formation curve is a sigmoidal curve

# B. Mechanism of Enzymatic Reaction

- Enzyme catalysis is due to a lowering of activation energy
- Proximity and orientation: Enzymes may help two molecules to get closer and into right orientation → lower energy barrier and increase reaction rate
- Such guidance in orientation of substrate can be done by electrostatic interaction (amino acid residues in enzymes may have different charges)
- Amino acid amphoteric→ can catalyze de-protonation or protonation of substrate
- May also be temporarily covalently bound with substrate
- Some metal ions may act as cofactors by charge shielding (situating in between two negatively charged surfaces to bring them together)
- Note that the lock-and-key hypothesis is not accurate in describing mechanism of actions of enzymes:

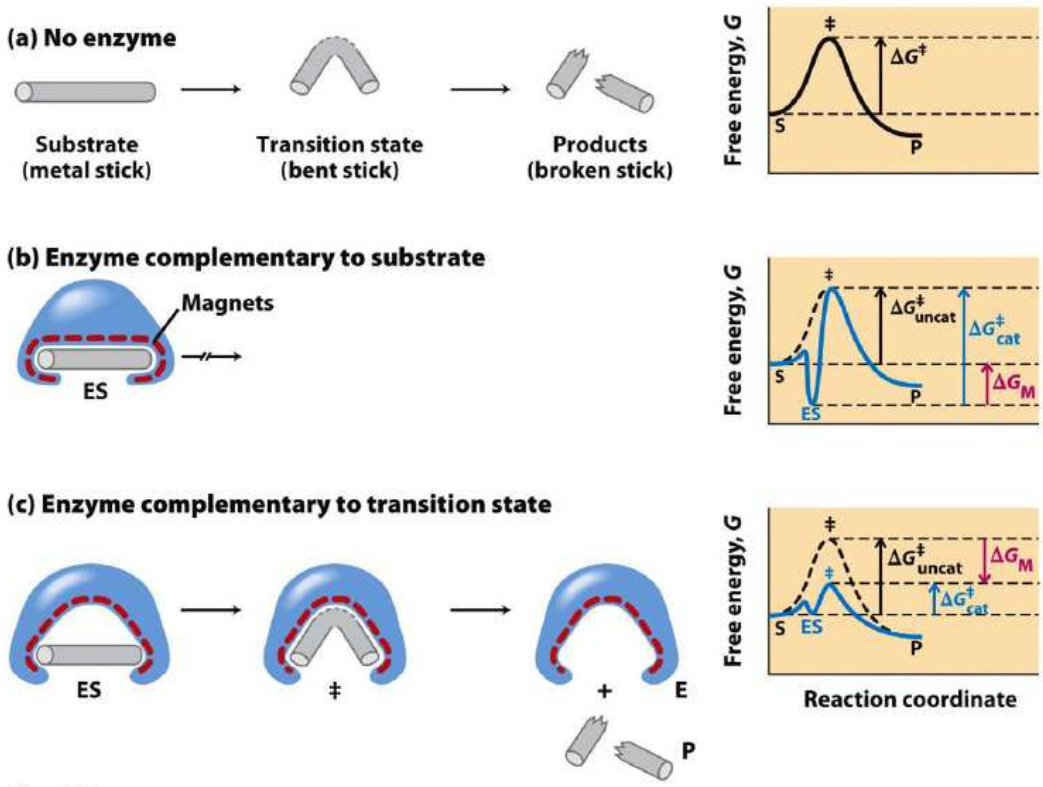


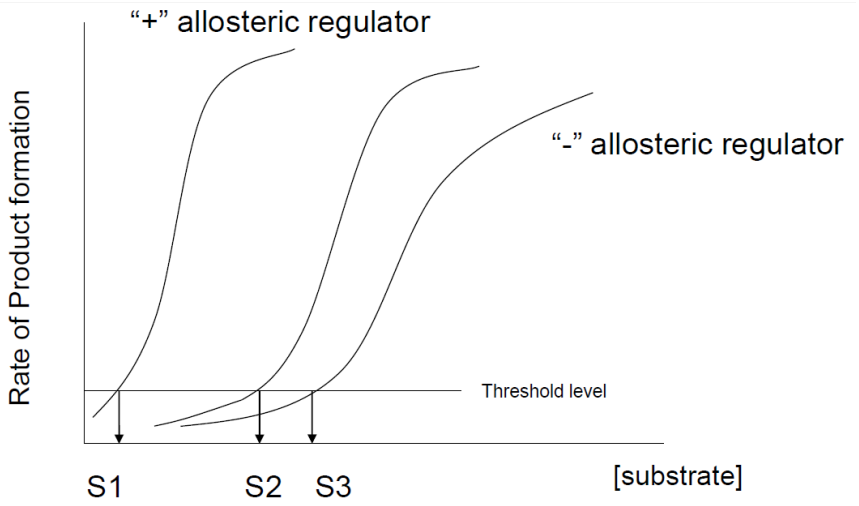

**Figure 6-5**
*Lehninger Principles of Biochemistry, Fifth Edition*


# C. Regulation of Enzymatic Activity

- Enzymes allow a particular reaction to take place at a particular time and location with a carefully adjusted rate
- Transcription of enzyme mRNA often arise from physiological/pathological cues
- With enzymes controlling metabolic activity, it provides a way to regulate metabolism effectively

# 1. Allosteric Regulators

- Oligomeric enzymes may have regulatory unit with regulatory sites binding to **allosteric regulators** (regulating molecules binding to sites other than the active site)
- Regulation of oligomeric enzymes by allosteric regulators:




# 2. Phosphorylation

- A phosphate group is added or removed from the enzyme to change its catalytic effect
- **Protein kinase** add a phosphate group to a protein
- **Protein phosphatase** remove a phosphate group from a protein
- Catalytic effect can either be increased or decreased by phosphorylation
- Characteristics: fast, reversible, involving protein kinases and protein phosphatases, alteration of kinetic parameters

## 3. By Adjustment of Rate of Synthesis and Breakdown of Enzyme Protein

- Rate of synthesis and breakdown of enzyme controlled to alter the abundance of the enzyme
- Enzyme 'life-cycle': gene → mRNA → protein → active enzyme protein → degradation
- Every step of the 'life-cycle' can be regulated
- Characteristics: slow, irreversible, usually long term regulation, alteration of enzyme abundance

## 4. By Proteolysis

- Protease is used to cut a part out of an enzyme
- May serves to activate/inactivate the enzyme
- Characteristics: fast, irreversible

## 5. By Activators or Inhibitors

- Addition of activators and inhibitors to enzymes to make them active and inactive respectively

# D. Importance of Enzymes in Medicine

## 1. Provide Valuable Information for Diagnosis

- Enzyme level at serum, plasma, urine, CSF can be tested
- Level of blood clotting enzymes → thrombotic tendency
- Intracellular enzymes are not supposed to be in blood, but upon tissue damage may leak into blood due to high cell:plasma ratio
- Measuring their level can give information about location of tissue damage and nature of disease
- Examples: transaminases for liver diseases, phosphatases for liver and bone diseases, amylases for pancreatic diseases

## 2. Enzymes as Therapeutic Targets

- Identify enzyme that is responsible for the regulation of a metabolic pathway
- Design chemical compounds which can inhibit the enzyme
- Examples:
  - Synthesis of prostaglandins in platelet aggregation by prostaglandin synthase
  - Production of angiotensin in high blood pressure by angiotensin converting enzyme
  - Synthesis of cholesterol in high blood cholesterol by HMG-CoA reductase
  - Synthesis of bacterial cell walls in bacterial infection by glocopeptidyl transpeptidase

# L7 Nutrition

## A. Key Concepts of Nutrition

- Balance and variety can ensure nutritional adequacy
- For each nutrient, there is a safety range: eat foods in moderation
- There is no 'one size fits all' diet
- Malnutrition includes under-nutrition and over-nutrition
- Nutrition is a dynamic science

## 1. Factors that Influence Our Choice of Food

- **Environmental**: economics, lifestyles, cultural and religious beliefs and traditions
- **Sensory**: flavor, texture, appearance
- **Cognitive**: social and emotional factors, nutrition and health beliefs, advertising
- **Health status**: physical restrictions due to disease, declining taste sensitivity, age and gender
- **Genetics**: taste sensitivity, preference for sweet and salty food, etc

## 2. Diseases and Dietary Practices

- Chronic disease that can be influenced by our diet:
  - Heart disease
  - Stroke, hypertension, diabetes
  - Obesity
  - Some forms of cancer

## 3. Scientific Information in Nutrition

- Types of nutritional studies:
  - Epidemiological studies
    - → Experimental (intervention) epidemiological studies
    - → Observational epidemiological studies
  - Animal studies
  - Cell culture studies
  - Human studies
- Experimental results are published in peer-reviewed journals but may be simplified/sensationalize by the media
- Results from nutrition studies can be conflicting as they may arise from different designs of the scientific investigation and different sample base
- **Nutrigenomics**: study of how different foods can interact with particular genes to affect a person's risk of developing nutrition-related diseases

# B. Essential Nutrients

- **Essential nutrients** are nutrients that when missing can lead to a deficiency disease
- Examples of essential nutrients for humans:
  - Water
  - Vitamins
  - Minerals
  - Essential fatty acids
  - Essential amino acids
  - Glucose

# 1. Major Functions of Nutrients in Body

- **Carbohydrates**: energy
- **Lipids**: energy, cellular development etc.
- **Proteins**: production of structural and functional components, growth, maintenance
- **Vitamins**: regulation of body processes, maintenance of immune function etc.
- **Minerals**: fluid balance ad metabolism, components of various tissues, etc.
- **Water**: maintenance of fluid balance, regulation of body temperature etc.

# 2. Daily Reference Intakes (DRIs)

## a. Estimated Average Requirement (EAR)

- **Estimated Average Requirement (EAR)**: the amount of the nutrient that should meet the needs of 50% of healthy people who are in a particular life stage/gender group
- Establishment of an EAR involves identification of a physiological marker that reflects proper functioning and can be measured to indicate whether the level of nutrient is adequate
- Conduct a nutritional study afterwards

## b. Recommended Daily Allowances (RDAs)

- **Recommended Daily Allowances (RDAs)** are the amounts of nutrients that meet the nutrient needs of 97.5% of all healthy individuals in a particular life stage/gender group
- Establishment of an RDA involves determination of EAR and addition of a safety margin

### c. Other DRIs

- **Adequate Intake (AI)** is estimated amount of nutrient required when there is no RDA and the evidence is not firm
- **Tolerable Upper Intake Level (UL)** is the maximum amount of nutrient that can be consumed that is shown not to cause any adverse effects
- **Estimate Energy Requirement (EER)** is the estimated total energy required for a certain individual in a period of time

# C. Nutrition Assessment Methods

- **Anthropometric measures**: physical measures of body eg. Height, weight
- **Biochemical tests**: measure a metabolite in body fluids, a storage or transport compound, an enzyme etc. eg. Blood cholesterol level
- **Clinical observations**: physical examination
- **Dietary intake**: collection of dietary intake data eg. Diet history, food record and frequency

# D. Nutrition and Weight Control

## 1. Body Mass Index (BMI)

- Body mass index (BMI) = $\frac{body\ weight(kg)}{(height(m))^2}$
  - <18: underweight
  - 18-23: normal
  - 23-24.9: overweight
  - >25: obese

## 2. Body Fat Distribution

- Location of body fat an important predictor of health risks
- **Upper body obesity**: related to CV diseases and type 2 diabetes (waist circumference >102cm in men and >88cm in women)
- **Lower body obesity**: less health risk but may change to upper body fat distribution after menopause

## 3. Body Fat Content

- Body fat content can be estimated by 'Siri formula':
  - Proportion of body fat = $\frac{4.95}{body\ density} - 4.5$
- Desirable body fat for adults:
  - Men: 8%-24%
  - Women: 21%-35%

# 4. Obesity

- Genes account for ~70% of weight differences between people
- Risks of being obese:
  - Child with no obese parent: 10%
  - Child with one obese parent: up to 40%
  - Child with both obese parents: up to 80%
- Gene pool has not changed much in last 50 years yet proportion of obese people risen rapidly → obesity epidemic also caused by lifestyle changes
- Adult obesity in female is rooted to childhood obesity whereas there is no strong links in men (obesity tends to start at 30)

# 5. Eating Disorders

- Exact cause unknown, genetic/social/psychological factors contribute to development
- Risk factors: female, low self-esteem, being teased about weight etc
- **Anorexia nervosa**: severe psychological disturbance with self-imposed starvation (affects ~1 in 200 women)
- **Bulimia nervosa**: cyclic episodes of overeating (bingeing) followed by purging (getting rid of food by gagging etc)

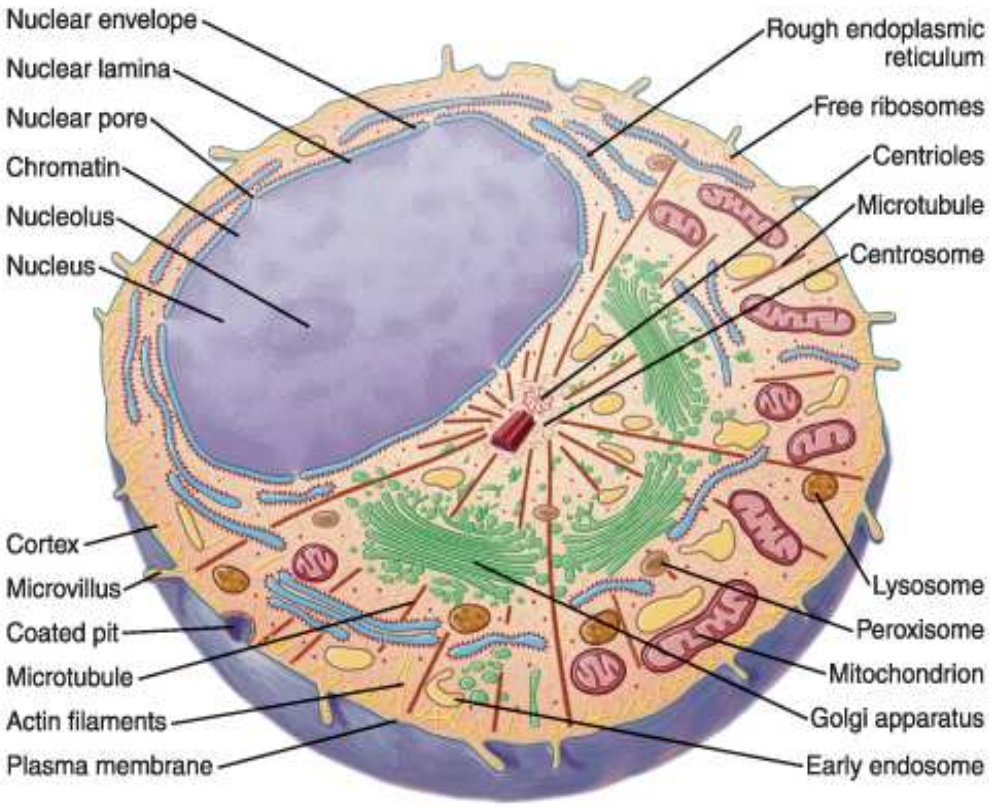
# L8 Structure and Function of Cells

## A. Diversity of Cells

- Most cells genetically identical (except lymphocyte → recombination of IgG gene) → diversity of cells given by <u>differential gene expression</u>
- Epigenetic changes: silencing or activating gene expression
  - Methylation of DNA (promoter/cytosine(C) residue of promoter) silences gene transcription)
  - Histone acetylation (activates) and deacetylation (inactivates) gene transcription

## B. Structures of Cell

- **Cell membrane**: surrounding wall of cell
- **Cytosol**: fluid part of cytoplasm (containing enzymes and metabolites)
- **Golgi**: organelle for packaging of protein
- **Lysosome**: organelle for breaking down things taken in from outside (with digestive enzymes)
- **Cytoskeleton**: internal scaffolding that controls the shape of cell and movement




- **Centrioles**: opposite poles for mitosis
- **Peroxisome**: organelle for metabolism of fatty acids
- **Nucleolus**: structure inside nucleus for rRNA transcription

# 1. Cell Membrane

- Lipid bilayer (phospholipid molecules **amphipathic** → spontaneously form a bilayer in water with hydrophobic ends inside)
- High fluidity → allow lateral diffusion of membrane proteins and facilitate cell movement
- Lipid bilayer → virtually impermeable to charged ions but variable permeability to water, $O_2$ and small hydrophobic molecules
- Break and tears are healed spontaneously → useful in modern molecular study during transfection of genes
- Membrane lipids:
  - Phospholipids (50%)
  - Cholesterol: stabilize mechanical property of membrane
  - Glycolipid: on outer side of membrane
- **Integral membrane protein**: penetrates whole membrane
- **Peripheral membrane protein**: penetrates only a part of membrane
- Membrane protein functions:
  - Attach cytoskeletal filaments to cell membrane
  - Attach cells to extracellular matrix (ECM)
  - Transport molecules in or out of cells
  - Receptors for cell signaling
  - Enzymatic activity, cell attachment and cell communication
- Membrane carbohydrates (**glycocalyx**; 2-20nm or more) in plasma membrane: precise composition varies with cell types
  - Cell type specific antigen
  - Major histocompatibility complex
  - Blood group antigens
  - Adhesion molecules

*Amphipathic: possessing hydrophobic and hydrophilic parts

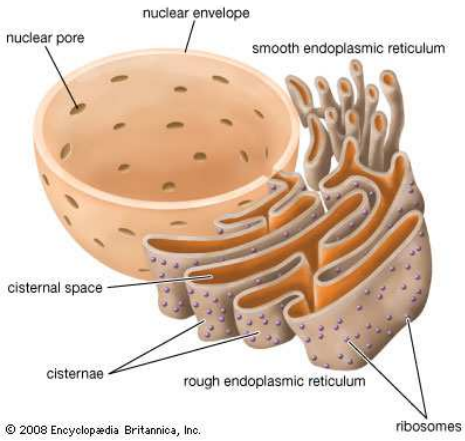
**Glycocalyx: glycoprotein-polysaccharide complex covering that surrounds plasma membranes of cells esp epithelial cells

## a. Transport in and out of Cells

- Diffusion
- Specialized membrane protein transport system or channels
- Endocytosis:
  - Phagocytosis: ingestion of large particles
  - **Pinocytosis**: ingestion of fluid and small molecules (from small vesicles 50nm)
  - Some viruses also use endocytic pathways to infect cells
- Clathrin-associated receptor-mediated endocytosis:
  - When certain ligands bind with receptors, clathrin (a type of special membrane-associated protein) binds to membrane and causes formation of a hexagonal lattice surrounding the vesicle
  - Only occur at specialized patches on plasma membrane (coated pits)
- Endocytic vesicles:
  - Clathrin-coated vesicles (100-150nm)
  - Uncoated vesicles (100nm)
  - Caveolae (50nm)
    - → Common in endothelial cell
    - → Formation due to caveolin (22kD integral membrane protein)
    - → High binding affinity to cholesterol
  - Phagosomes (large, 0.1-10µm)
    - → From phagocytosis, common in phagocytes
- Exocytosis:
  - Secretion (from *trans* face of Golgi apparatus), recycling of plasma membrane
- Endosomes (from endocytosis)
  - Major sorting compartment along endocytic pathway
  - Early endosome (pH 6.5), recycling endosomes (pH6.8), multivesicular bodies (pH 5.5) and late endosomes (pH 4.5)
  - Multivesicular bodieslate endosomes fuse directly with lysosomes (low pH in late endosomes activates lysosomal acid hydrolases to degrade endosomal content)
  - Endosomal pH affects fate of transported ligand and has profound effects on cell physiology

*kD = kilodalton i.e. 1000 a.m.u.

# 2. Endoplasmic Reticulum




- Complex intra-cytoplasmic membrane system
- Literal meaning of reticulum is ‘network’
- **Rough ER**: Flattened sheets of membranes and tubules with ribosomes attached
  - For protein synthesis (protein releases into ER cisternae) for export
  - Well-developed in protein-secretory cells eg. Exocrine pancreas
- **Smooth ER**: Flattened sheets of membranes and tubules without ribosomes
  - Different function in different cell types:
    - → Lipid metabolism and detoxification (eg. Hepatocytes)
    - → Steroid hormone production (eg. Leydig cells of testis)
    - → Calcium storage and release (eg. Muscle cells (as SR))

# 3. Golgi

- Stacked membranous cisternae (*sing.* cisterna) with vesicles
- *Cis* (forming) and *trans* (maturing) faces
- For modification and packaging of proteins (from RER)
- Formation of lysosome
- Recycling of cell membrane

- Movement of proteins through intracellular membrane system:

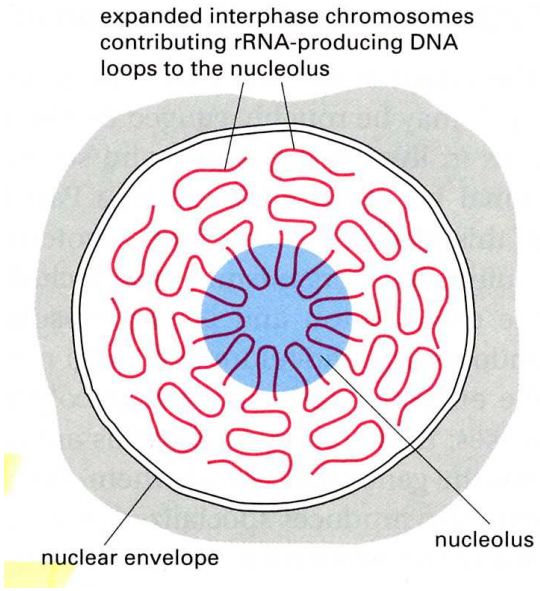
# 4. Nucleus

- Basophilic under H&E staining (blue)
- Bound by two concentric membranes:
  - Outer membrane: continuous with membrane of ER
  - Inner membrane: attached to filamentous proteins (lamins) of nuclear matrix inside nucleus
- Nuclear membrane perforated by many pores with special structures
- **Chromatin**: DNA + histones
  - **Euchromatin**: light-staining (electron-lucent i.e. low electron affinity) → active gene transcription
  - **Heterochromatin**: dense-staining area → highly condensed chromatin → non-coding DNA (eg. Centrosome and telomere) and inactive DNA (non-transcription form)

# 5. Nucleolus

- Site of most ribosomal RNA synthesis (28S, 18S, 5.8S) and ribosomal assembly
- Prominent in interphase nucleus
- Size increase with metabolic rate of cells
  - Tumour cells have prominent nucleolus
- rDNA located in C13, C14, C15, C21, C22
- Nucleolus helps transcribe rDNA and package rRNA with ribosomal proteins imported from cytoplasm to form ribosomes
- Newly formed ribosomal subunits translocated to cytoplasm through nuclear pore
- Many other novel fucntions to be unraveled (assembly of telomerase protein, cell cycle regulation etc)
- Detailed structure:
  - Clustering of tandemly repeated rDNA genes located on 5 pairs of chromosomes
  - Pale fibrillar region (non-transcribed DNA)
  - Dense fibrillar core (sites of rDNA gene transcription)
  - Granular regions (sites of ribosome assembly)

*S in 28S, 15S etc. refers to **Svedberg unit**, measuring rates of sedimentation



# 6. Mitochondrion

- ‘Respiratory system’ of cells:
  - Produce ATP, common energy currency in cells
  - Vary in number among different cells, more numerous in active cells
- Globular or elongated in shape, double-membraned
- Genetic system:
  - Circular DNA of maternal origin
  - Encodes some proteins within mitochondria
  - Most of the proteins in mitochondria are imported
- Suspected to have originated from a symbiotic bacterium → double membrane (outside is of the cell, inside is of the bacterium

# 7. Cytoskeleton

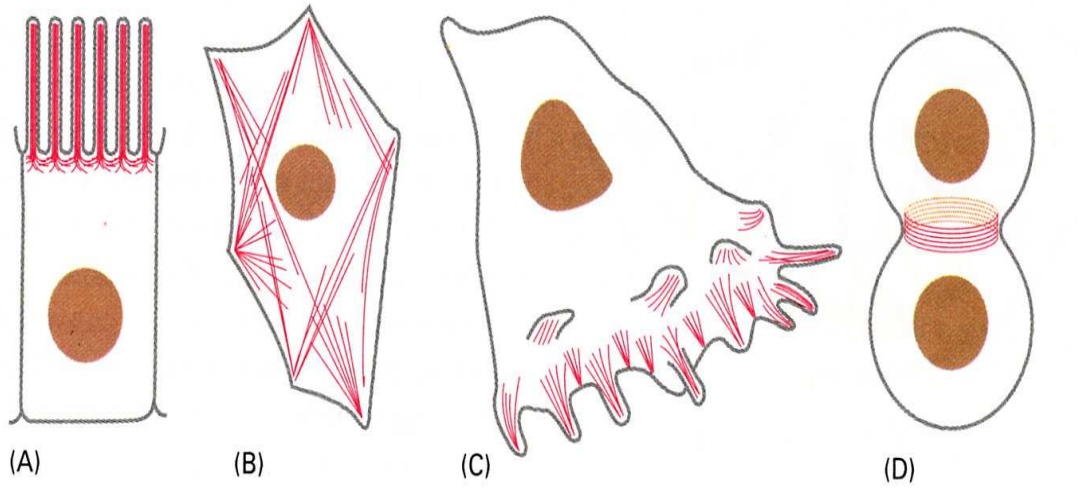
- Functions:

1) Mechanical support
2) Cell movement (*actin*)
3) Contraction (*actin and myosin* in muscles)
4) Transport of organelles, vesicles and macromolecules (*microtubules*)
5) Cell division (*microtubules and actin*)

- Three types: **microfilaments** (actin, <10nm), **intermediate filaments** (~10nm), **microtubules** (~24nm)
- Dynamic structure → growth and breaking down occur continuously in cell

## a. Actin Filaments

- Mainly involved in (amoeboid) movement, change in cell shape and cytokinesis
- Also cooperate with myosin in myocytes for contraction
- Roles of actin filaments in different parts of cells:




(A) Microvilli
(B) Stress fibres / **focal adhesion** / cell
(C) Filopodia / lamellipodia / cell migration
(D) Cytokinesis
*__focal adhesion__ is the structure that binds cytoskeleton onto ECM
**Filopodia/lamellipodia are 'feet' of cytoplasm that brings about amoeboid movement

## b. Intermediate Filaments

- Has a variety of functions in different cells and different places
  - Epithelial cells: tonofilaments (keratins) for cell adhesion via desosomes and hemidesosmes
  - Muscle cells: desmin filaments (desmin) for unknown function
  - Fibroblasts: vimentin for maintaining cell shape, fixing organelle position and control LDL transport
  - Neuron: neurofilament for structural support and regulation of axon diameter (affects nervous signal transport speed)
  - Glial cells: glial filaments

### i. Nuclear Lamina

- Nuclear cytoskeleton
- Network of protein intermediate filaments (20nm) underneath the internal nuclear membrane
- Composed of nuclear lamins A, B and C
- Interact with chromatin in the spatial organization of the nucleus

## c. Microtubules

- Tubular protein filament (made up of α-tubulin, β-tubulin) for intracellular transport
- Extend from **centrosome** to periphery of cell
- Movements involving microtubules:
  - Cell division
  - Flagellar and ciliary movements
  - Movement of organelles, vesicles, chromosomes, pigments
- Kinesin (away) and dynein (towards) motor proteins transport substances to and from centrosomes inside cells

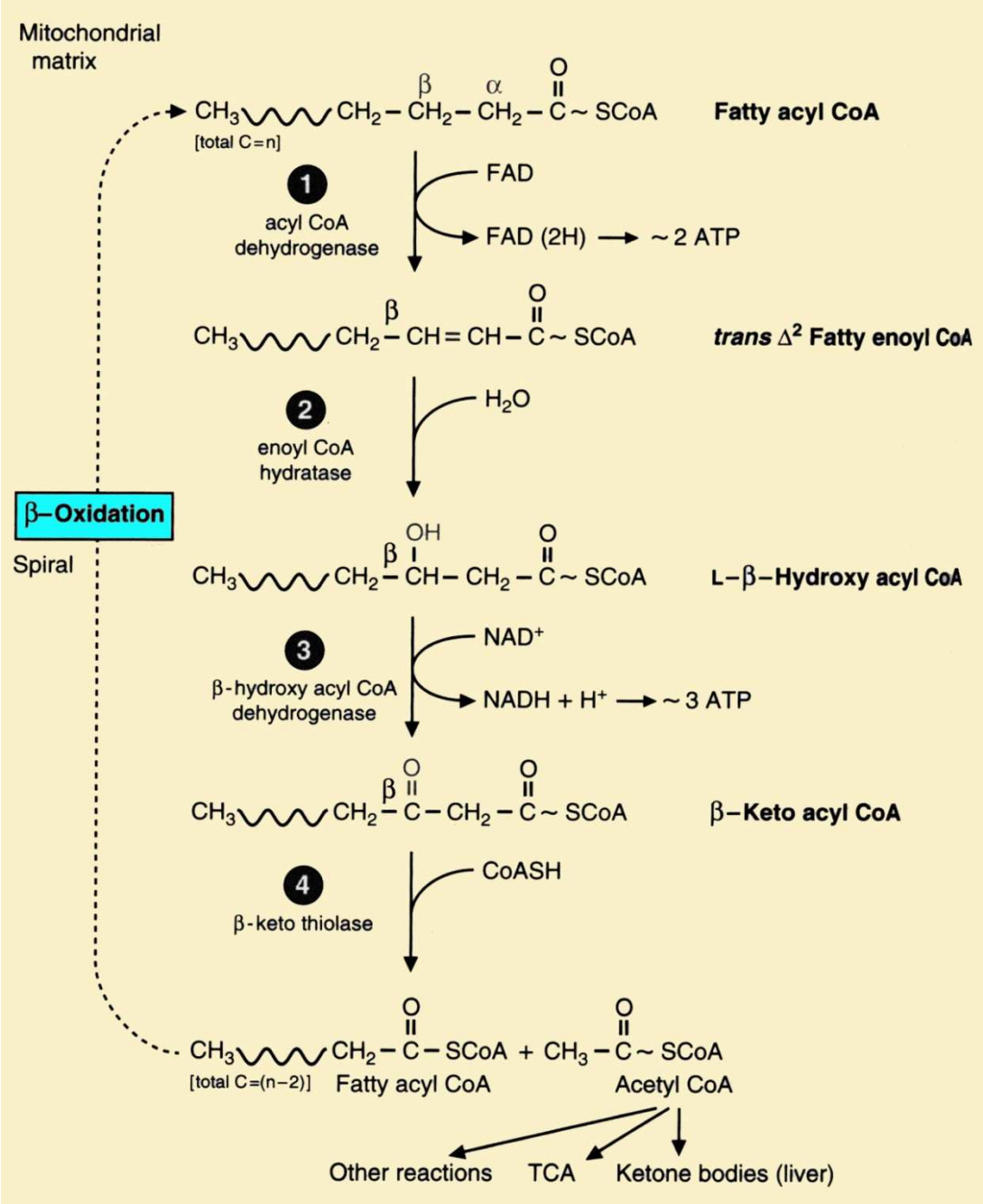
# L9 Lipids

## A. Properties of Lipids

- Main form: **triacylglycerol (TAG)** but also present in form of **cholesterol (Ch)**, **phospholipid** and **glycolipid**
- TAG can be classified into:
  - Saturated: without double bond
  - Unsaturated: with double bond(s)
    - → Most in nature are *cis*-fats → Has bent structure → inefficient packing → ↓intermolecular forces → liquid form
- Properties of lipids:
  - Hydrophobic
  - Uncharged
- TAG stored in adipose tissue a store of cellular energy
- Fatty acid salt, phospholipid and bile acid/salt are **amphiphiles**

# B. Fatty Acid Oxidation

- Also called β-oxidation
- Used by many body tissues esp by muscle cells
- Performed in <u>mitochondrial matrix</u> (and sometimes inside **peroxisomes**)
- More long-lasting than carbohydrate oxidation
- Consists of repeated removal of acetyl groups to form acetyl CoA
- Produces Acetyl CoA, $FADH_2$, NADH and ultimately ATP



# C. Cholesterol and Bile Salts

- Structure of **cholesterol**:

  - Four-ringed structure called ‘steroid nucleus’
  - Cholesterol synthesized from cytosolic acetyl CoA
  - Cholesterol then used to make bile salt, steroid hormones, blood lipoproteins and act as a component in cell membrane (strengthen cell membrane)
  - Linear shape allows it to pass through phospholipid bilayer

- Structure of **bile salt**:

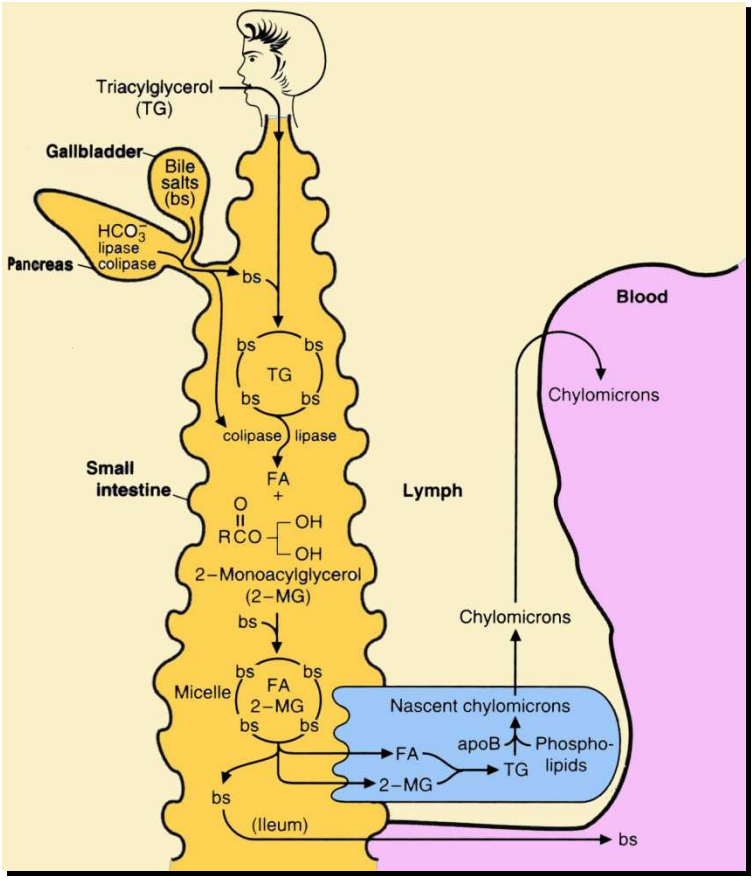
  - Steroid nucleus is derived from cholesterol
  - Negatively charged end → amphiphile → helps form **micelle** to emulsify lipids

*Micelle: one layered ‘bubble’ made up of amphiphiles with hydrophilic side facing outward

**Phospholipid molecule has two chains → overcrowded → cannot form micelle (can only form bilayered structure called **liposome**)

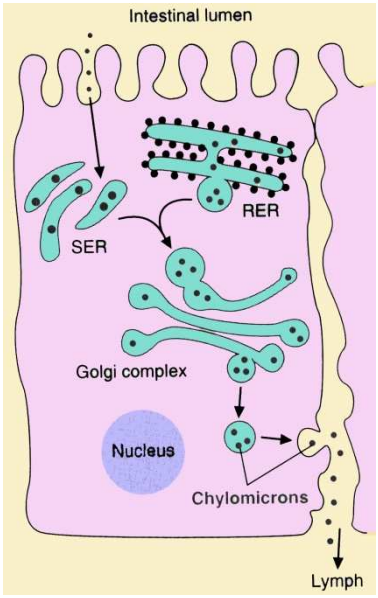
# D. Digestion of TAG

1) TAG emulsified by **bile salts** in bile to form micelles;
2) Pancreatic lipase work together with colipase to break down TAG into fatty acid (FA) and 2-monoacylglycerol (2-MAG);
3) FA and 2-MAG are taken into the intestinal wall and recombine into TAG;
4) TAG is packaged with apoB-48, phospholipids and cholesterol into **nascent chylomicrons** and secreted into lymph vessels.



# E. Chylomicrons and Exogenous Pathway of Lipid Metabolism

- **Lipoprotein**: Biochemical particles consisting of proteins, lipids, cholesterol, phospholipids and apolipoproteins that act as a vessel for lipid (and cholesterol) transport in blood plasma
  - Five types: chylomicron (cm), very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL), high density lipoprotein (HDL) [from lowest density to highest]
- **Chylomicron**: Lipoprotein containing large proportion of TAG and is secreted by intestines only
- Function: deliver dietary TAG from intestinal lumen to peripheral tissues for storage




## 1. Formation and Secretion

1) FA and 2-MAG enter intestinal wall cell by diffusion;
2) FA and 2-MAG re-esterify in SER to form TAG;
3) ApoB-48 synthesized in RER;
4) TAG, cholesterol and ApoB-48 packaged in Golgi;
5) Nascent chylomicrons secreted by exocytosis.

# 2. Metabolism and Fate of Chylomicrons

1) Nascent chylomicrons secreted by intestinal mucosal cells;
2) Nascent cm obtains ApoC-2 and ApoE from HDL circulating in blood and becomes mature cm;
3) Lipoprotein lipase (extracellular enzyme) at peripheral tissue capillary walls recognizes apoC-2 and breaks down TAG into FA and glycerol;
4) Most FA taken up by tissue cells while glycerol will return to liver by blood;
5) Free FAs that is not taken up by cells immediately are transported by serum albumin until taken up by cells;
6) Resultant cm remnants return ApoC-2 to HDL and is absorbed by sites with apoE-recognizing lipoprotein receptors at liver.

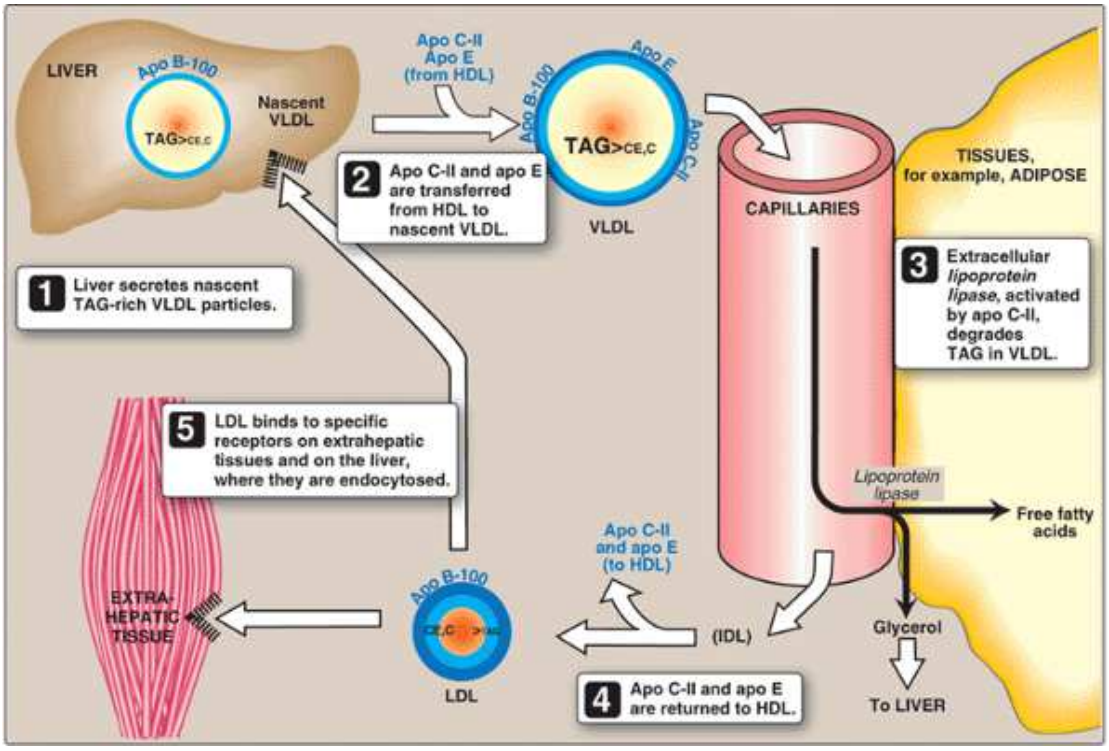
# F. VLDL, LDL and Endogenous Pathway of Lipid Metabolism

- Hepatocytes in liver can synthesize lipids from glucose via acetyl coA
- Also stores large amounts of TAG
- Hepatocytes secrete nascent VLDL into blood, which contains TAG, cholesterol, phospholipids and apoB-100
- Function of VLDL: transport of TAG from liver to periphery tissues for storage

## 1. Formation and Secretion of VLDL

1) RER synthesize apoB-100 apolipoprotein;
2) Golgi packages TAG with apoB-100, cholesterol and phospholipids;
3) VLDL is secreted into blood via exocytosis.

## 2. Metabolism and Fate of VLDL

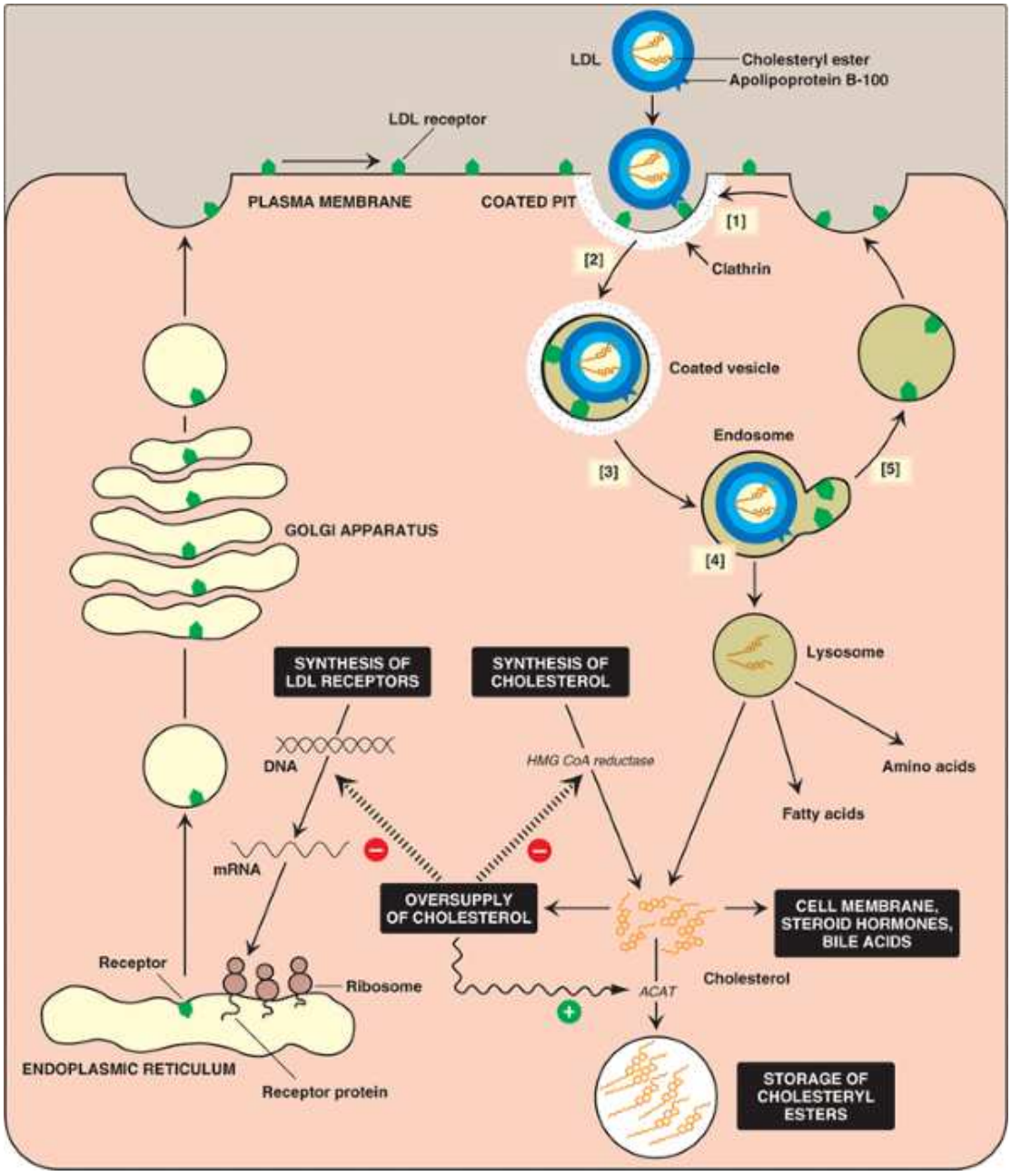



1) Nascent TAG-rich VLDL particles are secreted by liver;
2) Nascent VLDL obtains ApoC-2 and ApoE from HDL and becomes VLDL;
3) Lipoprotein lipase in peripheral tissue capillary walls break down TAG in VLDL to form FA and glycerol, in which FAs are taken up by tissues while glycerol returns to liver via circulation;
4) ApoC-2, ApoE are transferred to HDL;
5) Cholesteryl Ester Transfer Protein (CETP) helps transfer cholesterol from HDL to VLDL and TAG from VLDL to HDL, VLDL becomes LDL in the process (also note transitional state of IDL).

# 3. Metabolism and Fate of LDL

- LDL is endocytosed at specialized sites with LDLr (recognizes apoB-100) in peripheral tissues and liver
- Cholesterol in LDL is provided to tissue/liver cells for building hormones, cell membranes and storage
- Some LDL's lipid or apoB-100 components are oxidized → cannot be endocytosed by tissues and liver etc. → will be phagocytosed by macrophages via scavenger receptors
- Unlike LDLr, scavenger receptors not down-regulated by high cell cholesterol content → cholesterol accumulate in macrophages → becomes foam cells → formation of atherosclerotic plaques

## a. Effects of Uptake of LDL




1) Repress synthesis of HMG-CoA reductase → less *de novo* synthesis of cholesterol;
2) Stimulate *ACAT* → stimulate storage in esterified form;
3) Repress synthesis of LDLr.

*Rate-limiting step in cholesterol synthesis is the reduction of HMG-CoA into mevalonate by HMG-CoA reductase

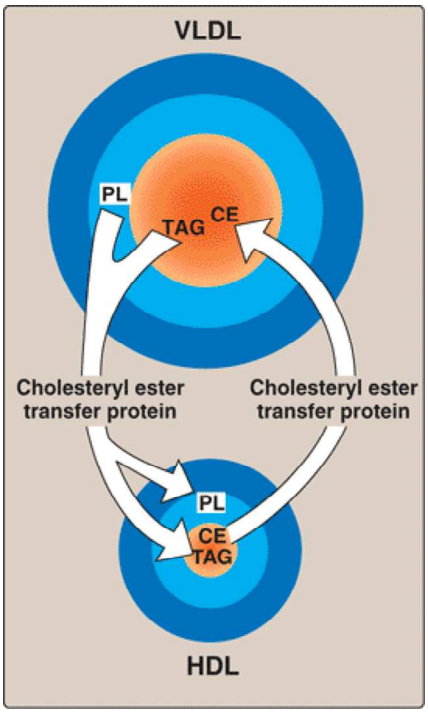
Statins, structural analogs of intermediate in the conversion to mevalonate → inhibits HMG-CoA reductase → reduces cholesterol synthesis → can be used to treat hypercholesterolemia

# G. HDL and the Reverse Cholesterol Transport

- HDL is secreted by liver and has a high proportion of proteins
- Excellent acceptor of unesterified cholesterol
- Functions of HDL:
  - Acts as a circulating reservoir of ApoC-2 and ApoE
  - Remove unesterified cholesterol from peripheral tissues and return them to the liver by LDL or themselves
- Three types:
  - Nascent (discoid) HDL: with very low cholesterol, precursor of HDL3
  - HDL3: with relatively low cholesterol level
  - HDL2: with high cholesterol level

## 1. HDL Secretion and Maturation

1) Nascent disc-shaped HDL is secreted by hepatocytes with apoA-1, apoC-2 and apoE;
2) Nascent HDL has high affinity for unesterified cholesterol → picks up unesterified cholesterol from lipoprotein particles and cell membranes of peripheral tissues;
3) Unesterified cholesterol is immediately esterified by PCAT enzyme in nascent HDL;
4) Nascent HDL becomes spherical in shape, now becomes HDL3;
5) HDL3 further accepts free cholesterol from peripheral tissues and becomes HDL2;
6) Cholesteryl ester transfer protein helps transport TAG from VLDL to HDL and cholesteryl ester from HDL to VLDL.



# 2. Reverse Cholesterol Transport

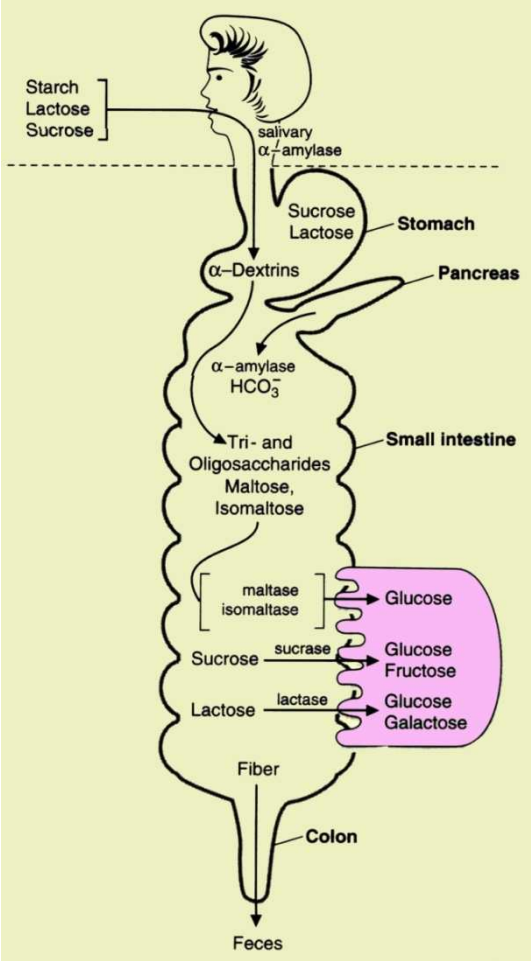
1) ABCA1 helps transport free cholesterol from peripheral tissue to HDL (incl. those deposited on arterial wall by macrophage);
2) Cholesterol is esterified by PCAT into cholesterol ester;
3) Some cholesterol is exchanged for TAG with VLDL;
4) Lipid-rich HDL2 binds to liver and steroidogenic cells and releases cholesterol in it (mediated by SR-B1 receptor in liver);
5) Cholesterol then used to form steroid hormones in steroidogenic cells and bile salts in liver;
6) Hepatic lipase helps degrade TAG (and phospholipids) in HDL2;
7) Lipid-deficient HDL3 is released.

# L10, 12 Carbohydrate Metabolism and Its Regulation

## A. Carbohydrate Digestion

- Common dietary carbohydrates:
  - Glucose
  - Fructose
  - Sucrose = glucose + fructose
  - Maltose = glucose + glucose
  - Lactose = glucose + galactose
  - Starch = n(maltose)
  - Glycogen = n(glucose)

1) Long-chained carbohydrates hydrolyzed by salivary α-amylase to form α-dextrins (low-molecular weight polysaccharides);
2) Dextrins further hydrolyzed by pancreatic α-amylase to form tri and oligosaccharides (short polysaccharide chains), maltose, isomaltose etc.;
3) Disaccharides broken down into monosaccharides by maltase, isomaltase, sucrase and lactase on intestinal wall;
4) Monosaccharides absorbed by intestinal wall.



# B. Carbohydrate Metabolism

## 1. Glucose

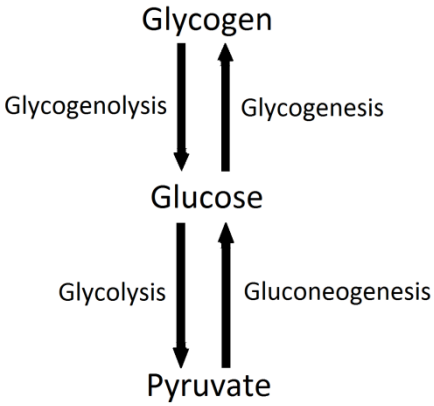
- 6-C sugar in ring form or in straight chain form:

  - Groups on LHS points upward
  - –CHO group with δ+, the other side with δ-

- Soluble → affects water potential → must be stored in insoluble form (i.e. glycogen) and level must be closely controlled → insulin in ↑Glc level and glucagon in ↓Glc level
- Glucose is transported into cells via facilitated diffusion and is $Na^+$ dependent

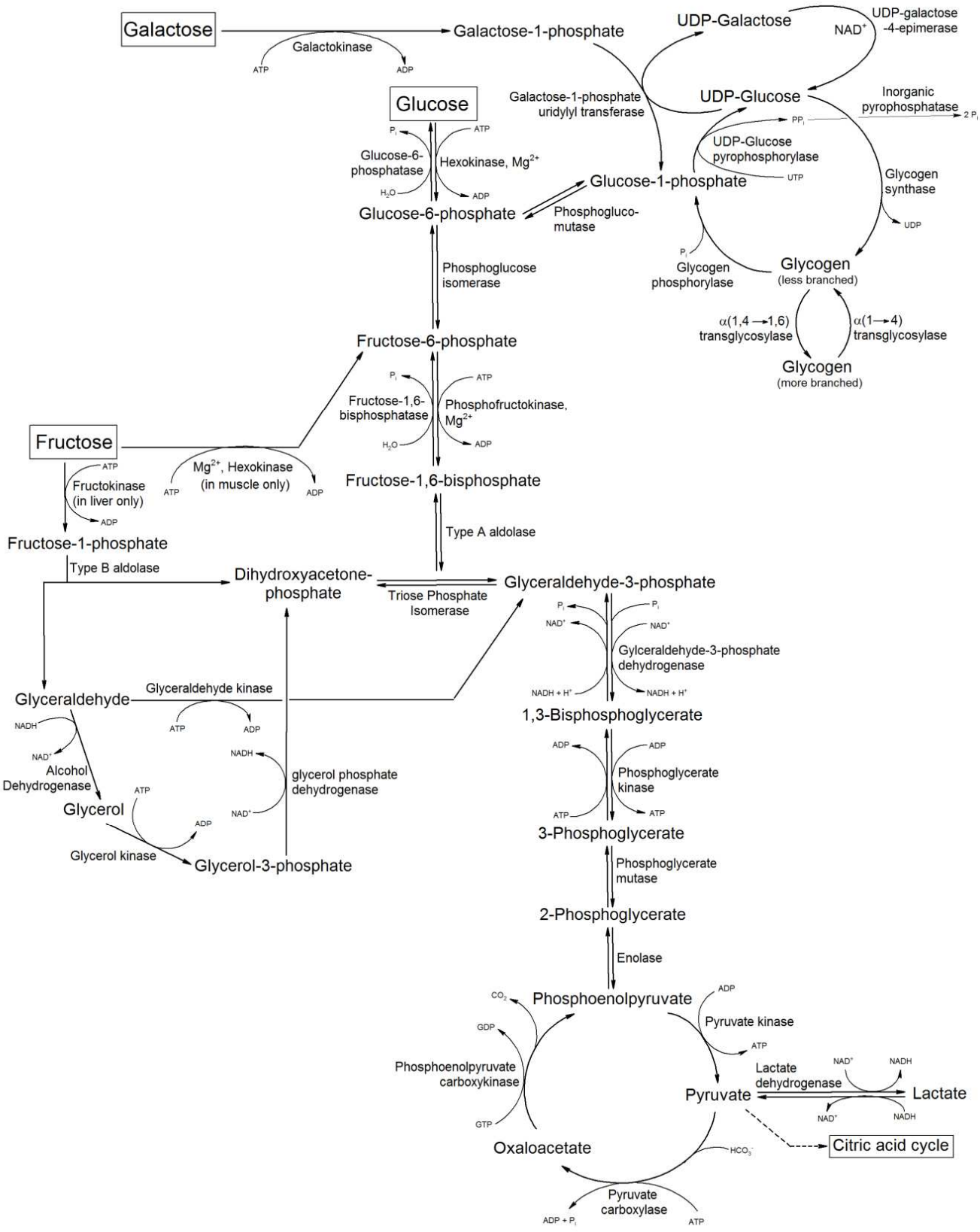
# 2. Glycolysis and related processes

- **Glycolysis**: conversion of glucose into pyruvate (in cytosol)
  - Provides metabolic energy
  - Precursor molecules for synthesis (eg AAs)
- **Gluconeogenesis**: generation of glucose from non-CHO substrates (eg pyruvate, glucogenic AAs, glycerol etc)
  - Maintains constant supply of glucose (esp in fasting state)
  - Mainly in liver
- **Glycogenolysis**: breakdown of glycogen into Glc-1-P
  - Storage of glucose
  - Muscle and liver
- **Glycogenesis**: synthesis of glycogen from glucose
  - Produces glucose from glycogen (in times of starvation, physical exercise and stress)
  - Muscle and liver
- Functions:
  - Control of blood glucose level
  - Production of ATP esp for anaerobic respiration of RBC (lacks mitochondria)
  - Conversion between important biological substances (AAs, carbohydrates, TAG, nucleic acids)
  - Conversion to storage forms of carbohydrates



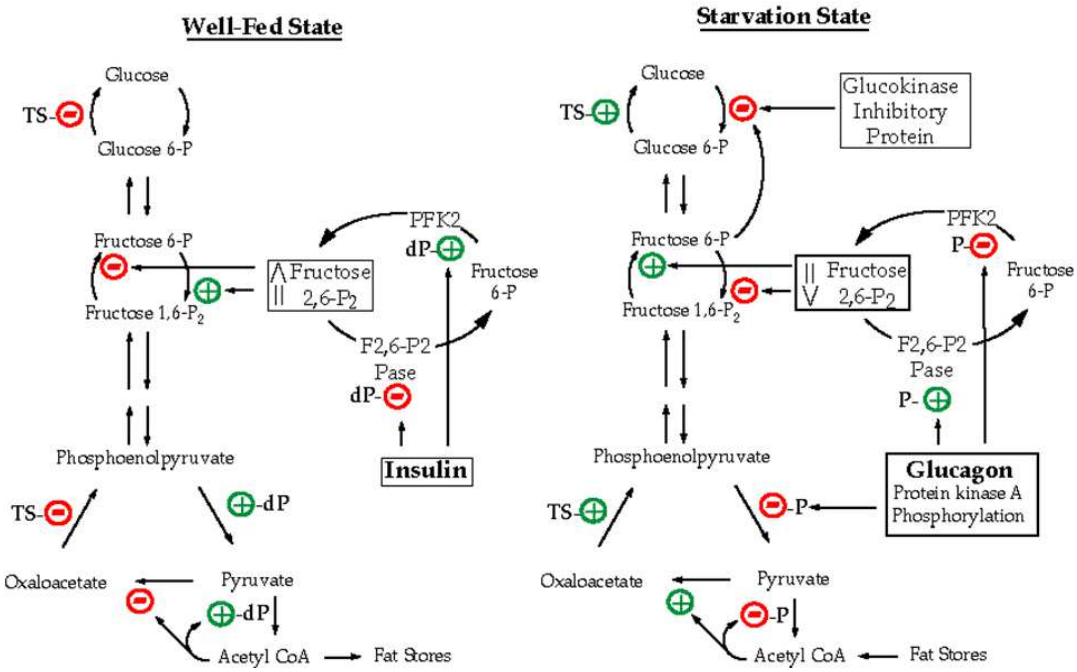

**Note that gluconeogenesis is not exclusively found in liver, but also carried out by kidney cortical cells as well as muscles. However, since muscle cells lack glucose-6-phosphatase, they cannot return free glucose to the blood, and thus its gluconeogenesis process is exclusively performed to provide glucose backbone for storage as glycogen*

- Complete metabolic pathway:



## a. Regulation of glycolysis and its related pathways

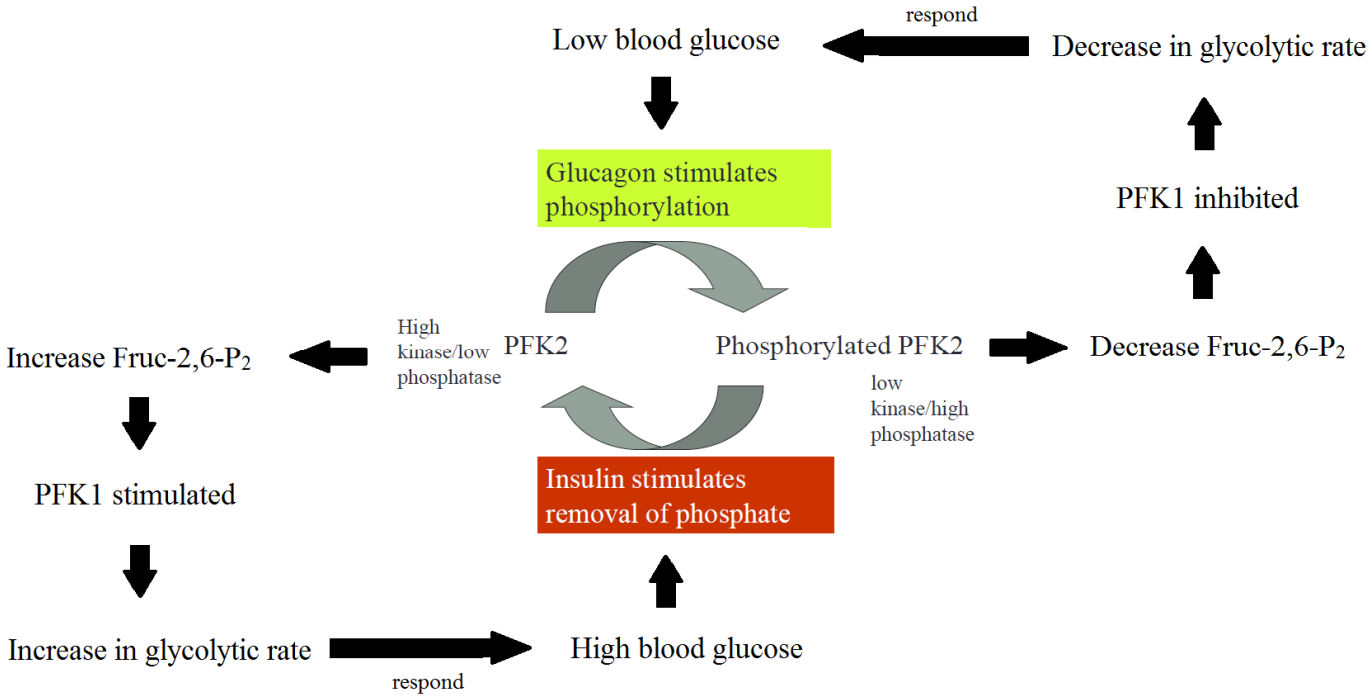
- **ATP**: ↑ glycolysis
- **AMP**: ↓ glycolysis
- **Alanine**: ↓ glycolysis
- **Insulin**: ↑glycolysis ↑glycogenesis ↓gluconeogenesis ↓glycogenolysis
- **Glucagon**: ↓glycolysis ↓glycogenesis ↑gluconeogenesis ↑glycogenolysis



## i. Regulation of Glycolysis

### (1) Regulation of Phosphofructokinase (PFK)

- Reaction: Fructose-6-P → Fructose-1,6-$P_2$ [PFK1]
  - ATP(-), AMP (+)
  - Fruc-2,6-$P_2$ (+)
- Note two types of PFK:
  - PFK1: only kinase domain, converts Fruc-6-P to Fruc-1,6-$P_2$
  - PFK2: with kinase and phosphatase domain, converts Fruc-6-P to and from Fruc-2,6-$P_2$
- Low BG → glucagon → phosphorylation of PFK2 → ↑phosphatase activity → ↓F-2,6-$P_2$ → ↓PFK1 activity → ↓glycolytic rate
- High BG → insulin → dephosphorylation of PFK2 → ↑kinase activity → ↑F-2,6-$P_2$ → ↑PFK1 activity → ↑glycolytic rate




### (2) Regulation of pyruvate kinase (PK)

- Reaction: Phosphoenolpyruvate → pyruvate [PK]
- Allosteric regulators:
  - F-1,6-$P_2$ (+)
  - ATP (-)
  - Alanine (-)
- Low BG → ↑glucagon → ↑phosphorylation of PK → deactivation of PK → ↓ glycolytic rate
- High BG → ↑insulin → ↑dephosphorylation of PK → activation of PK → ↑glycolytic rate

## ii. Regulation of Gluconeogenesis

**(1) Regulation of pyruvate carboxylase**

- Reaction: pyruvate → oxaloacetate [pyruvate carboxylase]
  - Acetyl CoA (+)
- Low BG → ↑glucagon ↓insulin → ↑gluconeogenesis + β-oxidation
- β-oxidation → ↑NADH:NAD ratio → OAA reduced to malate for shuttling to cytoplasm for gluconeogenesis + citrate formation inhibited
- ↑ gluconeogenesis rate → ↓ oxaloacetate → ↓ TCA cycle entry
- ↑ β-oxidation + ↓ TCA cycle entry → ↑acetyl coA → stimulates pyruvate carboxylase activity

**(2) Regulation of phosphoenolpyruvate (PEP) carboxykinase**

- Reaction: oxaloacetate → phosphoenolpyruvate [PEP carboxykinase]
- Insulin and glucagon inhibits and stimulates transcription of PEP carboxykinase gene → changes gluconeogenesis rate accordingly

**(3) Regulation of fructose 1,6-bisphosphatase (F-1,6-$P_2$ase)**

- Reaction: fructose-1,6-$P_2$ → fructose-6-P [fructose 1,6-bisphosphatase]
  - F-2,6-$P_2$ (-)
- Low BG → glucagon → phosphorylation of PFK2 → ↑phosphatase activity → ↓F-2,6-$P_2$ → ↑ F-1,6-$P_2$ase activity → ↑rate of gluconeogenesis
- High BG → insulin → dephosphorylation of PFK2 → ↑kinase activity → ↑F-2,6-$P_2$ → ↓F-1,6-$P_2$ase activity → ↓rate of gluconeogenesis

## iii. Regulation of Glycogenolysis and Glycogenesis

- Reaction: Glycogen → Glc-1-P [glycogen phosphorylase]
  - Insulin (-) glucagon (+)
  - AMP (+)
- Reaction: UDP-Glc → Glycogen [glycogen synthase]
  - Insulin (+) glucagon (-)
- BG↑ → insulin → glycogen synthase inhibited, glycogen phosphorylase stimulated → net conversion of glucose to glycogen → ↓ BG
- BG↓ → glucagon → glycogen synthase stimulated, glycogen phosphorylase inhibited → net conversion of glycogen to glucose → ↑ BG

## b. Pentose Phosphate (PP) Pathway

- Alternate pathway parallel to glycolysis:
  Glc-6-P → pentose phosphates → G3P
- Main function:
  - Synthesis of nucleotides (ribose backbone)
  - Production of NADPH for biosynthesis (reducing agent) and prevention of oxidative damage

## c. Other uses of Carbohydrates

### i. Synthesis of TAG

- Occurs in liver and adipose tissues
- Fatty acids formed from building up of acetyl coA units (exact opposite of β-oxidation)
- Glycerol formed from G3P
- Regulation:
  - Citrate (+): citrate level indicates availability of glucose; excess → conversion to TAG

*acetyl coA from citrate in TCA cycle (citrate act as carrier of acetyl coA from mitochondria to cytosol then cleaved to give OAA and acetyl coA, OAA then recycled into malate and return to mitochondria for TCA cycle)

### ii. Synthesis of AAs

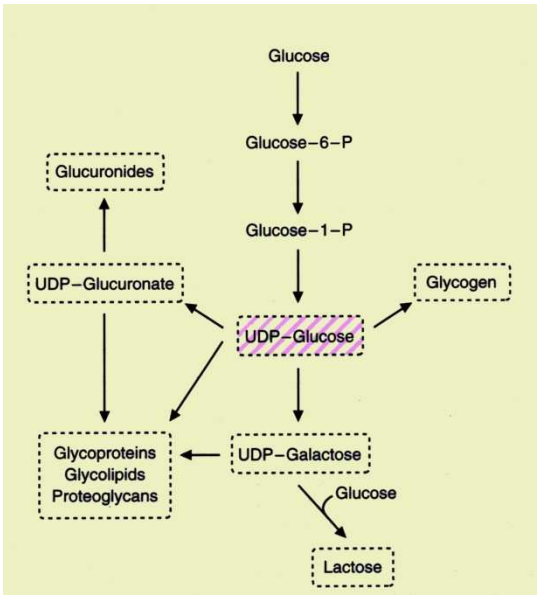
- AAs are formed from various intermediates of TCA cycle and glycolysis

### iii. Synthesis of Nucleic Acids

- Ribose backbone derived from PP pathway
- NADPH derived from PP pathway and glycolysis also aids conversion of NTP into dNTP

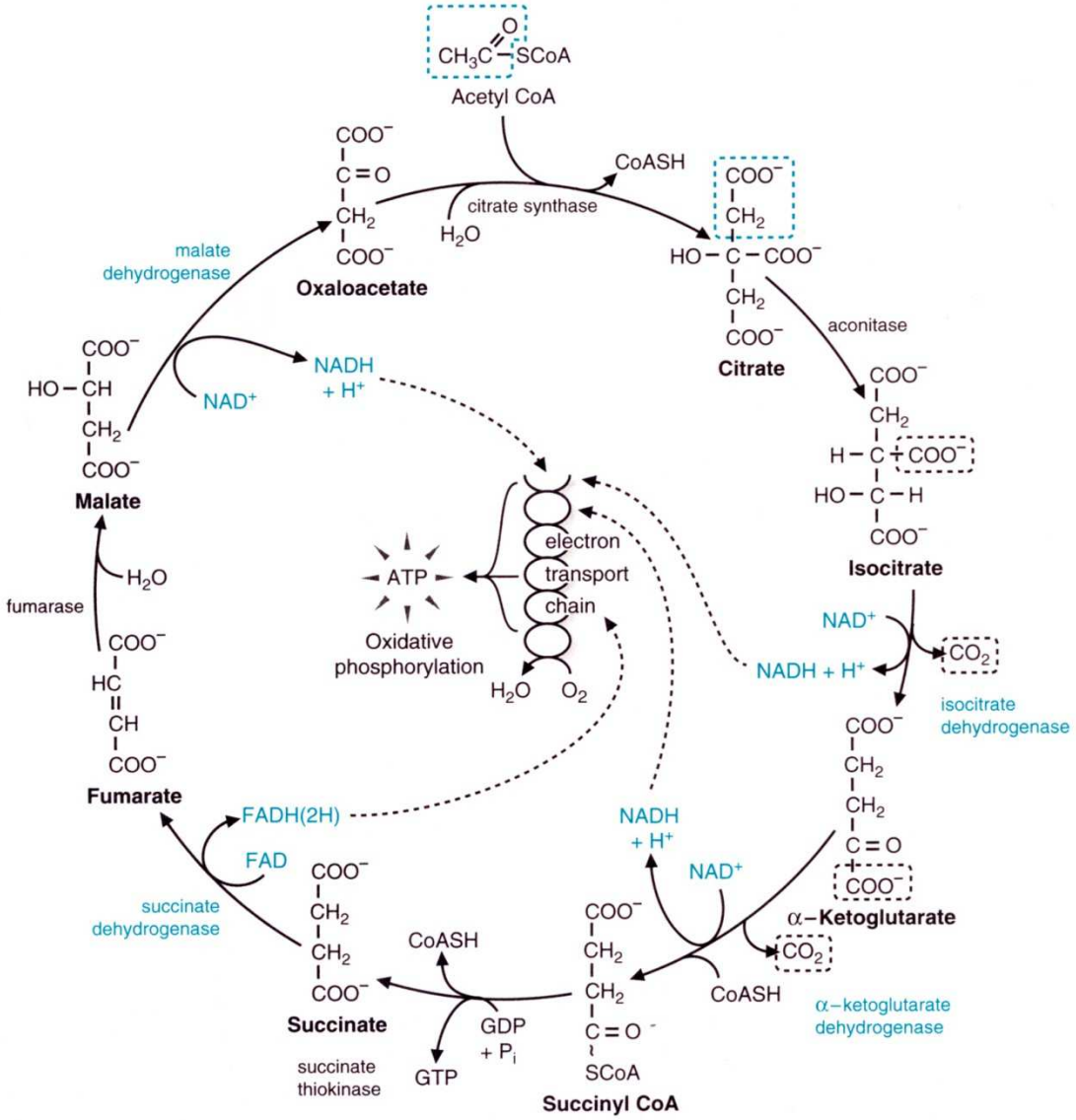
### iv. Synthesis of Glycoconjucates

- Glc-1-P converted to Uridine diphosphate(UDP)-Glc
- UDP-Glc can then be converted to glycolipids, glycoproteins, proteoglycans, glycogen and glucuronides



# 3. TCA Cycle and Electron Transport Chain

- Oxidation of acetyl CoA resulted in storage of reducing power in $FADH_2$ and NADPH → then used in electron transport chain to produce ATP
- Oxidation of $FADH_2$ and NADPH at e.t.c. pumps $H^+$ out of mitochondrial matrix → membrane potential used to drive ATP synthase



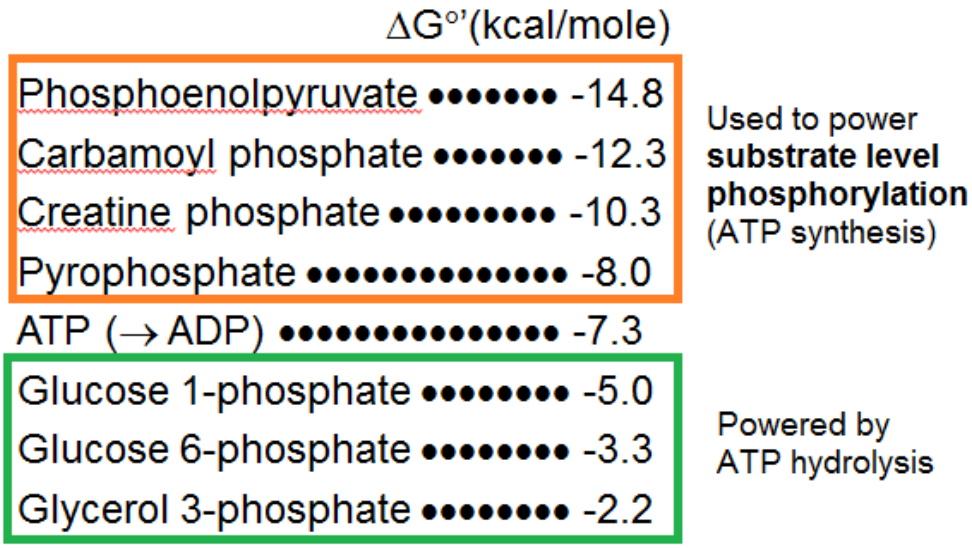
# L11 Generation of ATP

## A. Structure of ATP

- Structure of ATP:

- Negative phosphate ions repel each other → large amount of energy stored in high energy phosphate bonds → hydrolysis releases 7.3kcal/mol

## B. Mechanism of ATP Generation and Usage




### 1. ATP Usage

- ATP can be used to power thermodynamically unfavourable reaction ($\Delta G^o$ < 7.3kcal/mol):

kcal/mole

$$\text{Glucose} + Pi \rightarrow \text{glucose-6-P} + H_2O \qquad \Delta G^{o\prime} = +3.3$$

$$ATP + H_2O \rightarrow ADP + Pi \qquad \Delta G^{o\prime} = -7.3$$

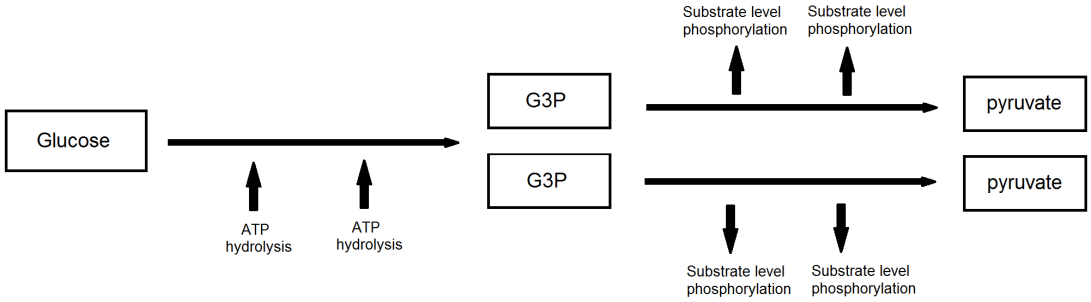
$$\text{Sum: Glucose} + ATP \rightarrow \text{glucose-6-P} + ADP \qquad \Delta G^{o\prime} = -4.0$$

- Coupling ATP hydrolysis with endergonic (+7.3 > $\Delta G^{o\prime}$ > 0) reaction → overall reaction becomes exergonic

# 2. ATP Synthesis

- Compounds with high-energy phosphate bonds ($\Delta G^o$ < -7.3kcal/mol) exhibit a high **$P_i$ transfer potential**
- **Substrate level phosphorylation**: Coupling of hydrolysis of high-energy phosphate bonds with formation of ATP from ADP
  i.e. $ROPO_3^{2-}$ + ADP → ROH + ATP
- Example:
  - 1,3-bisphosphoglycerate + ADP → 3-phosphoglycerate + ATP
  - PEP + ADP → pyruvate + ATP
- Note that substrate level phosphorylation is <u>independent</u> of $O_2$ availability
- **Oxidative phosphorylation**: ATP can also be synthesized by ATP synthase from transmembrane $H^+$ gradient generated by electron transport chain

*Note reason why glycolysis results in net production of ATP:



# L13 Amino Acids Metabolism

## A. Amino Acids Metabolism

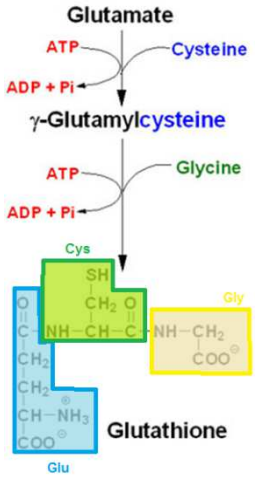
- Fed state:
  - Proteins
  - Enter CHO metabolic pathway to give ATP
  - Gluconeogenesis then stored as glycogen
  - TAG
  - Other essential N-containing compounds (glutathione, creatine, monoamine neurotransmitter)
- Fasting state:
  - Gluconeogenesis
  - Ketogenesis to form ketone bodies for energy

## 1. Transformation of AAs into fuel molecules

- Note three types of AAs:
  - Glucogenic AAs: can be used in gluconeogenesis
  - Ketogenic AAs (Leu, Lys): cannot be used in glucogenesis, used to generate ketone bodies via Ketogenesis pathway instead
  - Glucogenic and Ketogenic AAs (Ile, Phe, Trp, Try, Thr)
- Glucogenic AAs enter CHO metabolism pathway at TCA cycle or pyruvate, then used in gluconeogenesis
  - TCA cycle intermediates rerouted at OAA due to high activity of PEP carboxykinase (due to glucagon) → OAA leaves mitochondrion to perform gluconeogenesis
- Ketogenic AAs enter CHO metabolism pathway at acetyl coA only, then used in Ketogenesis to form ketone bodies, ultimately degraded into $CO_2$ in TCA cycle
  - Acetyl coA rerouted to Ketogenesis pathway because high PEP carboxykinase activity rerouted most OAA to gluconeogenesis → no OAA available for TCA cycle → rerouted

# 2. Production of Essential N-containing Compounds from AAs

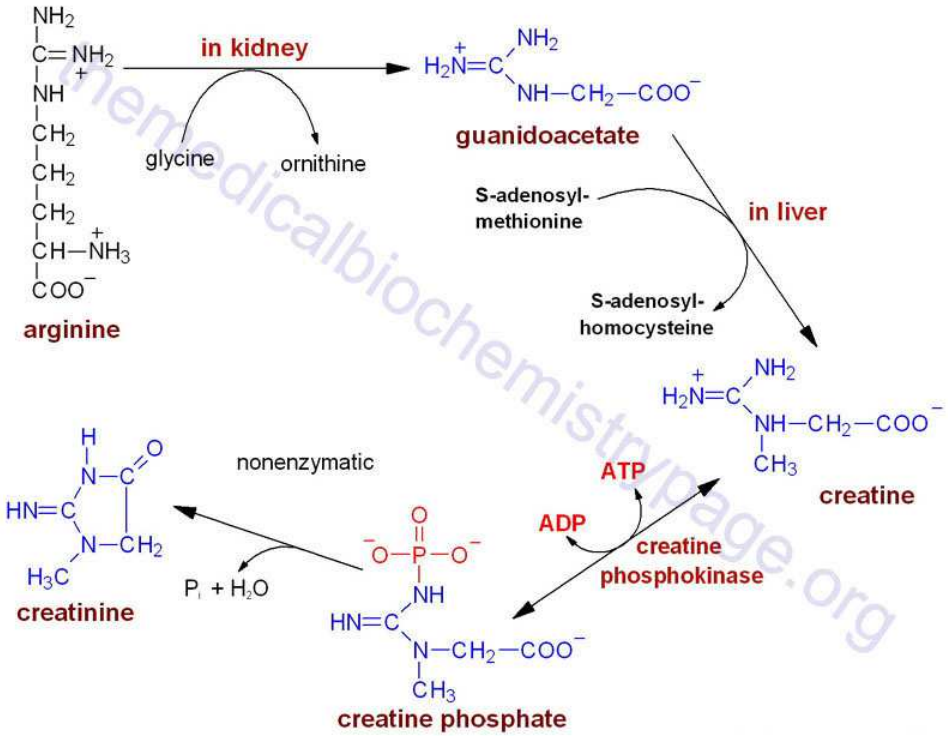
## a. Glutathione (GSH)




- Essential antioxidant in cells:
  - Oxidation: 2GSH → GSSG
  - Regeneration: GSSG + 2NADPH → 2GSH + 2NADP
- Reducing power given by **cysteine** residue in GSH
- Production pathway on the right

## b. Creatine

- Converted to and from phosphocreatine to act as alternative energy storage form
- Production pathway:






- Blood and urine creatinine level used to gauge renal function (specifically glomerular filtration rate i.e. GFR) because there is no reabsorption or secretion in renal tubules

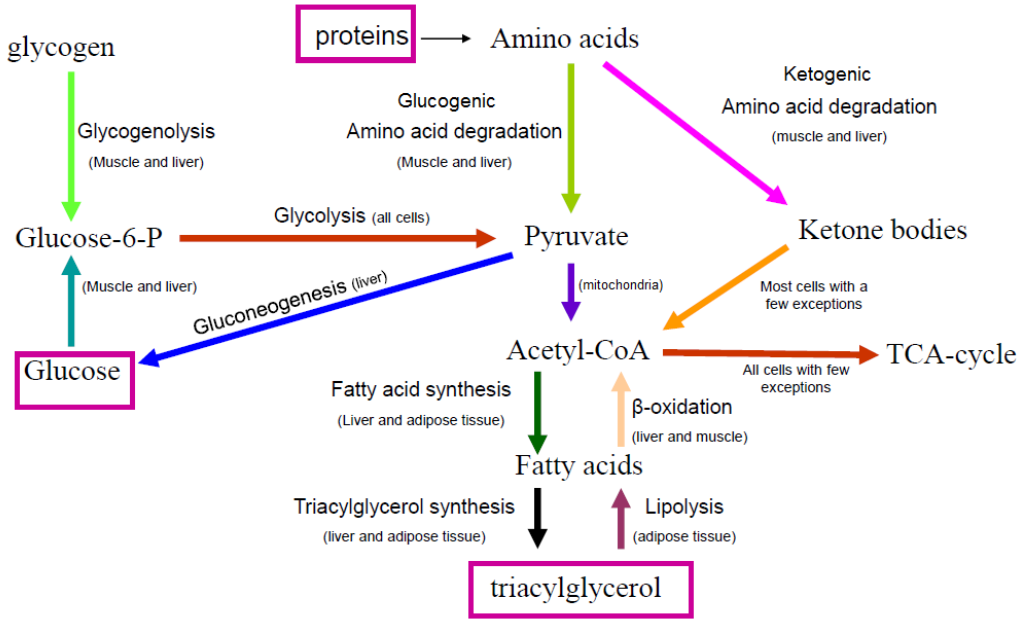
## c. Adrenaline, Noradrenaline, Dopamine, Serotonin

- Important hormones and neurotransmitters for the body
- First three produced from tyrosine, serotonin produced from tryptophan:

# L14 Metabolic Integration

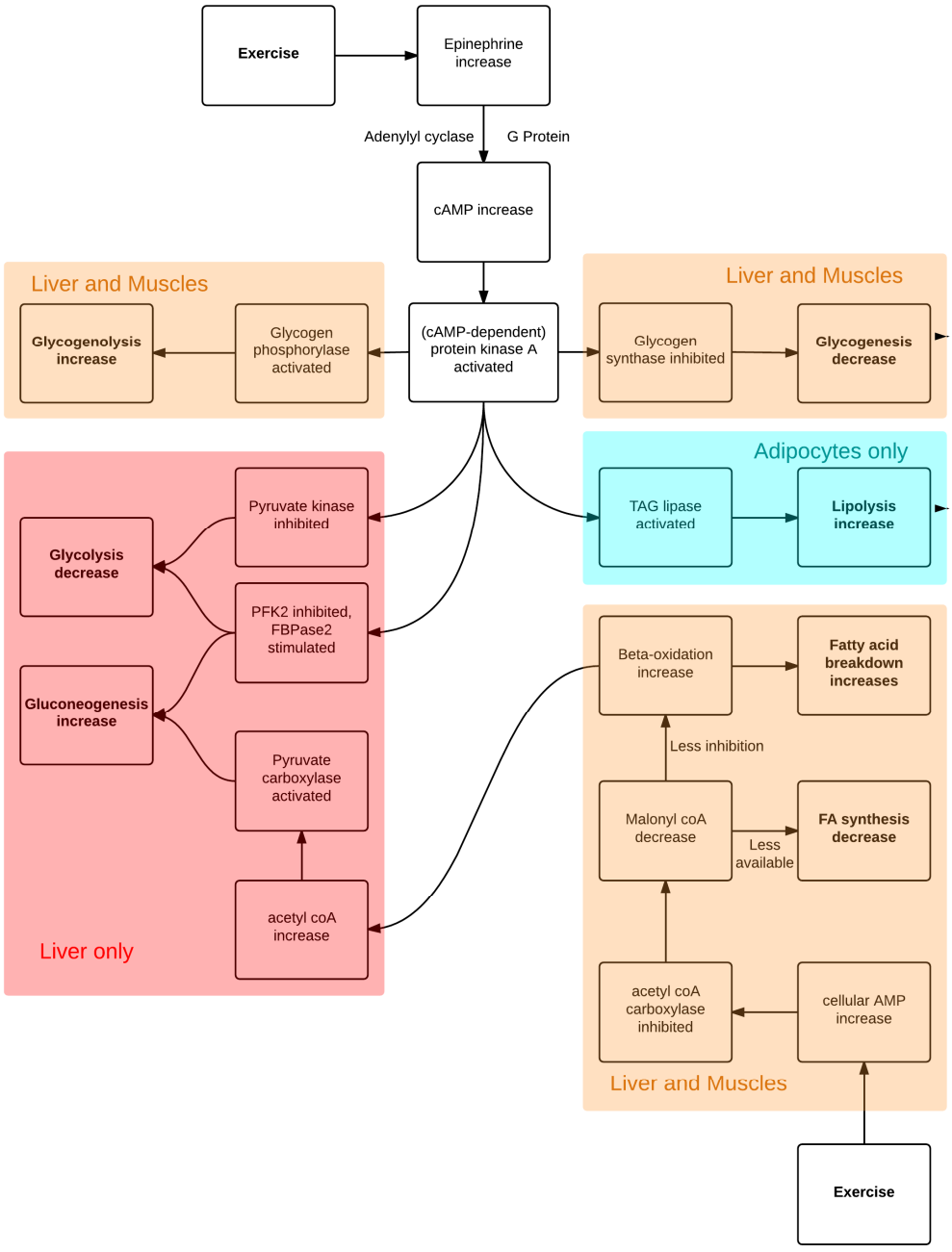
## A. Metabolic Integration

- **Metabolic integration**: interconversion of fuel metabolites to suit physiological demands
- Metabolic output can be regulated by enzyme at regulatory step through:
  - Synthesis and degradation
  - Allosteric regulation
  - Covalent modification
  - Proteolysis
- Metabolic pathway output usually regulated at <u>irreversible step</u> (eg glycolysis and gluconeogenesis)
- Interconversion of fuel metabolites:

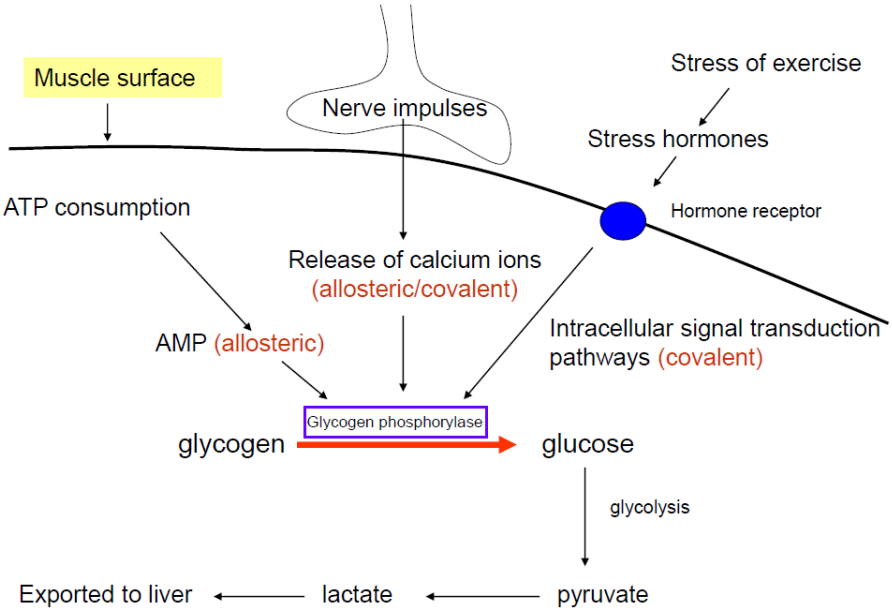


# B. Exercise State

- **Epinephrine** rises during exercise → G protein pathway activated → adenylyl cyclase activated → cellular cAMP↑ → protein kinase A activated (i.e. cAMP-dependent PK) → relevant enzymes phosphorylated → changes in cellular metabolic reactions:
  - Lipolysis ↑ FA synthesis ↓
  - Glycogenolysis↑ glycogenesis ↓
  - Glycolysis ↓ (↑ in cardiomyocytes) glyconeogenesis ↑
- Metabolic integration during exercise:



- Regulation of glycogenolysis can also be performed in other ways:




*Epinephrine also stimulates release of $Ca^{2+}$ (from cytosol) through $IP_3$ signaling for glycogenolysis (via protein kinase C pathway)

- **Glucose-alanine (Cahill cycle)**
  - Transaminase removes amino group from AA to form α-keto acid for energy/gluconeogenesis
  - Amino group transported to liver by alanine
  - Amino group disposed of as urea and glucose regenerated by gluconeogenesis from pyruvate
- Facilitation of anaerobic respiration by **Cori cycle**
  - Lactate generated by anaerobic respiration in muscles (releases ATP)
  - Lactate transported to liver and reconverted into glucose via gluconeogenesis (requires ATP)
  - Result: muscle ATP expenditure relocated to liver

# 1. Fuel Consumption in Different Exercise Intensity

- Heavy burst of energy:
  - ATP (muscle)
  - Phosphocreatine (muscle)
  - Glycogen (muscle) → glycogenolysis → glucose → glycolysis → ATP
- Moderately intense activity:
  - ATP
  - Phosphocreatine
  - Muscle glycogen (aerobic respiration involving oxidative phosphorylation)
- Less intense but prolonged activity:
  - Glycogen (liver)
  - AAs (muscles) via glucose-alanine cycle
  - FAs (adipose tissues)

*Note expts show that human cannot rely 100% on FAs

# C. Fed State

- **Insulin** increases (while glucagon drops) → signal transduction pathway → changes in metabolism
  - Glycolysis ↑ (by ↑F2,6$P_2$ and activation of pyruvate kinase)
  - Gluconeogenesis ↓ (by ↑F2,6$P_2$ and inhibition of PEP carboxykinase)
  - Glycogenolysis ↓ (by inhibition of glycogen phosphorylase)
  - Glycogenesis ↑ (by stimulation of glycogen synthase)
  - FA synthesis ↑
  - Lipolysis and FA breakdown ↓(by inhibition of adipose tissue lipase and of transport of FAs into mitochondria for β-oxidation)
  - Muscle protein breakdown ↓

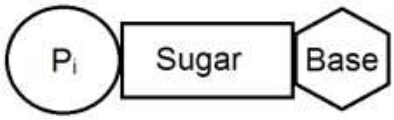
# D. Fasting State

- Main concern: fuel has to be provided without depletion of blood glucose (affect anerobic respiration + water potential) → FAs, AAs and ketone bodies used
- **Glucagon** increases (while insulin drops) → G-protein pathway activated → adenylyl cyclase activated → cAMP level ↑ → PKA activated → phosphorylation of a variety of metabolic enzymes → change in metabolism
  - Glycolysis ↓ (by ↓F2,6$P_2$ and inhibition of pyruvate kinase)
  - Gluconeogenesis↑ (by ↓F2,6$P_2$ and activation of PEP carboxykinase)
  - Glycogenolysis ↑ (by stimulation of glycogen phosphorylase)
  - Glycogenesis ↓ (by inhibition of glycogen synthase)
  - FA synthesis ↓
  - Lipolysis and FA breakdown ↑ (by activation of TAG lipase and ↓ malonyl coA reducing inhibitory effect on lipolysis)
  - Muscle protein breakdown ↑
- Consequence:
  - ↑ β-oxidation → acetyl coA accumulates
  - PEP carboxykinase activated → OAA converted to PEP → OAA↓
  - Acetyl coA↑ + OAA↓ → TCA cycle cannot handle all acetyl coA → acetyl coA rerouted to Ketogenesis pathway → ketone bodies generated
  - ↑acetyl coA → pyruvate carboxylase ↑ → pyruvate rerouted to gluconeogenesis pathway to form OAA

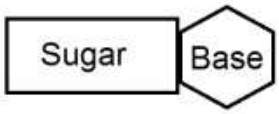
# L15 Nucleotide Metabolism

## A. Structure of Nucleotides and Variants

- **Nucleotide**: phosphate + 5-C sugar + nitrogenous base
  - Number of phosphates bound to nucleoside can vary from 1-3 to store different amounts of energy

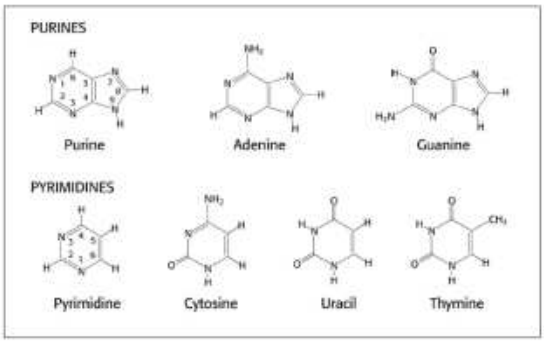



Nucleotide

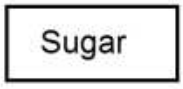


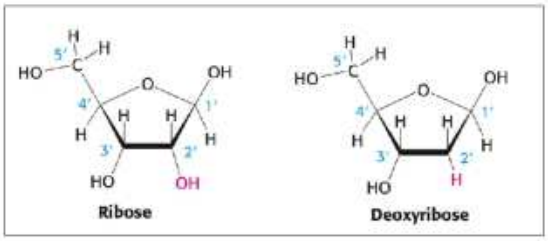

Nucleoside

- **Nucleoside**: 5-C sugar + nitrogenous base
  - Adenosine, thymidine, uridine, guanosine, cytidine

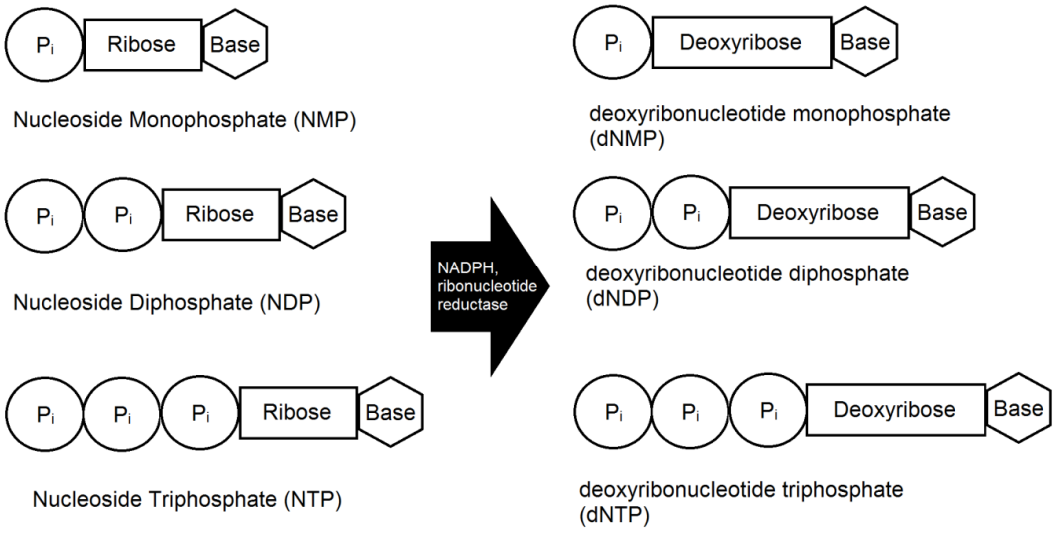




- Two types of bases:
  - Purine: two rings (A,G)
  - Pyrimidine: one ring (C, T, U)
- Two types of sugars:
  - Ribose: used in RNA
  - Deoxyribose: used in DNA



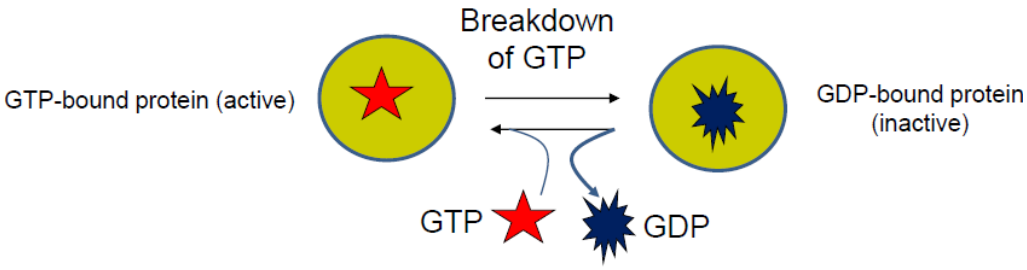




- **Nucleic acid**: polymer of nucleotides
- Nucleotides can also have added complexities for different functions:
  - **Nicotinamide adenine dinucleotide ($NAD^+$)**: Nicotinamide + $2P_i$ + adenosine
  - **Flavin adenine dinucleotide (FAD)**: riboflavin + $2P_i$ + adenosine
  - **Coenzyme A**: β-mercaptoethylamine + pathothenic acid + 3'-P-ADP
  - **UDP-glucose**: Glc + $2P_i$ + uridine (facilitate glycogen formation)




# B. Functions of Nucleotides

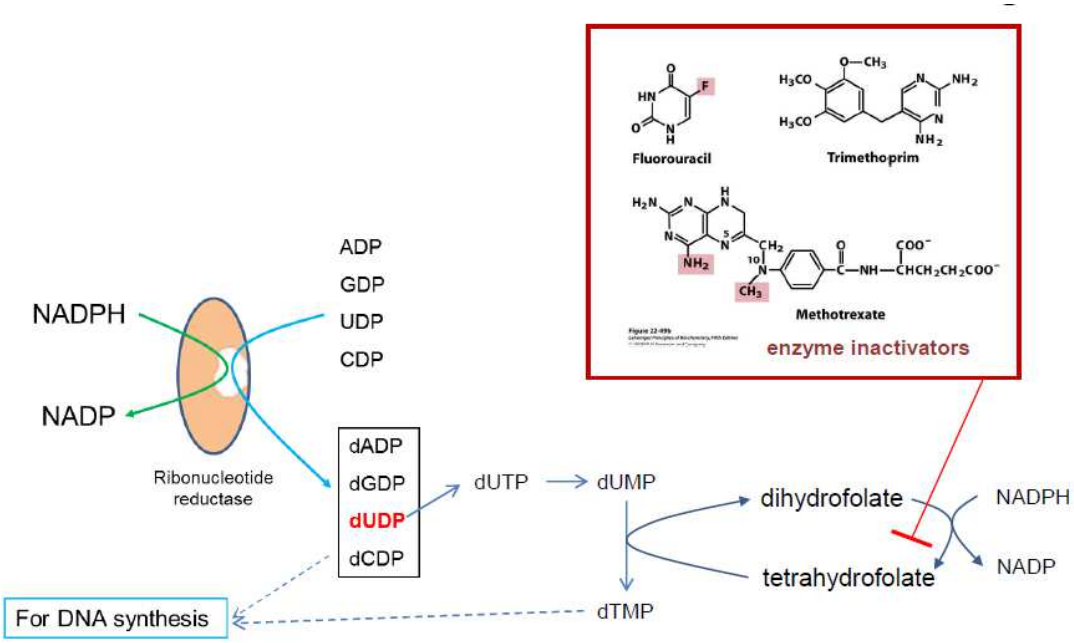
1) Metabolic work: Nucleotides switch from high energy form to low energy form to release energy for metabolic work;
2) Hormone-like molecules: adenosine receptor found in many cells: cardiomyocytes, neutrophils, endothelial cells, macrophages etc;
3) Molecular timers: GTP-bound protein is switched off by conversion into GDP-bound protein → can act as enzyme regulator




4) Synthesis of nucleic acids:
   RNA from NTP via RNA polymerase (transferal of genetic info)
   DNA from dNTP via DNA polymerase (preservation of genetic info)

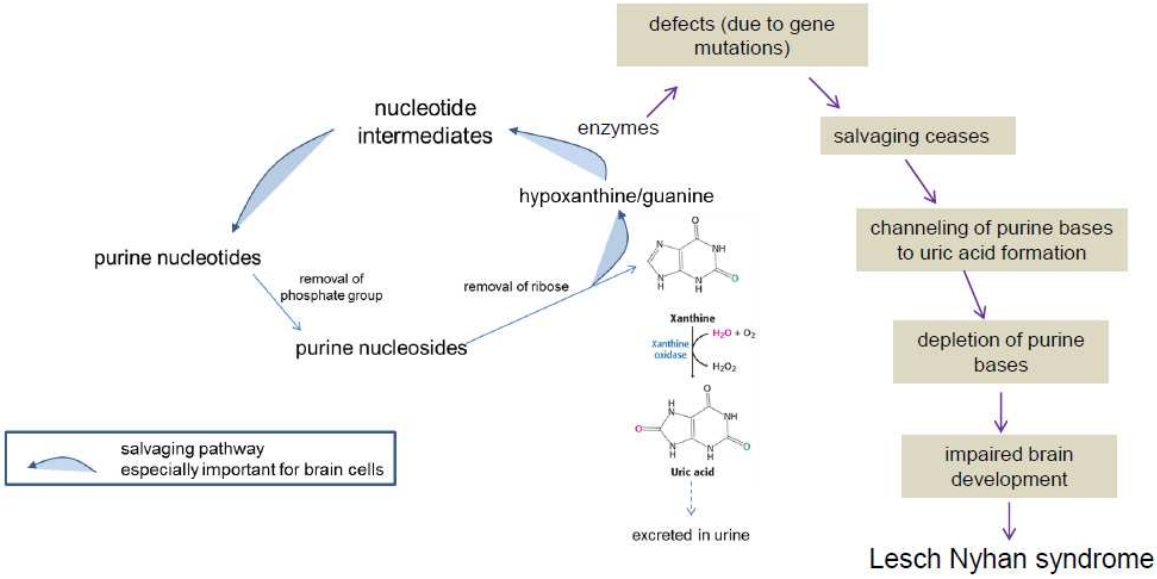
# C. Metabolism of Nucleotides

- **Supply of high-energy forms**: NDP/dNDP receives a $P_i$ from ATP (sometimes GTP) to form NTP/dNTP
- **Supply of deoxyribonucleotides**: NDP are converted to dNDP using ribonucleotide reductase and NADPH
- **Supply of dTMP**: from dUMP using tetrahydrofolate




*Anti-cancer drugs target regeneration of tetrahydrofolate → dTMP cannot be produced → DNA cannot be synthesized → cell division inhibited

- **De novo synthesis**: nucleotide synthesized by body from other substrates
  - 5-C sugar from glucose
  - Nitrogenous base synthesized from AAs and other nutrients
  - Metabolically costly (need ATP and other nutrients)
- **Purine nucleotide metabolism**: purine nucleotides degraded to uric acid and secreted → continuous loss of nucleotides
  - Salvaging pathway in place to recycle nucleotides
    → Brain relies heavily on salvaging pathway to maintain homeostasis (since de novo synthesis activity is low in brain)
  - When faulty → depletion of purine bases → impaired brain development → Lesch Nyhan syndrome



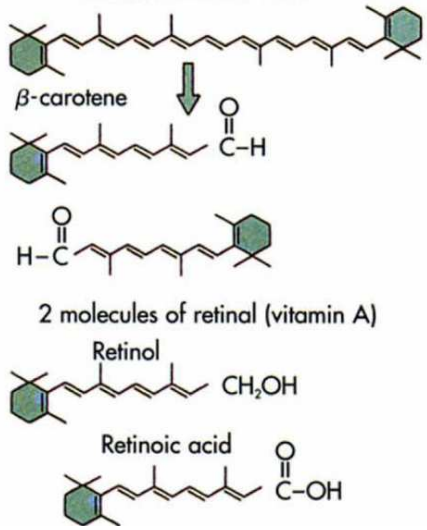
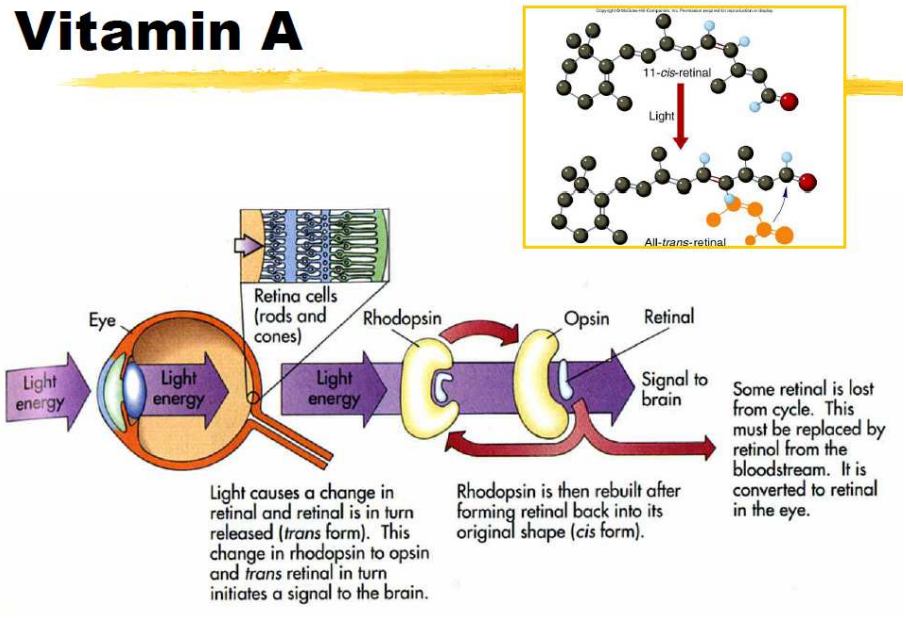

  - Also note when uric acid excretion is inefficient → uric acid accumulates in circulation → uric acid crystals form at joints → **gout**

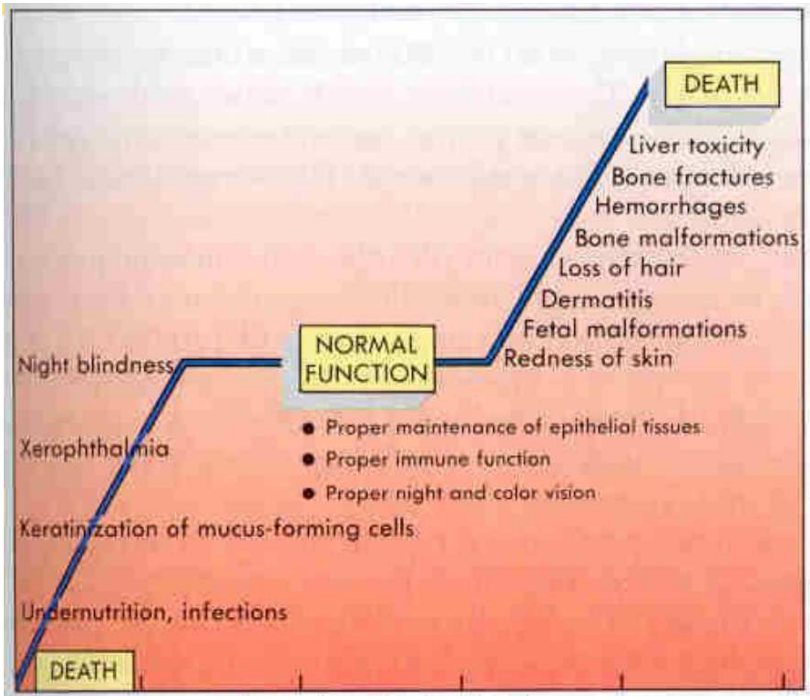
# L16 Nutrition: Vitamins and Minerals

## A. Vitamins

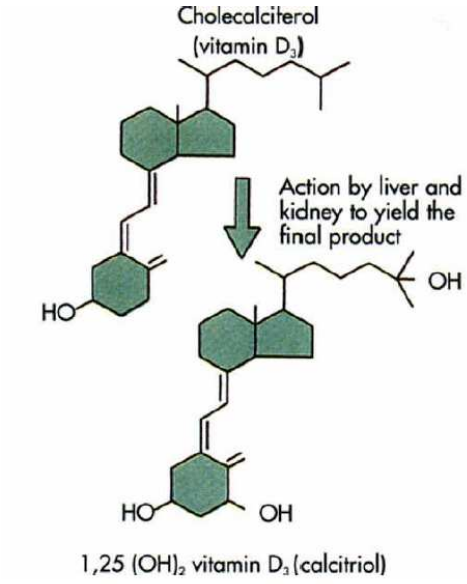
- **Vitamins**: naturally occurring organic molecules which are required in small amountsfor the normal health and functioning of the human body and must be provided in the diet
- Types:
  - Fat soluble: A, D, E, K
  - Water soluble: $B_1$, $B_2$, $B_3$ (niacin), $B_5$ (pathothenic acid), $B_6$, $B_9$ (folic acid), $B_{12}$, C
- Deficiency:
  - Possible causes:
    - → Inadequate intake
    - → Malabsorption due to disease states
    - → Increased tissue needs (eg pregnancy, fever, diabetes)
    - → Inborn errors of metabolism (causing altered enzyme affinity for coenzyme)
  - Usually lead to characteristic symptoms (**hypovitaminosis** / **hypervitaminosis**)

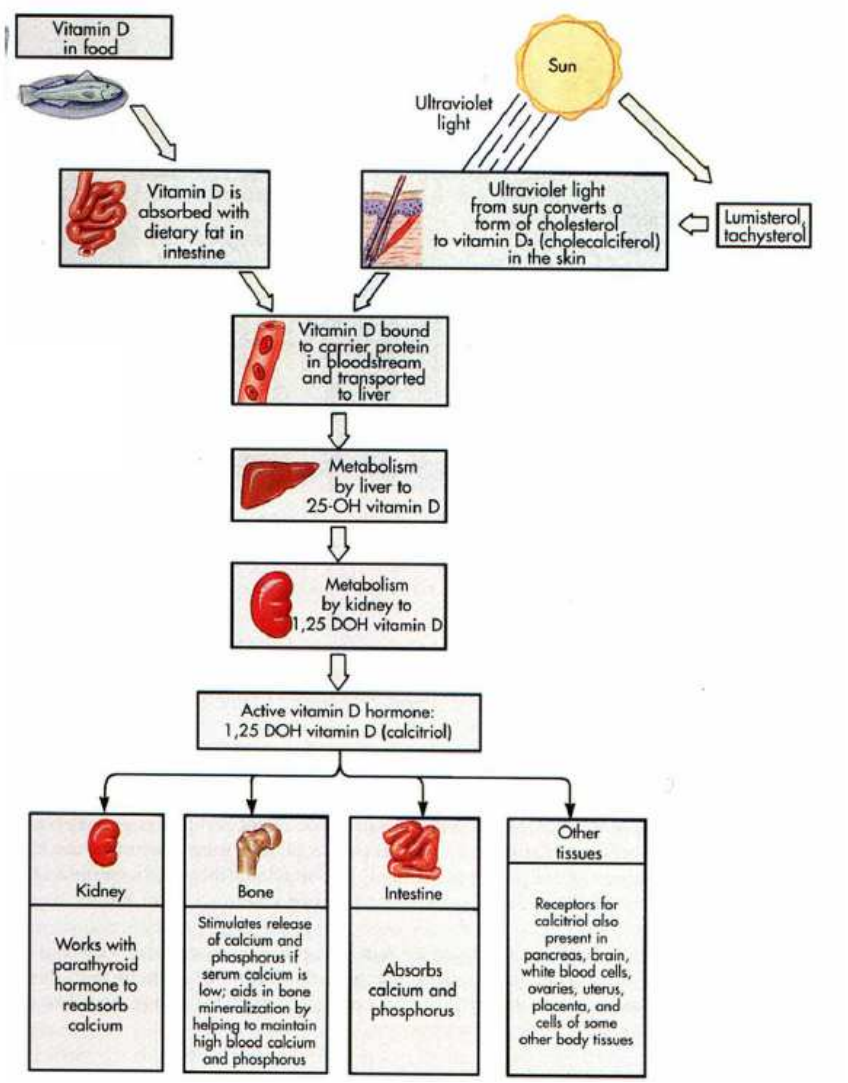
# 1. Vitamin A

| | |
|---|---|
| Definition | A group of chemicals including retinol, retinal, retinoic acid and few carotenoids that aids in retina detection of light |
| Structure |  |
| Function | **Retinal** is an essential light-sensitive molecular component of rhodopsin pigment (visual purple) [photopsin in cones] in the photoreceptors on the retina. Light changes retinal from *trans* form to *cis* form, leading to its release and a subsequent nerve signal to the brain:<br>  <br>**Retinoic acid** also serves as a hormone-like growth factor for epithelial and other cells. |

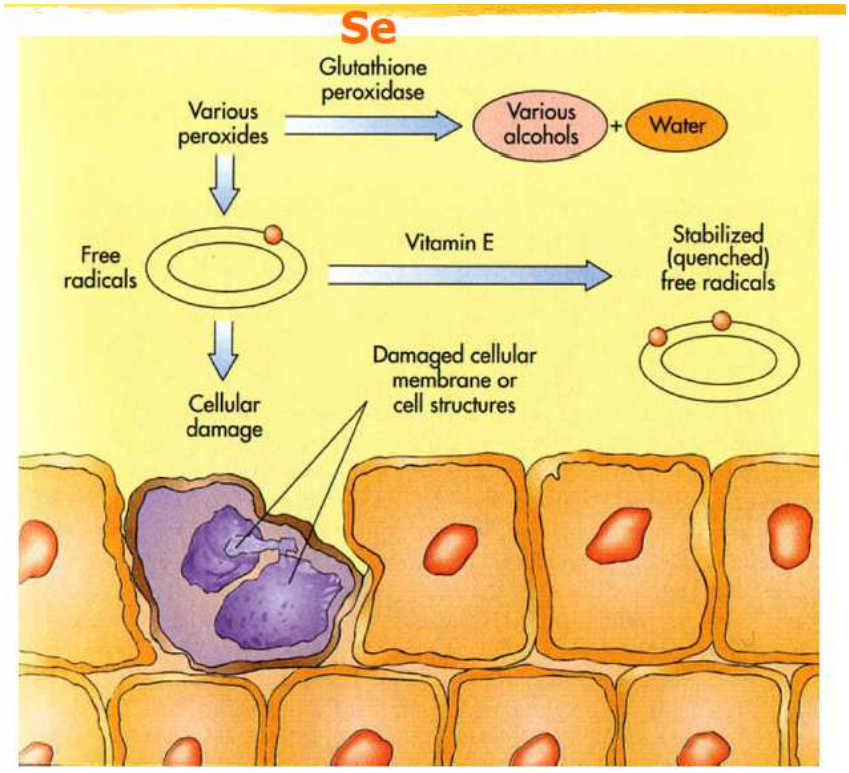
| | |
|---|---|
| Deficiency / excess |  <br>*Xerophthalmia: failure to produce tears by eyes |

# 2. Vitamin D

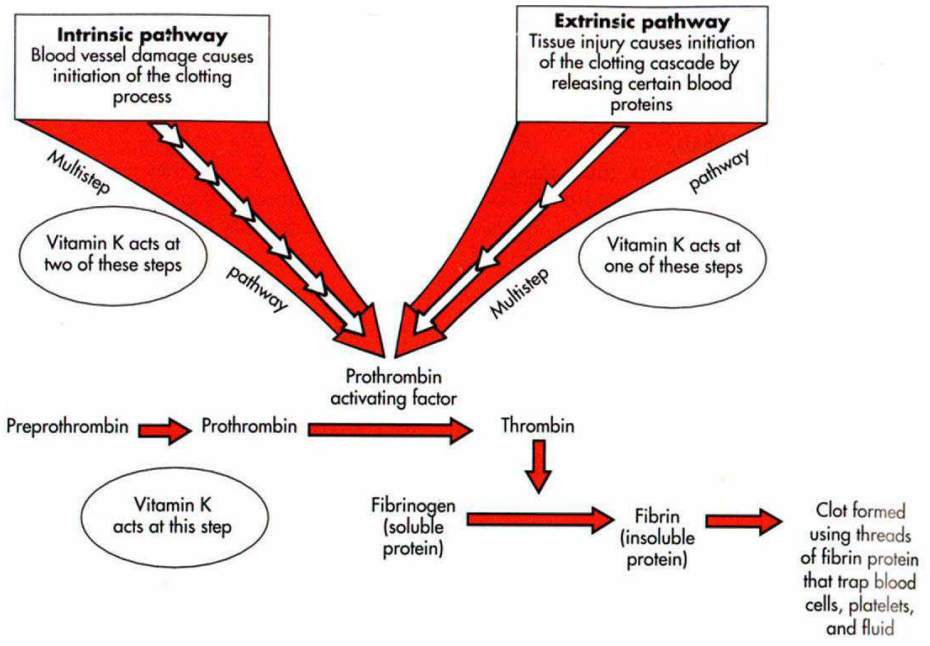
| | |
|---|---|
| Definition | A group of chemicals that promotes intestinal absorption of several minerals especially calcium and phosphate. |
| Structure |  |

| | |
|---|---|
| Function | Mediates (stimulates) $Ca^{2+}$ and $PO_4^{3-}$ absorption from intestine and deposition in bones (together with parathyroid hormone PTH)<br>  <br> |
| Deficiency / excess | Deficiency: rickets syndrome in children, **osteomalacia** in adult<br>*Rickets syndrome: poor bone mineralization before closure of epiphyseal plate<br>*Osteomalacia: bone softening due to inadequate $Ca^{2+}$ and $PO_4^{3-}$. |

# 3. Vitamin E

| | |
|---|---|
| Definition | A group of chemicals (including tocopherols) that protects biological membranes from oxidative damage |
| Structure | α-tocopherol |
| Function | Normally, $O_2$ is reduced as in $O_2 + 4e^- + 4H^+ \rightarrow 2H_2O$.<br>When there is not enough $e^-$, $O_2$ is not fully reduced → reactive oxygen species (ROS) formed (eg $.O_2^-$, .O)<br>Vitamin E helps provide $e^-$ for reduction of ROS:<br>ROO. + TocOH → ROOH + TocO.<br>ROO. + TocO. → ROOH + non-free radical product<br>*Note that ROO. is lipid peroxide, ROOH is its non-reactive form and TocO. is relatively stable radical<br>  <br><br>*Selenium (Se) is a cofactor for glutathione peroxidase |
| Deficiency / excess | Deficiency: skin diseases especially over-sensitivity to light<br>Deficiency is uncommon (rice is rich in vit E), secondary deficiency may be due to malabsorption or liver diseases |

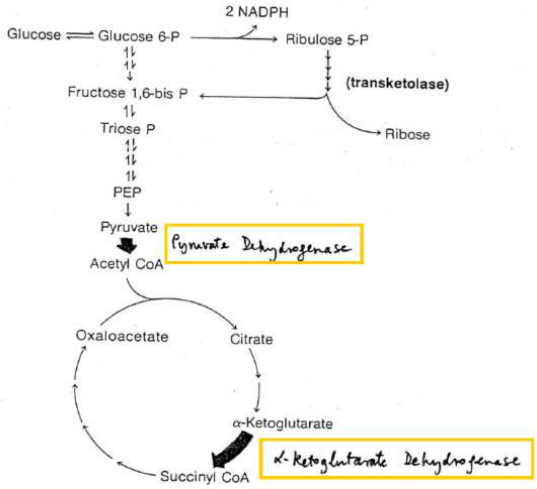
# 4. Vitamin K

| | |
|---|---|
| Definition | A group of chemicals (including phylloquinone) that is needed for blood clotting |
| Structure | phylloquinone |
| Function | Vitamin K is required for the synthesis of blood coagulation factors II (prothrombin), VII, IX and X by the liver<br>  <br><br>Also involved in carboxylation of glutamyl residues<br>(Gla is required in some clotting factors in clotting cascade) |
| Deficiency / excess | Deficiency: hemorrhagic disease in newborn |

# 5. Vitamin B

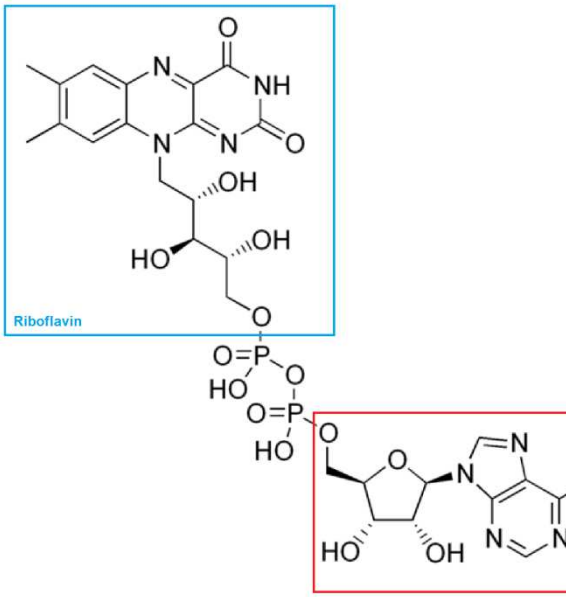
## a. Vitamin $B_1$ (thiamin)

- **Thiamin pyrophosphate (TPP)**: coenzyme of **pyruvate dehydrogenase** and **α-ketoglutarate dehydrogenase**, also activates **transketolase** (in PP pathway)




## b. Vitamin $B_2$ (Riboflavin (FMN))

- **Flavin adenine dinucleotide (FAD)**: Riboflavin + $2P_i$ + adenine




- Used as redox cofactor in cell metabolism (especially in electron transport chain)

## c. Vitamin $B_3$ (niacin, nicotinic acid)

- Derived to form nictotinamide ($+NH_2$) and then $NAD^+$ or $NADP^+$ as redox cofactors in cell metabolism

## d. Vitamin $B_6$ (pyridoxal phosphate and derivative)

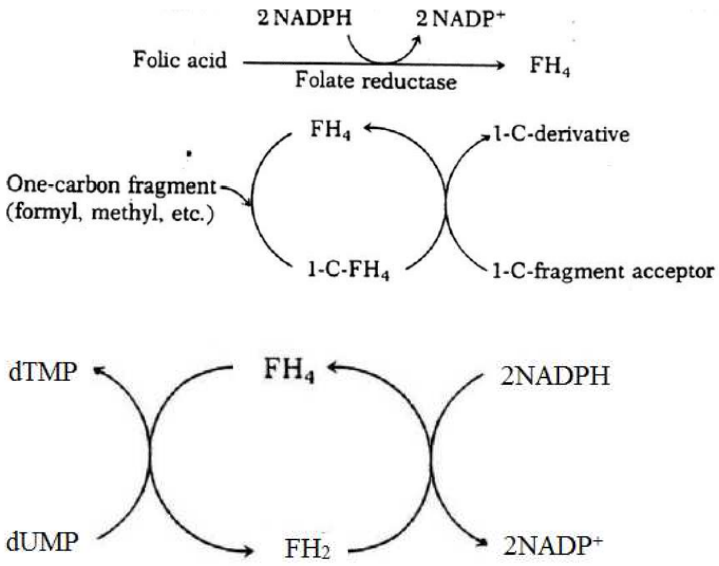
- **Pyridoxal 5'-phosphate**: cofactor for many enzymes in metabolism (incl. transaminase, biosynthesis of 5 important neurotransmitters and glycogen phosphorylase)
- Structure:

- Action:

## e. Vitamin $B_9$ (folic acid)

- Structure:

- Acts as a coenzyme for **transfer of 1-C units in synthesis of purines**, **thymidine**, **serine and methionine**
- Action:



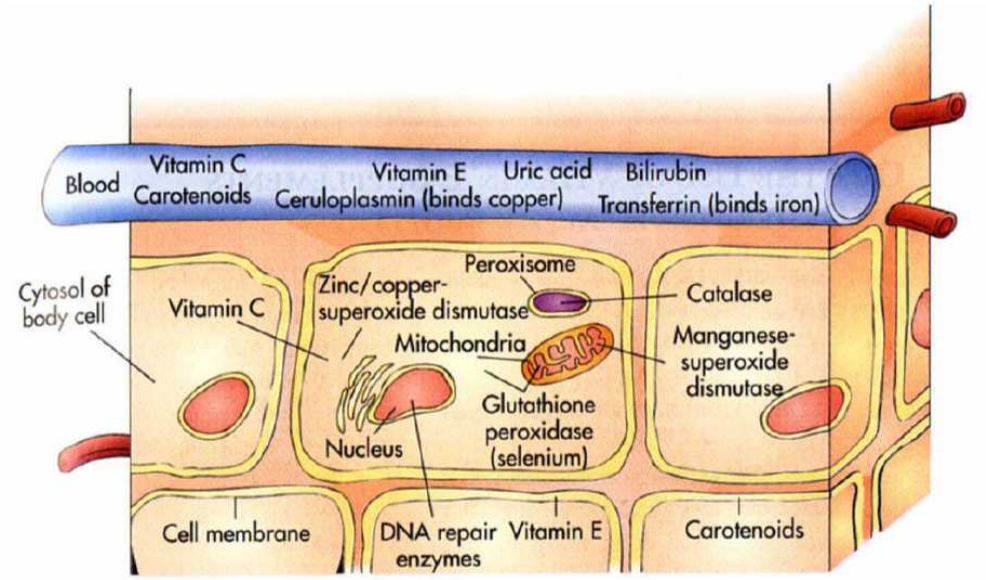

## f. Vitamin $B_{12}$ (cobalamin)

- Functions:
  - Intermediate in generation of methylated compounds (eg methionine, thymine)
  - Reducing ribonucleotides to deoxyderivatives
- Deficiency: pernicious anemia
  - Reduction in erythrocyte formation
  - Disorders in GI tract and nervous system

# 6. Vitamin C (ascorbic acid)

- Function:
  - Hydroxylation of proline in collagen synthesis → connective tissues
  - Degradation of tyrosine
  - Synthesis of epinephrine from tyrosine
  - Bile acid formation
  - Absorption of iron
  - Water-soluble free radical scavenger (due to reducing property)
- Deficiency: **scurvy**
  - Inability to form stable collagen → connective tissue weakness
  - Bleeding of mucous membrane, spongy gums, brown spots on skin

*Various types of antioxidants in body:



# B. Minerals

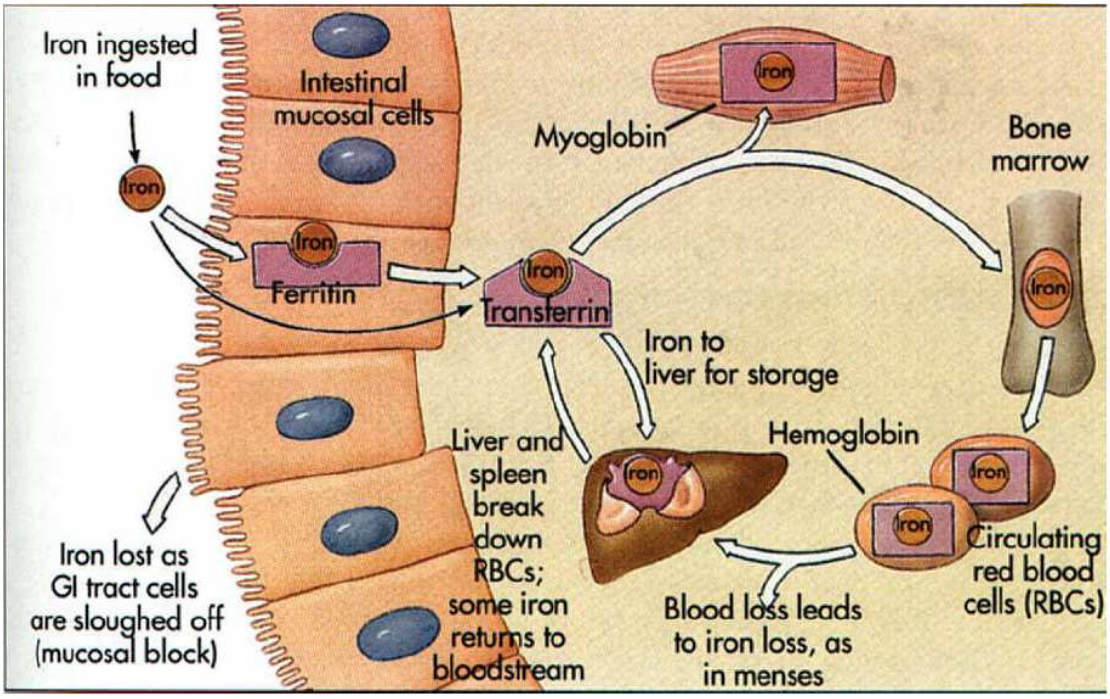
- Requiring >100mg/day:
  - For tissue structures: Ca, P
  - For cellular/ECF: Na, K, Mg
- Requiring a few mg/day:
  - Enzyme activators, prosthetic group of proteins: Fe, Cu, Zn, F, Mn
- Requiring a few μg/day:
  - Regulatory or catalytic processes: I, Se, Mo

# 1. Calcium

- Functions:
  - Structural: important component of bone
  - Important regulator of intracellular processes:
    - → Muscle contraction
    - → Ca-dependent intracellular signaling processes, eg protein kinase C
    - → Blood clotting
- Deficiency:
  - Osteomalacia due to inadequate $Ca^{2+}$ and vitamin D (more susceptible in pregnant woman)
  - Osteoporosis: complete loss of bone tissue in small areas within the bones → porous and brittle bones

# 2. Iron

- Functions: a wide range of functions connected with **oxidative reaction**
  - **Oxygen uptake** in haemoglobin and myoglobin
  - **Electron transport** in cytochromes and ferridoxins
  - **Activation of oxygen**: oxidases and oxygenases
  - **Activation of nitrogen**: nitrogenases
- Proteins for iron transport and storage:
  - Ferritin
    - → Stores iron as mobile, diffusible fractions
    - → May hold up to 4500 molecules of ferric ions
    - → Greatly elevated in iron overload
  - Transferrin
    - → Essential for efficient distribution of iron
    - → Plasma concentration rises in iron deficiency




# 3. Sodium

- Functions:
  - As an electrolyte
  - Maintain osmotic balance of body fluid
  - Maintain electrophysiological state of cells
  - Conduction of nerve impulse
- Deficiency: muscle cramps, nausea, vomiting, dizziness, shock and coma
- Excess: risk of hypertension

# L17 Cell Membrane Transport

## A. Plasma Membrane

- **Cell membrane** separates intracellular fluids from extracellular fluids
- Note that many substances occur at very different concentrations across cell membranes → selective permeability and transport of substances helps maintain the gradient for survival
- Selective permeability regulates **type** and **rate** of molecule traffic into and out of the cell
- Note that $H_2O$ **can** pass through phospholipid bilayer because it is small enough to squeeze through between phospholipid molecules

## B. Transmembrane Transport

### 1. Physical Transport

- Does not require a living cell nor outside energy
- Example: passive diffusion, osmosis

#### a. Passive Diffusion

- **Diffusion**: random movement of molecules from a higher to a lower concentration until equilibrium is reached
- A passive process for molecules to travel across a membrane
- No energy and special proteins
- Non-polar and lipid-soluble substances diffuse directly through the lipid bilayer
- Small lipid-insoluble substances diffuse through channel proteins

#### b. Osmosis

- **Osmosis**: diffusion of water across a <u>semi-permeable</u> membrane
- **Osmolarity**: total concentration of solute particles in a solution (in osmole/L)
- **Osmolality**: total concentration of solute particles in a solution (in osmole/kg)
- **Tonicity**: osmotic property of a solution (isotonic, hypotonic, hypertonic)

# 2. Biological Transport

- Requires a living cell and can either be active (against conc. gradient) or passive
- Example: facilitated diffusion, active transport, endocytosis and exocytosis

## a. Facilitated Diffusion

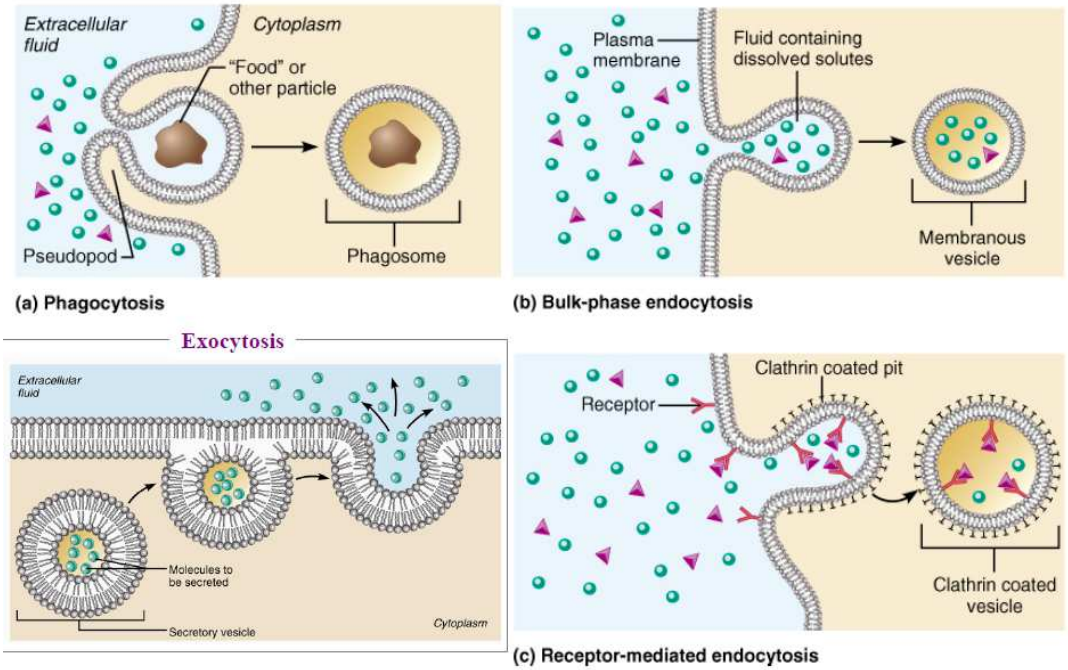
- Diffusion of large, polar molecules (eg simple sugars) across the cell membrane using protein carriers

## b. Active Transport

- Use of ATP to move solutes across a membrane with protein carriers
- **Primary active transport**: transport substances by conformational change of protein carrier with energy from hydrolysis of ATP (eg $Na^+/K^+$ pump)
- **Secondary active transport**: transport substances by conformational change of protein carrier with energy from electrochemical gradient (energy from bring an ion 'downhill') (eg $Na^+$/Glc symport transporter)
- Direction of transport:
  - **Symport system**: two substance ares moved across a membrane in the <u>same</u> direction
  - **Antiport system**: two substances are moved across a membrane in <u>opposite</u> directions
- Example: $Na^+/K^+$ pump:

## c. Vesicular Transport

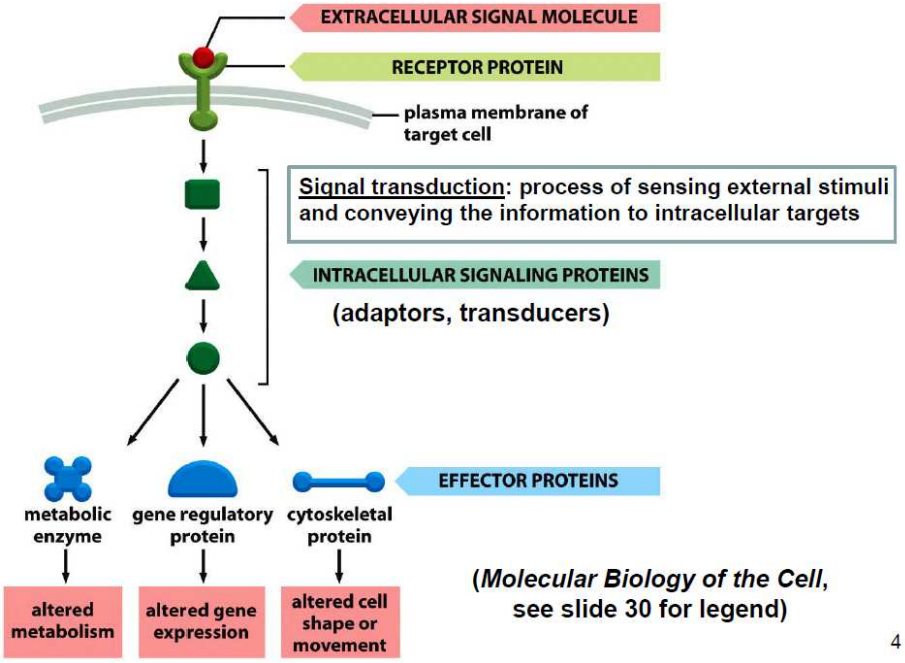
- **Vesicular transport**: Transport of large particles and marcomolecules across plasma membranes using vehicles
- **Exocytosis**: vesicular transport of large particles OUT of the cell
  - Examples: neurotransmitter release, hormone and mucus secretion
- **Endocytosis**: vesicular transport of large particles INTO the cell
  - Examples: macrophages and WBCs (phagocytosis), absorption of nutrients (bulk-phase endocytosis)
- **Receptor-mediated transport**: uses clathrin-coated pits as major mechanism for specific uptake of macromolecules
  - Examples: iron, insulin, enzyme, LDL absorption



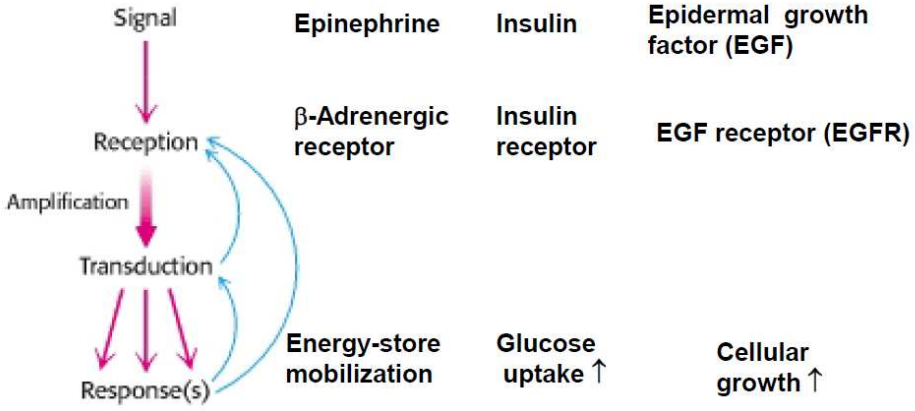

- Endocytosis often followed by fusing of **phagosome** with **lysosome** for digestion

# L18 Intracellular Communication: Signal Transduction

## A. Overview on Signal Transduction




- Three steps of signal transduction:
  - Ligand-induced receptor conformation change
    - → Receptor dimerization
  - Information-relaying by second messengers
    - → cAMP
    - → DAG/$PI_3$
    - → $Ca^{2+}$
  - Regulatory changes in metabolism
    - → Protein phosphorylation
    - → Protein ubiquitination
    - → GTP binding

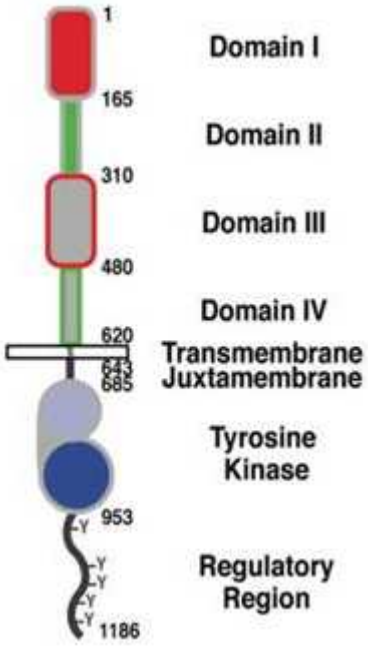



(***Biochemistry*** **6th ed; see slide 30 for legend)**

1) Release of signaling molecule → 2) Reception → 3) Signal transmission and amplification (second messengers) → 4) Activation of effectors → 5) Termination of signal (feedback inhibition)

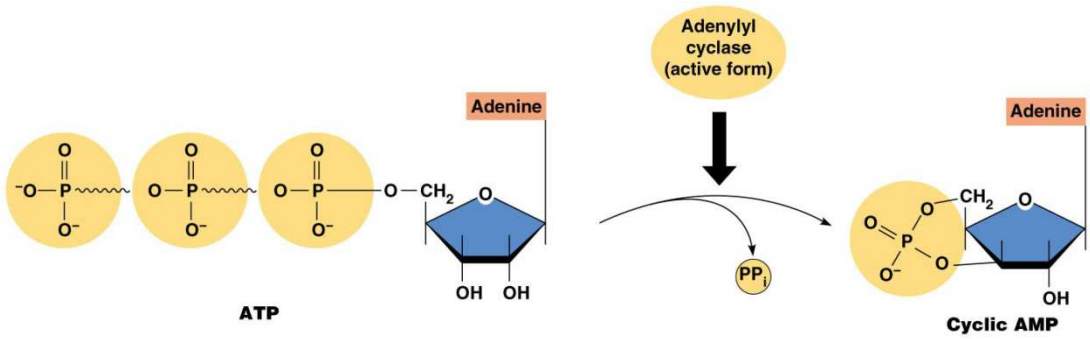
# 1. Ligand-induced receptor conformation change

- Ligand binding drives receptor to the active conformation (eg by dimerization)
- Example: ligand-induced dimerization of EGFR (EGF: epidermal growth factor)
  - Dimerization allows Tyr kinase to phosphorylate Tyr (Y) residues on each other
  - Phosphorylated Tyr domains can bind SH2 domains of downstream proteins → cellular growth
  - Clinical application: **trastuzumab** (monoclonal antibody) blocks EGFR dimerization
    → ↓cellular growth signals
    → target for cancer treatment



# 2. Second Messengers

- Concentration of second messengers can increase (or decrease occasionally) in response to ligand binding to receptor → diffuse to regulate activities of proteins at a distance
- Examples: cAMP, cGMP, DAG, $IP_3$ and $Ca^{2+}$
- Formation of cAMP (by adenylyl cyclase from ATP):




- Formation of DAG and $IP_3$ (by phospholipase C (PLC) from $PIP_2$, a minor component of phospholipid bilayer):

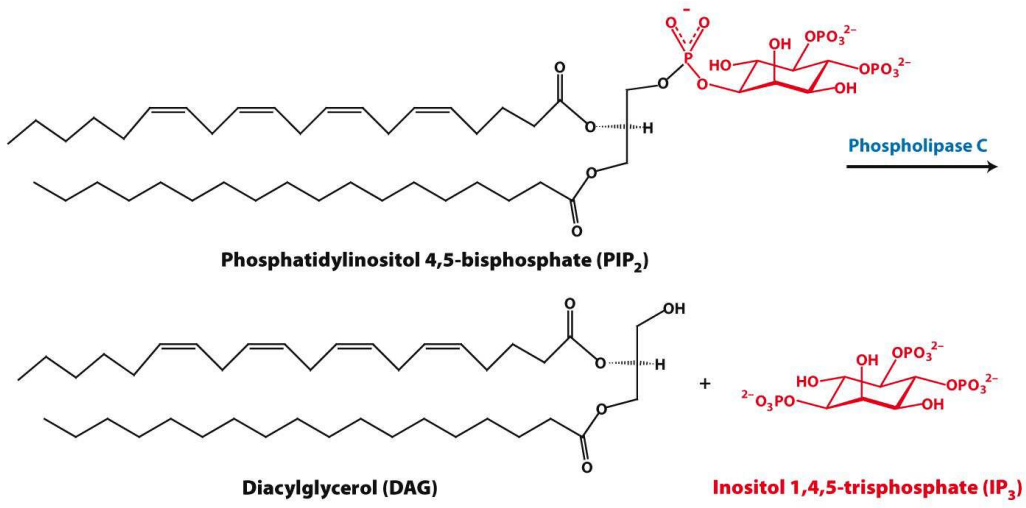



**Figure 14.12**
***Biochemistry*, Seventh Edition**

# 3. Metabolic Regulation Mechanisms

## a. Protein Phosphorylation (and Dephosphorylation)

- A phosphate group ($P_i$) is added to a hydroxyl-containing AA residue (i.e. Ser, Tyr, Thr) to modify its activity
- Catalyzed by **protein kinase** and **protein phosphatase**
- Source of $P_i$ usually from ATP to compensate for large $\Delta G$ of phosphorylation
- Can take place in less than a second or over a span of hours
- A single activated kinase can phosphorylate many target proteins → highly amplified effect
- Kinase inhibitors can be used to understand and treat human diseases
- Example: Bcr-Abl tyrosine kinase
  - Normally well-regulated
  - Mutant form is always activated → unregulated cell division → cancer
  - Bcr-Abl inhibitor Imatinib blocks ATP binding to Bcr-Abl kinase → anti-cancer effect
- Example: EGFR tyrosine kinase receptor
  - Normally important in cell cycle, cell proliferation/maturation, apoptosis, angiogenesis and metastasis regulation
  - Constitutively activated in many cancers due to mutations (EGFR level regulated by ubiquitination)
  - Tyrosine kinase inhibitors that blocks ATP binding sites can be used to treat cancer patients with mutated EGFR gene
  - EGFR signaling can also be inhibited by monoclonal antibodies

## b. Ubiquitination

- **Ubiquitin** (a protein) is used to 'mark' protein for proteolysis
- A few ubiquitin subunits form a chain and attach on proteins (polyubiquitination)

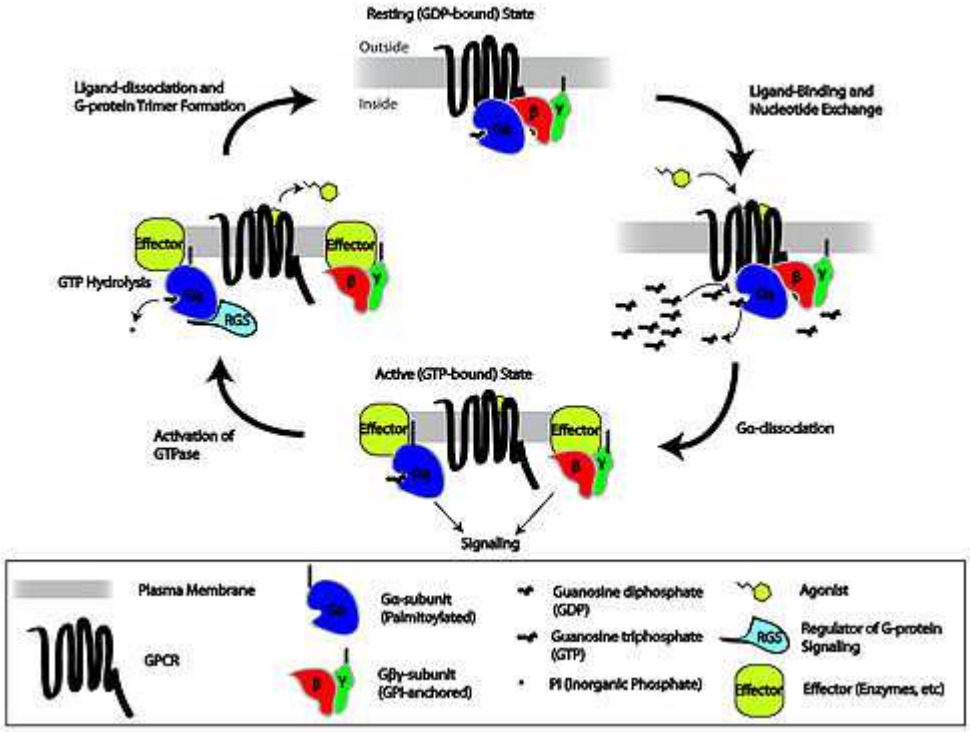
## c. GTP binding

- GTP-bound proteins switch between an active state when GTP is bound and an inactive state when GDP is bound
- **Activation** is achieved by **GTP binding** while **inactivation** is achieved by **hydrolysis of the bound GTP unit**
- Example: Ras GTP-bound protein
  - Ras signaling regulated by GTP binding
  - Mutant Ras in cancer constitutively binds GTP but not GDP

# B. G-Protein Coupled Receptor Pathways

- **G-protein coupled receptor (GPCR)**: important class of receptors that binds G-proteins
- **G-protein**: GTP-binding proteins responsible for acting as molecular switches
  - Has Gα, Gβ and Gγ subunits
  - Gα subunit: the GTP-binding part
  - Gβ and Gγ subunits usually associated together

## 1. Main Mechanism




1) Primary ligand binds to GPCR → Gα releases GDP and acquires a new GTP;
2) GTP-Gα and G-βγ subunits detach from GPCR;
3) GTP-Gα and G-βγ subunits bind to transmembrane intracellular effectors to produce downstream effect;
4) Gα soon hydrolyzes GTP into GDP → inactivation → re-association with Gβγ;
5) G protein recombines with GPCR → activated if ligand is still present.

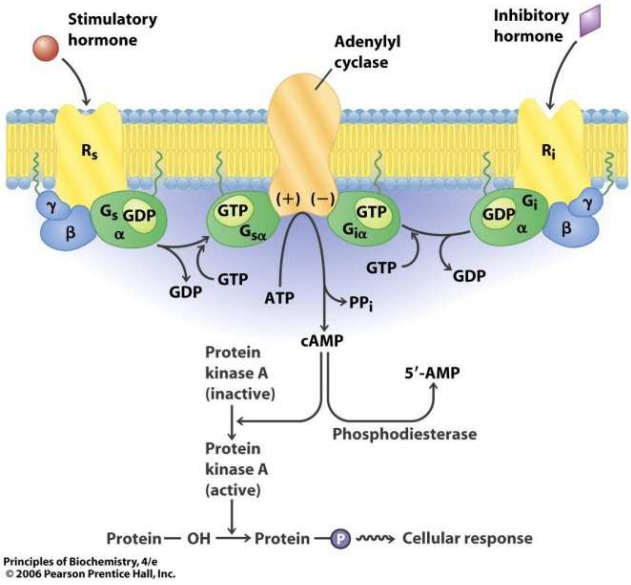
# 2. Main Classes of GPCRs and Their Effects

- Three main classes of GPCR: **Gs** (stimulatory), **Gi** (inhibitory) and **Gq**

## a. Action of Gs Proteins

- Mechanism:

1) Activation of Gs-associated receptors causes Gsα subunit to activate **adenylyl cyclase**;
2) Adenylyl cyclase converts cytosolic ATP into cAMP (and pyrophosphate);
3) cAMP binds to and activates **protein kinase A (cAMP-dependent protein kinase, PKA)**;
4) PKA phosphorylates a variety of downstream target proteins to produce cellular effects;




5) cAMP is then converted by **phosphodiesterase** into 5'-AMP to prevent constitutive activation.

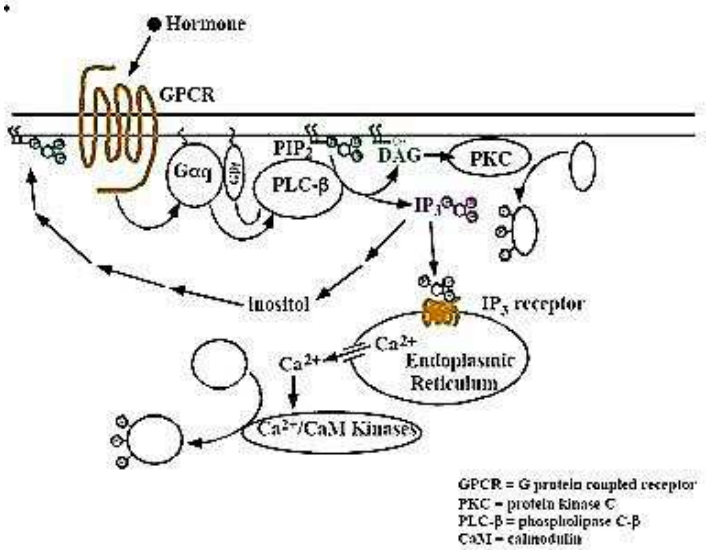
- Example: β-adrenergic receptor
- Downstream targets of PKA:
  - **L-type $Ca^{2+}$ channels** in cardiac muscles → <u>stimulatory</u>
  - **Myosin light chain kinase (MLCK)** in smooth muscles → <u>inhibitory</u>
  - **Phosphorylase kinase** which goes on to phosphorylate **glycogen phosphorylase** → <u>stimulatory</u>

**Note that although both smooth muscle and striated muscle contraction are controlled by intracellular calcium levels, smooth muscles lack the troponin complex found in striated muscles and thus rely on **MLCK** (activated by calcium-calmodulin complex) for calcium-dependent contraction.*

## b. Action of Gi Proteins

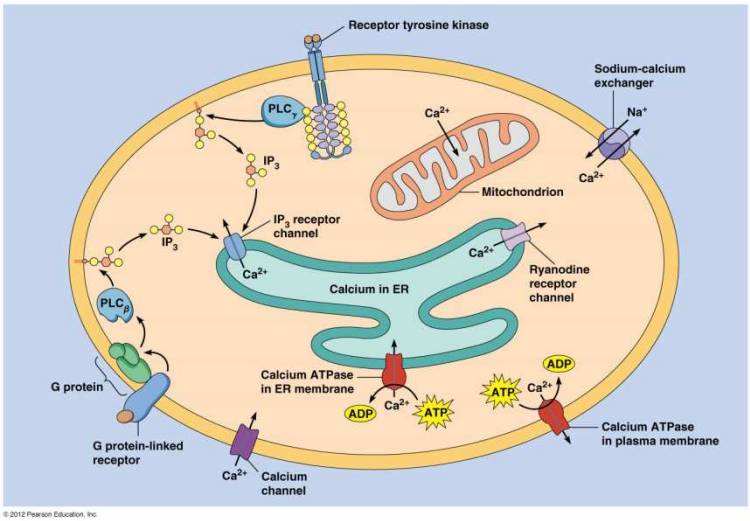
- Giα subunit binds to and <u>inhibits</u> adenylyl cyclase action → ↓cAMP
- Examples: $\alpha_2$-adrenergic, $M_2$ and $M_4$ muscarinic

## c. Action of Gq Proteins




- Mechanism:

1) Gqα subunit activates **phospholipase Cβ (PLCβ)**;
2) **PLCβ** cleaves $PIP_2$ on plasma membrane into $IP_3$ (released) and DAG (membrane-bound);
3) $IP_3$ binds **$IP_3$ receptor** at ER
   → $Ca^{2+}$ release from ER stores;
4) DAG activates downstream **protein kinase C (PKC)** which phosphorylates downstream protein for cellular effects.




- Example: $\alpha_1$ adrenergic (vascular smooth muscles), $M_1$, $M_3$ and $M_5$ muscarinic
- Intracellular calcium level is normally tightly controlled by **SERCA** (at SR) and **$Na^+/Ca^{2+}$ exchange (NCX)**
  - **RyR** binds calcium and causes Ca-induced Ca release from SR
- Increase in cytosolic $Ca^{2+}$ leads to $Ca^{2+}$ binding with **calmodulin** to form **calcium-calmodulin complex**
  → binds downstream protein kinases and phosphatases to produce effects
- Examples of Ca-CaM targets:
  - **MLCK** in smooth muscles → main mechanism for sm contraction control
  - **NO synthase** in endothelium → NO production → diffuse to vascular sm → activates guanylyl cyclase → ↑cGMP → protein kinase G activated → smooth muscle relaxation

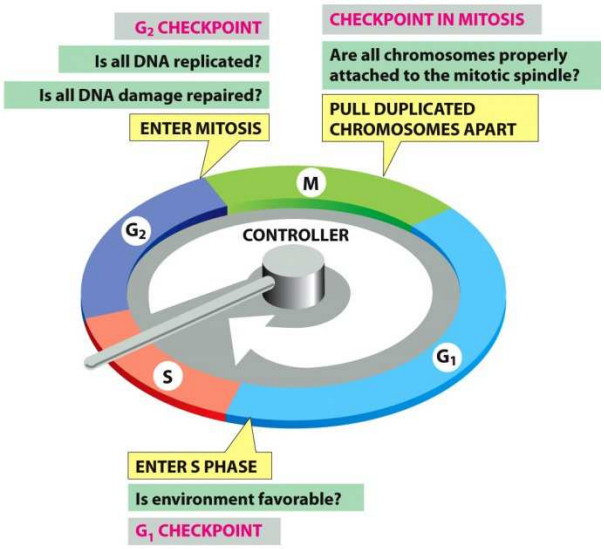
# L19 Cell Proliferation – Cell Division Cycle

## A. Cell Proliferation

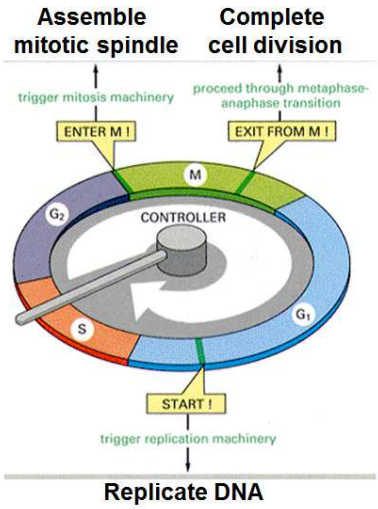
- ~$10^{14}$ cells in the body developed from one cell (zygote)
- Note various irreversible changes in cells during development:
  - Differentiation: Cells become more differentiated i.e. specialized during development
    - → **Cell potency**: Ability of differentiation into other cells
    - → During development, totipotent → pluripotent → limited potential
  - Proliferative: cells become less proliferative
- In adult,
  - Cell lost or died = cells reproduced → natural turnover with no net ↑ in cell number
  - Cells replaced by differentiated progeny (offspring) of proliferative stem cells
    - → Intestinal cells, WBCs: ~3-5 days, continuous regeneration
    - → Skin cells: 2-4 weeks, continuous regeneration
    - → RBCs: ~4 months, continuous regeneration
    - → Brain cells: slow loss with little regeneration
- Cancer results from genetic alterations that lead to abnormal regulation of cell divisions:
  - Benign tumour: excessive proliferation in defiance of normal constraints, remain clustered
  - Malignant tumour: invasive and colonize other sites

## B. Cell Cycle

- Cyclic process with defined events (phases) happening in a fixed sequence: $G_1 \rightarrow S \rightarrow G_2 \rightarrow M \rightarrow G_1 \rightarrow \ldots$
  - $G_1$, $G_2$ (gap): preparative stages, cell growth
  - S (synthesis): DNA replication
  - M (mitosis): nuclear division and cytokinesis
- **Interphase**: $G_1 + S + G_2$



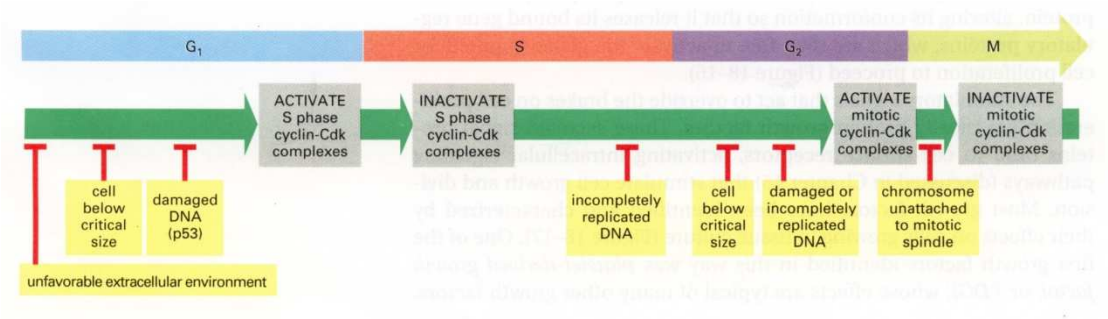
# 1. Checkpoint System for Cell Cycle




- Specific points along cell cycle can be stopped upon sensing of unfavourable signals
- Examples of unfavourable signals:
  - Intrinsic: cell size, DNA damage, extent of DNA replication, proper alignment of chromosomes on mitotic spindle
  - Extrinsic: environmental signals (soluble factors or factors presented on cell surface)

# 2. Cyclin Control of Cell Cycle

- **Cyclins**: group of proteins that control the cell cycle through cyclin-dependent protein kinases (Cdks)
- **Cyclin-dependent protein kinases (Cdks)**: Catalytic subunits that require association with cyclins (regulatory subunits) to become active serine/threonine kinase
  - Cyclin binding confers substrate specificity to the kinases
- Different cyclin-cdk complexes are cyclically activated in a cell cycle phase-specific manner (cyclin levels fluctuate periodically) → phosphorylate different target proteins → regulates cell cycle
  - G1 cyclin-cdks (cyclin D-Cdk 4/6) phosphorylate pRb leading to transcription of cyclin E and other genes needed for DNA replication → enter S phase
  - S cyclin-Cdk (Cyclin E-Cdk2) further phosphorylates pRb to drive S phase entry (positive feedback)
  - M phase cyclin-Cdk (Cyclin B-Cdk1) phosphorylates nuclear lamins and other proteins → breakdown of nuclear envelop → M phase entry




- Regulation of Cdk activities:
  - Periodic synthesis (regulated transcription) and degradation (regulated proteolysis of cyclins
  - Phosphorylation/dephosphorylation by other kinases and phosphatases
  - Cdk inhibitors (CKIs): CIP/KIP and INK4 proteins that mediate DNA-damage checkpoint control
- Mutations of cell cycle regulators may lead to cancer

# L21 Thermoregulation

## A. Normal Body Temperature

- Body temperature is maintained at a stable level because temperature affects speed of metabolic reaction
- Balance between heat production and heat loss determines core body temperature
- Various parts of body set at different temperatures:
  - Core body temperature ($37^{o} \pm 0.5^{o}C$)
    - → Regulated by thermoregulatory mechanisms
    - → Displays **diurnal rhythm**: lowest in predawn hours and rises in the afternoon
    - → Rectal temperature is best representative of core temperature
  - Surface temperature
    - → Fluctuates widely in healthy adults depending on environmental temperatures
    - → Temperature of extremities cooler than rest of the body

## 1. Heat Gain

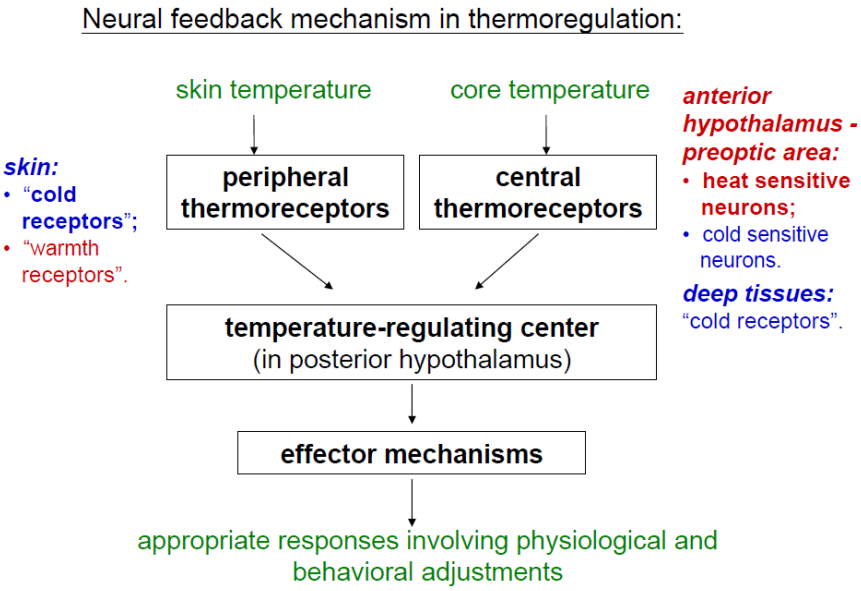
- Heat gain = heat production + heat transferred from environment
- Heat production from:
  - Basal rate of metabolism
  - Muscle activity including exercise or shivering
  - Extra metabolism by effect of thyroxine on cells
  - Extra metabolism by effect of epinephrine, norepinephrine and sympathetic stimulation on cells
  - Extra metabolism caused by increased temperature of body (due to heat gain from environment)
- Most heat produced generated in the deep organs → transferred to skin

## 2. Heat Loss

- Heat is loss from the skin by radiation, conduction, convection and evaporation of sweat (and insensible water loss)

# B. Body Temperature Regulation

- Temperature regulated by negative feedback mechanisms:
  - Control centre: temperature-regulating center in posterior hypothalamus
  - Receptors: peripheral thermoreceptors (cold/warm receptors on skin), central thermoreceptors (preoptic area in anterior hypothalamus




# 1. Temperature Sensors

## a. Thermoreceptors in Hypothalamus

- **Anterior hypothalamic-preoptic area** contains large numbers of heat-sensitive neurons and about a third as many cold-sensitive neurons
  - Heat-sensitive neurons ↑ firing rate when temp ↑
  - Cold-sensitive neurons ↑ firing rate when temp ↓
  - More sensitive to temperature↑ → initiates heat-losing mechanism
- **Posterior hypothalamus** contains cold-sensitive neurons
  - Temperature ↓ → initiates heat-conserving mechanisms

### b. Superficial and Deep Thermoreceptors

- **Skin** contains both cold and warmth receptors
  - Cold receptors ~10x warmth receptors → peripheral temp detection mainly concerns detecting coldness instead of warm temperatures
  - Rate of firing ∝ to both rate of change of temperature and steady-state temperature
  - Receptors unevenly distributed: particularly high density of cold-receptors on face (esp tip of nose) and hands
- **Deep thermoreceptors** present in certain part of body
  - Mainly in spinal cord, abdominal viscera, great veins
  - Function differently from skin receptors (exposed to core temperature)
  - Mainly detect cold rather than warmth
- Likely that both types are concerned with preventing hypothermia

## 2. Temperature-regulating Center

- Signals that activate the hypothalamic thermoregulatory center come:
  - Temperature-sensitive cells in the anterior hypothalamus
  - Peripheral temperature receptors, especially cold receptors
- Reflex effector mechanisms activated by **warmth** controlled primarily from **anterior hypothalamus**
- Reflex effector mechanisms activated by **coldness** controlled from posterior hypothalamus
- Temperature signals from preoptic area and peripheral thermoreceptors are integrated and compared to the set-point value in **posterior hypothalamus**, any difference → trigger heat-conserving/heat-losing mechanisms

## 3. Temperature-regulating Effector Mechanisms

### a. Response to Heat

- ↑**Heat loss**:
  - **Vasodilation of cutaneous arterioles** (by inhibition of sympathetic centers in posterior hypothalamus that causes vasoconstriction)
  - **Sweating**: increase heat loss by evaporation
- ↓ **Heat production**:
  - **Anorexia** (loss of appetite)
  - **Apathy** and **inertia** (inactivity)
- **Behavourial response**: changes in clothing, choice of surroundings, decrease voluntary activity

## b. Response to Coldness

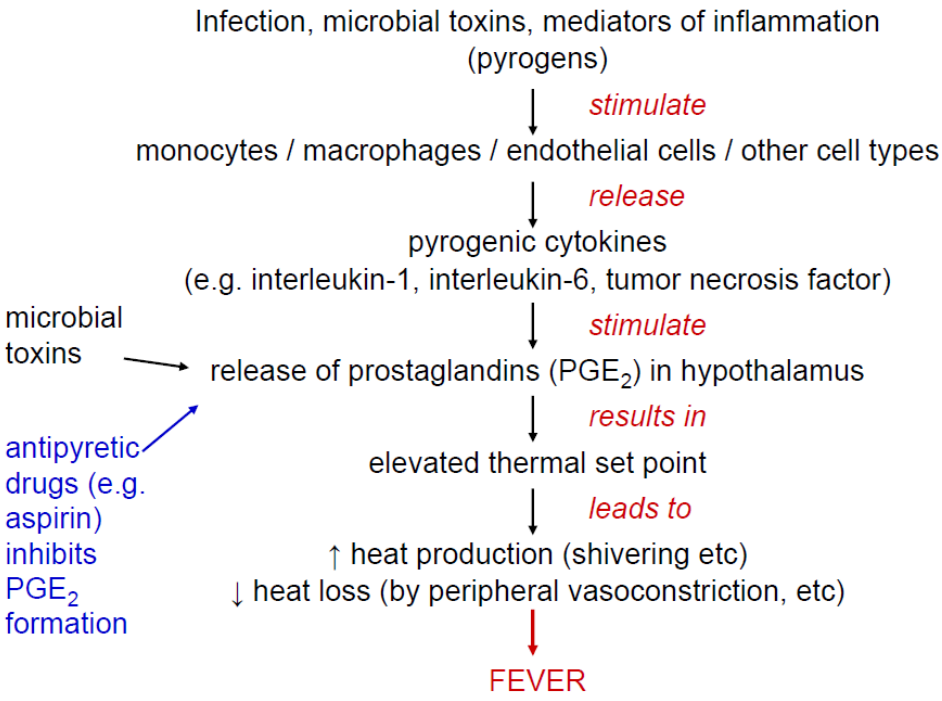
- ↓ **Heat loss**:
  - **Cutaneous vasoconstriction** (by stimulation of sympathetic centers
  - **Piloerection** (contraction of arrector pili muscles → piloerection → improves insulation)
- ↑ **Heat production**:
  - **Hypothalamic stimulation of shivering**:
    - → Primary motor centre located in dorsomedial portion of the posterior hypothalamus near the wall of the third ventricle
    - → Normally inhibited by heat center (in anterior hypothalamic-preoptic area), excited by cold signals from skin and spinal cord
    - → When body temp < critical temperature level → shivering center activated
    - → Signals transmitted through **bilateral tracts** down brain stem → **lateral columns** of spinal cord → **anterior motor neurons** → ↑ tone of skeletal muscles throughout body
    - → When tone > a certain critical level, shivering begins
    - → Body heat production can ↑ as high as 4-5x normal during max shivering
  - **Sympathetic 'chemical' excitation of heat production**:
    - → Chemical thermogenesis stimulated by increased sympathetic stimulation and circulating catecholamines (epinephrine, dopamine etc)
    - → In infants, brown fat mediated chemical thermogenesis
  - ↑ **thyroxine secretion**
    - → Long-term response (may take several weeks for thyroid gland to hypertrophy before reaching new level of thyroxine secretion)
    - → Exposure to cold → ↑TRH in hypothalamus → ↑TSH in pituitary → ↑thyroxine secretion by thyroid gland → ↑ cellular metabolic rate throughout the body

*Muscle tone: residual tension of muscle

**Thermoregulatory response mainly dominated by sympathetic nerve, no role by parasympathetic nervous system

# C. Fever

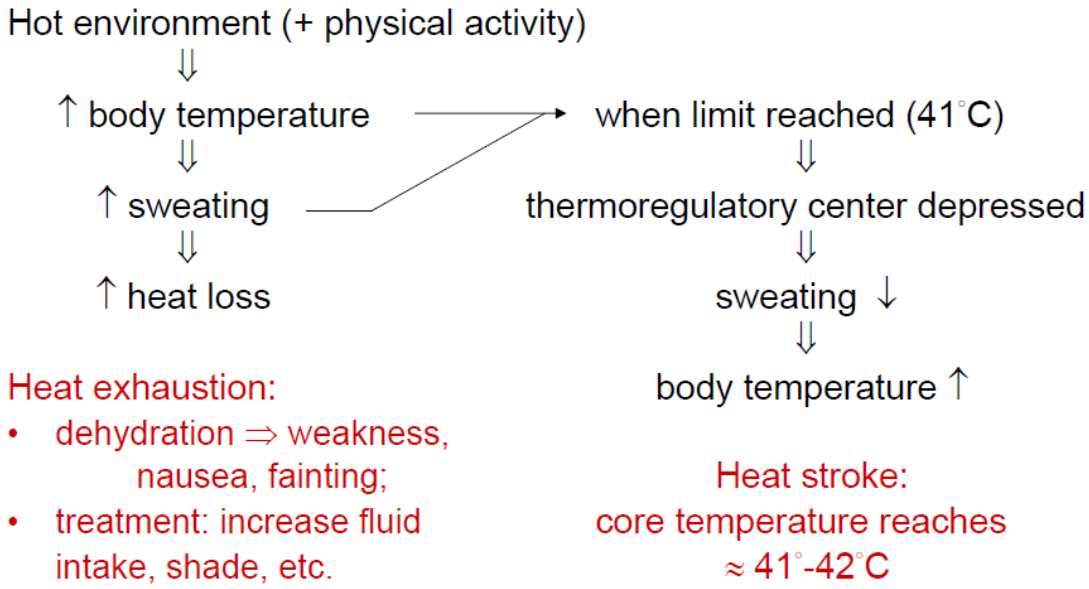
- **Fever (pyrexia)**: an increased body temperature caused by elevation in thermal set-point
- Mechanism of pyrexia:




- Note that since set point is raised in pyrexia, fever will result in **chills** and **rigors** (physical sign of shivering)
- Pulsatile release of pyrogenic cytokines may also lead to **sudden reduction of set-point** → feels hot, vasodilation, sweating
- **Crisis**: removal of pyrogen → ↓ thermal set-point → body effects responses to lose heat → **vasodilation** and **sweating**

# D. Hyperthermia

- **Hyperthermia**: increase in body temperature above thermal set-point
- Note difference in heat exhaustion and heat stroke:
  - **Heat exhaustion**: dehydration causing problems in negative feedback system (skin is moist)
  - **Heat stroke**: temperature limit reached → depression in thermoregulatory center → positive feedback (skin is dry)
    - → Strenuous physical exertion in high ambient temperature and humidity → profuse sweating and salt and water depletion
    - → Dehydration + ↓BP → ↓blood flow to kidneys, splanchnic (organs) and brain
    - → CNS symptoms: ↑ brain temp and ↓ cerebral blood flow → fatigue, confusion, unconsciousness




*Acclimatization to heat: body may get used to high temperature when lived in hot regions for a long time

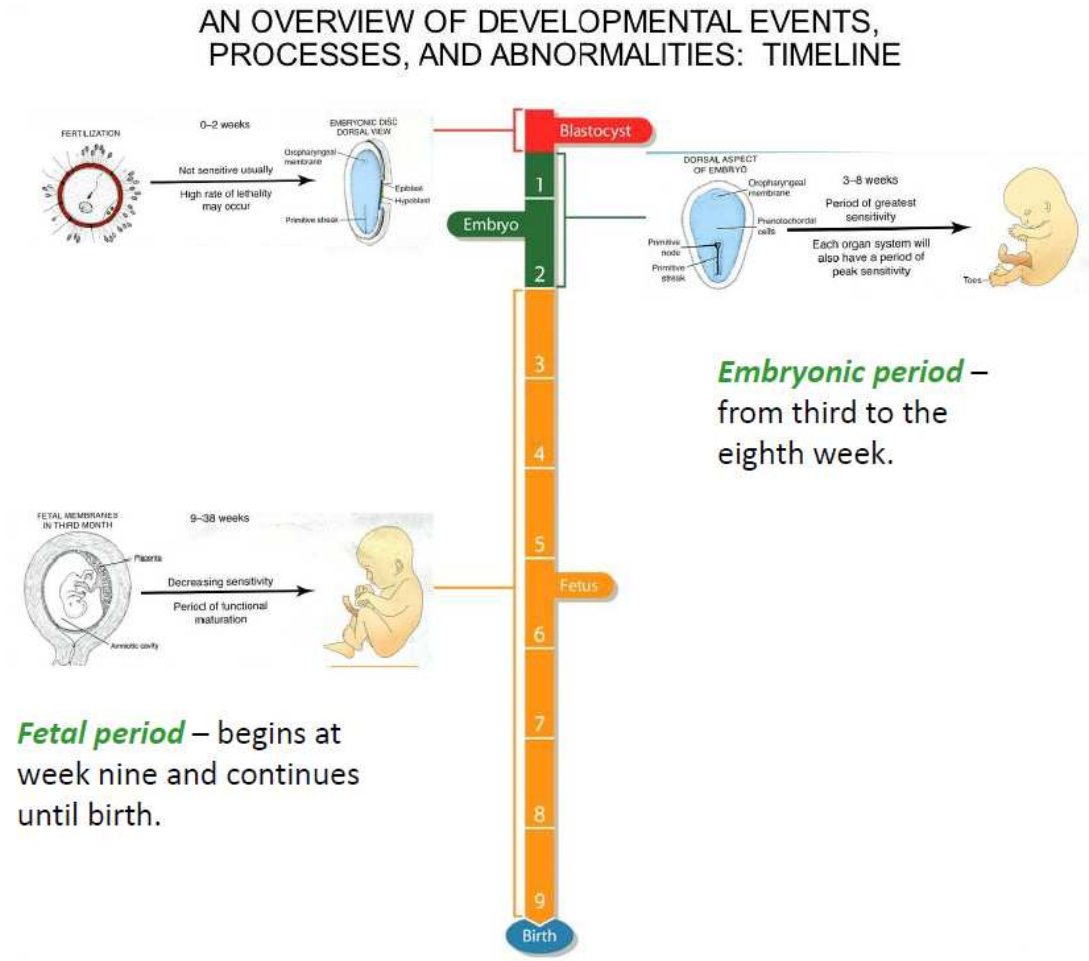
Physiological changes:

- ↑max rate of sweating
- ↑ plasma volume
- ↓ NaCl concentration in sweat and urine (due to ↑aldosterone secretion)

**Hypothermia: core temp <35$^{o}$C, lethal when core temp <32$^{o}$C (due to arrhythmia)

# L20, 22, 23 Embryology: Embryogenesis

## A. Overview on Prenatal Development




- **Clinical (gestational) age**: time since mother's last menstrual period (LMP)
- **Postovulatory age**: clinic age – 14 days
- Three stages:
  - **Germinal period**: week 1-2, formation of primitive germ layers
  - **Embryonic period**: week 3-8, organogenesis
  - **Fetal period**: week 9-38, organ systems grow and mature
- Three trimesters:
  - **First trimester**: period of embryonic and early fetal development, most critical stage, rudiments of the major organ systems appear
  - **Second trimester**: complete development of organ systems
  - **Third trimester**: rapid fetal growth (most of organ systems are fully functional during early stage of this period)

# 1. Gametogenesis

- Gametes derived from primordial germ cells (PGC)
- PGC in epiblast → yolk sac (2nd week) → gonads (4-5th week) → mitosis, stop at prophase (in yolk sac) → gametogonia (oogonia/spermatogonia)

## a. Oogenesis

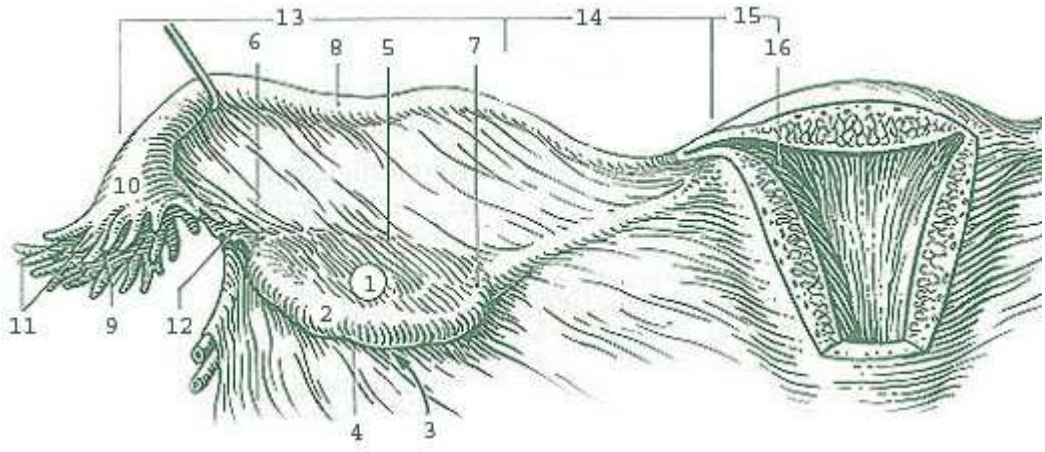
- **3rd moth of development**: oogonium → mitosis → primary oocyte → arrest at meiosis I prophase
- **First half of menstruation cycle**: primary oocyte → meiosis I → secondary oocyte + first polar body → arrest at meiosis II metaphase
- **Fertilization**: secondary oocyte → meiosis II → mature oocyte + second polar body
- Note oocyte surrounded by **corona radiata** (associated cells) and **zona pellucida** (tough barrier for sperms, belongs to oocyte)

## b. Spermatogenesis

- Entire process occurs after puberty
- Spermatogonium → mitosis → primary spermatocyte → meiosis I → secondary spermatocytes → meiosis II → spermatids → spermiogenesis → sperm
- **Spermiogenesis**: modification of round spermatids to produce functional (elongated) sperms
  - Loss of cytoplasm
  - Development of tail
  - Formation of acrosome (cap)

# B. Fertilization

- **Fertilization**: combination of genetic materials from <u>haploid sperm cell</u> and <u>haploid secondary oocyte</u> into a single diploid nucleus
- Site: ampullary region of uterine tube (#13 in figure)




- Functions:
  - Stimulate penetrated oocyte to **complete 2nd meiotic division**
  - **Restore diploidy**
  - **Initiation of cleavage** and **metabolic changes** in zygote
  - **Sex determination**
  - Confer **genetic variability** by random fertilization
- 3 phases of oocyte penetration:

1) Penetration of **corona radiata** by squeezing through by flagellum action
2) Penetration of **zona pellucida** by secretion of enzyme from acrosome
3) Fusion of cell membrane (of oocyte and sperm)

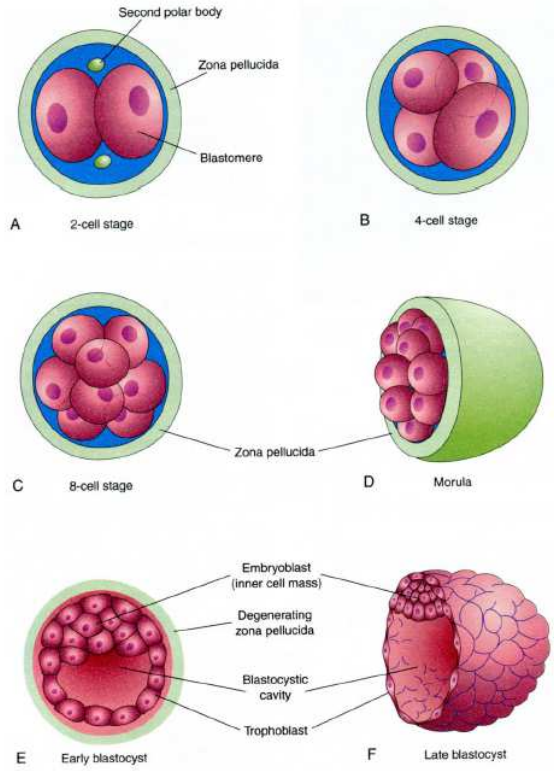
- Prevention of polyspermy:
  - **Cortical reaction**: cortical granules of oocyte release contents (hydrolytic enzymes and polysaccharides) upon first sperm penetration
  - **Zonal reaction**: contents released in cortical reaction hydrolyzes zonal sperm receptors and render zona pellucida impenetrable to other sperms
- Male and female pronuclei then fuse together to complete fertilization

# C. Cleavage

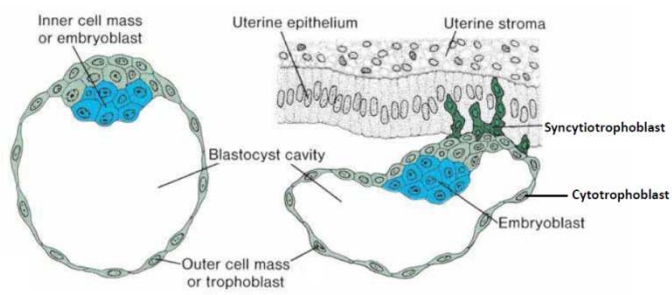
- **Cleavage**: Repeated cell division (mitosis) with little or no growth in early embryo
- Importance:
  - Restore normal cytoplasm : nucleus ratio (note oocyte C:N ratio is very large (to provide energy reserve) due to polar body formation)
  - Active transcription and protein synthesis
  - Changes from PP pathway (provide more building blocks eg nucleotides) to normal glycolytic pathway (also called **Embden Meyerhof pathway**, provide more energy)
  - Maternal recognition of pregnancy
  - Cell fate determination
- Cell becomes **morula** (a solid ball of ≥12 cells) and then undergoes **compaction** (formation of tight junction)

# D. Blastogenesis

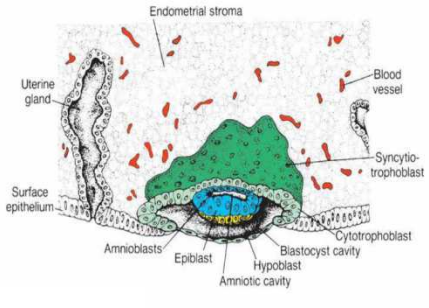
- Cell becomes **blastocyst** as zona pellucida disappears and embryo takes in fluid in oviduct to form a **blastocystic cavity**
- Separation of **blastomeres** (cells produced by cleavage) into two parts:
  - **Trophoblast**: thin outer cell layer, gives rise to **embryonic part of placenta**
  - **Embryoblast**: centrally located inner cell mass, gives rise to the **embryo**
- Shedding of zona pellucida allows blastocyst to increase in size



# E. Implantation




Blastocyst (4-5 Days) Implanting blastocyst (6 Days)



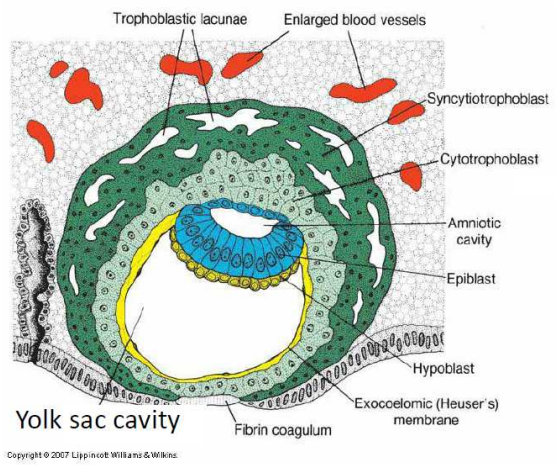

Implanted Embryo (7.5 Days)

- **Attachment phase**: increase in vascular permeability in area of **stroma** (connective supportive framework in organs) underlying the **conceptus** (embryo + associated structures), oedema, change in ECM composition
- **Invasion phase**: cytotrophoblast cells fuse together and erode adjacent endometrial tissues
- Two germ layers form: **epiblast** and **hypoblast**

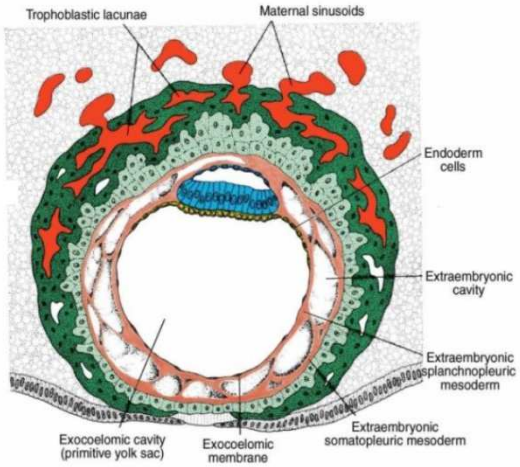
*If blastocyst attach elsewhere → **ectopic pregnancy** (pregnancy outside uterus)

Possible sites: intestinal **mesentery** (part of peritoneum that attaches organs onto peritoneum), oviduct, ampulla, **internal os** (internal narrowing of uterus at cervix) of uterus

# F. Formation of Bilaminar Germ Disk

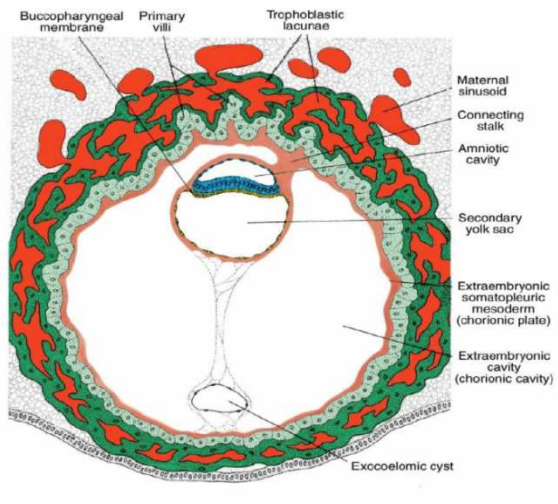



9 Days



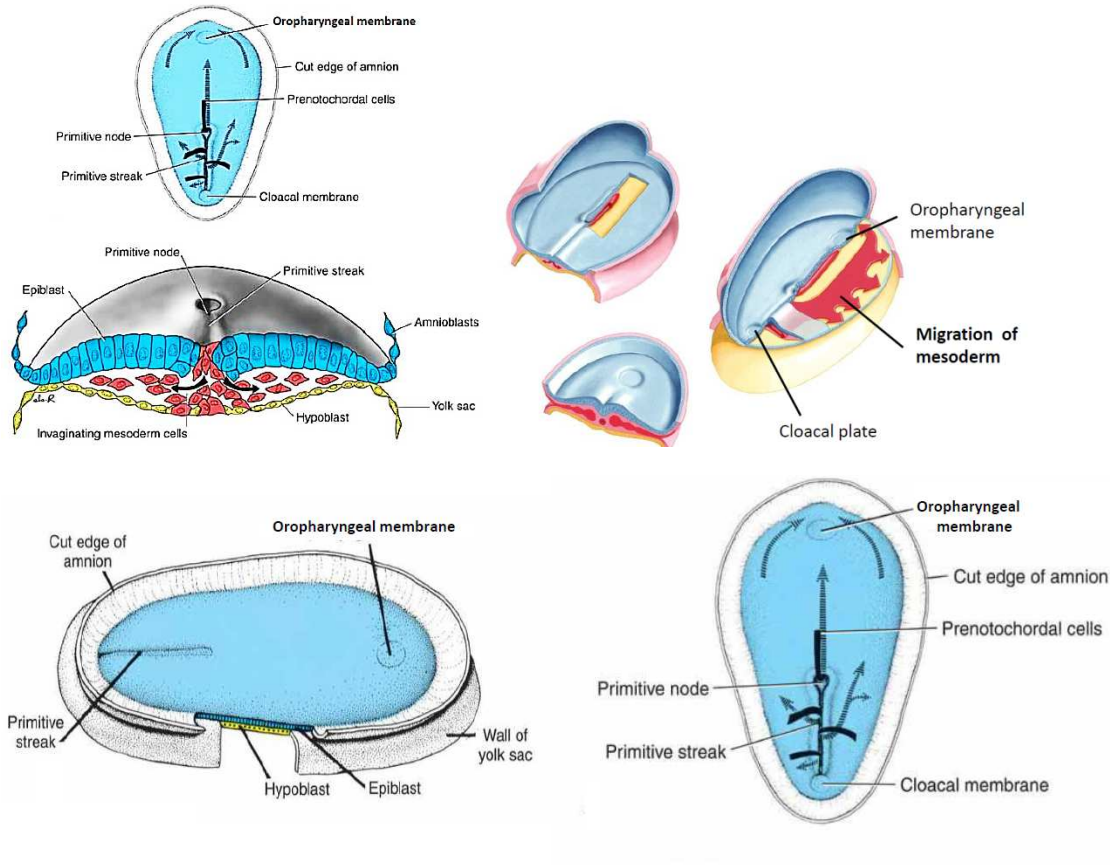

12 Days

- **2nd week of development**: inner cell mass (ICM) forms **bilaminar** germ disc (**epiblast** and **hypoblast**)
- **Cytotrophoblast**: syncytiotrophoblast and cytotrophoblast (wall of blastocyst)
- **Extraembryonic mesoderm**: Visceral (splanchnic, of organ; covers yolk sac) and parietal (somatic, of 'walls'; covers amnion) layers
- **Trophoblastic lacunae**: precursor of maternal blood space, will fuse together to form part of placenta
- **Amnioblast**: secretes amniotic fluid to form amniotic cavity
- **Day 15**: formation of primitive streak and establishment of **cranial-caudal axis**
- NODAL protein from primitive node to regulate laterality




13 Days

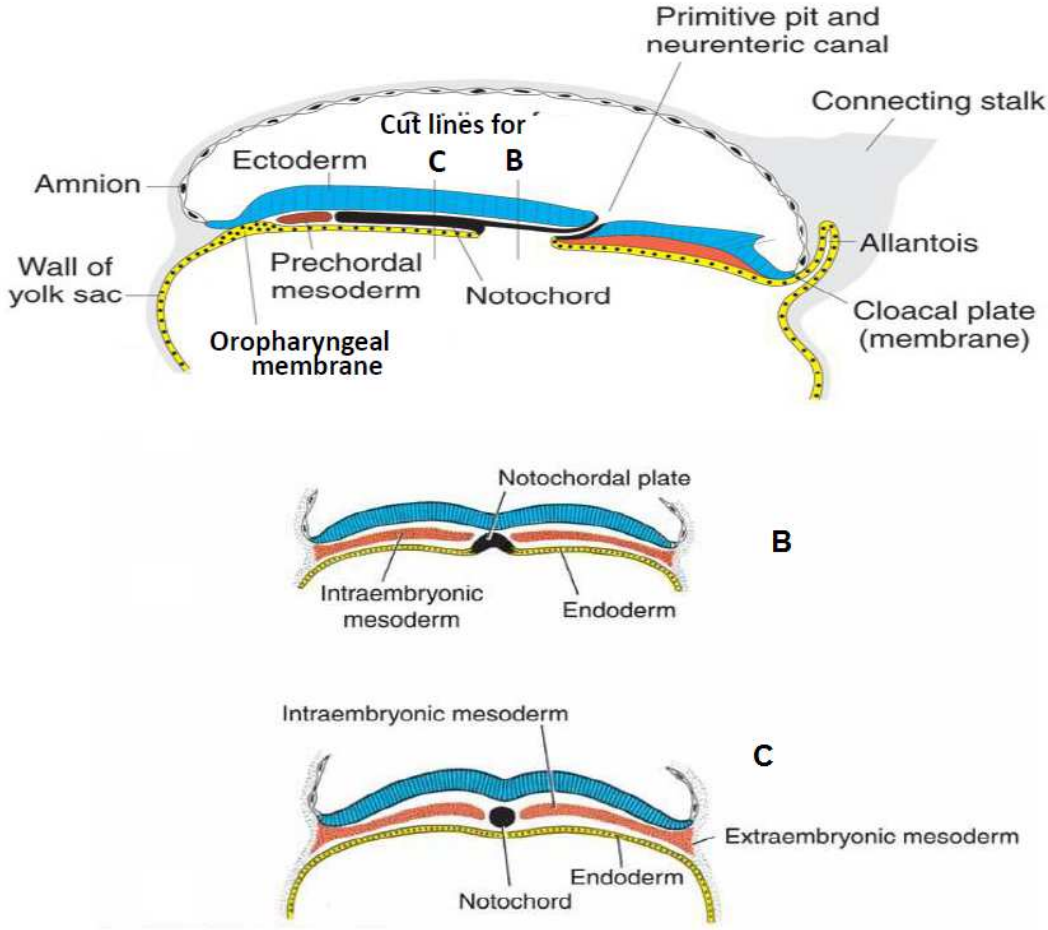
# G. Gastrulation




14 Days 16 Days

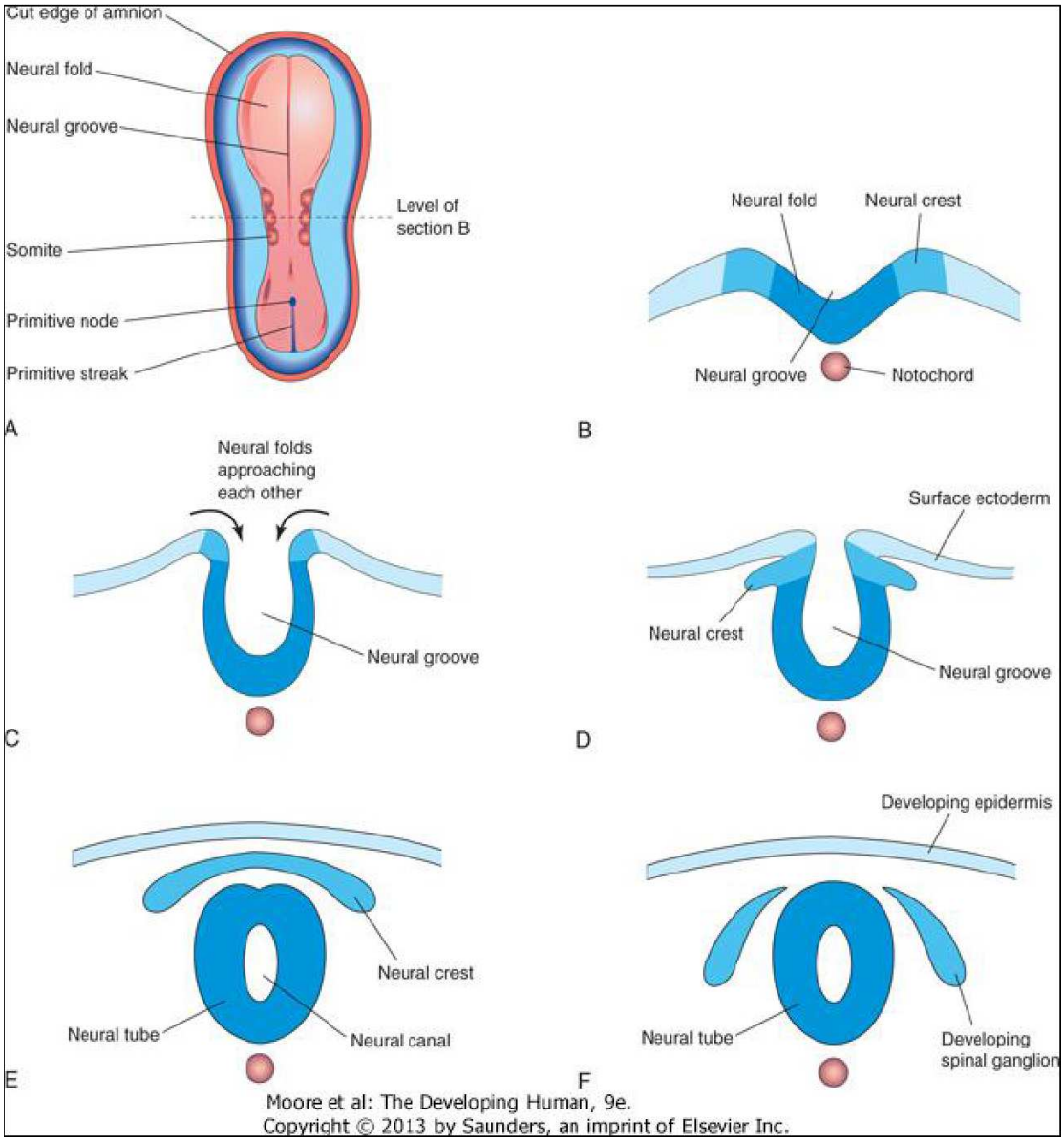
- **Gastrulation**: formation of **endoderm** and then **mesoderm** from **epiblast**
- **Epiblast** becomes the **ectoderm**
- **Hypoblast** shed away during gastrulation
- Derivatives of the three germ layers:
  - **Ectoderm**: skin, CNS, PNS, eyes, internal ear, neural crest cells (bones and c.t. of the face and part of the skull)
  - **Mesoderm**: bones, c.t., urogenital system, cardiovascular system
  - **Endoderm**: gut and gut derivatives (liver, pancreas, lungs etc.)

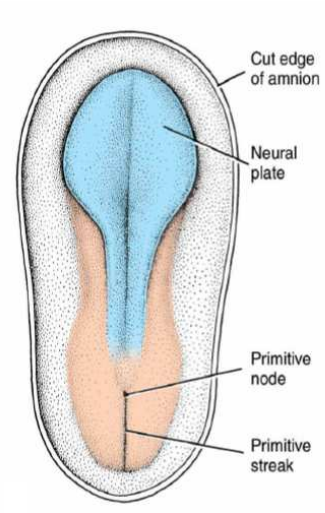
- Formation of prechordal plate and notochord:
  - Prechordal plate induces forebrain and midbrain regions
  - Notochordal cells induce hindbrain and spinal cord regions



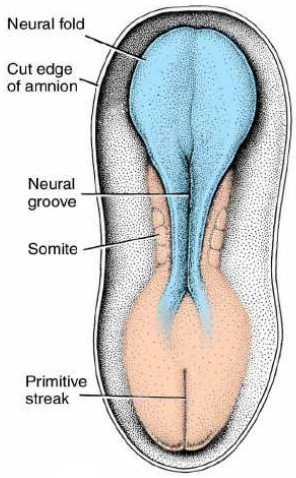
# H. Neurulation

- **4th to 8th weeks**: formation of **neural tube** (**neurulation**)
- **Notochord** and **prechordal mesoderm** induces the overlying ectoderm to form **neural plate** (neuroectoderm) → intiation of neurulation
  - **Prechordal plate** induces forebrain and midbrain formation (↑FGFs ↓BMPS)
  - **Notochord** induces hindbrain and spinal cord formation (↑FGFs ↑WNT3a)
- **Neurotube** formed by folding along the midline:

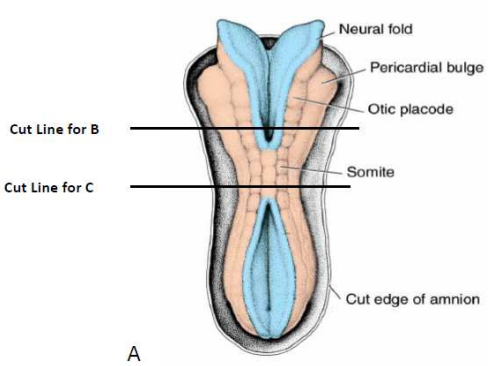




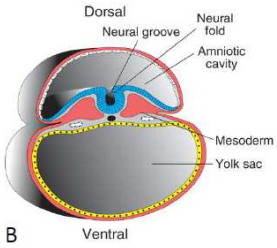

18 Days

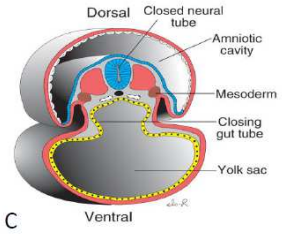


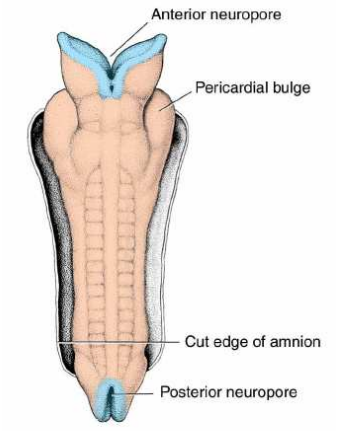

20 Days



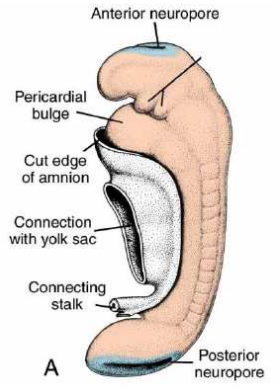

22 Days



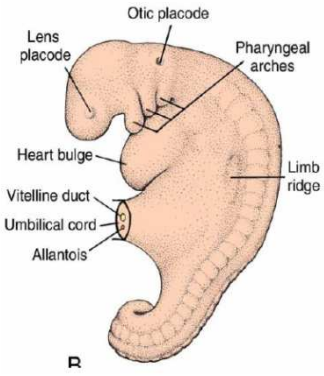




23 Days




25 Days

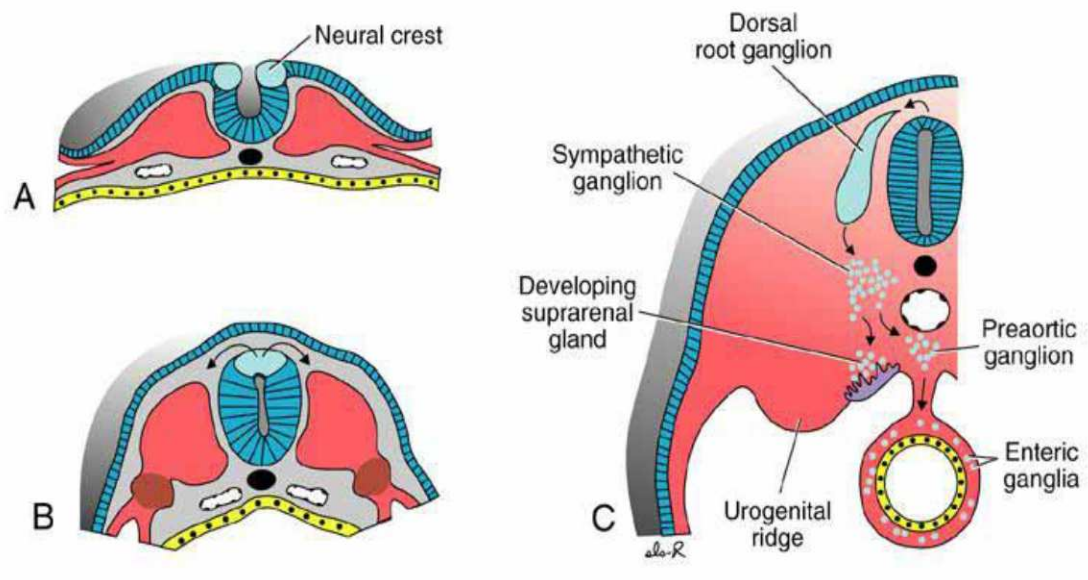



28 Days

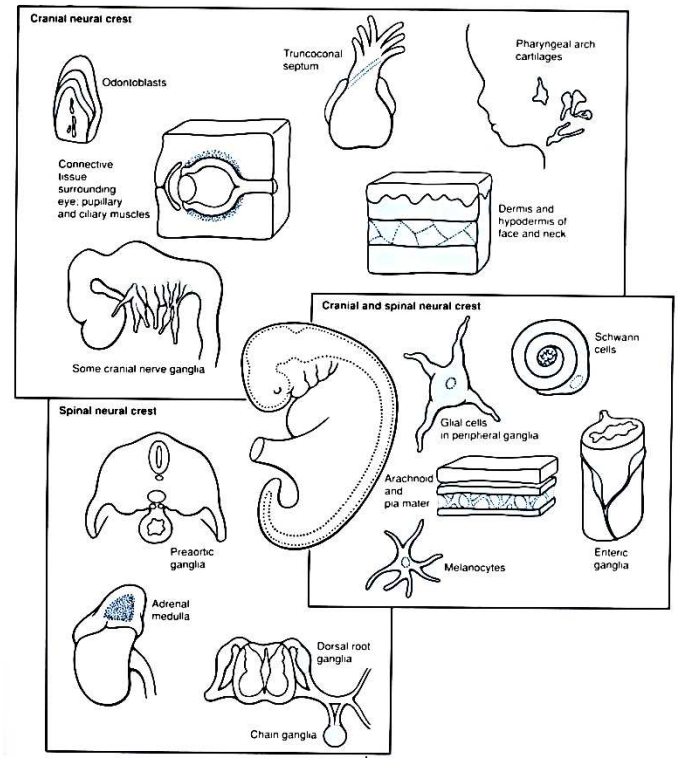
- **28th Day**: Neural tube closed completely
- Eye (optic vesicle), ear (otic vesicle), mouth, heart, **somites** etc. have also formed over this same time period

*Defect in neural tube closure → **anencephaly** (unclosed anterior neuropore, fatal) and **spinal bifida** (unclosed posterior neuropore)

- **Neural crest** forms when sides of neural tube come together at midline
  - Some of the cells break away and migrate along the side of neural tube
  - Migrate throughout embryo to form many different tissues

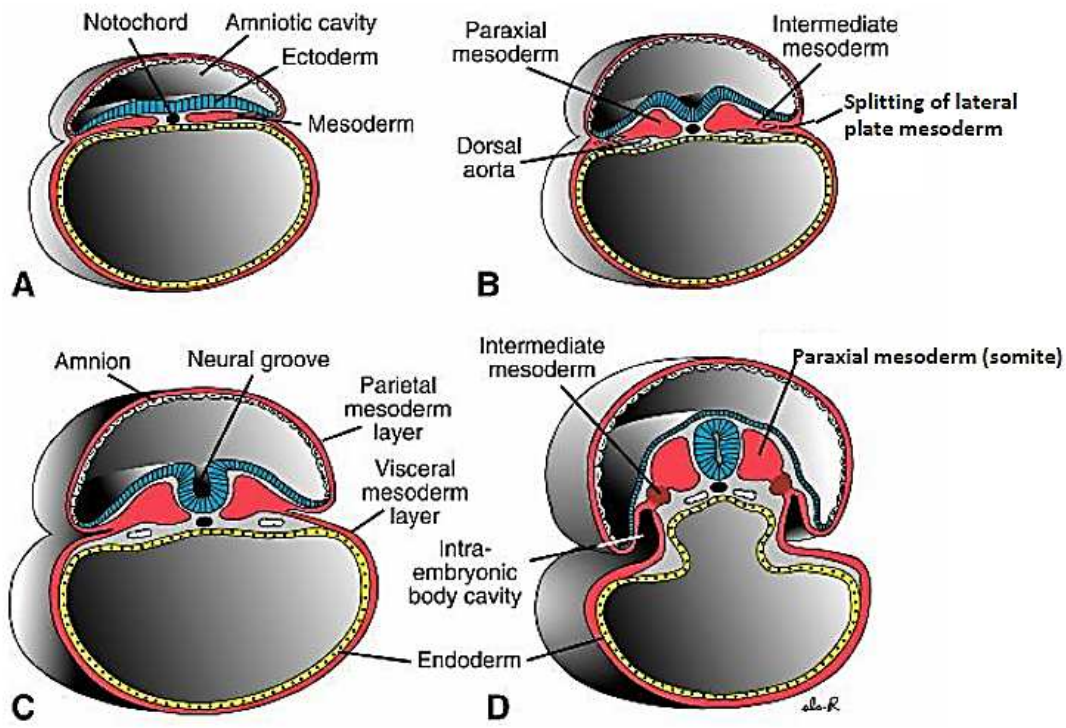



  - Forms:
    - → Sensory and post-ganglionic autonomic portions of PNS
    - → Adrenal medulla (centre of adrenal gland)
    - → Melanocytes of skin (melanin-producing cells)
    - → Part of skull, dentin of teeth, some skeletal muscles
    - → General c.t. of the head (mesenchyme)



# I. Mesodermal and Somite Development

- Mesoderm layer develop into three parts (from notochord to periphery):
  - **Paraxial mesoderm**: derived to form **somite**
  - **Intermediate mesoderm**: derived to form urogenital system
  - **Lateral plate mesoderm**: derived to form skin and limb, bones
    - → Further splits to form **parietal** (lines amniotic cavity) and **visceral** (lines yolk sac) **lateral plate mesoderm**

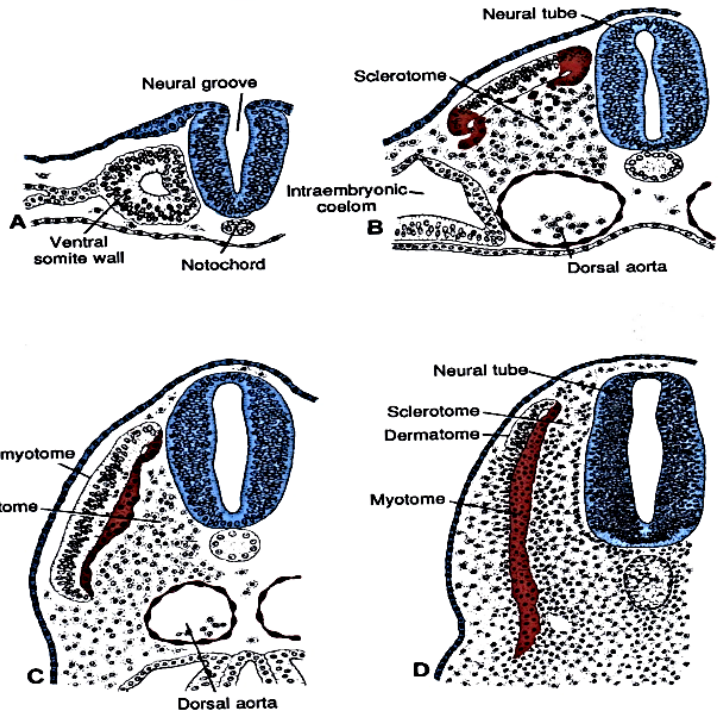


- **Somites** form from paraxial mesoderm along the neural tube
  - Forms skeletal muscles, bones and c.t. (incl. skin dermis)
  - Development of a somite:

Sclerotome:
vertebrae and ribs

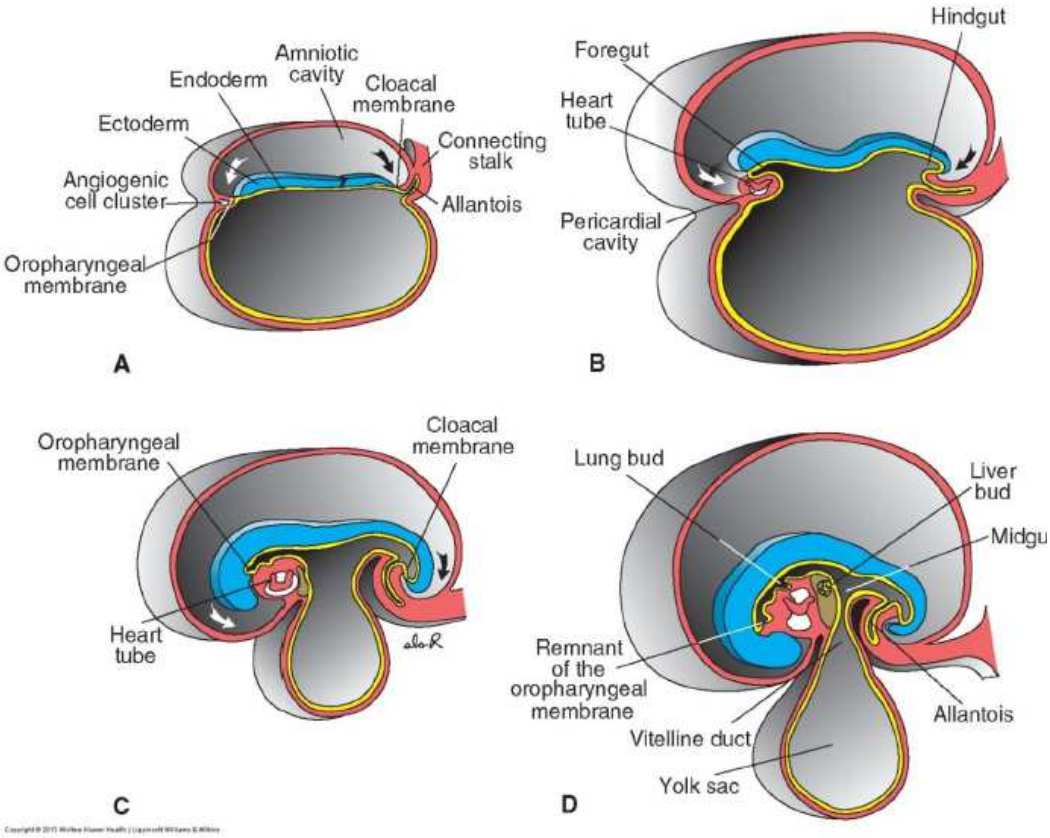
Dermatome:
Skin dermis

Myotome:
Muscle

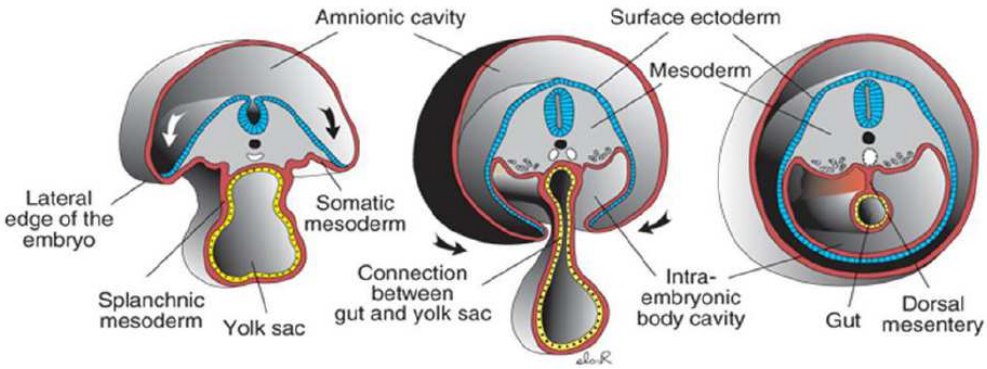


# J. Embryo folding

- Embryo folds both along **cephalocaudal** axis and laterally
- Amniotic cavity now surrounds the whole embryo
- Connection with yolk sac now reduced to a narrow **vitelline duct**
- Part of **chorionic cavity** enclosed by embryo to form **intraembryonic body cavity**
- Endoderm surrounding the part of yolk sac enclosed by embryo folding forms the **gut tube**
- **Cephalocaudal** folding:




- Lateral folding:




*__Caudal dysgenesis__ (mermaid syndrome) occurs when there is not enough mesoderm cells for caudal development

# K. Fate of the Three Germ Layers

## Ectodermal derivatives

| Primordia | Derivatives or Fate |
|---|---|
| Surface ectoderm | Epidermis of the skin<br>Sweat, sebaceous, and mammary glands<br>Nails and hair<br>Tooth enamel<br>Lacrimal glands<br>Conjunctiva<br>External auditory meatus |
| (Stomodeum and nasal placodes) | Oral and nasal epithelium<br>Anterior pituitary |
| (Otic placodes) | Inner ear |
| (Lens placodes) | Lens of eye |
| Neural tube | Central nervous system<br>Somatomotor neurons<br>Branchiomotor neurons<br>Presynaptic autonomic neurons<br>Retina/optic nerves<br>Posterior pituitary |
| Neural crest | Peripheral sensory neurons<br>Postsynaptic autonomic neurons<br>All ganglia<br>Adrenal medulla cells<br>Melanocytes<br>Bone, muscle, and connective tissue in the head and neck |
| Amnion | Protective bag (with chorion) around fetus |

## Mesodermal derivatives

| Primordia | Derivatives or Fate |
|---|---|
| Notochord | Nucleus pulposus of an intervertebral disc<br>Induces neurulation |
| Paraxial columns (somites) | Skeletal muscle<br>Bone<br>Connective tissue (e.g., dorsal dermis, meninges) |
| Intermediate mesoderm | Gonads<br>Kidneys and ureters<br>Uterus and uterine tubes<br>Upper vagina<br>Ductus deferens, epididymis, and related tubules<br>Seminal vesicles and ejaculatory ducts |
| Lateral plate mesoderm | Dermis (ventral)<br>Superficial fascia and related tissues (ventral)<br>Bones and connective tissues of limbs<br>Pleura and peritoneum<br>GI tract connective tissue stroma |
| Cardiogenic mesoderm | Heart<br>Pericardium |

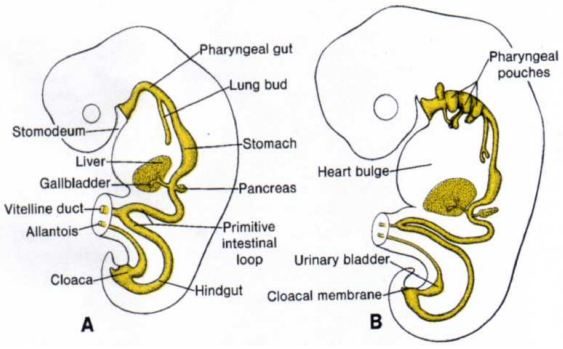
*GI*, Gastrointestinal.

## Endodermal derivatives

| Primordia | Epithelial Derivatives or Fate |
|---|---|
| Gut tube endoderm | GI tract (enterocytes)<br>Mucosal glands of GI tract<br>Parenchyma of GI organs (liver, pancreas)<br>Airway lining (larynx, trachea, bronchial tree)<br>Thyroid gland<br>Tonsils |
| Cloaca (part of hindgut) | Rectum and anal canal<br>Bladder, urethra, and related glands<br>Vestibule<br>Lower vagina |
| Pharyngeal pouches (part of foregut) | Auditory tube and middle ear epithelium<br>Palatine tonsil crypts<br>Thymus gland<br>Parathyroid glands<br>C cells of the thyroid gland |
| Yolk sac | Embryonic blood cell production (mesoderm)<br>Pressed into umbilical cord, then disappears |
| Allantois (from yolk sac, then cloaca) | Embryonic blood cell production (mesoderm)<br>Vestigial, fibrous urachus<br>Umbilical cord part disappears |

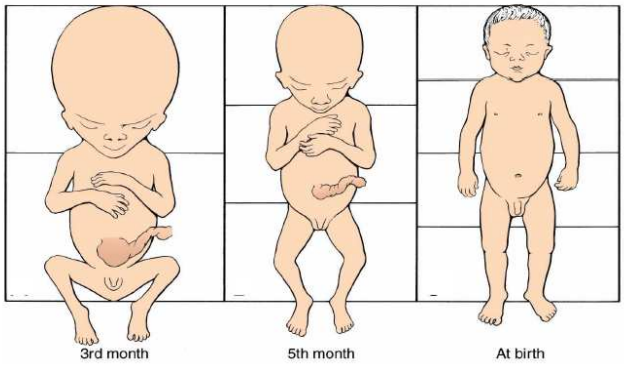
*GI*, Gastrointestinal.

Derivatives of endoderm



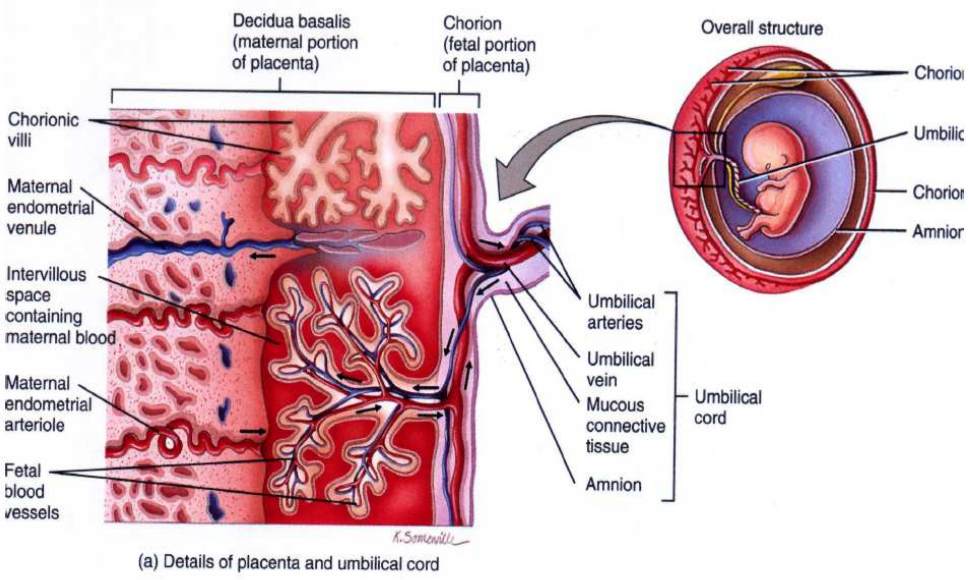
# L. Fetal Growth Period

- **9th week to 38th week**: fetal growth period
- Characterized by **rapid body growth** and **differentiation of tissues and organ system**
- Relative slowing of head growth compared with that of the rest of the body
- Most of the weight gained during last 3 months




Length: 3-6 months Weight: 7-9 months

- **Placenta**: act as barrier between fetal and maternal blood
  - Formed from fetal endothelium, fetal c.t., cytotrophoblast, syncytiotrophoblast




(a) Details of placenta and umbilical cord

# M. Birth Defects

## 1. Causes

- 15% genetic, 10% environmental, 20% multifactorial , 50-60% unknown
- **Teratogens**: factors that cause birth defects

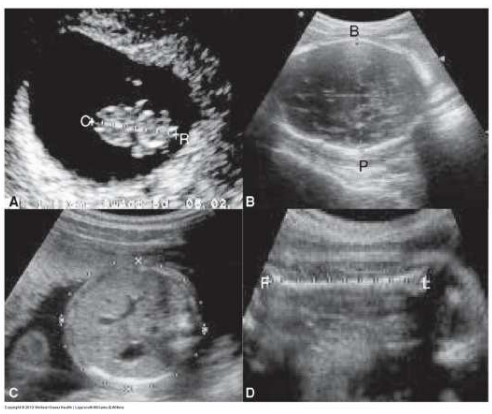
### a. Human Teratogens

- Drugs:
  - Cigarette smoking, Caffeine
  - Alcohol: **Fetal alcohol syndrome** in chronic alcoholic mother will induce pre-and post-natal growth deficiency, mental retardation
  - Progesterone and androgen: masculinization of external genitalia
  - Anti-coagulants: causes hypoplasia (underdevelopment) of nasal cartilage and epiphysis (round end of long bone); CNS defects
  - Diethylstilbesterol: causes congenital abnormal uterus and vagina
  - Anti-convulsants, anti-neoplastic agents, tranquilizers, thyroid drugs
- Environmental:
  - Organic Hg; Pb (growth retardation)
  - Infectious agents: rubella, HIV, herpes, simplex virus
  - Radiation
  - Mechanical factors

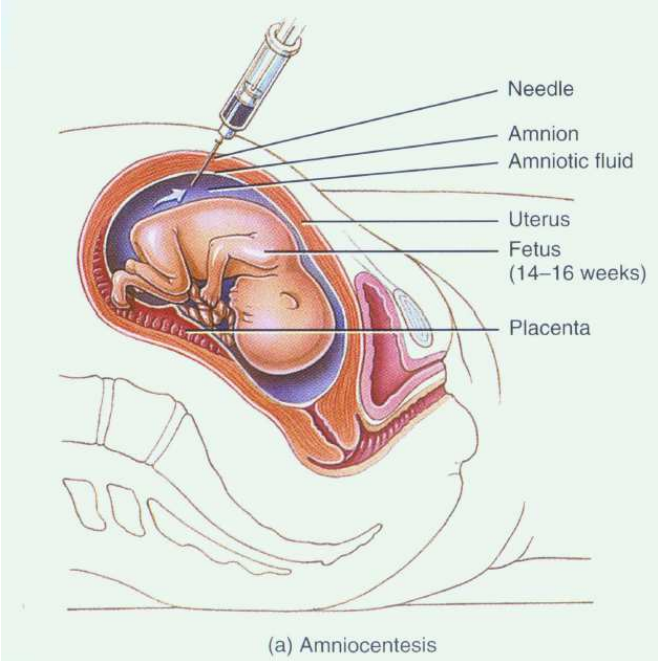
## 2. Prenatal Diagnosis

- Methods:
  - Ultrasonography:
    - → Chorionic sac and its contents visualized during embryonic and fetal period
    - → Placental/fetal size, multiple births, abnormal presentation can be determined
    - → Can also measure biparietal diameter of fetal skull, gonads and nasal bone

A. Crown-rump length (CRL)-7 weeks
B. Biparietal diameter of the skull
C. Abdominal circumference
D. Femur length

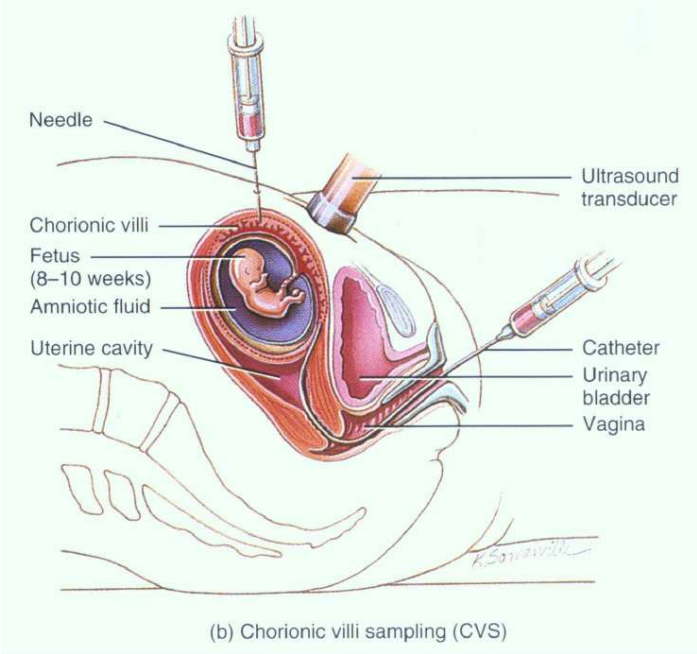


- Maternal serum screening for α-fetoprotein (AFP) → level can be used to screen for diseases such as neural tube defect (NTD), Down syndrome, trisomy 18, sex chromosome abnormalities
- Amniocentesis (genetics, AFP, Ach)
  - → Removal of amniotic fluid by syringe at gestational age of 16-18 weeks
  - → Fetal cells cultured for **karyotyping**
  - → Amniotic fluid assayed for α-fetoprotein
  - → Risk to induce abortion is ~1/200
  - → Rare complication: maternal infection



(a) Amniocentesis

- Chorionic villus sampling (genetics)
  - → Fetal tissue for analysis through aspiration from villous area transcervically guided by ultrasound
  - → Performed at gestational age 9-12 weeks (more actively dividing cells)
  - → Can detect chromosomal abnormalities, inborn errors of metabolism and X-linked disorders
  - → Fetal loss rate ~1%
  - → Detection methods include karyotyping, chromosomal banding/painting, DNA sequencing, mRNA detection, proteins (eg. AFP in NTD, low lecithin-spigomyelin ratio in lung abnormalities)

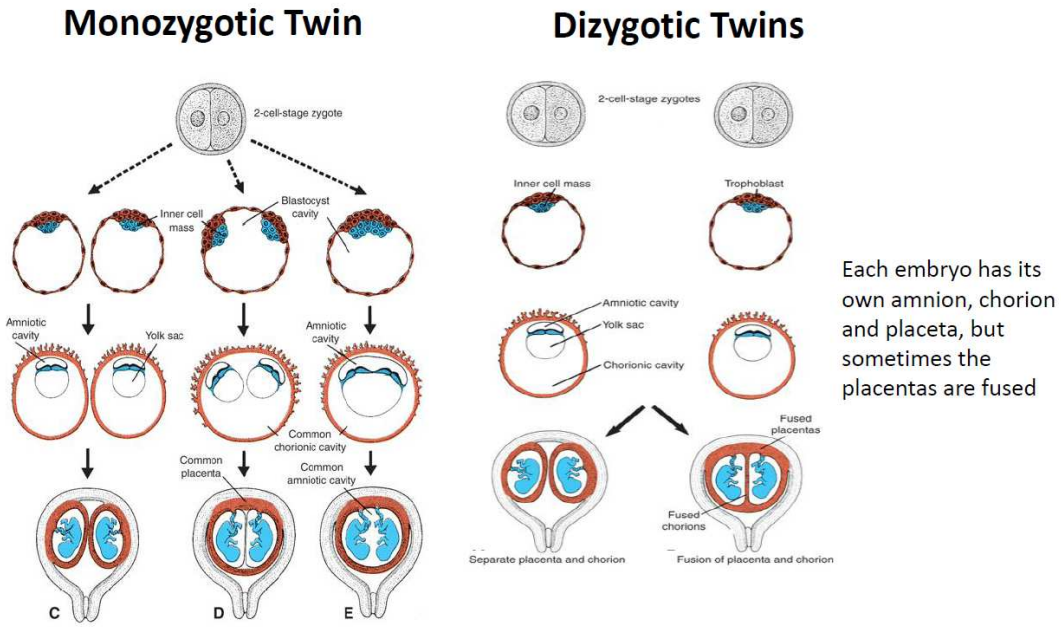


(b) Chorionic villi sampling (CVS)

- Indication for prenatal diagnosis:
  - Maternal age >35
  - Previous child with a *de novo* chromosomal abnormality (recurrent risk 1%)
  - Presence of a structural chromosomal abnormality
  - Family history of some genetic defect: known neural tube defect (risk 2-5%), other types (risk >1%)
  - X-linked disorders

# 3. Twinning

- Incidence: ~1 in 85 pregnancies
- 10-20% die at birth
- 12% premature infants are twins
- Two types:
  - **Monovular** (identical)
    - → **Dichorial**, **diamniotic**
    - → **Monochroial**, **diamniotic**
    - → **Monochorial**, **monoamniotic**
  - **Biovular** (fraternal)



- Abnormality: **conjoined twins**

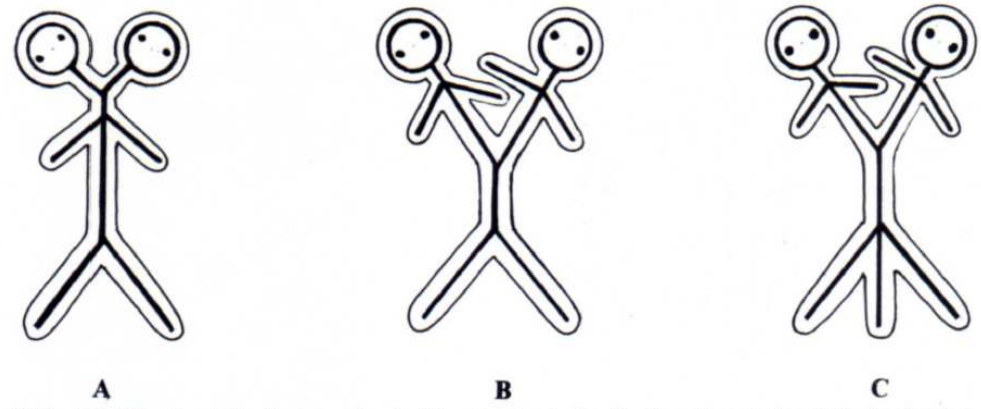
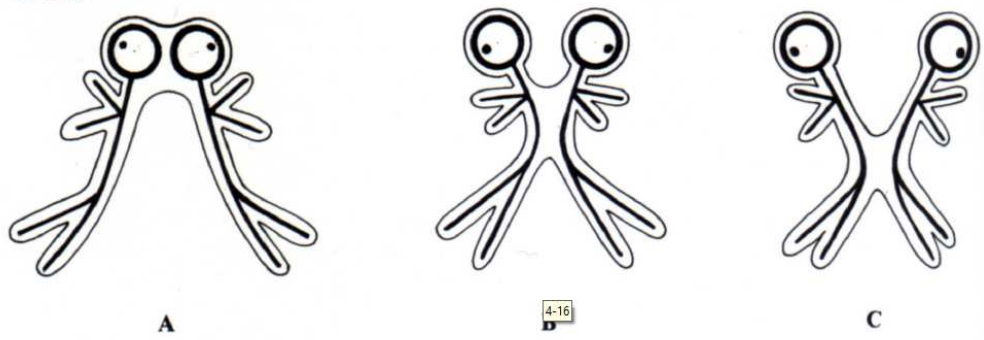



FIG. 7-2. Results of duplication of primitive streak: **A**, duplication of rostral end; **B**, duplication of rostral half; **C**, rostral and caudal duplication.

FIG. 7-3. Results of incomplete duplication of germ layers: **A**, rostrally; **B**, centrally; **C**, caudally.




craniopagus thoracopagus pygopagus

# 4. Chromosomal Anomalies

- **Nondisjunction**: failure of homologous pair to separate in anaphase, meiosis I
- **Monosomy**: only one chromosome of a homologous pair is found
  - Cause: non-disjunction in one of the gametes
  - E.g. XO or **Turner's syndrome**
- **Trisomy**: an extra chromosome (for a certain homologous pair) is found
  - Cause: dispermic fertilization, non-disjunction in one of the gametes
  - E.g. trisomy 21 or **Down's syndrome**
  - E.g. trisomy 17-18 or **Edward's syndrome**
  - E.g. trisomy 13-15 or **Patau's syndrome**

*Chromosomal anomalies more common in later (smaller) chromosomes (∵ ↓ loss in genetic material → ↓ disruption on genetic expression → ↑ survival chance)

## a. Edward's Syndrome

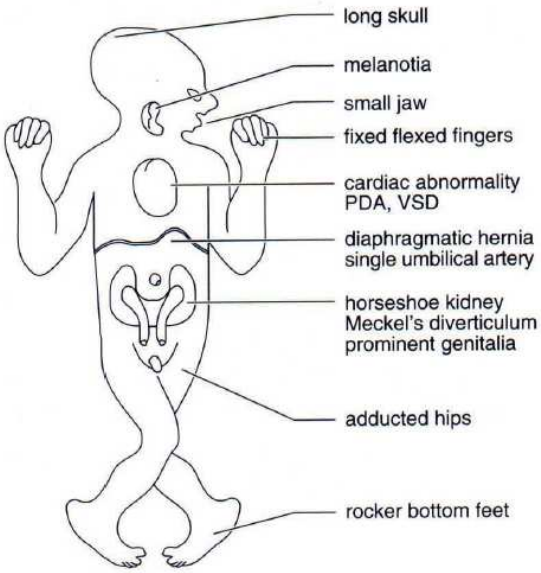



**FIGURE 6** Edward's syndrome: abnormalities in trisomy 17–18.

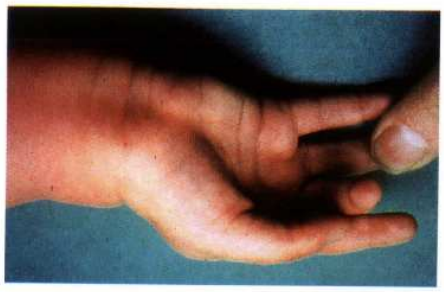


**FIGURE 7** Edward's syndrome: flexed fingers cannot be extended (child, 18 months).

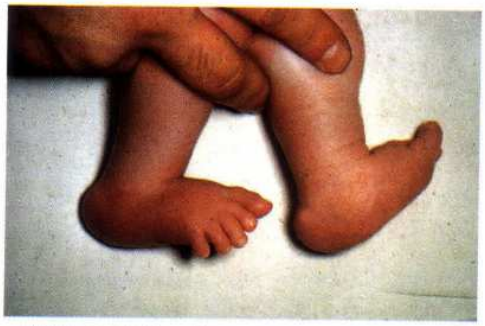


**FIGURE 8** Edward's syndrome: "rocker bottom" feet in a neonate.

## b. Down's Syndrome

FIGURE 2 Down's syndrome: characteristic facie

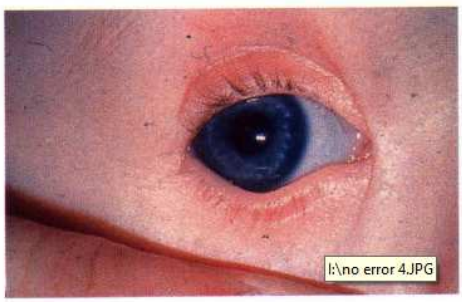



FIGURE 3 Down's syndrome: notched eyelids and epicanthic fold.

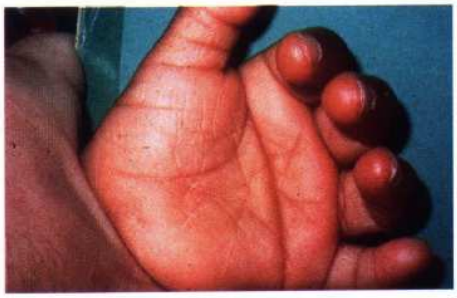


FIGURE 4 Down's syndrome: characteristic palmar "simian" crease.

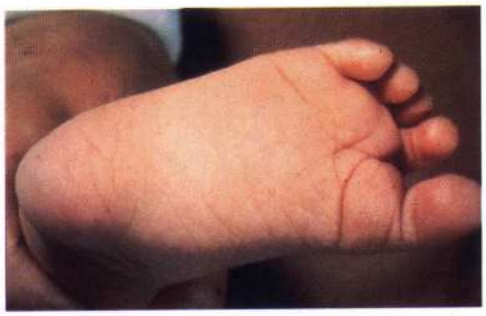


FIGURE 5 Down's syndrome: transverse crease in the sole of the foot, with separation of the hallux.

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- Note that incidence of Down syndrome in newborn infants rises with maternal age

# L24 Do Doctors Really Matter?

## A. Public Health

- Role of doctors
  - Improving health for **individuals** (Hippocratic oath)
  - Improving health for **humanity** (declaration of Geneva)
- **Public health**:
  - Prevention of disease and improvement in health in populations rather than individuals (older definition)
  - Also concerned with the broader determinants of health (eg. Social structure) rather than individual risks

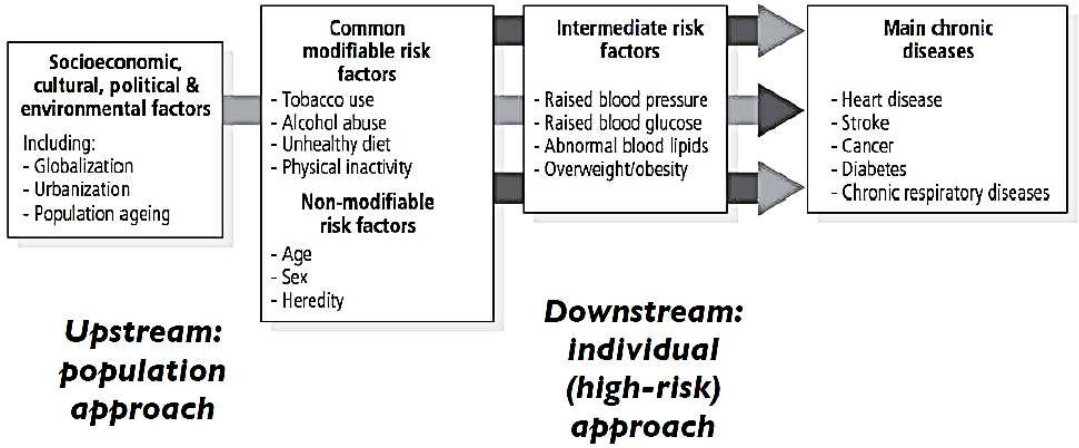
## B. Preventive Approach in Medicine

### 1. Levels of Prevention

| Level | Phase of Disease | Aim | Target | Actions |
|---|---|---|---|---|
| Primordial | Underlying economic, social and environmental determinants (eg poverty) | Establish and maintain **conditions that minimize hazards to health** | Total population or selected groups | Public policies and inter-sector action (eg sanitation, clean air) |
| Primary | Specific causes and risk factors (eg smoking) | Reduce **incidence** of disease | Total population, selected groups or high-risk individuals | Public health programmes and health promotion (eg. Smoking cessation, vaccination |
| Secondary | Early stage | Reduce **prevalence** of disease | Individuals with **early disease** | Early diagnosis and treatment (eg. Cancer screening) |
| Tertiary | Late stage | Reduce disease **complications and disability** | Individuals with established disease | Rehabilitation (eg. Stroke rehab) |

# 2. Preventive Approaches

- Cause of **cases** vs. cause of **incidence**:
  - A population-oriented knowledge
  - Characteristics of population (not individuals) have to be studied to find determinants of prevalence and incidence




## a. Individual (High-risk) Approach

- ✓ Intervention **appropriate to individual** (tailor-made)
- ✓ Subject motivation
- ✓ Physician motivation
- ✓ Cost-effective use of resources
- ✓ **Benefit** : **risk ratio favourable**
- × Difficulties and costs of screening
- × Palliative and temporary – not radical
- × Limited potential for individuals and populations
  - Large number at small risk may give rise to more cases of diseases than the small number who are at high risk
- × Behaviourally inappropriate

## b. Population Strategy

- ✓ Radical – attempts to remove underlying causes that make the disease common
- ✓ Large potential for population
  - Attempts to shift the whole distribution of exposure in a favourable direction
- ✓ Behaviourally appropriate – changes norm
- × 'Prevention paradox': a preventive measure which brings much benefit to the population **offers little benefit to each participating individual**
- × Poor motivation of subject
- × Poor motivation of physician
- × **Benefit** : **risk ratio** worrisome

# C. Medicine as a Social Science

- Epidemics are 'indications of large disturbances of collective life' → **elimination of social inequality** to prevent epidemic
- **McKeown thesis**: population growth primarily due to ↓ mortality from disease due to ↑ social conditions (living standard)
  - Criticized medicine as placing too much emphasis on 'cure' rather than 'care'
- **Preston's theory**: life expectancy rose between 1930 and 1960 regardless of income level
  - Factors **exogenous to income** accounted for most of the gain in life expectancy → major effect of mortality
- **Illich's theory of iatrogenesis**: medicine does more harm than good to general population health
  - **Clinical iatrogenesis**: injury done to patients by ineffective, toxic and unsafe treatment
  - **Social iatrogenesis**: 'medicalisation of life' → unrealistic health demands → more treatments → individuals lose autonomous coping skills and become more reliant on institutional care
  - **Cultural iatrogenesis**: destruction of traditional ways of dealing with and making sense of death, pain and sickness → people less tolerant to diseases
  - Health more dependent on individual action than on new treatments
  - Iatrogenesis theory rebutted by Bunker: 17% of gain in life expectancy since 1900 attributed to medical and public health intervention; loss of life expectancy due to iatrogenesis only 6-12 months

- Reality is something in between: both improvements in social conditions and healthcare contributed to increase in life expectancy:
  - Social conditions are 'fundamental causes' of disease and death
  - People with more resources (higher income) have better health
  - Note average BP↓, self-rated health↑, subjective happiness ↑ and family harmony↑ as income ↑
- Overall life expectancy increase attributed to:
  - Economic wellbeing/standard of living
  - Public health
  - Personal healthcare
  - Individual health-related behaviour
- **'Ladder of political activism' for doctors**:
  - **1st rung**: political passivism; info on health risk and opportunities for health improvement is exchanged within the health sector only
  - **2nd rung**: public health professionals actively disseminate relevant information among politicians
  - **3rd rung**: public health professionals try to directly influence the political process
  - **4th rung**: public health professionals become politicians themselves

# L25 What is Medicine? What is Public Health?

- Four key health challenges:
  - **Unfinished** epidemic of infectious diseases
  - **Emerging** epidemic of chronic conditions
  - **Unethical** epidemic of inequalities
  - **Unnecessary** epidemic of environmental insults
- Systematic solution to challenges:

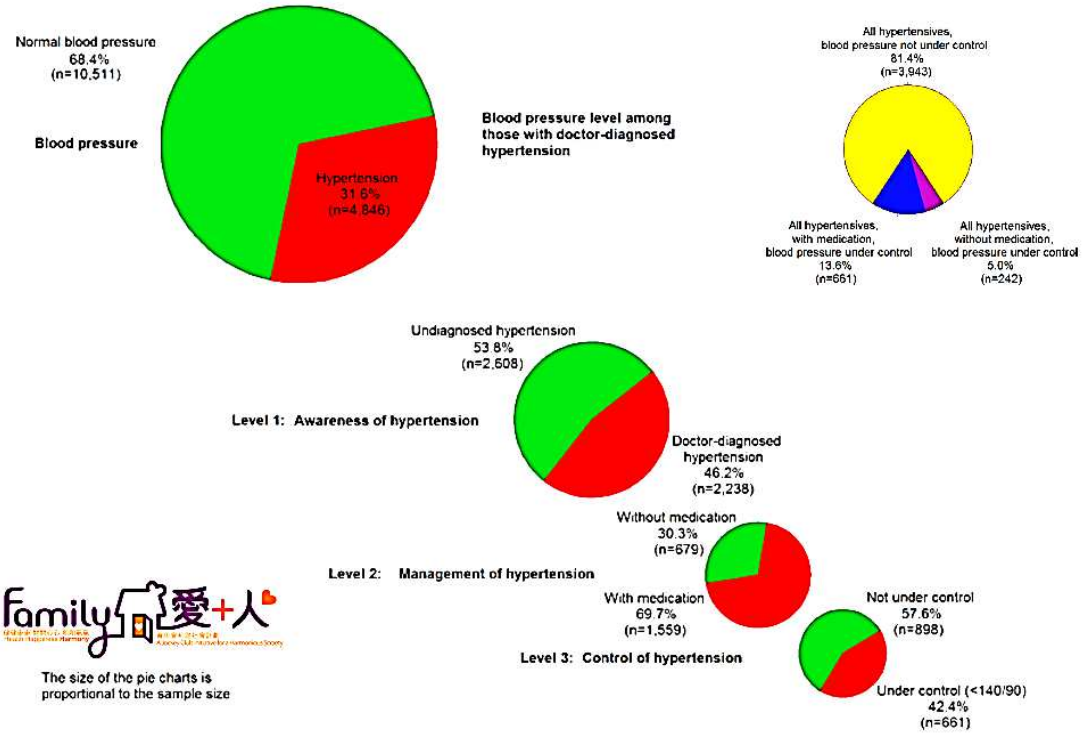
1) Identify the problem;
2) Break down the problem into manageable, soluble components;
3) For each component, deploy optimal combination of resources (human, financial, capital etc) in a targeted fashion (optimal = more efficient/value-added)

## A. Unfinished Epidemic of Infectious Diseases

- Examples: animal-origin influenza, antibiotic resistance, vaccine-preventable infections, aetiologic (causal) potential associated with non-communicable diseases
- Methods adopted:
  - Control on poultry supply chain
  - Childhood immunization programme (CIP)

# B. Emerging Epidemic of Chronic Conditions

- Lifestyle determinants: smoking, alcohol, total and form of energy intake, physical activity, dietary salt intake, fruits and vegetables
- Note that non-communicable diseases (NCDs) account for >85% of all deaths (esp neoplasm, CVD etc.)
- Major health risks:
  - Overweight/obesity: 51.8%
  - Hypertension: 31.6%
  - Tobacco: 11.5%
  - Type II diabetes: 9.8%
- Obesity dependent on diet and exercise
  - Intake (food availability and portion size, high (trans) fat diets and high energy density foods)
  - Expenditure (exercise already displaced as preferred mode of leisure activity and lack of conducive built environment (reliance on transportation)
- **Rule of Halves in Hypertension in HK**:
  - 50% high BP (31.6%)
  - 50% diagnosed (46.2%)
  - 50% with medication (69.7%)
  - 50% under control (42.4%)



# C. Unnecessary Epidemic of Environmental Insults

- Problems:
  - Air pollution, incl indoor (secondhand/thirdhand smoke)
  - Environmental contamination of food chain
- Tobacco control:
  - Health education
  - Fiscal: 50% rise in tobacco duty in 2009/10 budget
  - Legislative: Smoking (Public Health) Ordinance
  - Challenges:
    - → Legal and judicial interpretation of new law (advertisement, definition of 'indoor area'
    - → Illicit import and sales
    - → Tobacco lobby (eg product differentiation of age and gender-specific markets, pressure through media and other PR strategies)
    - → Improvement in provision of smoking cessation across all sectors
- Air pollution problem:
  - 1990, EPD restricted S content of fuel to 0.5% by weight
  - Both $SO_2$ concentration in air, prevalence of bronchial hyperresponsiveness in primary school children and increase in deaths from heart and lung diseases reduced after the restriction

# D. Unethical Epidemic of Inequalities

- Social determinants of health
- Pathways to ill health: psychosocial, neomaterial, cultural, behavioural, lifecourse
- Commoditization of healthcare → inverse care law: availability of good healthcare varies inversely with the need of population group (better income → less need but better healthcare available)

# E. Public Health

- Public health is:
  - Population based
    Emphasises collective responsibility for health, its protection and disease prevention
  - Recognises the key role of the state, linked to a concern for the underlying socio-economic and wider
  - determinants of health, as well as disease
  - Emphasises partnerships with all those who contribute to the health of the population
- Difference between medicine and public health:

**Medicine**

- Primary focus on individual
- Personal service ethic, in the context of social responsibilities
- Emphasis on disease diagnosis, treatment, and care for the individual patient
- Medical paradigm places predominant emphasis on medical care
- Uniform system for certifying specialists beyond professional medical degree
- Lines of specialization organized, for example, by:
  - organ system (cardiology, neurology)
  - patient group (obstetrics, pediatrics)
  - aetiology and pathophysiology (infectious disease, oncology)
  - technical skill (radiology, surgery)
- Biological sciences central, stimulated by needs of patients; research moves between laboratory and bedside
- Numerical sciences increasing in prominence, though still a relatively minor part of training
- Social sciences tend to be an elective part of medical education

**Public Health**

- Primary focus on populations
- Public service ethic, as an extension of concerns for the individual
- Emphasis on disease prevention and health promotion for the whole community
- Public health paradigm employs a spectrum of interventions aimed at the environment, human behavior and lifestyle, and medical care
- Variable certification of specialists beyond professional public health degree
- Lines of specialization organized, for example, by:
  - analytical method (epidemiology, toxicology)
  - setting and population (occupational health, global health)
  - substantive health problem (environmental health, nutrition)
- Life sciences central, with a prime focus on major threats to the health of populations; research moves between laboratory and field
- Population sciences and quantitative disciplines essential features of analysis and training
- Social and public policy disciplines an integral part of public health education

*Source: Harvard School of Public Health*

- Specialty of community medicine in HK to do public health work

# L26 How is healthcare organized in Hong Kong?

## A. Health System

- Well-functioning health system responds (in a balanced way) to a population's needs and expectations by:
  - □ Improving health status
  - □ Defending population against health threats
  - □ Protecting population against financial consequences of ill health
  - □ Providing equitable access to healthcare
  - □ Making it possible for people to participate in decisions affecting their health and their health system

## 1. Components of a health system

1) Individuals and bodies that deliver healthcare:
   - Public vs private
   - Western vs traditional
   - Licensed vs unlicensed
   - Persons vs institutions
2) Money flows that finance healthcare:
   - General revenue
   - Social insurance
   - Private insurance
   - Out-of-pocket payments
   - Medical saving accounts
3) Activities providing specialized inputs into the healthcare process:
   - Medical and nursing schools
   - Drug manufacturers
   - Medical device manufacturers etc.
4) Financial intermediaries, planners and regulators who control, fund and influence provider of healthcare:
   - Government: ministries of health and finance
   - Insurance companies
   - Regulatory bodies, etc.
5) Activities of organizations that deliver preventive services:
   - Immunisation
   - Family planning
   - Infectious disease control
   - Health promotion activities, etc.

# 2. Health System Reform

- Forces driving reform:
  - Healthcare is central to improvement in health status and general development of populations
  - Rising cost of healthcare
  - Rising expectations of the public
  - Limits on government's capacity to pay
  - Growing skepticism about conventional approaches
- **'Control knobs' for health system reform**: areas of a health system that significantly determine how the system affects the population and can be adjusted by government action
  - **Financing**: mechanisms for raising money that pays for healthcare
  - **Payment**: methods for transferring money to healthcare providers, creating incentives for providers
  - **Organizations**: mechanisms to affect the mix of providers, their roles and functions and how they operate internally
  - **Regulation**: use of coercion by the state to alter the behavior of providers, insurance companies and patients
  - **Behaviour**: efforts to influence how providers and patients behave

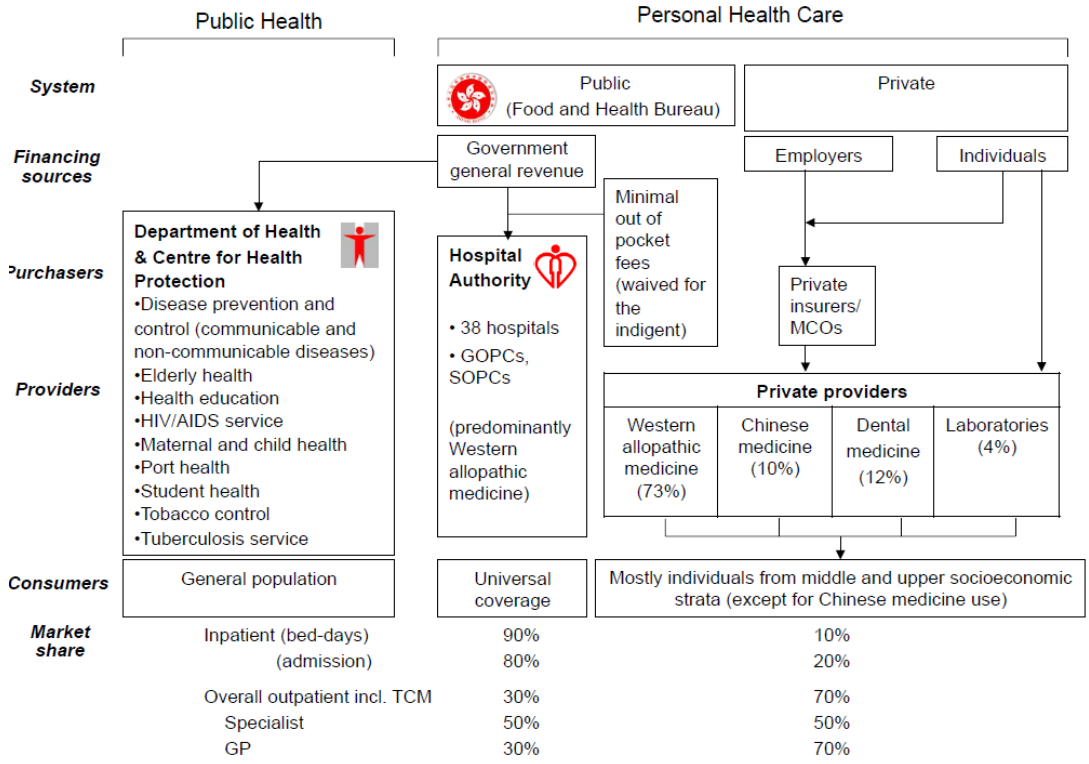
# B. Health System in Hong Kong

- Total expenditure on health (TEH):
  - 5.1% of gross domestic product (GDP)
  - 49% public sources and 51% private sources
- Comparison with other economies:
  - **Comparable quality and health outcomes at relatively low total and public health expenditure (HE) as % GDP**
- Health financing sources:
  - Household out-of-pocket payments accounted for 68% of private HE
  - Employer-provided group medical benefits and individually purchased private health insurance each accounted for 14% of private HE
- Healthcare providers:
  - Spending at providers of ambulatory care and hospitals accounted for 73% of TEH
  - Public HE was mostly incurred at hospitals (69%)
- Healthcare functions:
  - Public HE mostly incurred in inpatient curative care (32%) and ambulatory care (i.e. outpatient care) (26%)
  - Private HE concentrated in ambulatory care (42%), inpatient curative care (22%) and medical goods outside patient care setting (19%)
- Note: healthcare professionals (doctors, nurses, pharmacists etc.) per population still significantly lower than world average

# 1. Organization

- **Food and Health Bureau** oversees the entire system
- Most public health functions carried out by **Department of Health**
- **Food and Environmental Hygiene Department** for food safety and inspection (Centre for Food Safety) and environmental hygiene
- **Agriculture**, **Fisheries and Conservation Department** for prevention and control of animal and plant disease as well as regulation of animal husbandry (agriculture) and fishing practices

## Macro-organisation of the Hong Kong health system



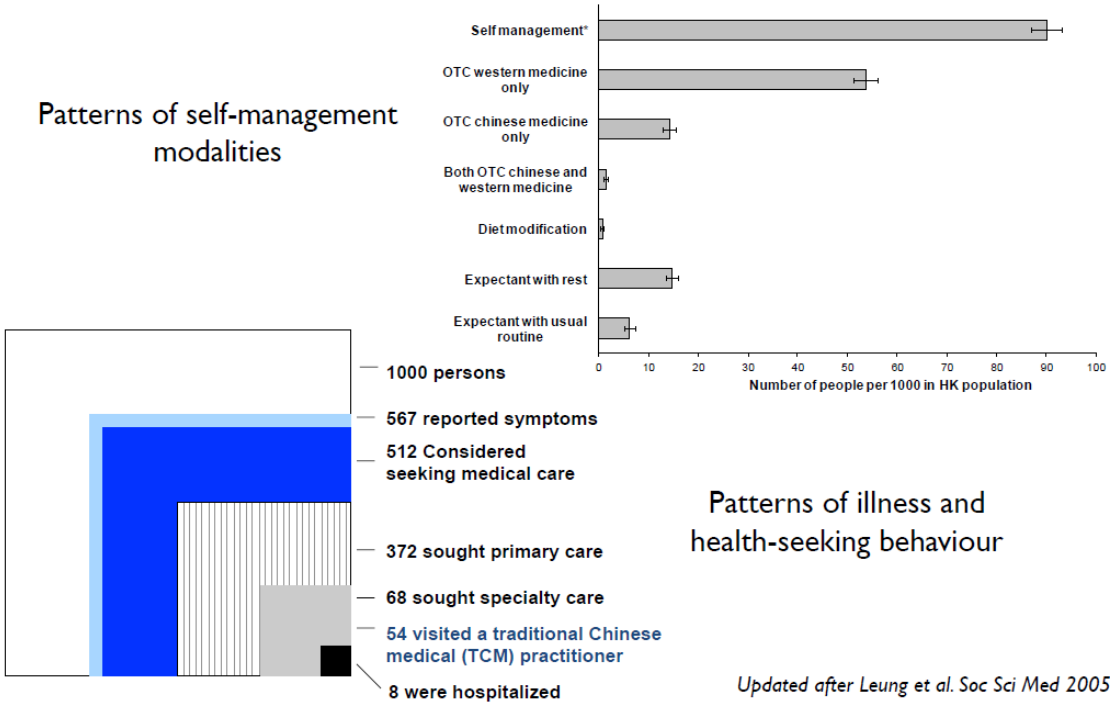

## a. Department of Health (DH)

- Disease surveillance, prevention and control (Centre for Health Protection)
- Health promotion
- Statutory and regulatory functions (Chinese medicine, drugs, port health, tobacco control, medical devices, private healthcare institutions)
- Preventive clinical services (elderly health, maternal and child health, student health, HIV/AIDS, tuberculosis)
- Other clinical services (forensic pathology, clinical genetics, child assessment, primnary health and dental care for civil servants and dependants)

## b. Hospital Authority (HA)

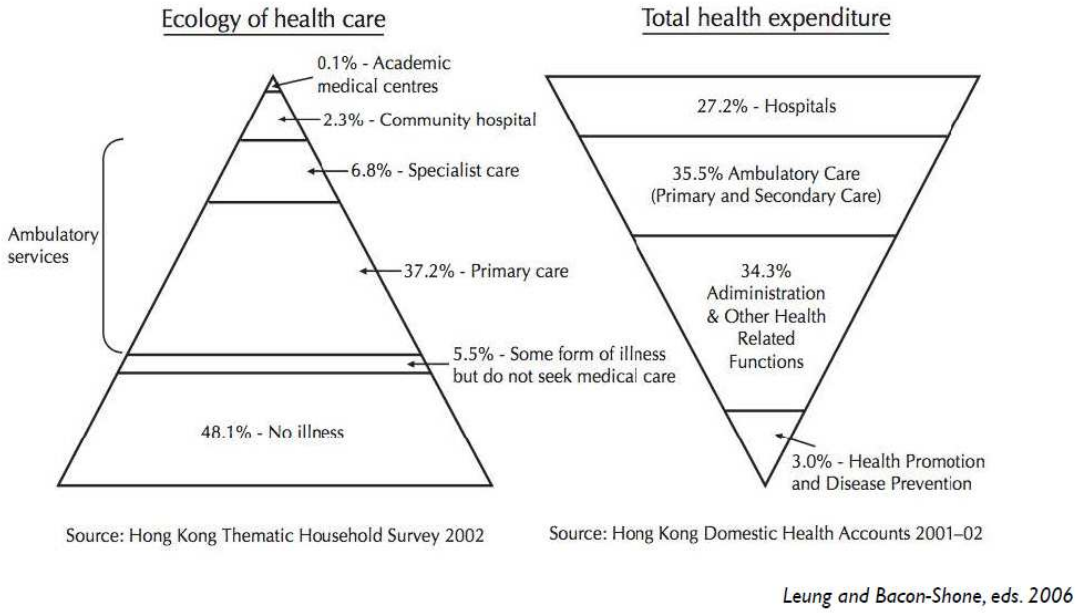
- Public statutory body directly accountable to the Food and Health Bureau
- Manages **public hospital system**:
  - 42 public hospitals and institutions
  - 48 specialist out-patient clinics
  - 73 general out-patient clinics
  - Organized into 7 geographical clusters

# 2. Ecology




*Updated after Leung et al. Soc Sci Med 2005*

# 3. 'Health Financing Paradox'




Source: Hong Kong Thematic Household Survey 2002

Source: Hong Kong Domestic Health Accounts 2001–02

*Leung and Bacon-Shone, eds. 2006*

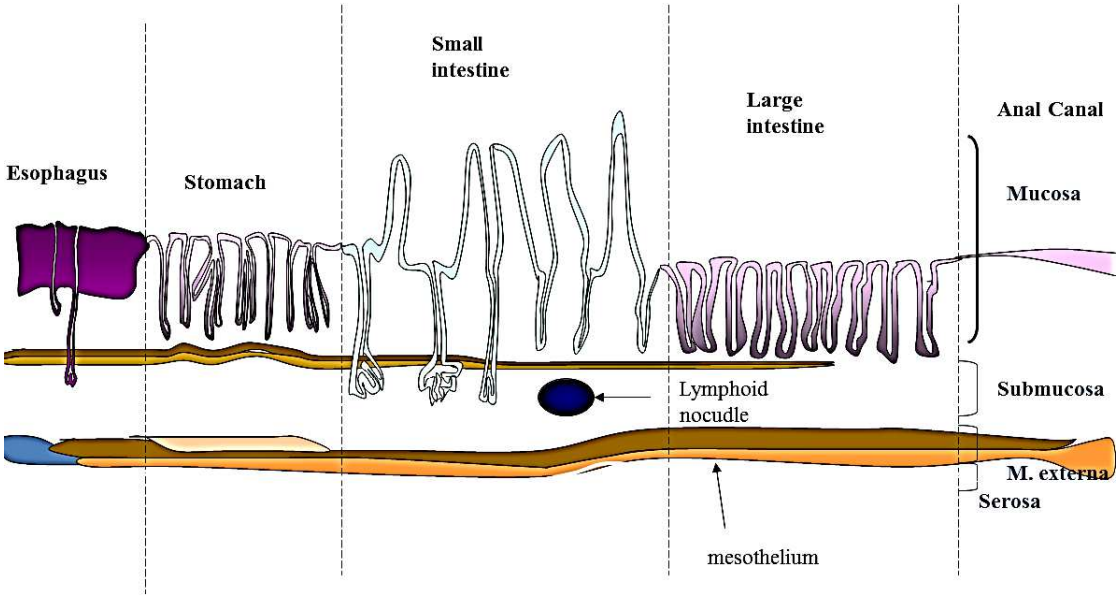
# 4. Future Reform

## a. The Harvard Report (1999)

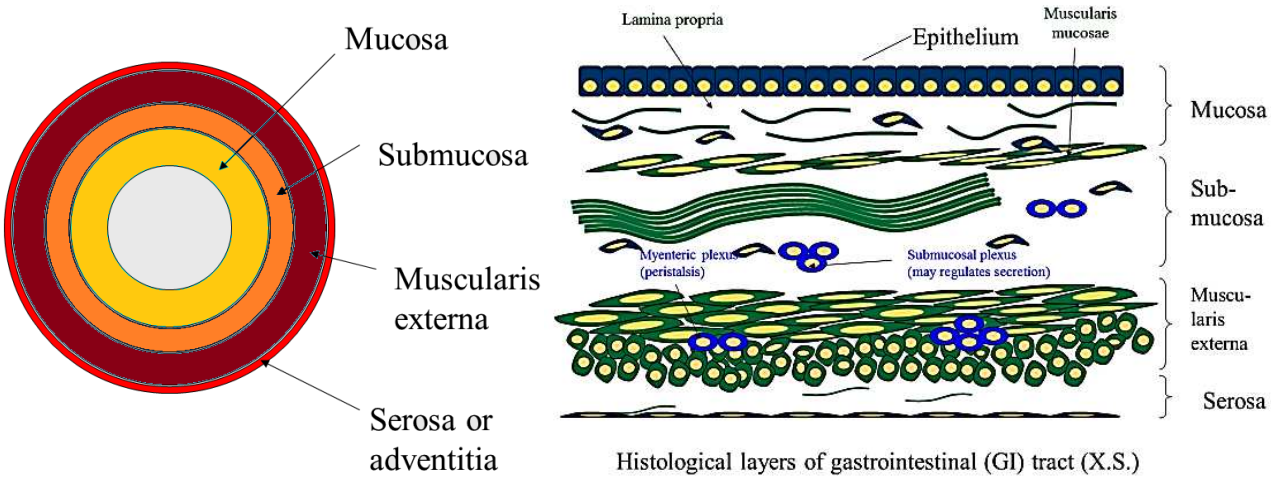
- Assessment of HK health system by Harvard University, commissioned by HK government
- Criticisms:
  - Compartmentalized, hospital-based delivery system
  - Incoherent financing
  - Questionable financial sustainability
  - Supplier-dominated decision-making
- Proposal:
  - Financing:
    - → **Compulsory social insurance scheme** to pool risk across entire population (health security plan)
    - → **Long-term health savings account** (MEDISAGE)
  - Organization:
    - → Reorganization of HA into competing integrated health systems
  - Payments:
    - → Payments made on per episode or packaged basis to reduce oversupply; to be negotiated between Health Security Fund and providers

# L28 Gastrointestinal Tract

## A. Histological Layers




Summary of histological layers of GI tract




Histological layers of gastrointestinal (GI) tract (X.S.)

# 1. Mucosa

- Functions: absorption, secretion, protection
- Epithelial lining:
  - Oesophagus: stratified squamous non-keratinizing epithelium
  - Stomach: protective simple columnar epithelium (predominantly mucus-secreting)
  - Intestines: simple columnar epithelium (absorptive cells and mucus-secreting cells)
- Lamina propria:
  - Accommodates the mucosal gland (epithelial invagination)
  - Loose connective tissues
  - Lymphatic and fenestrated blood capillaries
  - Supports and nourishes the epithelium
  - Unencapsulated lymphoid nodules and plasma cells (for protection)
- Muscularis mucosae:
  - Thin layers of smooth muscle (inner circular and outer longitudinal)
  - For local movement and folding of the mucosa (controlled by **Meissner's plexus** and some paracrine hormones)
  - Modulates the heught of villi in small intestines

# 2. Submucosa

- Loose c.t. with larger blood vessels and lymph vessels
- **Meissner's plexus**: submucosal plexus of ANS ganglion cells and nerve fibres
- Contains mucus-secreting glands in duodenum and esophagus only

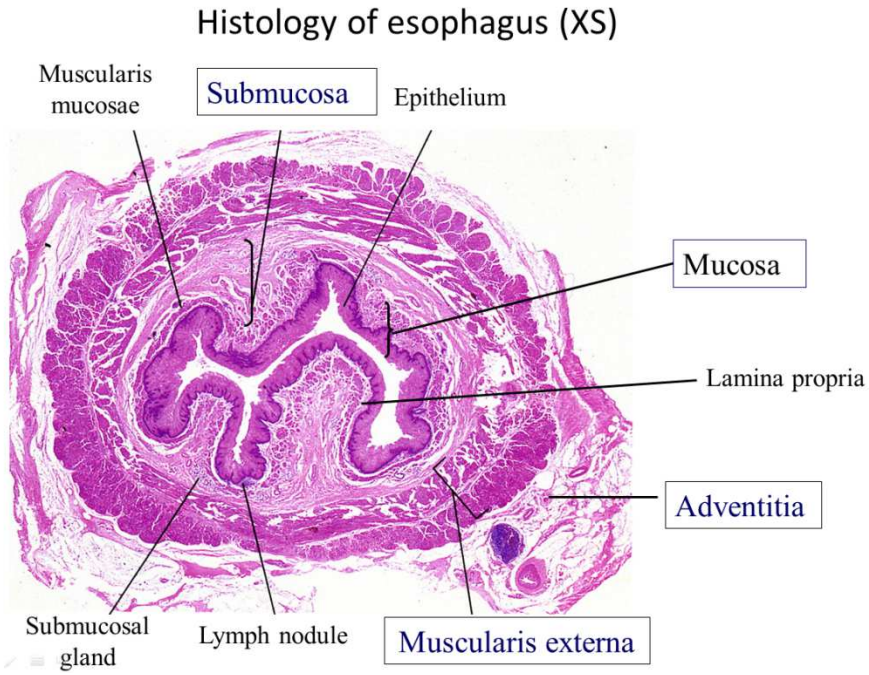
# 3. Muscularis Externa

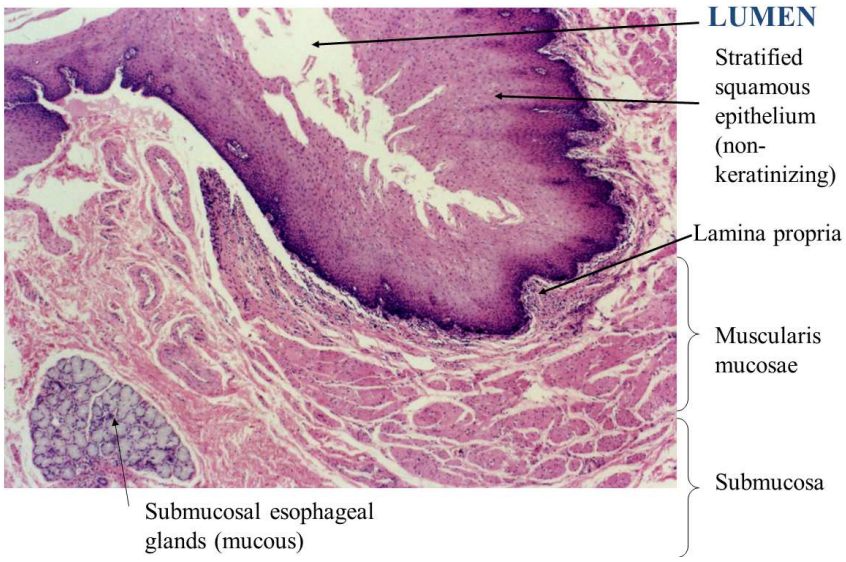
- Two layers of smooth muscles: inner (circular) and outer (longitudinal)
- Regulate luminal diameter of the intestine
- Moves luminal contents along the tract by peristalsis
- Peristaltic waves coordinated by **Auerbach's (myenteric plexus)** (between circular and longitudinal muscle layers and by paracrine hormones

# 4. External Layer

- **Serosa**: visceral (of organ) peritoneum (mesothelium (simple squamous) + c.t.), i.e. serous membrane
- **Adventitia**: loose connective tissues in esophagus and retroperitoneal (retro- = behind) segment of intestines

# B. Oesophagus

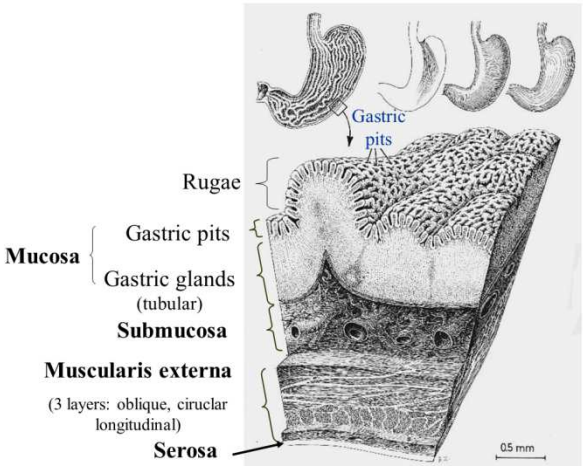



- Muscular walls to convey chewed food from pharynx to the stomach
- Stratified squamous non-keratinized epithelium to withstand abrasion
- **Esophageal cardiac glands** (simple tubular, mucous) in lamina propria at upper submucosa to eases passage of ingested food
- Substantial **muscularis mucosae**
- **Muscularis externa**:
  - Striated in the upper third, smooth in lower third, mixed in middle third
  - Physiologic sphincters at two sites: pharyngoesophageal and gastroesophageal
- **Adventitia** (not serosa) as outermost layer

# C. Stomach

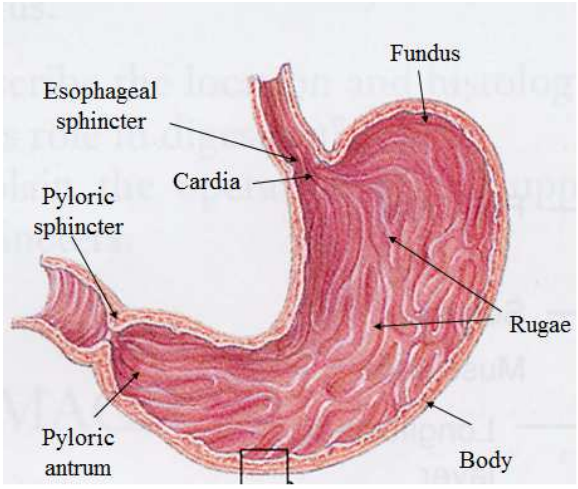
- Function: for breaking down ingested food and as beginning of digestion (into **chime**)
- Gastric mucosa (simple columnar epithelium) raised into folds (**rugae**)
- Mucosal simple tubular glands: HCl (parietal), mucus (neck), digestive enzymes (zymogen), hormones
- Mucous lining at the surface for protection from acidity
- No submucosal glands except in region close to duodenum
- Three layers of muscles in muscularis externa:
  - Innermost (oblique)
  - Middle (circular)
  - Outermost (longitudinal)
- Serosal covering (continuation of mesogastrium – gastric mesentery)




# 1. Division of Stomach

## a. Cardia

- Epithelium changed drastically from **stratified squamous** in esophagus to **simple columnar** in cardiac region
- Mucosal cardiac gland
- Secretory cells: mucus and lysozyme (antibacterial)
- Few parietal cells for HCl



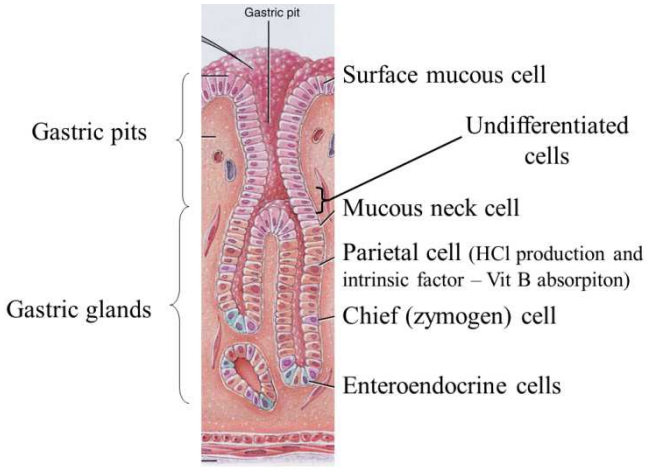

## b. Fundus and Body of Stomach

- Surface epithelium: **simple mucous columnar cells** (not goblet cells)
- **Gastric pit (foveola)**: tiny epithelial recess where gastric glands open into
  - Lined by mucous columnar cells
- **Gastric (fundic) gland**: straight, branched at base
  - Secretes gastric juice (water, HCl, mucus, digestive enzymes, electrolytes)

## c. Pylorus

- **Pyloric glands**:
  - Deeper pits
  - Shorter gland and more branched
  - Proximal region: secrete HCl and mucus
  - Other regions: entirely mucous secreting
  - Fewer enteroendocrine cells: secretion of serotonin (neurotransmitter), gastrin (↑ gastric acid secretion), somatostatin (↓ gastric acid secretion)
- **Pyloric sphincter**: Substantial circular middle layer of muscularis externa at outlet of stomach

# 2. Gastric Glands




- **Simple branched mucosal gland** in lamina propria:
  - **Isthmus** (opening into gastric pits, uppermost)
  - **Neck**
  - **Base** (lowest)
- Isthmus and neck: germination zone (replace all cells in glands, pits and luminal surface)
- Regulated by **vagus nerve** and by several hormones (cells in gastric and duodenum):
  - **Gastrin**: stimulate HCl secretion
  - **Somatostatin**: inhibit release of gastrin
  - **Urogastrone**: inhibit HCl secretion

## a. Mucous Neck Cells

- In the neck region
- Mucus secreting and mitotic

## b. Parietal (Oxyntic) Cells

- Large pale-staining, pyramidal
- Concentrated in the upper and middle part of gastric glands
- Intracellular channels (canaliculi) to ↑ surface area
  - HCl production
  - Lined by numerous mitochondria and SER (active transport of $H^+$ ions) → acidophilia in H&E staining
  - Numerous interdigitation and long microvilli
- Mucous coating to protect gastric lining
- Secrete **gastric intrinsic factor**
  - For vitamin B12 absorption in small intestine
  - Deficiency → impaired RBC formation i.e. pernicious anemia

## c. Chief (Zymogenic) Cells

- Concentrated at lower half of the gland
- Many **zymogen** granules (enzyme precursors: pepsinogen and precursor of rennin and lipase)
  - Pepsinogen → pepsin by acidic pH
- Extensive rER (basophilic), basally located nucleus
- Prominent Golgi complex

## d. Enteroendocrine Cells

- Small number (of numerous variety)
- Produce peptide hormones (serotonin etc.)
- Referred to as the difuse **neuroendocrine system**:
  - Some GI peptides and amines are neurotransmitters
  - **Paraneurone**: neurotransmitter-secreting cells
  - Many belongs to **APUD cells system** (amine precursor uptake and decarboxylation)

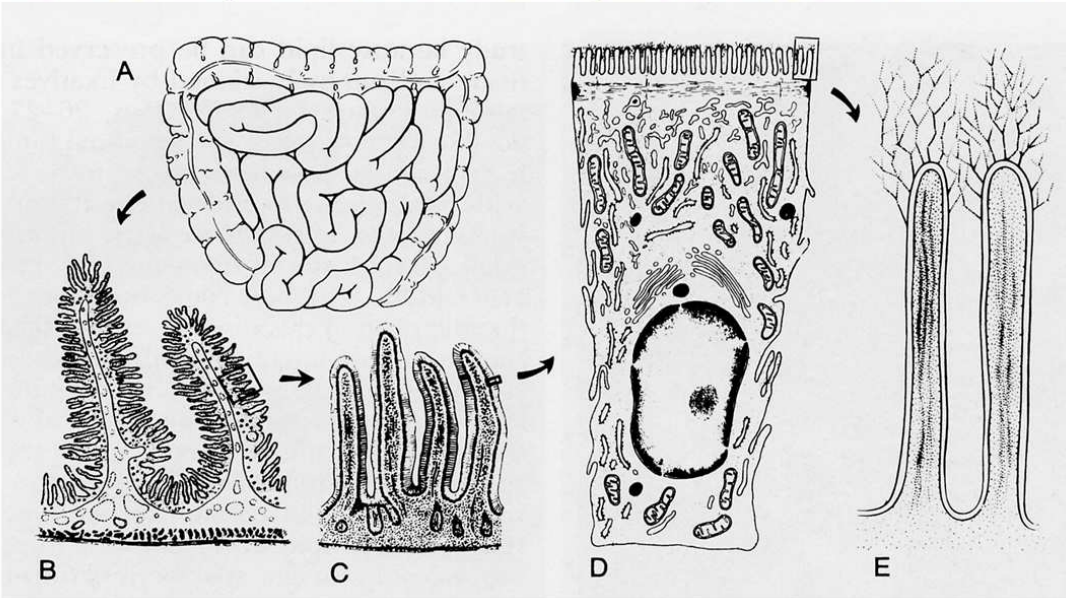
## e. Undifferentiated Cells (Neck and Isthmus)

- Germination region
- High mitotic rate
- Epithelium replaced in 4-6 days

# D. Small Intestine

- Composed of **duodenum**, **jejunum**, **ileum**
- Functions: Complete digestion, absorbs nutrients, produces a variety of GI hormones
- Digestion:
  - Digestive juices from pancreas:
    - → Alkalinity to counteract gastric acidity
    - → Digestive enzymes for digestion
    - → Bile from liver to augment pancreatic lipase
  - Mucus from:
    - → Submucosal (**Brunner's**) glands in duodenum
    - → Mucosal glands in lamina propria of mucosa in GI tract (**crypts of Lieberkuhn** or intestinal crypts in small and large intestine)
    - → **Goblet cells** of mucosal epithelium
- Absorption area expanded by:
  - **Plicae circulares** (approx. 2-3x surface area)
  - **Intestinal villi** (approx. 10x surface area)
  - **Microvilli** (approx. 20x surface area)
  - Collectively approx. 400-600x surface area

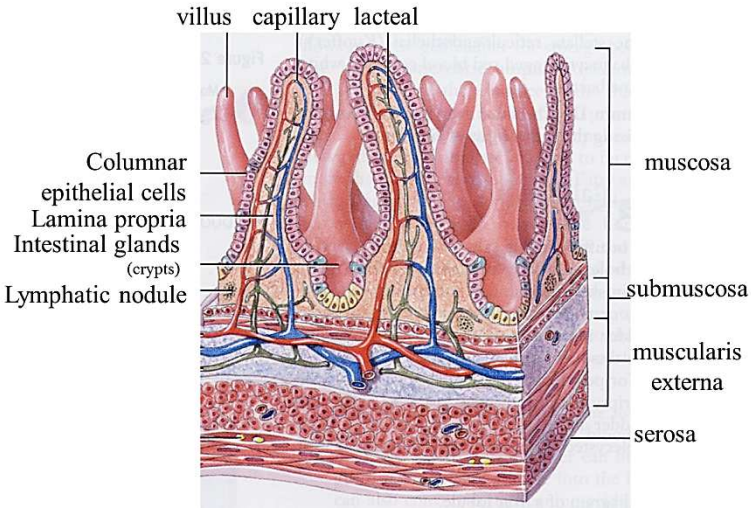
Levels of amplification of the absorptive surface of the intestine




(A) convolution; (B) plicae circulares; (C) villi; (D) microvilli; (E) oligosaccharide chain of integral protein

# 1. Features

## a. Villus




- Tall absorptive columnar cells with abundant goblet cells and occasional enteroendocrine cells interspersed
- Contain a profuse network of fenestrated blood capillaries for absorption of nutrients
- Absorption of fats by lymphatic capillaries (**lacteal**)
  - Absorbed fat in **monoglycerides** and **free FAs**
  - Packaged as lipid (in SER) in **chylomicrons** and secreted into lacteal
  - **Chylomicrons** then enter blood via thoracic duct
- Smooth muscle cells extend into villi from muscularis mucosae → modulate height of villus
- Numerous cell type (lymphocytes, plasma cells, eosinophils) in lamina propia

## b. Intestinal Glands

- Also called **Crypts of Lieberkühn**
- Main cell types: **goblet cells**, **paneth cells**

## c. Peyer's Patches

- Aggregated lymphoid nodules
- Particularly prominent in ileal walls
- Extended to submucosa
- **Gut-associated lymphoid tissue (GALT)** for mucosal immunity
- Antigen-presenting epithelial cells (**M cells**) overlying aggregated lymphoid nodules: ingest foreign antigen → deliver them to macrophages or lymphocytes → B cells differentiate into IgA producing plasma cells → IgA secreted onto free surface of epithelia → primary defence against mucosal infection

# 2. Cell Types in Small Intestine

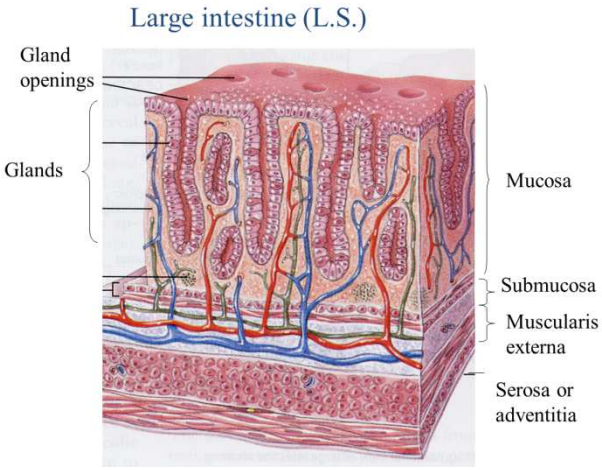
- All cell types derived from small crypt base columnar cells (stem cells)
- Epithelia cells on villi renew about every 5-6 days
- **Villous columnar cells**:
  - For absorption (microvilli → striated/brush border)
  - **Brush border enzymes**: disaccharidases and peptidases, enzymes are integral membrane glycoprotein of cell membrane
  - Junctional complexes: tight junctions (sealing) and adhering junctions
- **Goblet cells**:
  - In both villi in crypts
  - ↑ in number from duodenum to ileum
- **Paneth cells**:
  - At lower part of crypts
  - Have large acidophilic zymogen granules
  - Extensive ER and prominent Golgi apparatus
  - Major source of **lysozyme**
- **Enteroendocrine cells**:
  - GI hormones including secretin and cholescystokinin-pancreozymin

# 3. Regional Variations in Small Intestines

| | Duodenum | Jejunum | Ileum |
|---|---|---|---|
| Plicae circulares | Present | Present | Proximal half |
| Villi | Broad, tongue-like | Narrow | Narrow |
| Submucosal gland | Brunner's gland | Absent | Absent |
| Lymphoid nodules | Present | Present | Extensive as Peyer's patches |
| Outermost layer | Adventitia (mostly retro-peritoneal) | Serosa | serosa |

# E. Large Intestines

- Consists of **colon**, **rectum**, **anal canal**, **appendix**
- Functions:
  - Complete absorption and retrieve water (and electrolyte) from luminal content
  - Produces abundant protective mucus, some GI hormones, no digestive enzymes secreted
  - House bacteria that produce vitamin B12 and K
- No villi, numerous crypts (long and straight)
- No Paneth cells
- Surface epithelium: tall absorptive columnar cells with striated border, goblet cells (↑ in number from ascending colon to rectum)
  - Replaced ~ every 6 days by new cells arising from lower parts of crypts




- No submucosal glands
- Caecum and colon, longitudinal muscle (muscularis externa) arranged mostly as three longitudinal bands (**teniae coli**) → continuous contraction
- Colon has **sacculation** (formation of sacs (**haustra coli**)), absent in appendix
- Presence of **appendix epiploica** (pouches of peritoneum filled with fat on colon)
- Retroperitoneal segment of colon and rectum have an adventitia, others serosa
- At anus,
  - **Internal anal sphincter**: circular smooth muscle
  - **External anal sphincter**: circular band of skeletal muscle → voluntary control of defecation
  - Epithelium changes: simple columnar epithelial lining changes to stratified squamous non-keratinizing then to keratinizing epidermis of skin

# 1. Hemorrhoids (piles)

- Mucosal lining of anal canal lacks crypts, raised into longitudinal ridges (**anal columns**) joined to form **anal valves**
- Discontinuous muscularis mucosa that terminates at **anal valve**
- Contains a plexus of small vein (**anastomosis** ('bridge vessel') between portal venous system and systemic venous system)
- **Hemorrhoid**: Chronic congestion of anal venous plexus → dilat and varicosed → anal mucosa bulges (**internal hemorrhoids**) → protrude under anal skin (**external hemorrhoids**)

# 2. Appendix

- Blind end appendage of **caecum**
- Microscopically resembles large intestine
- Prominent lymph nodules: involves deep into submucosa (confluent and surround entire lumen)
- **Appendicitis**: obstruction of lumen → bacterial infection → perforation → **peritonitis**
- **Appendectomy**: surgical removal of inflamed appendix

# L29 Epithelial and Glandular Tissue

## A. Epithelial Tissue

- One of the four basic types of body (epithelium, connective tissues, muscle tissue and nerve tissue)
- Derived from all three germ layers (**ectoderm**, **mesoderm**, **endoderm**)
  - **Ectoderm**: epidermis of skin; epithelial linings of sweat glands, duct oral surface vagina and anal canals etc
  - **Mesoderm**: epithelial linings of blood vessels (endothelium), surfaces of body cavities (mesothelium), genital ducts, urinary ducts and tubules etc
  - **Endoderm**: epidermis of esophagus, epithelial linings of GI tract and lower respiratory tract epithelium, epithelial parts of liver and pancreas etc
- Composed of closely packed and contiguous (touching) cells
- Form membranous sheets covering surface of the body (skin and GI tracts) and cavity of body (eg thoracic, pleural, abdominal)
- Properties:
  - All cells have **junctional structures** (**desmosome** between cells, **hemidesmosome** for cell-to-matrix) at lateral and basal surfaces (to form intact sheet to cover a surface)
  - All cells rest on **basement membrane**
  - **Cytokeratin** as **intermediate filament** (→ detection in c.t. indicates cancer)
  - **Avascular**: derived nutrients by diffusion from blood vessels in underlying c.t.
  - Supported by c.t. underneath
  - Little or no intercellular matrix (unlike c.t.)
  - Frequently renewed and replaced (→ most possible site of cancer)
    - → Presence of self-renewal stem cells (adult stem cells)
    - → Intestinal epithelium renew in approx. a week's time (stem cells at base of crypts)
    - → Skin epithelium renew in approx. a month's time (stem cells in **stratum basale**)

- Functions:
  - Secretion (as glandular epithelium): endocrine (hormones), exocrine (sweat, digestive enzymes, mucin)
  - Absorption: digestive epithelium
  - Transport: lining of kidney tubules
  - Protection: epidermis of skin (dermis is c.t.)
  - Sensory: retina and olfactory epithelia
- All epithelia separated from underlying c.t. by **basement membranes** (structure under light microscope)
  - **Basal lamina**: lamina lucida (cell membrane) + lamina densa (collagen IV) (derived from epithelium)
  - **Protein layer**: collagen VII + fibrilla
  - **Lamina reticularis**: collagen III (derived from c.t.)
- **Mesothelium**: epithelium covering serous body cavity (pleural or abdominal) → secretes serous fluid
- **Endothelium**: epithelium covering heart chambers, blood and lymph vessels
- Classification:

1) **Number of cell layers**: simple or stratified
2) **Cell shape**: **squamous**, cuboidal, columnar
3) **Presence or absence of keratinized (dead) cell laye**r: keratinized or non-keratinized
4) **Presence of cilia**: ciliated or non-ciliated

*Basement membrane contains collagen IV → cancer cells secrete type IV collagenase to invade tissues

# 1. Classification

- **Simple squamous**: e.g. parietal layer of Bowman's capsule, endothelium of blood vessel, thin segment of loop of Henle (in kidney), respiratory epithelium (alveli)
- **Simple cuboidal**: e.g. lining of most ducts, thyroid gland
- **Simple columnar**: e.g. absorptive epithelium of intestine and gall bladder
- **Stratified cuboidal**: e.g. ducts of sweat gland
- **Stratified columnar**: e.g. lining of large excretory ducts, conjunctiva of eye
- **Stratified squamous (non-keratinized)**: lines moist surfaces, e.g. esophagus, vagina
- **Stratified squamous (keratinized)**: lines dry surfaces, eg. Epidermis of skin
- **Pseudostratified columnar**: multiple layers of nuclei but with all cells touching the basement membrane, eg. Linings of trachea, bron chi and epididymis (with cilia)
- **Transitional**: present in urinary epithelium, cell shape changes from cuboidal (unstretched) to squamous (stretched); present in bladder and ureter

*__Metaplasia__: chronic change of environment → change from one type to the other (e.g. smoking causes squamous metaplasia in respiratory epithelium (Pseudostratified columnar))

# 2. Polarity of Epithelial Cells

- Apical surface:
  - **Cilia** (in respiratory epithelium and lining epithelium of oviduct)
  - **Microvilli** (in absorptive cells of GI tract)
  - **Stereocilia** (long microvilli present in epididymis → absorb excess fluid used to propel sperm from testis as they gain motility)
  - **Flagella**: (movement of spermatozoa from **seminiferous tubules** in testis)
- Lateral surface:
  - **Junctional complex** for adhesion and barrier to passage of material
  - **Gap junction** for communication (by connexon)
  - Membrane interdigitation (in active absorptive cells eg kidney tubules)
- Basal surface:
  - **Hemidesmosome** (half desmosome, attaches epithelial cells onto basement membrane)

## a. Junctional Complex

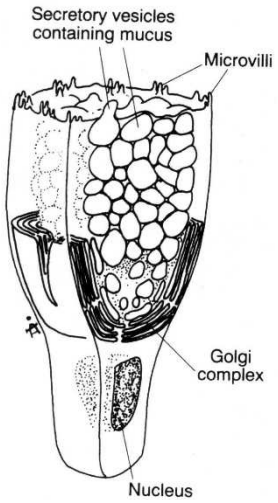
- **Zonula occluden**: tight junction, belt-like, prevent passage of fluid between epithelial cells, associated with special protein complexes
- **Zona adherens**: adhering junction, belt-like, for adhesion, associated with actin → form a net to separate upper and lower part of epithelial cells
- **Desmosome**: spot-like adhering junction, associated with intermediate filaments (keratin tonofilaments)

*__Pemphigoid__: Antibody against desmosomal protein → blistering AI skin disease

# B. Glandular Epithelium

- **Glandular epithelium**: Epithelial cells specialized for secretion
- Present as downgrowth of epithelia into underlying c.t.
- **Exocrine gland**: with excretory duct; deliver secretion to epithelial surface
- **Endocrine gland**: ductless; deliver secretions (hormones) into blood

## 1. Classification




- **Cell number**:
  - Unicellular eg. Goblet cell
  - Multicellular eg. Most types of glands
- **Shape of glands**:
  - Tubular (branched or unbranched)
  - **Acinar** (acinus, 'ball'-like)
  - Mixed or **tuboacinar**
- **Duct of gland**:
  - Unbranched duct → simple gland
  - Branched duct → compound gland
- **Nature of secretion**:
  - **Serous**: watery with protein (enzymes); basophilic cytoplasm (abundant RER for protein synthesis)
  - **Mucous** (mucinous): mucin (rich in proteoglycan), thick and slimy
  - Mixed (eg salivary gland)
- **Mode of secretion**:
  - **Merocrine**: secretion pass to outside by **exocytosis** without significant loss of cytoplasm eg pancreas
  - **Apocrine**: loss of a portion of apical cytoplasm as secretory product eg mammary gland
  - **Holocrine**: lysis of whole cell during the secretory process eg sebaceous gland

*Mucous and serous membranes:

**Mucous membrane (mucosa)**:

- Lines cavities connected with outside of body (alimentary tract, respiratory tract etc)
- Mucous secretion
- Epithelium + lamina propria (c.t.) + muscularis mucosa

**Serous membrane (serosa)**:

- Lines peritoneal, pericardial and pleural cavity
- Watery fluid
- Mesothelium + c.t.

# L30 Connective Tissues

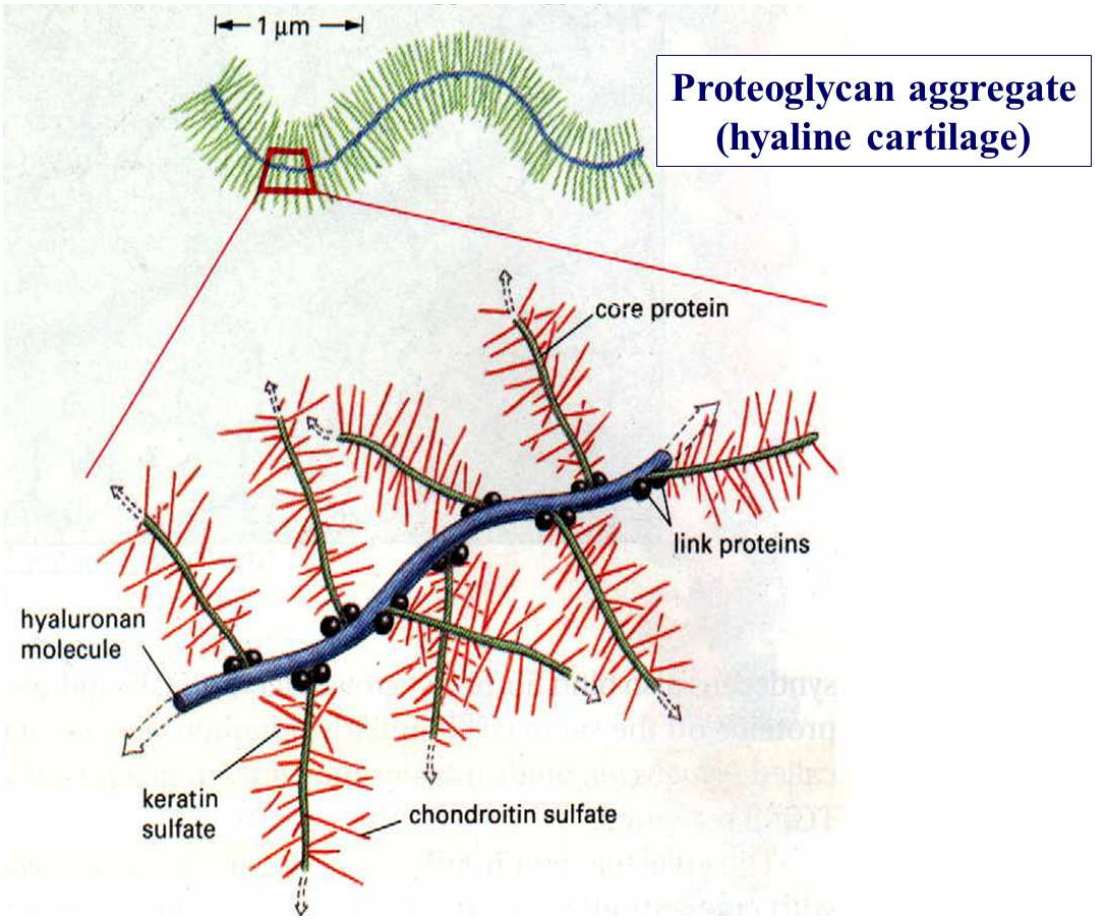
## A. Connective Tissues

- **Origin**: embryonic mesenchyme (mesodermal germ layer)
- **Functions**:
  - Cohesion of structures: ECM plays crucial role in regulating behavior of cells
  - Structural: support epithelial cells, others (eg. ligaments, tendons)
  - Nutrient diffusion and waste removal
  - Protection (eg. prevent spread of infection)
  - Tissue repairs
- Examples of specialized c.t.:
  - Cartilage and bone: for support
  - Adipose tissues: storage of lipid
  - Hemopoietic tissue: formation of blood cells
- Consists of:
  - **Extra-cellular matrix**: ground substance (fluid) + fibrous component
  - **Cells**: fibroblasts, adipocytes, lymphocytes, macrophages etc.
- Classification:
  - By relative abundance of fibres: **loose** or **dense**
  - By arrangement of fibres: **irregular** or **regular**
  - By nature of fibres: **white** for collage, **yellow** for elastic
- Types:
  - Loose c.t.: mesentery, Wharton's jelly in umbilical cord, lamina propria in GI tract
  - Dense c.t.: dense irregular (dermis) and dense regular (tendon, ligament)

# 1. Extra-cellular Matrix

## a. Ground substance

- Amorphous (can change shape), highly hydrated gel (resist compressive force)
- Complex mixture of **proteoglycans** and **glycoproteins**:
  - **Proteoglycans**: core protein + glycosaminoglycan (GAG) side chains
    → **Glycosaminoglycan**: $[\text{amino sugar + uronic sugar}]_n$ → highly extended and osmotically active → absorb water and form hydrated gel
  - **Glycoproteins**: proteins + oligosaccharide side chain (→ adhesion of cells to substrate)



## b. Fibrous Components

### i. Collagen Fibres

- Present in all kinds of c.t.
- Major components in skin and bone
- Acidophilic
- Unbranched molecules
- Abundant in hydroxyproline and hydroxylysine
- Consists of parallel fibrils (cross-striated under EM) of triple helical tropocollagen molecules
- >27 subtypes, most common is type I (almost everywhere)
- Note type IV in basal lamina in epithelial cells

### ii. Reticular Fibres

- Extremely fine fibres of **collagen type III**
- Form extensive network to support soft organs and tissues
- Not visible under H&E but easily visible under silver stain (**argyrophilic**)
- PAS (polysaccharide staining) positive: high content of glycoproteins

### iii. Elastic Fibres

- Stretchable (with cross-linked molecules) fibres
- Branched and rejoined to form a loose network in loose c.t.
- Amorphous core of **elastin** surrounded by micro-fibrillar glycoprotein (fibrillin)
- When abundant → yellow colour
- Difficult to stain with H&E
- Distribution: loose network in loose c.t., aortic walls, vertebral column

# 2. Cells of Connective Tissues

## a. Fibroblasts

- Most common cell type
- Synthesize fibrous component and ground substance
- Active state: fibroblast; quiescent state: fibrocyte
- Respond to tissue damage and synthesize new matrix
- Some fibroblasts may be precursor cells for smooth muscle cell, adipocyte, chondroblast, osteoblast
- Excessive proliferation → fibrosis

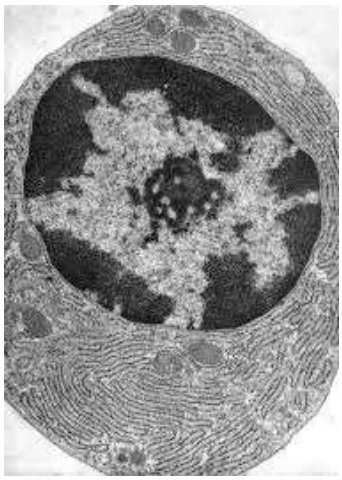
## b. Macrophages

- Phagocytic, derived from circulating **monocytes**
- Distributed throughout whole body and present in most organs
- Constitute **mononuclear phagocyte system**: regeneration of blood cells and defense against microorganism
- Oval or kidney-shaped nuclei, eccentrically located
- Irregular surfaces (actively involved in pinocytotic and phagocytic activities)
- Many lysosome
- Long-living
- Form **multinuclear giant cells** in pathologically conditions
- Surface receptors for Fc (antibody) and C3 (complements) – **opsonization**: facilitation of phagocytosis by antibodies and other substances
- Functions:
  - Ingestion of particles and their digestion by lysosomal enzymes
  - Immune defense (antigen-presentation, secretion of growth factors and cytokines)

## c. Mast cells

- Oval to round in shape
- Nucleus obscured by cytoplasmic granules
- Specific surface receptors – **IgE** (similar to basophils)
- Mast cell granules are **metachromatic** (show different colour from stain)
- Content of mast cell granules: histamine, neutral protease, ECF-A (eosinophil chemotactic factor of anaphylaxis → allergic reaction), leukotrienes
- Release of granules triggered by binding of antigen to **IgE**
- Involved in immediate hypersensitivity reactions (anaphylactic shock i.e. serious allergy)

## d. Plasma Cells



- Few in c.t.
- Differentiated from B cells
- Synthesis of Ab
- Large ovoid cells with basophilic cytoplasm (due to abundant RER involved in antibody synthesis)
- **Juxtanuclear** (near nucleus) Golgi complex
- Eccentrically placed nucleus, heterochromatin clump (with appearance of **clock-face nucleus**)

## e. Leukocytes

- Migratory cells from blood (more during inflammation)
- Major types: neutrophil, eosinophil, basophil, lymphocyte

## f. Adipose cells

- Two types:
  - **Unilocular (yellow) adipose tissue**
    - → Cells only have one large fat vacuole
    - → Common form
    - → Main energy source
  - **Multilocular (brown) adipose tissue**
    - → Cells have several fat vacuoles
    - → Numerous mitochondria, large number of blood capillaries
    - → Transform stored chemical energy to heat when stimulated (thermogenesis)
    - → Important in first few months of postnatal life

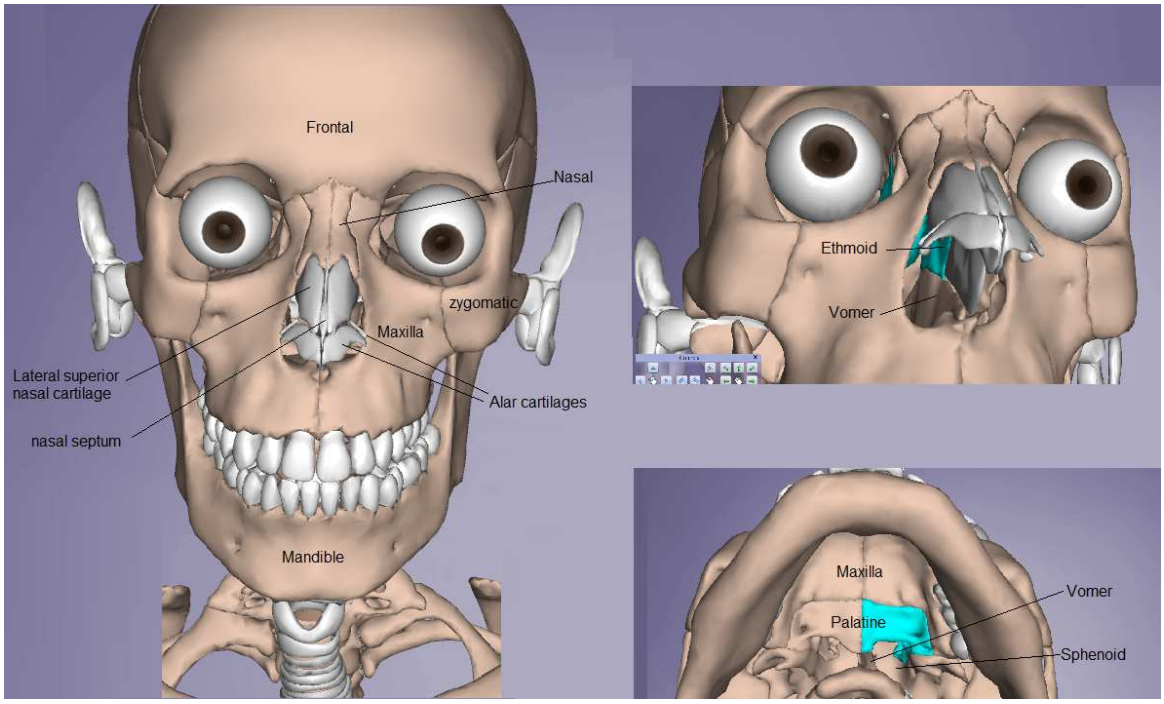
# L32 Structural Organization of the Respiratory System

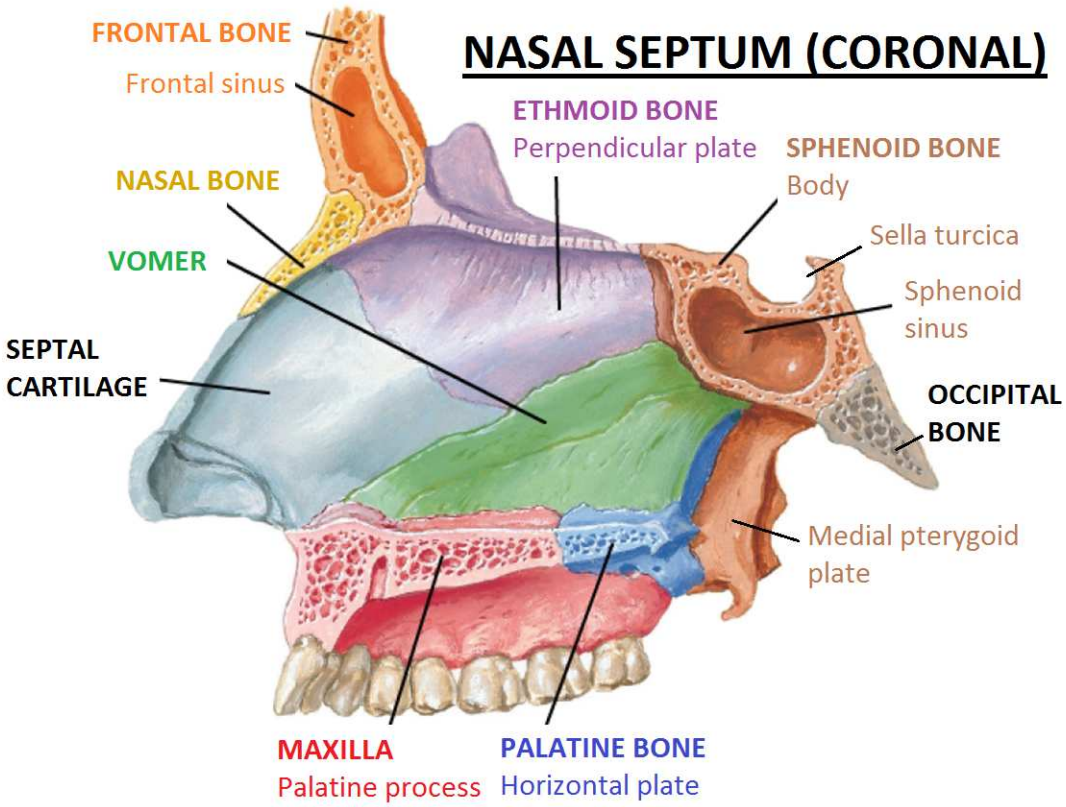
## A. Respiratory System

- Major organs: nose, pharynx, trachea, bronchi, lungs, muscles of respiration and diaphragm
- Function: provide pathway for entry of oxygen into body and excretion of $CO_2$ into the atmosphere

## B. Nasal Cavity

- Nasal cavities considered **upper part of respiratory system**, the rest is the lower part
- **Nose**: immovable bony bridge supported by (1) **nasal bones** (2) frontal processes of **maxillae** (3) nasal part of **frontal bone**



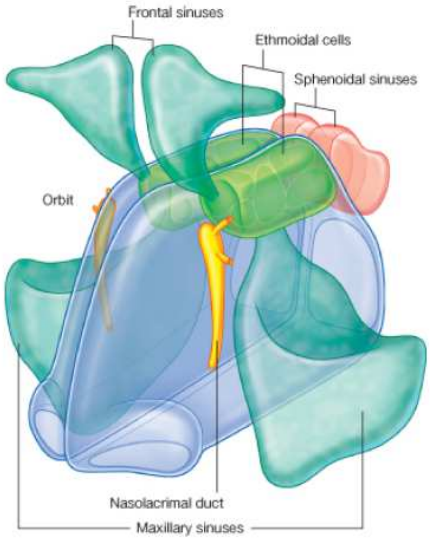



- **Nose** opens anteriorly as **anterior nares aperture** and posteriorly as **posterior nares aperture**
- **Nose** divided into right and left nasal cavities by **nasal septum**
  - **Nasal septum** made up of: (1) perpendicular plate of **ethmoid** bone, (2) **vomer**, (3) septal cartilage
- **Roof** of nasal cavity formed by **frontonasal**, **ethmoidal** and **sphenoid bones**
- **Floor** of nasal cavity formed by palatine process of **maxilla** and horizontal plate of **palatine** bone
- **Medial wall** is formed by nasal septum
- **Lateral wall** is formed by three curvature plates (curve downwards) known as **conchae** (or **turbinates**): **superior concha**, **middle concha** and **inferior concha**
- Beneath each concha there is a potential space (**meatus**) for drainage of **paranasal sinuses** and **nasolacrimal ducts**
- Space above **superior concha** is known as **spheno-ethmoidal recess**
- Nasal cavity and paranasal sinuses lined by **pseudostratified ciliated columnar epithelium**

- Near roof, lined by **olfactory epithelium** containing cell bodies of **olfactory nerve (CN I)**
  - Other parts innervated by branches of **trigeminal nerve (CN V)**
  - **Nasal (pterygopalatine) ganglion** formed from **maxillary nerve (CN $V_2$)** and **facial nerve (CN X)** for sensory (through CN $V_2$) and autonomic nervous system
- Functions:
  - Respiration
  - **Olfaction** (smelling)
  - Filtration of dust
  - Humidification of air
  - Drainage of paranasal sinuses (air-filled extension of nasal cavities)
- Blood supply:
  - Branches of **maxillary artery** (from external carotid artery)
  - Branches of **facial artery** (from external carotid artery, for mucosa)
  - Branches of **ophthalmic artery** (from internal carotid artery, for structures around orbit)
  - Blood is drained into **pteryogoid plexus**, **facial vein**, **infraorbital vein** and **ophthalmic vein**

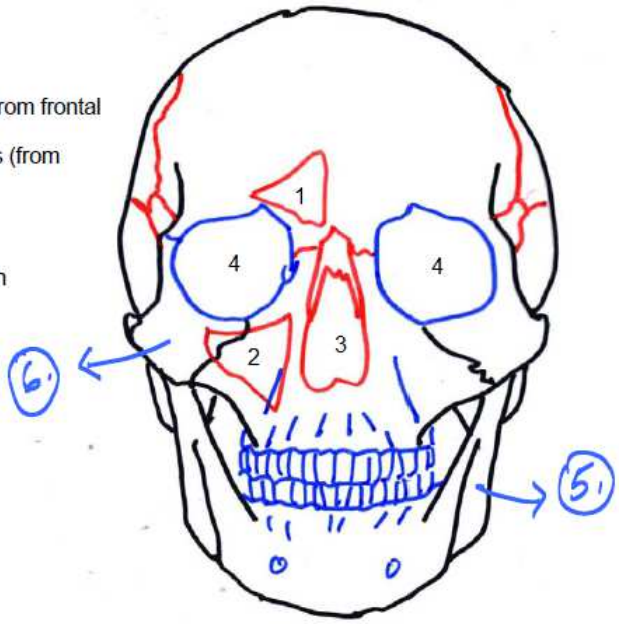
# C. Paranasal Sinuses

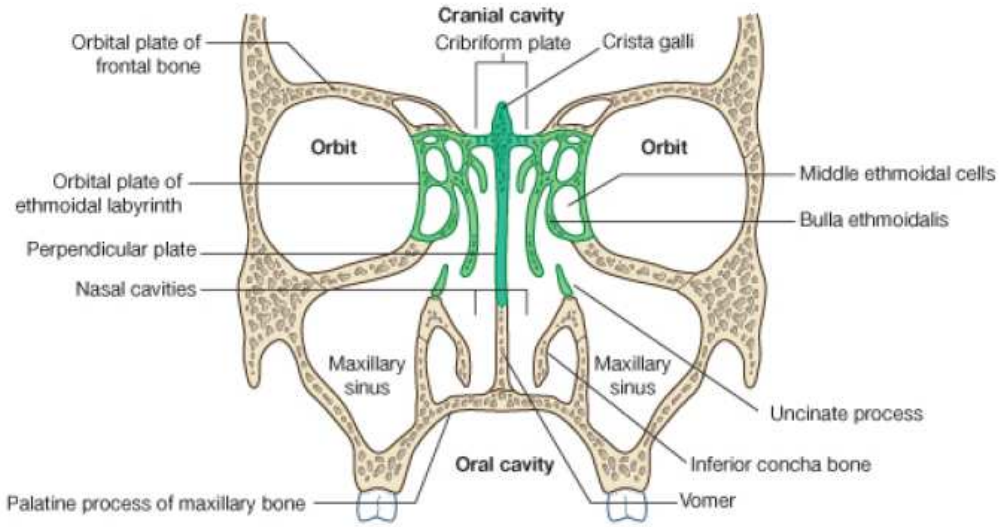
- **Paranasal sinuses**: air-filled extension of the nasal cavity
- Location: **frontal sinuses**, **ethmoid sinuses**, **sphenoid sinuses**, **maxillary sinuses**
  - Ethmoid sinuses divided into anterior/middle/posterior
  - Maxillary sinus commonly infected due to inefficient drainage



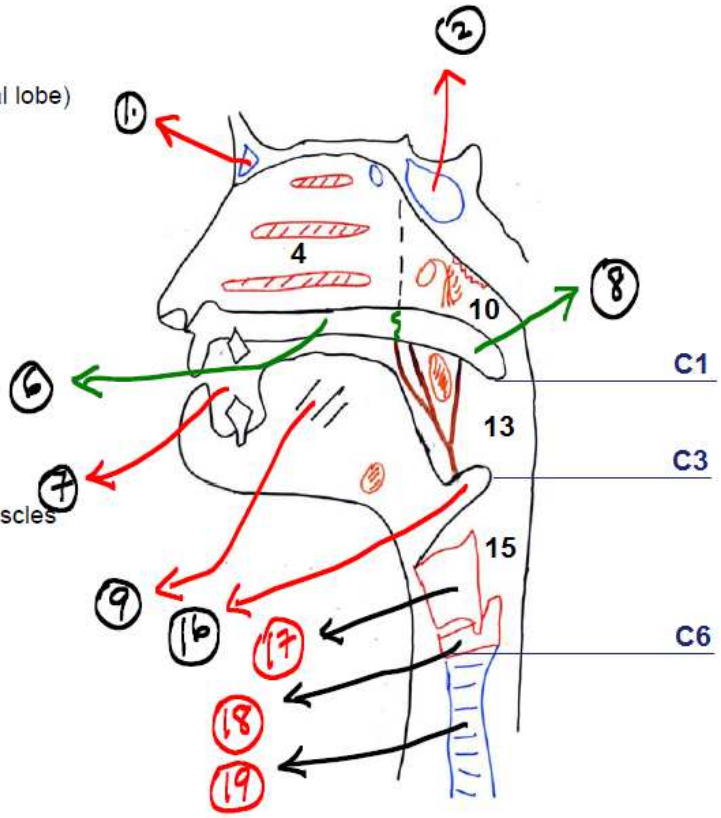

- Function not well-defined but mainly for resonance of voice and reducing weight of skull
- Drain into **meatuses** of the **nasal cavity** (if not, **sinusitis** may develop)
- Mucosal lining innervated by branches of **trigeminal nerve (CN V)** (ophthalmic nerve (CN $V_1$) and maxillary nerve (CN $V_2$)
- Blood supplied via **ophthalmic artery** and **maxillary artery**
- Also note **nasolacrimal duct**: carry excess tears from eye (lacrimal sac) to nasal cavity (inferior meatus)

1. frontal sinus (from frontal bone)
2. maxillary sinus (from maxillary bone)
3. nasal cavity
4. orbit
5. mandible
6. zygomatic arch



1. frontal sinus
2. sphenoid sinus
3. opening of sphenoid sinus
4. nasal cavity
5. anterior cranial fossa (frontal lobe)
6. hard palate
7. oral cavity
8. soft palate
9. tongue
10. nasopharynx
11. opening of auditory tube
12. adenoids
13. oropharynx
14. palatine tonsils
15. laryngopahrynx
16. epiglottis
17. larynx
18. cricoid cartilage
19. trachea
20. pharyngeal constrictor muscles




# D. Pharynx and Soft Palate

- **Pharynx** about 12-14cm in length, commences at base of skull and ends at **C6**
- Divided into three segments: **nasopharynx**, **oropharynx**, **laryngopharynx**
- **Pharynx** composed of three layers of tissue:
  - **Mucous membrane lining** (pseudostratified ciliated columnar epithelium at nasopharynx, stratified squamous epithelium at oropharynx and laryngopharynx → continuous with oesophagus)
  - **Fibrous tissue**
  - **Muscle tissue** (composed of several muscle groups of **constrictor muscles** involved in swallowing)
- Functions:
  - Pathway for air and food
  - Taste (CN I nerve endings found at oral cavity and pharynx)
  - Hearing (auditory tube allows balancing pressure of middle ear)
  - Warming and humidifying
  - Protection (by lymphoid tissue)
  - Speech (by acting as a resonating chamber)

# 1. Nasopharynx

- **Nasopharynx** lies above soft palate and behind nasal cavity
- **Roof**: collection of adenoid tissue called **pharyngeal tonsils (adenoids)**
  - Lymphoid tissues that are prominent in children ≤ 7
- **Auditory tube** opens on lateral wall → allows connection between nasal cavity and middle ear
  - Middle ear infection common amongst children, get infected via this route
  - **Tubal elevation**: Elevated part of **auditory tube**
  - Space called **pharyngeal recess** behind **tubal elevation** → common site of origin for nasopharyngeal carcinoma

# 2. Soft Palate

- **Palate** divided into hard and soft palate
  - **Hard palate**: floor of nasal cavity (maxillary, palatine)
  - **Soft palate**: mobile fold of tissue attached to posterior part of hard palate
- **Uvula**: conical projection in the midline of soft palate
- Five muscles regulate movement of soft palate → elevate and tense soft palate
  - Attached to bone and **aponeurosis** (flat tendon) of pharynx
  - Innervated by **pharyngeal plexus**
- Swallowing → soft palate separates oral and nasal cavities

# 3. Oropharynx

- **Oropharynx** located behind the mouth and extends below **C3**
- Anteriorly, a pair of folds of mucosa enclose **palatine tonsils**, a collection of lymphoid tissues

# 4. Laryngopharynx

- **Laryngopharynx** extends from level of **C3** to **C6**
- Starts at lower level where oropharynx ends and continues down with oesophagus at level of **C6**
- Just behind larynx and is continuous with oesophagus (with simple squamous epithelium)

# E. Larynx

- **Larynx (voice box)** is located at the level **C3** to **C6**
- Consists of several irregular shape cartilages bound by ligaments
- Superiorly related to **hyoid bone**
- Inferiorly continuous with **trachea**
- Anteriorly, **suprahyoid muscle** and **infrahyoid muscle**, groups of muscles attached to the hyoid bone
- Posteriorly, **laryngopharynx** is behind pharynx and is continuous with oesophagus
- Laterally, two lobes of **thyroid gland**
- Primary function: production of **sound**

# F. Trachea

- **Trachea**: continuation of larynx
- Extends from **C6** to level of **T4-T5** where it bifurcates to two main **bronchi**
- Posteriorly, oesophagus separates trachea from vertebral column
- Laterally, related to lungs and thyroid gland
- Trachea made up of **C-shaped cartilages** and behind it consists of **ciliated columnar epithelium** and **smooth muscle layer**
- Functions:
  - Support patency of airway
  - Excretion of particles
  - Assists in cough reflex
  - Humidification, warming and filtration of air
- Blood supply:
  - **Inferior thyroid artery** (branch from subclavian artery)
  - **Bronchial artery** (from thoracic aorta)
  - Drains into inferior thyroid vein and brachiocephalic veins
- Nerve supply: recurrent laryngeal nerve, vagus nerve and sympathetic cervical ganglia

# G. Lung Airways

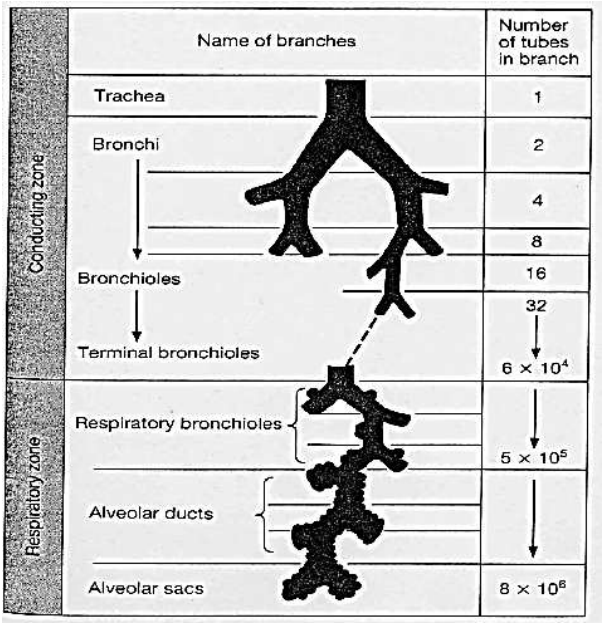
- Two primary **bronchi** formed from trachea bifurcation at **T4-T5**
- **Bronchi** further divides into **lobar bronchus** (distributed to lobes), **segmental bronchus** (into bronchpulmonary segment of lobes), **bronchioles**, **alveolar ducts**
- **Alveolar ducts** open into alveolus
- Function of **conducting part of airway** is for control of airflow
- **Respiratory bronchioles** and **alveoli** involved in external respiration, immune defense, warming and humidification of air
- **Lungs** located in **thoracic cavity**:
  - **Right lung** has three lobes: **upper**, **middle** and **lower lobes**
  - **Left lung** has two lobes: **upper** and **lower lobes**
- **Lungs** enveloped by **pleura**

# L33 Mechanisms of Breathing

## A. Respiratory System

- Components: nose, pharynx, larynx, conducting airways, respiratory airways, lungs, alveoli, blood vessels
- Functions:
  - Provides oxygen
  - Eliminates carbon dioxide
  - Regulates the blood pH level
  - Forms speech sound (phonation)
  - Defends against microbes
  - Converting angiotensin I to angiotensin II (in lungs, renin-angiotensin system to increase BP via vasoconstriction)
- Steps of respiration:
  - Neural control: voluntary control and involuntary one due to rhythmic activity from lower brain stem
  - Muscle control: contraction/relaxation of respiratory muscles (intercostal, diaphragm and abdomen)
  - Ventilation by **bulk flow**: unidirectional flow driven by pressure gradient
  - Pulmonary gas exchange: diffusion of respiratory gases
  - Gas transport: via blood and CVS
  - Tissue gas exchange by diffusion
  - Cellular respiration

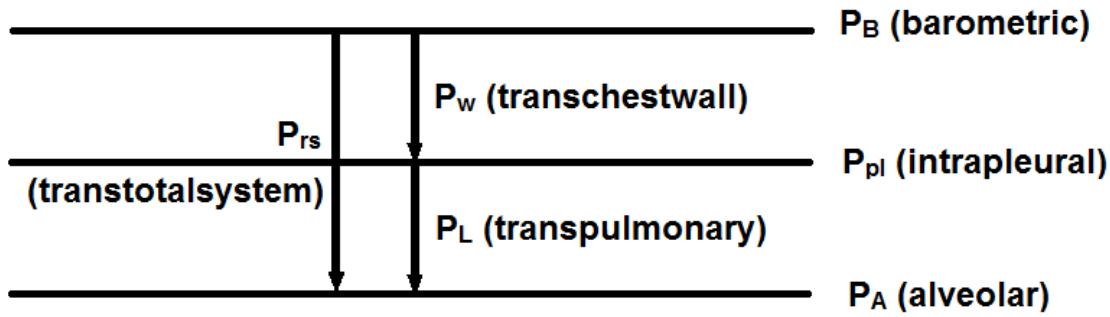
- Airway branching:




- Note total cross-sectional area of airways increase significantly after terminal bronchioles → forward velocity very slow → gaseous diffusion is chief mode of ventilation
- Note that a **pulmonary surfactant** is secreted at alveoli → ↓ surface tension of water → ↑ ability of alveoli to expand → easier breathing
- Lungs are surrounded by **pleura**: **visceral pleura** (inner) and **parietal pleura** (outer)
- Circulations that supply the lungs and airways:
  - **Pulmonary circulation**: right heart → pulmonary artery → pulmonary capillary → pulmonary vein → left heart
  - **Bronchial circulation**: aorta → conducting airways → pulmonary veins (1-2% of cardiac output) [adds deoxygenated blood to the systemic circulation]

# B. Mechanics of Breathing

- Force generated by respiratory muscles counteracts forces raised by the mechanic characteristics of respiratory system (elastic recoil of lungs) (static component) and resistance to airflow (dynamic component)
- Force for driving airflow is **difference between alveolar and atmospheric pressure divided by airway resistance**
- **Transmural pressures ($P_{tm}$)**: $P_{inside} - P_{outside}$




- **Boyle's law**: pV = constant (=nRT)
- **At end expiratory position (EEP)**,
  - **$P_{pl}$ = -4 mmHg**
  - **$P_L$ = 0 – (-4) = 4 mmHg**
  - Positive transpulmonary pressure counteracts inward elastic recoil of lungs
  - **$P_{rs}$ = 0 – 0 = 0 mmHg**
  - **$P_{cw}$ = -4 – 0 = -4 mmHg**
  - Negative trans chest wall pressure counteracts outward elastic recoil of chest wall
- Note: **$P_L$** controls lung inflation/deflation, **$P_W$** controls elastic recoil of chest wall (outward) and **$P_{rs}$** drives airflow

# 1. Inspiration

1) Inspiratory muscles contract;
2) Volume of thoracic cavity increases;
3) Pressure in intrapleural space reduces to below resting value (-4 to -7 mmHg);
4) Transpulmonary pressure increases;
5) Lungs expand in volume;
6) Due to Boyle's law, $P_A$ reduces to below atmospheric level;
7) Negative $P_{rs}$ drives air inwards into the alveoli.

# 2. Quiet Expiration

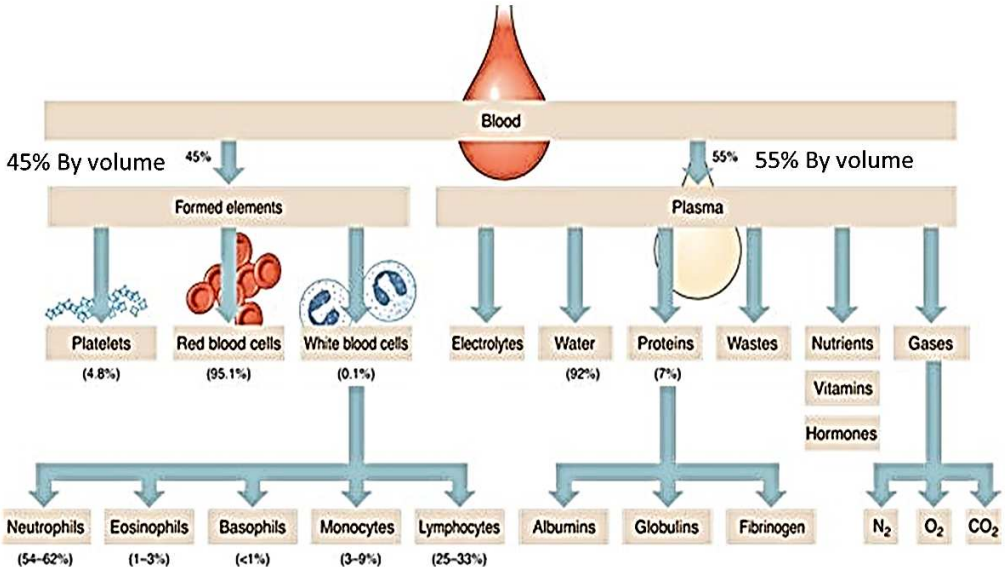
1) Inspiratory muscles relax;
2) Chest wall moves inward to its resting position;
3) $P_{pl}$ moves toward resting value (-7 to -4 mmHg);
4) $P_L$ decreases;
5) Lungs recoil due to elastic properties of lung tissue;
6) Lung volume reduces;
7) $P_A$ raises to above atmospheric level;
8) Positive $P_{rs}$ drives air out of alveoli.

*Abdominal muscles contract to push diaphragm upwards on forced expiration

# L34 Blood Cells

## A. Blood

- A liquid connective tissue consisting of blood cells and extracellular matrix
  - **Matrix**: clear, light yellow blood plasma (~55% by volume)
  - **Formed elements**: RBCs (45% by volume), WBCs and platelets (<1% in volume)
- Part of circulatory system
- Functions:
  - **Transport** oxygen/$CO_2$, nutrients, metabolic wastes
  - **Protection**: limiting infection, platelets for blood clotting
  - **Regulation**: regulating pH and water balance, maintain body temperature
- **~4-6L** of blood in adults, ~8% of body weight



# 1. Plasma

- Function: clotting, defense and transport
- Contents:

| | |
|---|---|
| Water | 92% by weight |
| Proteins | Serum albumin, globulins, fibrinogen, clotting factors, enzymes and others |
| **Nutrients** | Glucose, amino acids, lactic acid, lipids (cholesterol, fatty acids, lipoprotein, triglycerides, and phospholipids), iron, trace elements and vitamins |
| **Electrolytes** | Salts of sodium, potassium, magnesium, calcium, chloride, bicarbonate, phosphate and sulfate |
| **Nitrogenous wastes** | Urea, uric acid, creatinine, creatine, bilirubin and ammonia |
| **Gases** | Oxygen, carbon dioxide and nitrogen |

*α- and β-globulin for transport, γ-globulin for defense, fibrinogen for clotting, **albumin** to draw water into capillaries at capillary bed by osmosis

# B. Blood Cells

## 1. Hematopoiesis

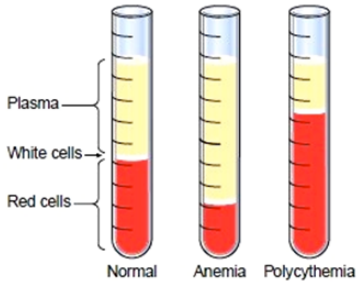
- Generation of blood cells in red bone marrow

# 2. Erythrocytes (RBCs)

- Most abundant in blood
- Biconcave, anucleate, can deform easily (squeeze through small capillaries)p
- No nucleus and DNA → no protein synthesis and mitosis → more flexible but with limited life span
- No mitochondria → generate ATP by anaerobic respiration
- High SA:V ratio: facilitate rapid diffusion of $O_2$
- Function: transport $O_2$ from lungs to tissues and $CO_2$ from tissues to lungs (catalyze bicarbonate formation and carries some $CO_2$ as carbamate at hemoglobin amino residue)
- Lifespan: 120 days
- Carries **hemoglobin**: 4 globin + 4 heme groups

## a. Blood Count

| | |
|---|---|
| Mean fraction of body weight | 8% |
| **Hematocrit** (% of RBC by volume) | Female: 37% - 48%<br>Male: 45% - 52% |
| **Hemoglobin** | Female: 12-16 g/dL<br>Male: 13 – 18 g/dL |
| **Mean RBC Count** | Female: 4.2 – 5.4 million/uL<br>Male: 4.6 - 6.2 million/uL |
| Platelet Count | 130,000 – 360,000/uL |
| Total WBC Count | 5,000-10,000/uL |



## b. Erythropoiesis

- Pluripotent stem cell → erythrocyte colony-formation unit (CFU) → erythroblast → reticulocyte (enters blood, 0.5%-1.5% in blood) → erythrocyte
- Whole process take 3-5 days
- Erythroblast multiply and synthesize hemoglobin
- Iron, vitamin $B_{12}$ and folate ($B_9$) required
- Modifications:
  - Reduction in cell size
  - Increase in cell number
  - Synthesis of hemoglobin
  - Loss of nucleus ad organelles
- Lives ~120 days after release from BM, then phagocytosed by macrophages in liver and spleen (~2.5M destroyed every second)
- Regulation by blood $O_2$:
  - **Hypoxia** (low blood $O_2$) stimulates liver and kidney (90%) to secrete **erythropoietin (EPO)** into bloodstream → red bone marrow increase erythropoietic rate → increase in $O_2$ carrying capacity → inhibits EPO secretion

## c. Blood Types

- **ABO** and **Rh** systems
- Chemical composition of glycolipids (**agglutinin**) on RBC surface act as antigens for immune activation
- Blood plasma contains antibodies (**agglutinogen**) that react against incompatible antigens on foreign RBCs → agglutination (clumping up of cells)
- **ABO system**: A and B antigens
- **Rh system**: 49 antigens, D, C, E, c, e among most significant
  - Usually denoted as Rh+ and Rh- (D-antigen)

## d. Anemia and Polycythemia

- **Anemia**: reduced number of RBC → hematocrit < 35%
- Causes: Nutritional (iron/B9/B12 deficiency), hemorrhage, diseases
  - Iron deficiency anemia
  - Heavy menstrual periods
  - Bleeding in digestive or urinary tract
  - Surgery, trauma, pregnancy (plasma increase faster than RBC in pregnant women)
  - Sickle cell anemia, thalassemia
- **Polycythemia**: excess numbers of RBCs
  - Primary: intrinsic to RBC precursors (inherited), myeloproliferative diseases
  - Secondary: natural or artificial increases in EPO production (due to chronic hypoxia caused by COPD, high altitudes, tumors etc.)

### i. Sickle Cell Anemia

- Mutation of hemoglobin: Glu → Val
- RBC produce abnormal hemoglobin causes deformity into sickle-shapes
- RBCs get stuck and block flow in small blood vessels → risk of infection
- Treatment: bone marrow or cord-blood stem cell transplant

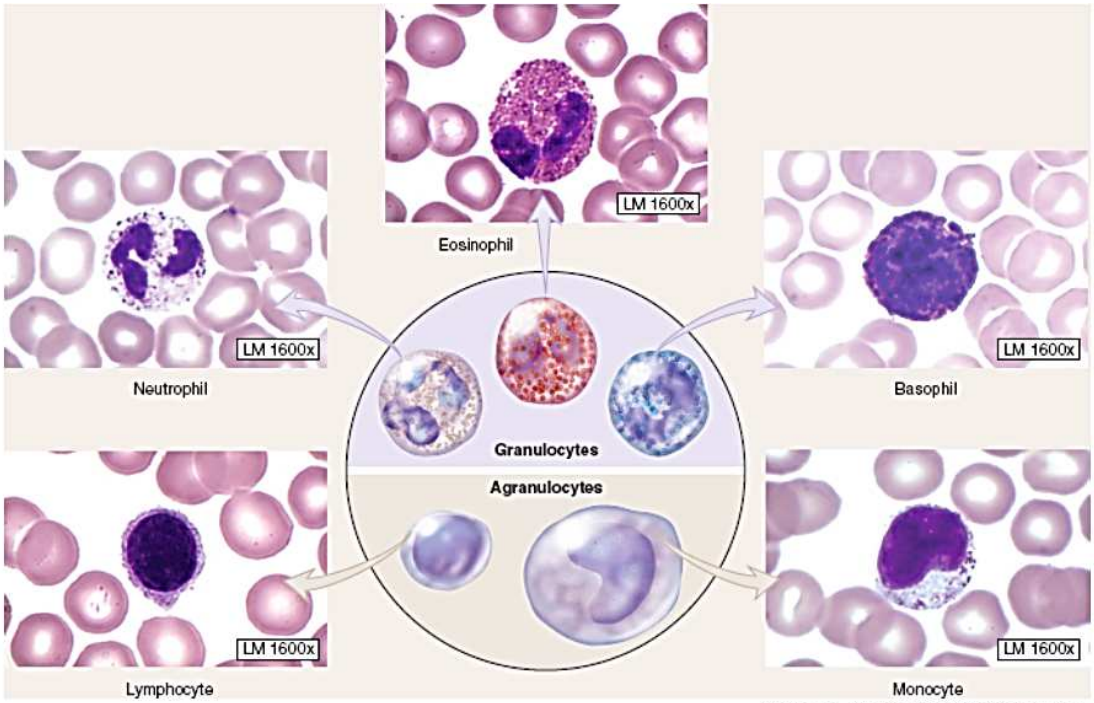
### ii. Thalassemia

- A group of genetic blood disorders involving abnormal formation of hemoglobin → mild or severe anemia
- Alpha thalassemia (4 genes) vs beta thalassemia (2 genes)
- Symptoms:
  - Slowed growth and delayed puberty
  - Bone problems – expanded bone marrow
  - Enlarged spleen

## e. Bone Marrow Transplant

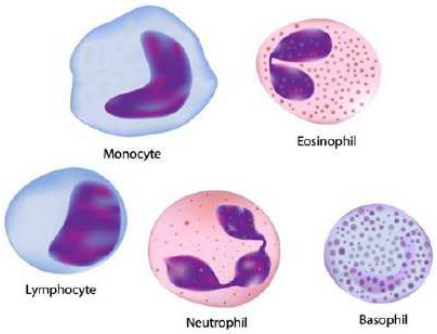
- Applicability: leukemia, lymphoma, sickle-cell anemia, some forms of anemia and other disorders
- Replace cancerous or defective bone marrow with donor stem cells (cord blood or bone marrow)
- Prior chemotherapy or radiation to prevent rejection

# 3. White Blood Cells (WBCs)



Human Anatomy McKinley 3e

- **5 main types of white blood cells:**
  - **Neutrophils**
    - most numerous
    - fight infections by **killing & ingesting bacteria** & fungi & by ingesting foreign debris (phagocytosis)
  - **Lymphocytes**
    - consists of 3 types:
      - T lymphocytes
      - Natural killer cells
        - both help protect **against viral infections & destroy some cancer cells**
      - B lymphocytes
        - develops into cells that **produce antibodies**
  - **Monocytes**
    - **phagocytize dead or damaged cells & help defend many infectious organisms**
  - **Eosinophils**
    - **kill parasites, destroy cancer cells & are in allergic responses**
  - **Basophils**
    - **secretes histamine, participate in allergic responses**

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- 5k – 10k WBCs/μL
- **Granulocytes**: **neutrophil**, **eosinophil**, **basophil**
- **Agranulocytes**: **lymphocytes (B/T)**, **monocyte**, **natural killer cell**, **dendritic cell**

*Blood smear stained by mixture of acid (eosin) and basic (methylene blue) dyes → nucleic acids stained by methylene blue and proteins stained by eosin (red)

| | |
|---|---|
| Nuclei | Purple to violet |
| Lymphocytes | Plasma Blue |
| Monocytes | Plasma Blue |
| Granulocytes: | |
| Neutrophils | Violet granules |
| Eosinophils | Red-violet granules |
| Basophils | Strong violet granules |
| Thrombocytes | violet |
| Erythrocytes | Weak red |

## a. Granulocytes

### i. Neutrophils

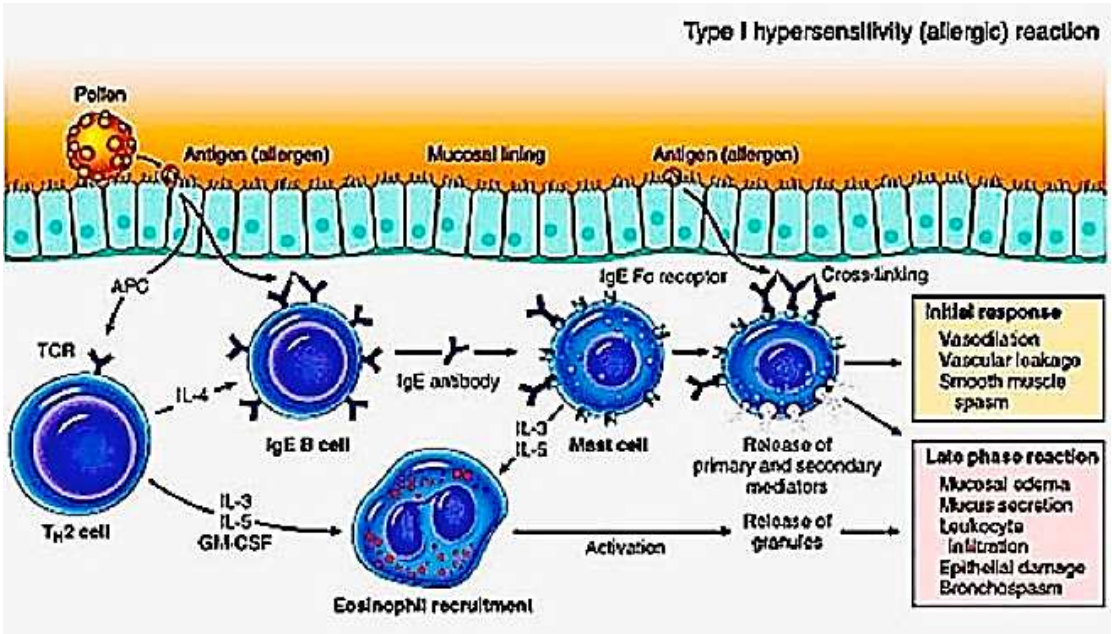
- Most abundant: 60-70% of total WBC
- Circulate in blood for ~6-10 hr
- High in **bacterial infection**
- Functions:
  - Phagocytose microorganisms and other substances
  - Specific granules filled with enzymes
  - **Azurophilic** (stained by methylene blue) granules (lysosomes and antibicrobicidal)
  - Acute inflammatory responses to bacterial infection
- Neutrophil granules:
  - Primary: similar to lysosomes
  - Secondary: specific to neutrophil, 2x primary but smaller; involved in inflammatory response (secretory)
  - Tertiary: contain enzymes secreted by cell into extra-cellular environment
- Cytoplasm contains few organelles apart from granules

## ii. Eosinophils

- Only 2-4% of WBCs, count fluctuates
- Increase in **parasitic infections**, **allergies**, collagen diseases and diseases of spleen and CNS
- Involved in **immediate hypersensitive late-phase reaction**
- Functions:
  - Phagocytose antigen-antibody complexes, allergens and inflammatory chemicals
  - Secrete enzymes that weaken or destroy parasitic worms
- Granules contain anti-histamine

## iii. Basophils

- Rarest: only 1%, count relatively stable
- Increase in **viral infections**, **inflammation** etc.
- Involved in **immediate hypersensitivity reactions**
  - IgE receptor on surface
  - High in allergic reactions
- Functions:
  - Structural and functional similar to **mast cells** (in c.t.)
  - Accumulate at sites of infection
  - Degranulation (**histamine**) to increase blood flow and promote inflammation
  - Secrete **heparin** to promote mobility of other leukocytes in the area
  - Release chemical signals → attract eosinophils and neutrophils to site of infection



## b. Lymphocytes

- Smallest, 20-50% of WBCs
- B, T, NK cells
- B cells mature in red bone marrow
- T cells mature in thymus gland

### i. T Lymphocytes

- Thymus-dependent
- Cell-mediated immunity (adaptive)
- **T helper (CD4+)**, **cytotoxic T (CD8+)**, **regulatory T** and **memory T cells**
- Functions:
  - Destroy cancer cells, infected cells and foreign cells
  - Coordinate actions of other immune cells to regulate immune system
  - Suppress immune responses

### ii. B Lymphocytes

- Activated by:
  - Interaction with T cells
  - Directly by antigens in blood/on bacteria
- Functions:
  - Antigen-presenting cells
  - Coordinate actions of other immune cells
  - Secrete antibodies
- Differentiate into **plasma cells** and **memory B cells**

**(1) Plasma Cells**

- Terminally differentiated antibody-secreting B cells
- Prominent RER
- Secrete (a specific type of) antibodies up to 2k molecules per second for 4-5 days
- Germinal center: lymphatic system

### iii. Natural Killer Cells (NK Cells)

- Attack and lyse bacteria, transplanted tissues, non-self cells (cancer, infected cells)
- 'Natural' because it does not require MHC-marked antigen (marked by antigen-presenting cells) or antibody to function (unlike cytotoxic T cells)
- Function: immune surveillance
- **Innate defense**: non-specific, no immunolofical memory
- Small granules such as **perforin** (drill holes into target cells membrane) and **proteases** (granzymes)

## c. Monocytes

- Largest, 2-10% of WBCs
- Circulating: precursor of tissue macrophages
- Circulate in blood for 1-3 days then migrate into body tissues as macrophages
- Count increases in viral infections and inflammation
- Functions:
  - Replenish resident macrophage
  - Migrate to site of inflammation to differentiate into macrophage

## d. Macrophage

- Tissue-based, highly phagocytic (pathogens, dying or dead cells and foreign cells)
- Antigen-presenting cells: phagocytosis then present Ab at cell surface with MHC marker
- Examples:
  - **Kupffer cells** in liver sinusoids: phagocytose RBC
  - **Alveolar macrophages** in lungs: immune surveillance
  - **Microglia** in CNS: scavenges CNS tissues for infected cell
  - **Osteoclasts** in bone: bone resorption and remodeling

## e. Dendritic Cells

- Tissue-based professional antigen-presenting cells
- Immature in blood and once activated → migrate to lymph nodes to activate T cells
- Two types: myeloid dendritic cell and plasmacytoid dendritic cell
- Examples: Langerhans cells (skin)

## f. Mast Cells

- Immature form in blood and mature in tissue
- Major effector cell of immediate hypersensitivity (allergic) reaction
- Recent studies – roles in controlling infection (unclear yet)
- Reside in most tissues adjacent to blood vessels
- Granules rich in histamine and heparin
- Similar in both appearance and function to basophil

# 3. Platelets (thrombocyte)

- Function: blood clotting
- Formed from **megakaryocyte** fragments
- No nucleus but complex internal structure → lysosomes, mitochondria, microtubules, microfilaments, granules and open **canalicular** system
- High platelet count → unnecessary clotting → possible strokes and heart attacks

## a. Hemostasis (blood clotting)

1) Secretion of vasoconstrictors;
2) Formation of temporary platelet plugs;
3) Secrete procoagulants / clotting factors;
4) Secrete chemicals that attract neutrophils and monocytes;
5) Secrete growth factors → help maintain and repair blood vessels.

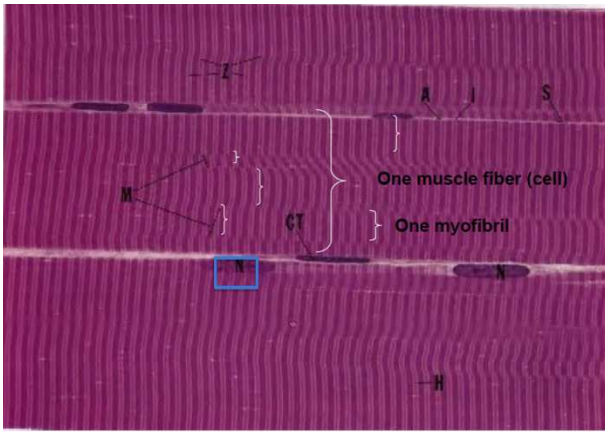
# L35 Movement-generating Tissue: Muscle

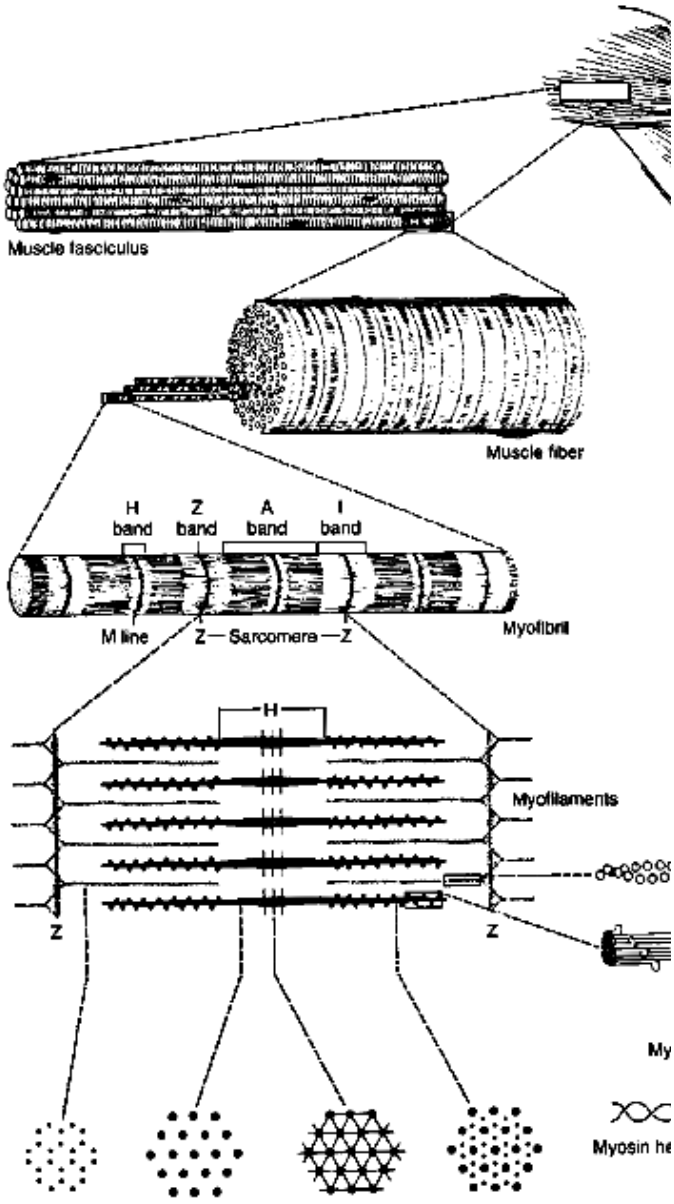
## A. Muscles

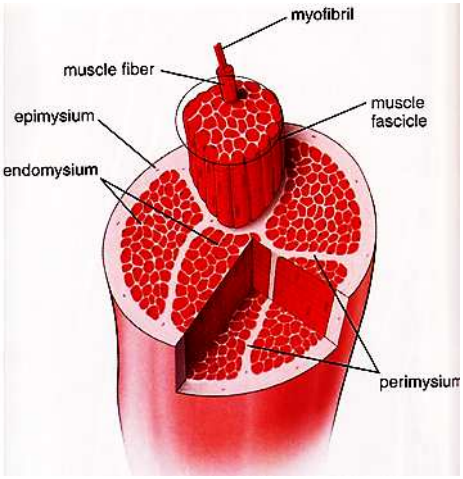
- Muscles are made up of **muscle cells** containing **myofilaments**:
  - Thin filament: primarily **F-actin**
  - Thick filament: **myosin**
- Two types of muscle cells:
  - Striated muscle (cross-striations at light microscope level)
    - → Skeletal muscle (movement of skeleton)
    - → Cardiac muscle (heartbeat)
  - Smooth muscle (no cross-striations) (walls of blood vessels, intestines, uterus etc)

## B. Skeletal Muscles

- For locomotion and movement of structures like eyeballs
- Organization:
  - **Muscle fascicle**: group of muscle cells
  - **Muscle fibre**: individual muscle cells
  - **Myofibrils**: fibrous structure in muscle fibres
  - **Myofilaments**: filaments involved in muscle contraction
  - **Sarcomere**: each contractile unit





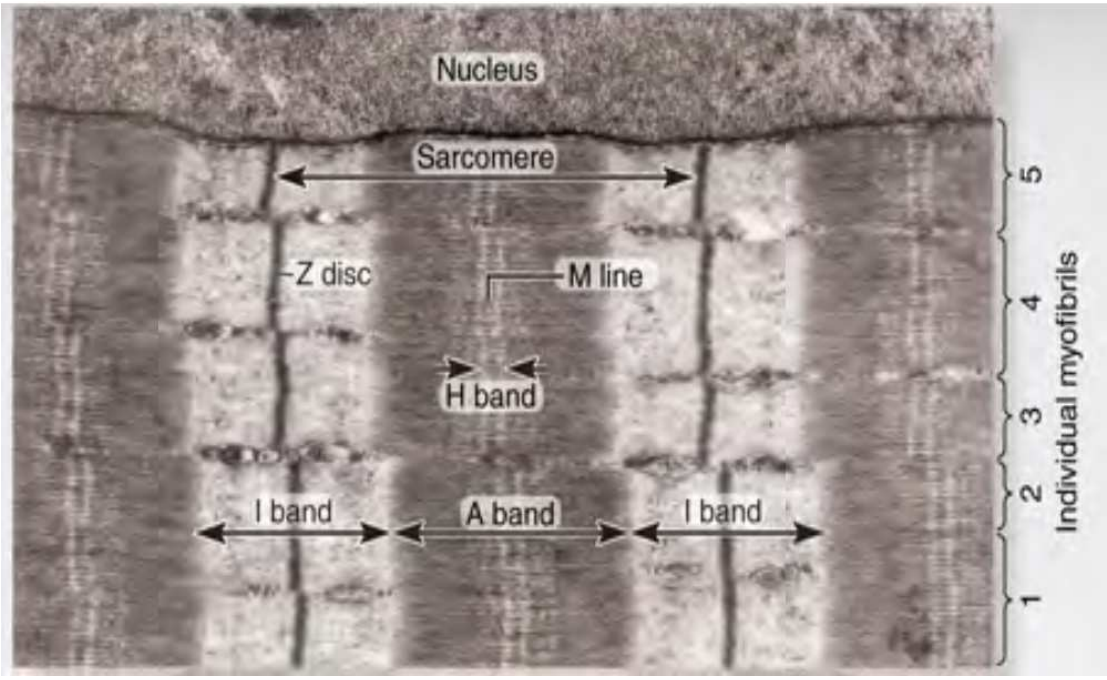

- Each muscle cell is a multinucleated **syncytium** (multinuclear cell formed from fusion of several cells) formed by fusion of **myoblasts**
- Connective tissue organization:
  - **Epimysium** surrounds whole muscle (and is continuous with tendons)
  - **Perimysium** separates muscle fascicles
  - **Endomysium** separates individual muscle fibres in a muscle fascicle

# 1. Physiological types

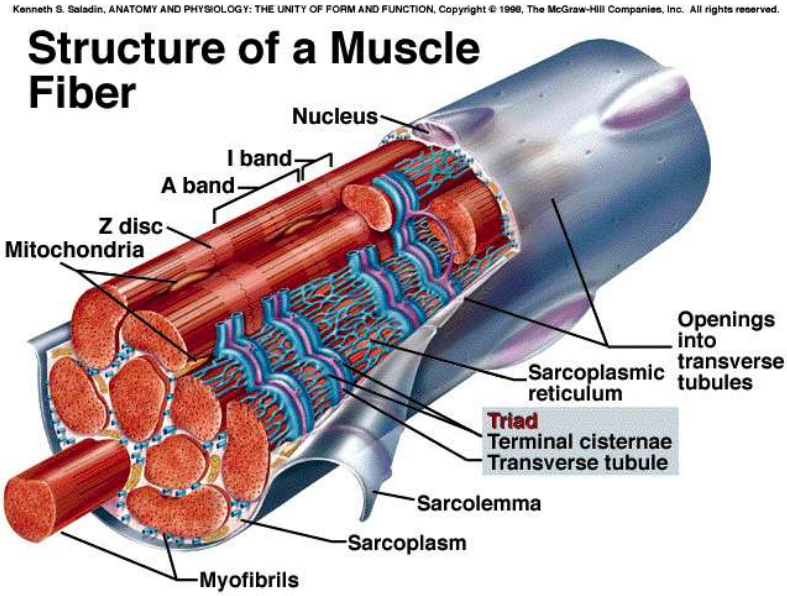
- **Type I (slow oxidative) fibres**
  - Slow-twitch fatigue-resistant
  - Large amounts of **myoglobin** (red), numerous mitochondria and blood capillaries
  - Long and slow contraction (postural muscle)
  - Metabolic pathway: **oxidative metabolism**
  - For marathon runners
- **Type IIa (fast oxidative glycolytic) fibres**
  - Intermediate in properties and function between type I and type IIb fibres
  - Fast-twitch
  - 400-800M athletes
- **Type IIb (fast glycolytic) fibres**
  - Fast-twitch
  - Fatigue-prone
  - Lower amount of myoglobin (white) and mitochondria
  - High anaerobic enzyme activity
  - Metabolic pathway: **glycolysis**
  - **Larger** in fibre size
  - Present in biceps and triceps
  - Short-distance sprinters

# 2. Structure of Myocytes and Myofibrils

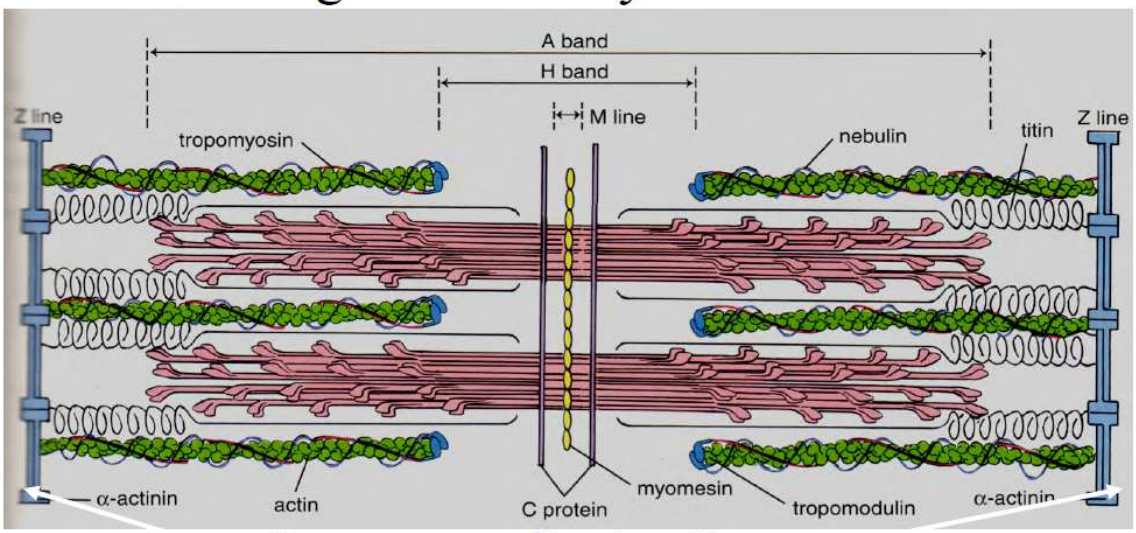
- **Myofibril**: structural and functional unit of muscle fibres
- Composed of **thick filament myosin** and **thin filament actin**
- **Sarcomere** as contractile units




- Banding due to arrangement of thick (A band) and thin (I band) filaments:
  - D**a**rk/**l**i**g**ht: **A** band is the dark band and **I** band is the light band
  - HAZI: **H** band (lighter region) in A band and **Z** disc (darker line) in I band
- Ultrastructural features:
  - **Sarcoplasmic reticulum**: enlarged endoplasmic reticulum, helps pump and store $Ca^{2+}$
  - **Transverse tubules (T tubules)**: invagination of **sarcolemma** (myocyte cell membrane) at A-I junction

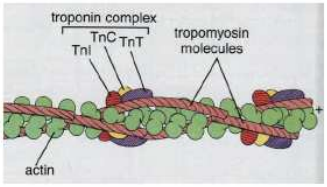


# Arrangement of myofilaments

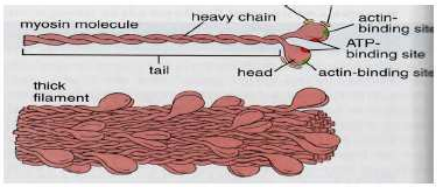



**Sarcomere: z-line to z-line**

Actin



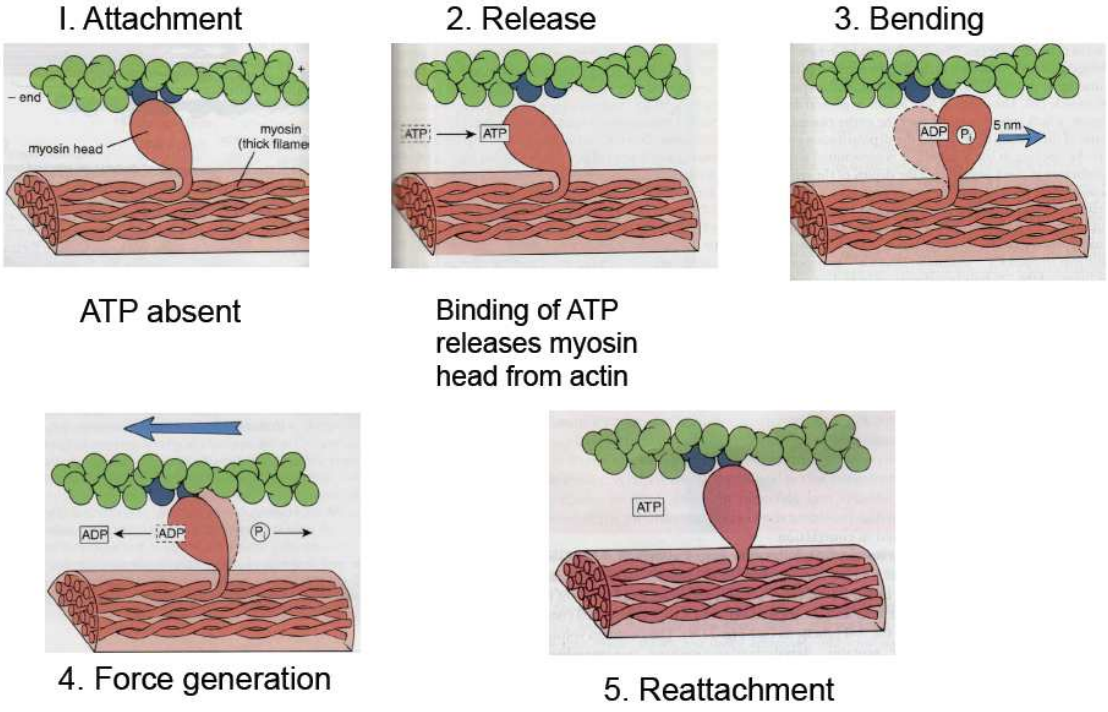

Myosin




## 3. Excitation-Contraction Coupling (E-C coupling)

1) Nerve impulse arrives at axon end of neuromuscular junction;
2) ACh neurotransmitters are released into the synapse;
3) Ach binds with receptor at sarcolemma, triggering opening of ligand-gated (sodium) ion channels;
4) Membrane depolarized and the resultant electrical impulse travels along T-tubule;
5) Voltage-dependent $Ca^{2+}$ channels on sarcoplasmic reticulum open and $Ca^{2+}$ flows into the myofibrils;
6) $Ca^{2+}$ bind to **troponin** and displaces **tropomyosin** to expose **myosin** binding site at **actin**;

# 4. Contraction Mechanism

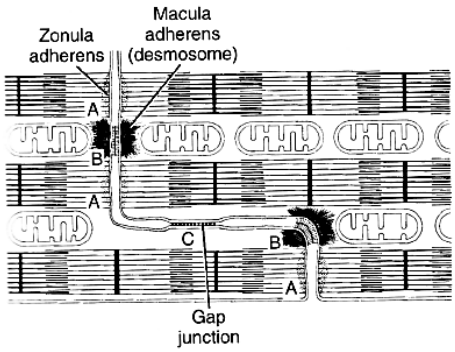



1) **Myosin** head originally attached to **actin** filament;
2) ATP binding triggers release of myosin head from actin;
3) Hydrolysis of ATP provides energy for bending and extension of myosin head, facilitating binding of myosin at a new binding site;
4) **Power stroke** is delivered to pull actin. At the same time, ADP and $P_i$ are released.
5) Steps (1) – (4) repeat to generate a macroscopic muscle contraction.

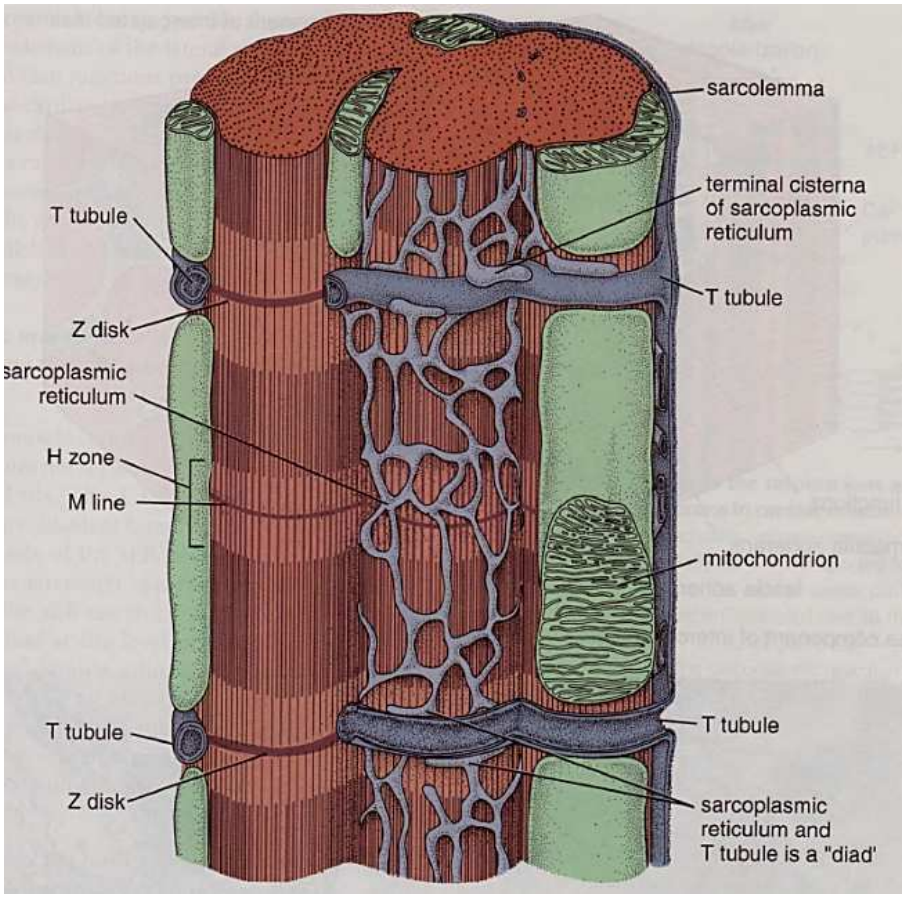
# 5. Innervation

- One somatic motor neurone often innervate >1 myocytes → all myocytes joined to one neurone contract upon receiving the same signal → **motor unit** for stronger contraction
- **Motor end plate**: pocket formed around motor neuron by sarcolemma
- **Muscle spindles**: sensory receptors to detect length of muscle to regulate contraction

# C. Cardiac (heart) Muscles

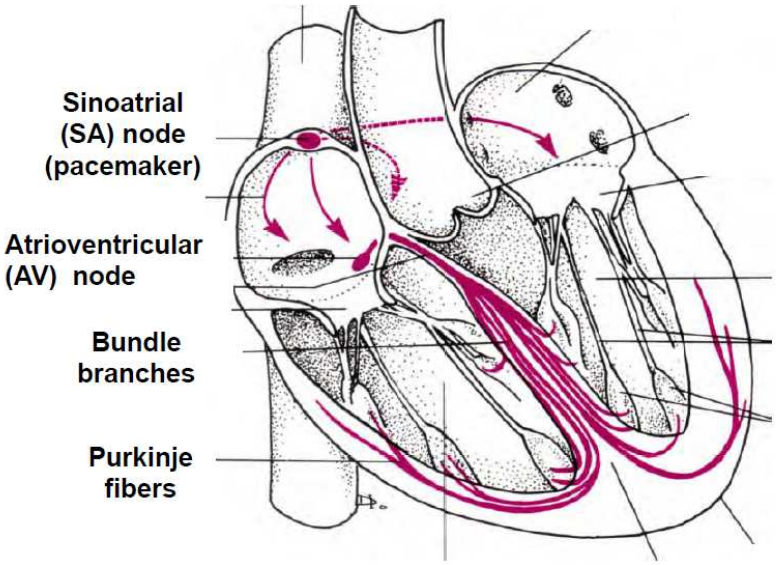



- Striated
- Some modified to form **Purkinje fibres** to conduct nerve impulse
- Differences from skeletal muscles: **intercalated disc**, branching of cardiac muscle fibers, centrally located nuclei (skeletal muscle nuclei are peripherally located)
- Note: **T-tubule at Z-line** instead of A-I junction



## 1. Innervation

- Cardiac muscles innervated by **autonomic nervous system** and **Purkinje fibres** in heart
- Few nerve fibres in cardiac muscle




**Impulse conducting system of the heart**

# D. Smooth Muscle

- Bundles of sheets of elongated fusiform (spindle-like) cells with finely tapered ends
- Found in walls of small blood vessels, intestine and uterus
- Interconnected by **gap junction** to regulate contraction of entire bundle or sheets of smooth muscle cells
- Nuclei centrally located
- Specialized for **slow, prolonged contraction**
- Innervated by autonomic nervous system
- Capable of dividing to maintain or increase their number: only form of muscle that is capable of regeneration
- Also contract by myosin/actin filament sliding
- **Dense bodies** act as Z disks and are fixed by intermediate filaments (desmin)

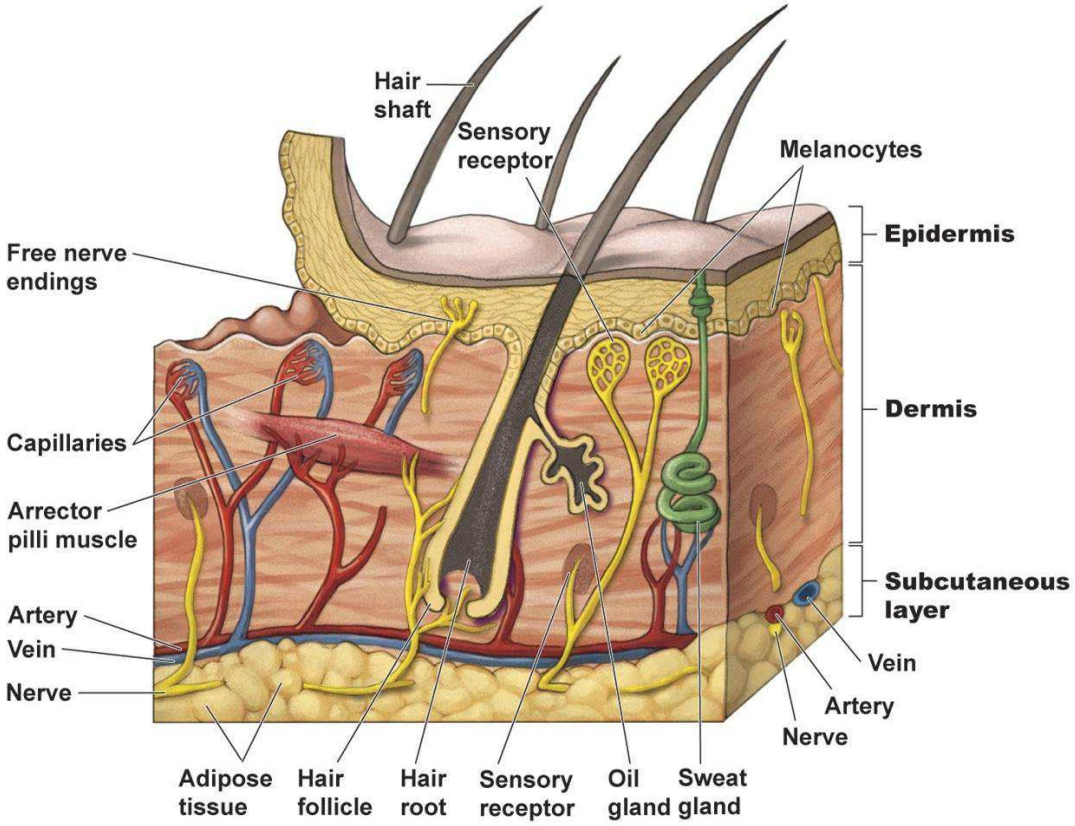
# E. Clinical Consideration of Muscles

- Muscle growth and **atrophy** (wastage):
  - Skeletal muscle fibres incapable of mitosis → numbers relatively unchanged
  - Loss of nerve innervation → denervation atrophy
  - Lack of exercise → disuse atrophy
  - Aging → senescence atrophy
- Muscular **dystrophy** (degeneration): hereditary diseases in which skeletal muscles degenerate
  - Most common form: **Duchene muscular dystrophy (DMD)** due to defective gene for dystrophin

# L36 Introduction to the Skin

## A. Skin Anatomy

- Largest organ in the body
- Weight: 5kg in average 70kg man
- Body SA: $2m^2$
- 3 distinctive layers: **epidermis** (stratified, cellular), **dermis** (connective tissue), **subcutis** (fat, skin appendages)
- Function: protect underlying structures (fascia, muscle)



# 1. Epidermis

- Thickness: 0.05 – 0.1mm
- 30-day regeneration cycle (basal → surface)
- Composed of **keratinocytes** capable of proliferation and differentiation
- Stratified structure:
  - **Stratum corneum** (cornified dead cells)
  - **Stratum granulosum** (granulated layer where living keratinocytes flatten and die)
  - **Stratum spinosum** (cells begin keratinization here)
  - **Stratum basale** (stem cells divide to form keratinocytes above, produces **melanin**)

# 2. Dermo-epidermal Junction (DEJ)

- Complex network of protein and glycoprotein
- **Basement membrane**: formed from basal keratinocyte (of epidermis) and superficial dermis
- Importance:
  - Adhesion (destruction → blister eg. pemphigoid)
  - Cellular migration (wound healing)
  - Cellular signaling (epithelial-mesenchymal signaling)

# 3. Dermis

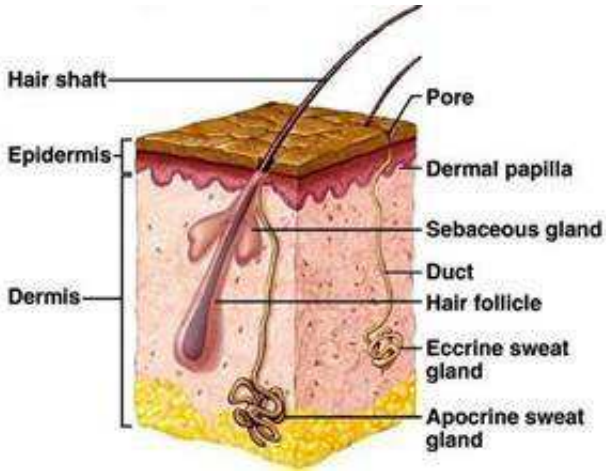
- Connective tissue:
  - Supporting matrix for strength
    - → Collagen (80-85% of dry weight) for tensile strength
    - → Elastic tissues (2-4%, elastin, microfibrils) for elasticity
  - Ground substance (i.e. **extrafibrillar matrix**, water, glycoproteins and proteoglycan) for water-retention
- Dermal collagens: types I, III (dermal interstitum) and type IV (basement membrane)
- Polysaccharides in dermis (0.1 – 0.3%):
  - Hyaluronic acid (a type of GAG)
  - Water-binding capacity → 60% of dermis by weight is water
- Rich in blood supply: superficial and deep **vascular plexus**
- **Adnexal structures** (appendage): **pilosebacceous unit**, **eccrine** and **apocrine** sweat glands

## 4. Subcutis

- Adipose tissue
- 80% of body's fat reserve
- Arterioles, venules, lymphatics
- Functions:
  - Calorie reserve
  - Cushion effect
  - Insulation

# B. Skin Appendages

## 1. Pilosebacceous Unit




- Originated from **epidermal downgrowth**
- Developed between 10-14 of **gestational age**
- Four classes:
  - **Terminal** (scalp, beard area) → thick, long, dark hair
  - **Vellus** (majority of skin) → short, pale hair
  - **Apopilosebaceous** (**axilla** (armpit), groin) → associated with apocrine gland
  - **Sebaceous** (face, chest, back) → only sebaceous gland

### a. Hair Follicles

- Number of follicles remained unchanged until middle life
- Terminal : vellus ratio changes throughout life
  - **Androgenetic alopecia**: androgen controls conversion between terminus and vellus pilosebacceous unit → androgen disorder causes terminal hair to change to vellus hair → loss of hair (**alopecia**)
- **Terminal hair** on scalp: largest follicle size and extension into subcutis
- **Vellus hair** on forehead: small follicle size and large sebaceous gland

## b. Scalp Hair

- Scalp hair growth: 1cm/month
- Scalp hair: 100k terminal hair follicle in average

### i. Hair Cycle

- **Anagen**: active growth phase
  - Up to 90% of hair follicles
  - Length: 3 years
- **Catagen**: regressing/involuting phase
  - ~1% of hair follicles
  - Length: 3 weeks
- **Telogen**: resting/quiescent phase
  - ~10% of hair follicles (~10k)
  - Length: 3 months
  - In average, 100 hair shed in one day

*__Telogen effluvium__: physical or psychological stress → up to 70% of hair enter **telogen** phase prematurely

**Eyebrow: hair cycle completed in 4 months

## c. Sebaceous Glands

- Differentiated at 13-15 weeks of gestational age
- Large and well-developed in fetus
- Size rapidly reduced after birth
- Regain of function at puberty (due to androgen control)
- Examples of diseases:
  - **Seborrhoeic dermatitis** (infants): excess sebum → fungal element growth triggering an AI response
  - **Acne vulgaris** (adolescents): blockage in hair follicles → infection and inflammation

*__Vulgaris__: common

**Two types of human skin:

- **Glabrous skin** (no hair):
  - Palms, soles
  - Compact **stratum corneum** (10 times more flexures)
  - Encapsulated sense organs (dermis)
  - Lack of hair follicles and sebaceous glands
- **Hair-bearing skin**
  - Hair follicles + sebaceous glands
  - Lack of encapsulated sense organs

# 2. Sweat Glands

- 1.6 – 4M
- Two types: **apocrine** / **eccrine**

## a. Eccrine Sweat Gland

- Diameter: 30 – 50μm
- Length: 2 – 5 mm
- Responsible for thermoregulatory sweating
- Distributed nearly entire body surface
- Identifiable over palms, soles in 16$^{th}$ week
- Key structures:
  - **Bullous** (large vesicle-like) secretory coil in lower dermis
  - Secretory duct in dermis
  - Opening pore at surface
- Secretion mechanism: **eccrine** (secretion by exocytosis)

## b. Apocrine Sweat Gland

- Distribution: axilla (armpit), genitalia, mammary areas
- Secretion mechanism: **apocrine** (secretion by decapitation)
- Low secretory output
- Lipid-rich production

## c. Human Perspiration

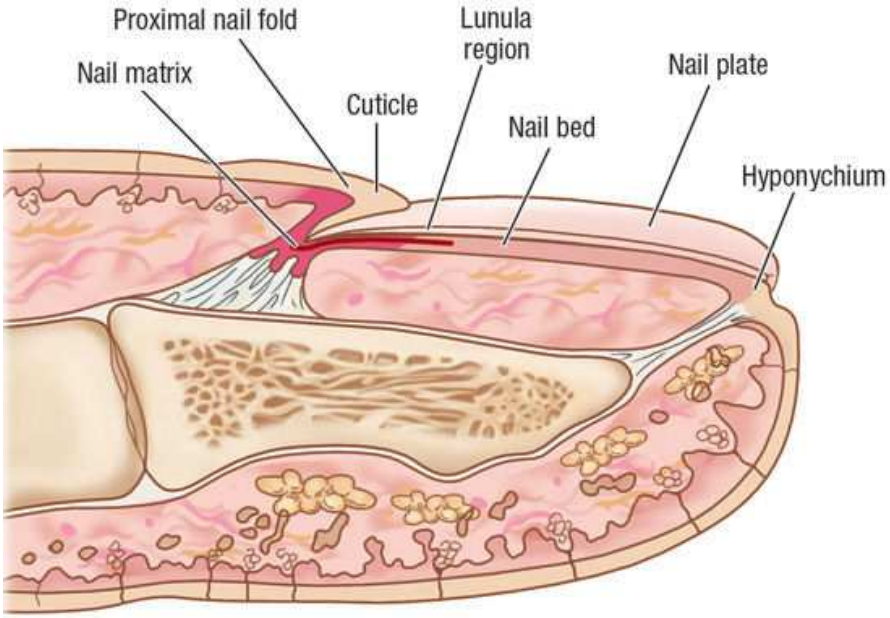
- Two types: insensible perspiration, active sweating (mainly **eccrine** glands)
- Insensible perspiration:
  - Passive water evaporation from skin surface
  - Depends on temperature and humidity
- Active sweating:
  - For thermoregulation
  - Mental/emotional (mental stimuli) → palms and soles
- Innervation:
  - Sympathetic in nature
  - **Cholinergic** (acetylcholine, ACh) in character
  - ↑ due to **pilocarpine** (parasympathetic stimulator), ↓ due to **atropine** (sympathetic stimulator)

***Despite sweating is a sympathetic response in nature, pilocarpine/atropine effects on sweating are opposite from expectation:**

- **Pilocarpine** and **atropine** are **agonist** and **antagonist** to **muscarinic acetylcholine receptors (mAChRs)** respectively
- **mAChRs** normally found in **parasympathetic nervous system** → pilocarpine and atropine stimulate and inhibit PN respectively
- Sweat gland nervous pathway, although sympathetic in nature, uses mAChRs → pilocarpine and atropine have reversed effect on sweating

# 3. Nails

- Development since 8-9 weeks of gestation
- Growth:
  - Finger nails: 3mm/month
  - Toe nails: 1mm/month
- Structure:
  - Nail plate (keratin)
  - **Proximal nail fold**
  - **Nail matrix** (tissue with nerves, lymph and blood vessels underneath proximal nail fold)
  - **Nail bed** (epidermal tissues underneath nail plate)
  - **Hyponychium** (epithelium beneath nail plate at junction of nail and fingertip)
  - **Lunula region**: visible part of nail matrix under the nail plate




- Functions:
  - Mechanical protection
  - Enhance sensory discrimination
  - **Dexterity** (fine motor skills) for scratching and grooming (cleaning body)
  - Cosmetic accessory

# B. Development of Skin

- From ectoderm and mesoderm:
  - Ectoderm → nervous system, epidermis
  - Mesoderm → dermis, skin appendages (c.t.)
- Structural components:
  - Hair follicles, mails (9 weeks)
  - Sweat glands (9 weeks: palms and soles; 15 weeks: others)
  - Sebaceous gland (15 weeks)

# C. Functions of Skin

1) **Mechanical barrier**: prevention of physical injury, preservation of water and electrolytes;
2) **UV protection**: by melanin in epidermis (stratum basale)
3) **Thermoregulation**: by vessels and sweat glands
4) **Immunity**: innate and adaptive
5) **Sensation**: pain, touch, temperature etc
6) **Endocrine**: vitamin D synthesis
7) **Communication**

## 1. As a Barrier

- Skin acts as a physical barrier against external environment
- **Stratum corneum**:
  - Cornified cell envelope
  - Highly insoluble layer
  - Glu-Lys isodipeptide bonds → protein cross-linkage → insolubility
  - Rich in **ceramides** (waxy lipids with amides), free sterols, free FAs
- Prevent inward and outward passage of water and electrolytes

## 2. Protection from UV

- UV may cause DNA damage → mutation → carcinogenesis
- UV absorption in **stratum corneum**, **epidermal keratinocyte** and **melanin** (in stratum basale)
- **Melanocytes**:
  - Pigment-producing cells
  - Located at basal epidermis (stratum basale)
  - Production of **melanin**: **eumelanin** (brown/black), **phaeomelanin** (yellow/red)
  - Melanin transferred as **melanosomes** (organelle for handling of melanin)

# 3. Thermoregulation

- Sweating and alteration of circulation in skin to maintain constant body core temperature:
  - Sweating controlled by hypothalamus → ↑ heat loss by evaporation → ↓ body temperature
  - Vasoconstriction/vasodilation: Skin arterioles constrict/dilate → skin capillaries blood flow changes as blood is redirected to shunt vessels (**arteriovenous anastomosis**)

# 4. Immunity

## a. Innate Immunity

- **Anti-microbial peptide**:
  - Direct anti-microbial action
  - Eg. cathelicidins, β-defensins
- **Alarmins**:
  - Enhance host defense system
  - Chemotactic: movement of WBCs by chemical signals
  - Angiogenetic: formation of new blood vessels → ↑ blood flow
- **Phagocytosis**:
  - Dermal dendritic cells
  - Macrophages

## b. Adaptive Immunity

- Antigen-presenting: Langerhans' cells (dendritic cell of skin and mucosa), dendritic cells, macrophages
- Cellular immunity (Th1 response)
- Humoral immunity (Th2 response)

## 5. Sensation

- Afferent fibres → sensory root
- Efferent fibres → autonomic motor root
- Specialized sensory receptors: **Meissner's corpuscles** (light touch mechanoreceptors), **Merkel's receptors** (texture mechanoreceptor)

## 6. Endocrine

- Production of **vitamin D** upon sunlight exposure: modification of cholesterol into cholecalciferol ($D_3$)
- Function of vitamin D: enhance intestinal absorption of $Ca^{2+}$, $PO_4^{3-}$

## 7. Communication

- Visual appeal, texture, smell
- Role in social and sexual aspects
- Organ of communication
- Enhancement by clothing, cosmetics

# D. Skin Homeostasis

- Skin and its appendages are capable of regeneration
- Proliferation and differentiation from stem cells
- Location of stem cells:
  - Bulge area of follicles → follicle
  - Basal area of inter-follicular epidermis → epidermis
  - Base of sebaceous gland → sebaceous gland

# L37 Introduction to Musculoskeletal System

## A. Skeletal System

- Two regions:
  - **Axial skeleton**: skull, thoracic cage, vertebral column
  - **Appendicular skeleton**: bones of limbs and limb girdles
- Consists of **bones**, **cartilage**, **joint**
- Functions of skeletal system:
  - Support
  - Protection of internal organs
  - Act as levers
  - Site for manufacturing blood cells (in bone marrow)
  - Stores $Ca^{2+}$ and $PO_4^{3-}$
- Comparison of bone and cartilage:

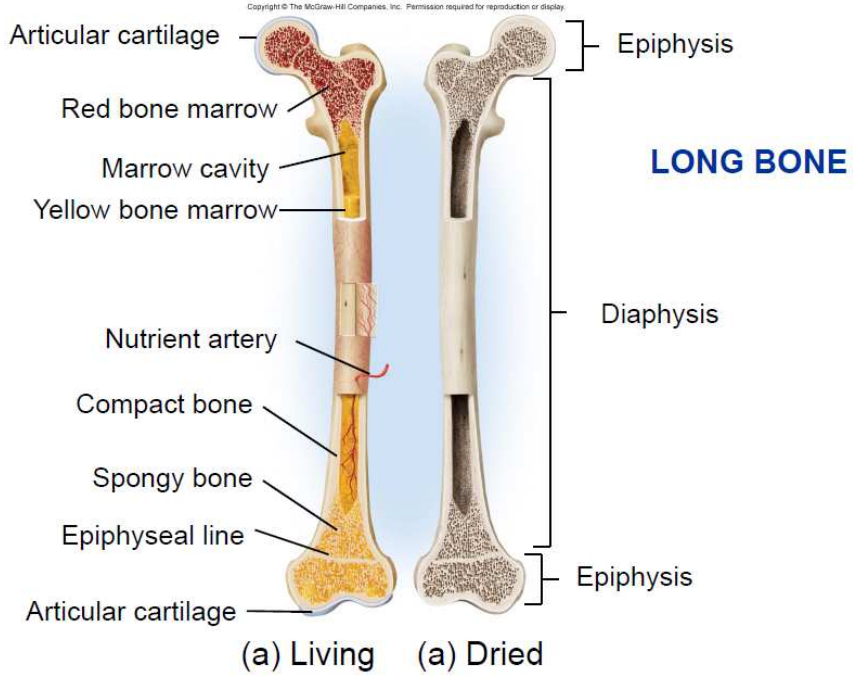
| | Bone | Cartilage |
|---|---|---|
| Cells | **Osteocytes** | **Chondrocytes** |
| Intercellular matrix | ▶ Collagen fibres for tensile strength<br>▶ Inorganic calcium and phosphate for compressive strength | ▶ Collagen or elastic fibres<br>▶ Organic proteoglycan |
| Blood vessels and nerves | Well-supplied | Lacking (supplied by diffusion from neighboring matrix) → doesn't heal as quickly as the bone |
| Growth | **Appositional** | **Appositional** and **interstitial** |

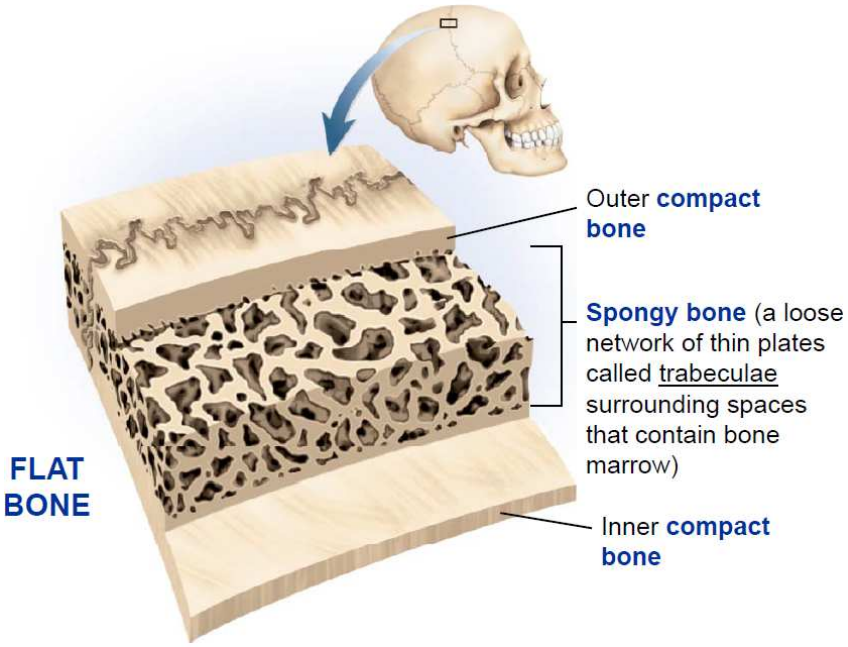
*Bone growth:

- **Appositional**: addition of new layer
- **Interstitial**: growth in the interior

# 1. Bones

- Bone tissue grow by **osteoblast** differentiation to form **osteocyte**
- Bone tissue resorbed by **osteoclasts** (bone macrophages)



# 2. Cartilage

## a. Hyaline (glassy) Cartilage

- Glassy, translucent, flexible, elastic
- High proportion of ground substance
- Low proportion of collagen fibres
- Examples: costal cartilages, articular cartilages, tracheal rings

## b. Fibrocartilage

- Large amount of collagen fibres (for toughness)
- Small amount of ground substance
- Examples: intervertebral disk (shock-absorber), pubic symphysis

## c. Elastic Cartilage

- Opaque, yellowish
- Very elastic because of large numbers of elastic fibres
- Will not be calcified → will remain as cartilage throughout lifetime
- E.g. **ear auricle (pinna)**, nose

# 3. Joints

## a. Fibrous Joints

- **Sutures** in skull: interdigitation of bones joined by collagen fibres
- **Gomphosis** between tooth and socket: joined by periodontal ligaments
- **Syndesmosis (interosseous membrane)**: fibres joining relatively long bones (eg. tibia/fibula joint)

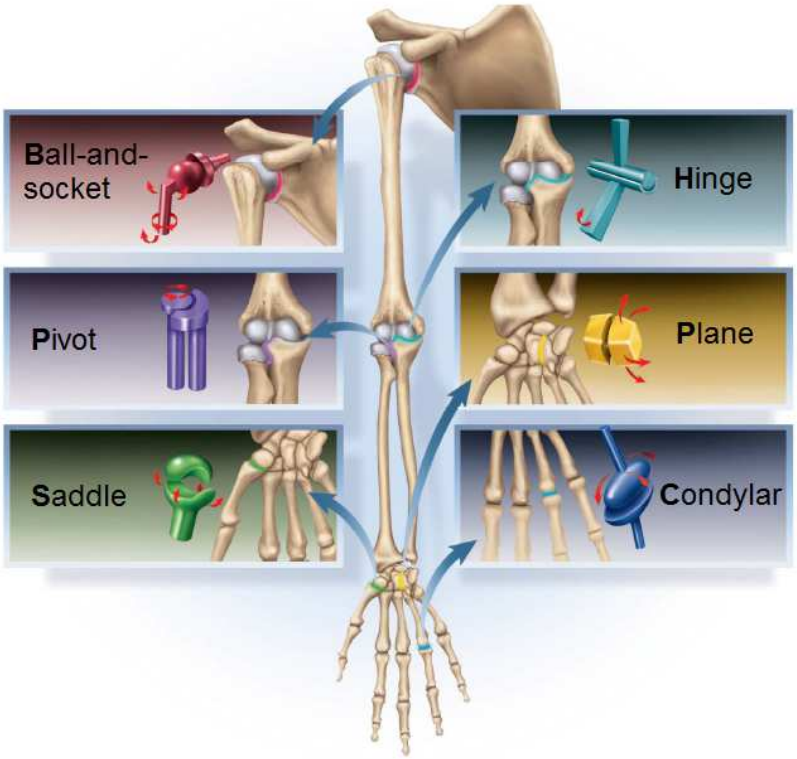
## b. Cartilaginous Joints

- **Primary cartilaginous joint** (**synchondrosis)**: eg. epiphyseal plate (growth plate in adolescents, hyaline cartilage in nature, converted into bone in adults (epiphyseal line))
- **Secondary cartilaginous joint (symphysis)**: hyaline cartilage + fibrocartilage + hyaline cartilage (eg. intervertebral joints, pubic symphysis)

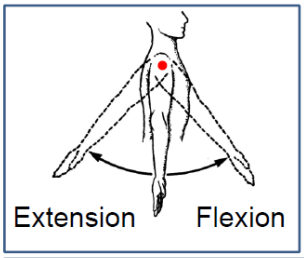
## c. Synovial Joints

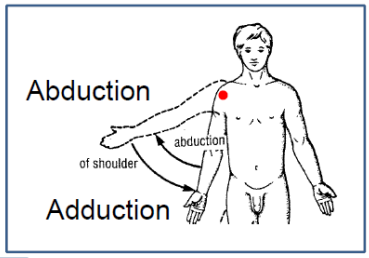
*Note that **synovial membrane** does not cover articular cartilage

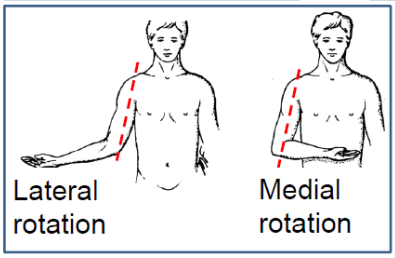
- Range of motion and stability depends on (1) shape of articular surface (2) ligaments (3) muscle tone (residual tension)
- Types: **P**raying **H**ard **P**rovides **C**hildren **S**trong **B**eliefs
  - **P**lane: intercarpal joint
  - **H**inge: elbow joint
  - **P**ivot: proximal radioulnar joint
  - **C**ondylar: metacarpophalyngeal joint
  - **S**addle: carpometacarpal joint of thumb
  - **B**all and socket: pectoral girdle joint

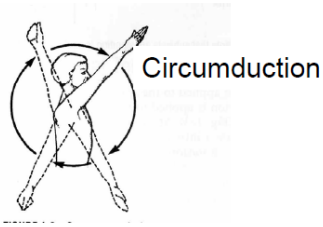


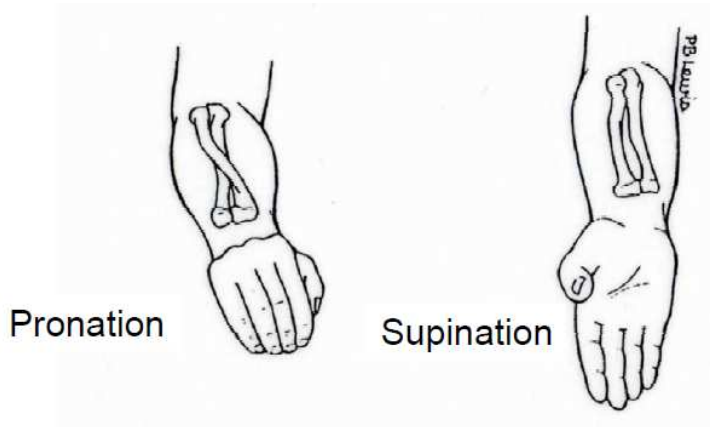

*Note terminology of limb movement:



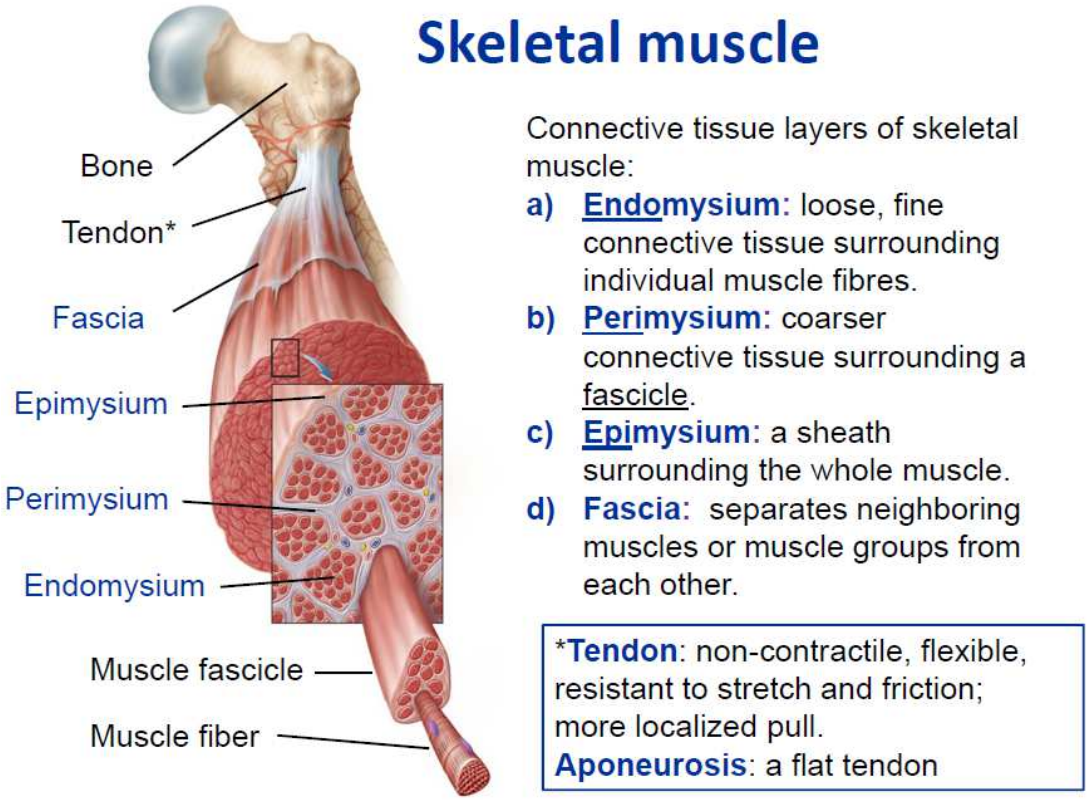



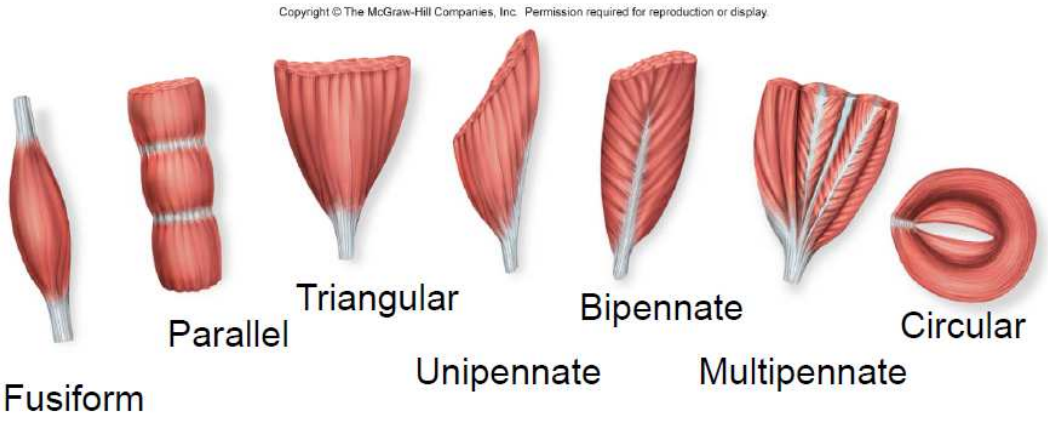
# B. Muscular System

## 1. Muscles

- Classification: skeletal, cardiac, smooth
- Skeletal muscle structure:




- Muscle shapes and fascicle arrangement:




*pennate = feather-like

## 2. Muscle Origin and Insertion

- **Origin**: attachment that moves the least
- **Insertion**: attachment that moves the most
- Contraction of muscle brings insertion closer to origin → movement

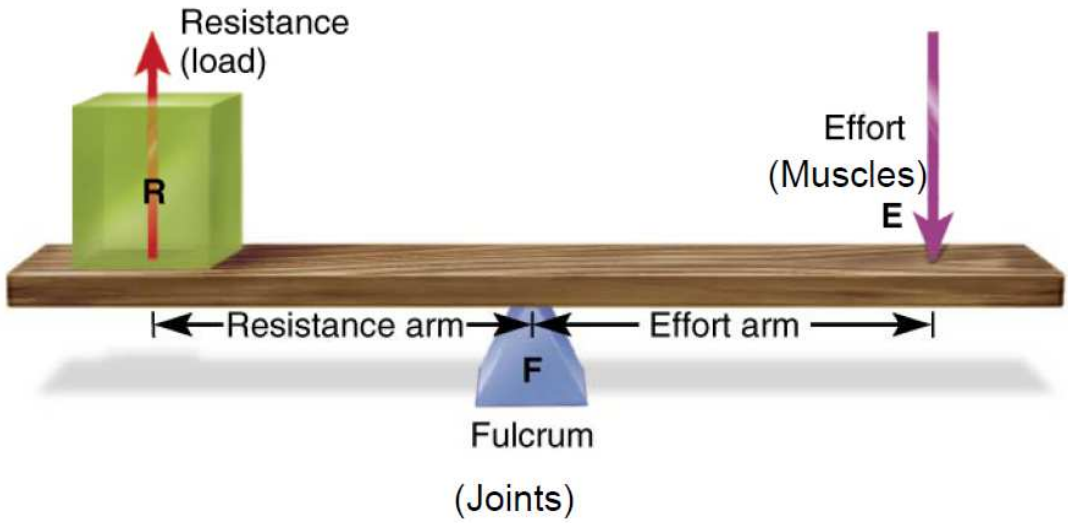
*Note: origin and insertion are interchangeable (eg. pectoralis minor muscle can act as muscle for movement of scapula or accessory respiratory muscle to aid inhalation)

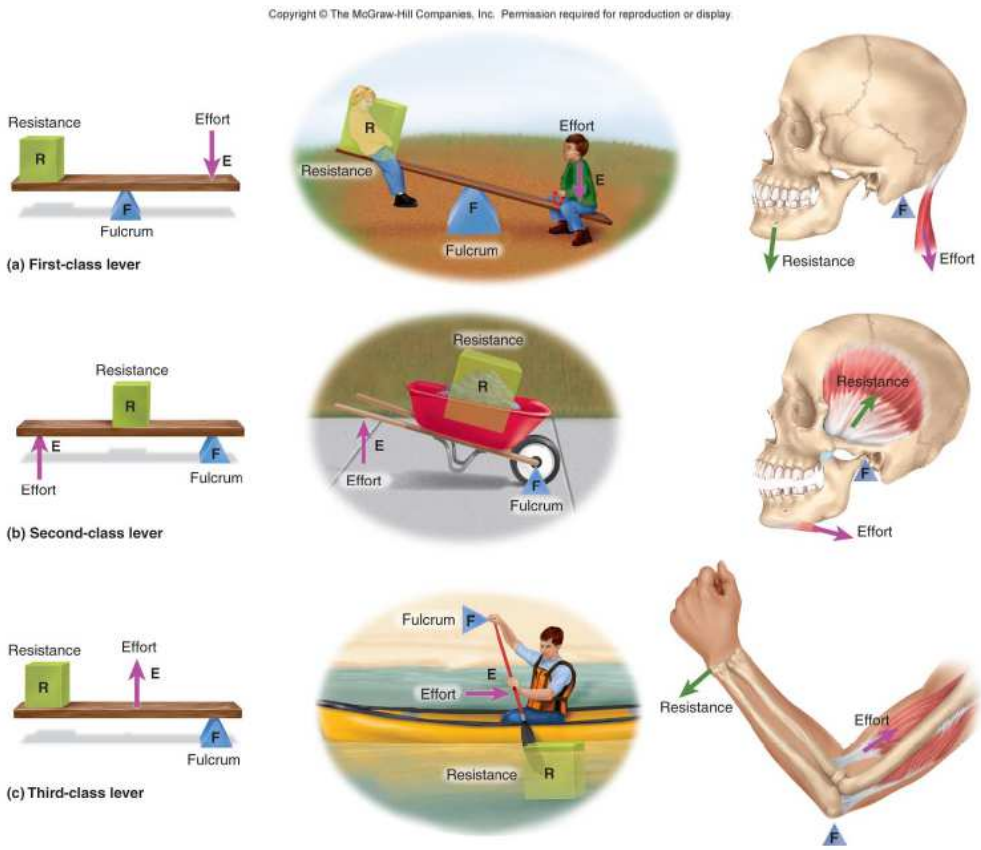
## 3. Functional Groups of Muscles

- **Prime mover (agonist)**: muscle that produces most of the force during a particular joint action
- **Antagonist**: a muscle that opposes the prime mover
- **Synergist**: a muscle that helps the prime mover to produce more power
- **Fixator**: a muscle that prevents a bone from moving so as to prevent undesirable movement

# 4. Muscle Action

- Muscle act as the effort in a lever system to bring about locomotion



# L38 Introduction to Endocrinology

## A. Hormones

- **Classical hormones**: complex substances produced by glands, secreted into blood, carried to target at some distant sites (endocrine action)
- **Local hormones**: those act at or near site of production (less needed and produced) (paracrine action)
- Chemical natures: mostly peptides or proteins, or steroids, some derivatives of AAs
- Receptor:
  - Binding of hormone to receptor triggers a response
  - Both **affinity** and **number of receptors** are important
  - Actions of hormone depend on conc. and receptors in responsive tissues
  - Receptor on plasma membrane (peptides, proteins) → fast actions (eg through signal transduction to activate enzymes)
  - Receptor in nucleus (thyroxine, steroids) → slow action (eg affect synthetic rate of proteins)

## 1. Metabolism of Hormones

- Hormone level in blood depends on both **rate of secretion** and **rate of removal**
- **Metabolic clearance (MCR)**: volume of blood completely cleared of a hormone per unit time
  - MCR × conc. of hormone = volume completely cleared
- **Half-life ($t_{1/2}$)**: time for hormone level to decrease to half its initial value
- Clearance rate is related to affinity to plasma protein: stronger binding → long half-life

# 2. Hormonal Action

| Hormone | Nature | Secretion | Effect |
|---|---|---|---|
| **Growth Hormone (GH)** | Peptide | Pituitary | Metabolic:<br>- ↑ Gluconeogenesis, Glc uptake in liver<br>- ↑ Protein synthesis<br>- ↑ Lipolysis<br>Blood minerals:<br>- ↑ $Ca^{2+}$ retention in bone<br>Growth:<br>- ↑ growth, strengthen bones |
| **Thyroxine ($T_4$)** | Tyr-based | Thyroid gland | - Metabolic:<br>- ↑ blood glucose<br>- ↑ protein synthesis (excess ↓)<br>- ↑ lipolysis (excess ↓)<br>Growth:<br>- ↑ protein synthesis<br>*(excess → early closure of epiphyseal plate and stunting of growth)* |
| **Cortisol** | Steroid | Adrenal cortex | Metabolic:<br>- ↓ protein synthesis<br>- ↑ blood glucose (via gluconeogenesis)<br>- ↑ lipolysis<br>Growth:<br>- ↓ protein synthesis and bone growth<br>- Early closure of epiphyseal plate and stunting of growth<br>*(a stress hormone that triggers anti-stress and anti-inflammatory response → medical use as topical cream)*<br>*(controlled by CRH in hypothalamus and then ACTH in pituitary)* |
| **Insulin** | Peptide | Pancreas | Metabolic:<br>- ↑ protein synthesis<br>- ↓ blood glucose<br>- ↑ fat formation<br>Growth:<br>- ↑ protein synthesis<br>- ↑ bone growth |

| | | | |
|---|---|---|---|
| **Glucagon** | Peptide | Pancreas | Metabolic:<br>- ↑ blood glucose (by ↓ glycolysis and ↑ gluconeogenesis) |
| **Adrenaline** | Tyr-based | Adrenal medulla | Metabolic:<br>- ↑ blood glucose<br>- ↑ lipolysis |
| **Aldosterone** | Steroid | Adrenal cortex | Blood volume:<br>- ↑ water and $Na^+$ reabsorption in distal tubule and collecting duct<br>- ↑ blood volume<br>Blood minerals:<br>- ↑ excretion of $K^+$ in kidney<br>- ↓ $Na^+$ reabsorption |
| **Angiotensin** | Peptide | Liver | Blood volume:<br>- ↑ water and $Na^+$ reabsorption at proximal tubule<br>- ↑ blood volume<br>- ↑ aldosterone |
| **Anti-diuretic hormone (ADH)** | Peptide | Hypothalamus via pituitary | Blood volume:<br>- ↑ water reabsorption at collecting duct<br>*(excess → ↓ blood $Na^+$ level)*<br>**Exercise → ↑ ADH secretion*<br>∴ drinking excess water during exercise → hyponatremia |
| **Atrial natriuretic peptide (ANP)** | Peptide | Atrium (heart) | Blood volume:<br>- ↓ water and $Na^+$ reabsorption at proximal tubule<br>- ↓ blood volume<br>Blood minerals:<br>- ↓ $Na^+$ reabsorption at proximal tubule |
| **Parathyroid hormone (PTH)** | Peptide | Parathyroid gland | Blood minerals:<br>- ↑ bone breakdown<br>- ↓ excretion of $Ca^{2+}$ in kidneys<br>- ↑ $Ca^{2+}$ level |
| **Gonadotrophin-releasing hormone (GnRH)** | Peptide | Hypothalamus | Reproductive cycle:<br>- ↑ secretion of FSH/LH from anterior pituitary<br>**release of GnRH is **pulsative***|

| | | | |
|---|---|---|---|
| **Follicle-stimulating hormone (FSH)** | Glyco-protein | Anterior pituitary | Reproductive cycle:<br>- ↑ spermatogenesis/follicle development |
| **Luteinizing hormone (LH)** | Glyco-protein | Anterior pituitary | Reproductive cycle:<br>- ↑ testosterone/oestrogen/ progesterone release<br>- Stimulate ovulation |
| **Sex steroids (eg. testosterone, oestrogen, progesterone)** | Steroid | Gonads | Reproductive cycle:<br>- Important for development of gonads, sex accessory glands (prostate, uterus etc) and secondary sexual characteristics<br>Growth:<br>- ↑ Protein synthesis and bone growth<br>*(excess → early closure of epiphyseal plates, stunting of growth)* |

# 3. Time Frame of Hormonal Action

- Hormones with short-term actions have short half-lives
- Long-term action, nuclear receptors, transcription/translation are required
- Some hormones (eg. $T_4$, insulin) have both long and short-term actions

# 4. Regulation of Hormone Secretion

## a. Negative Feedback

- Most common
- A close-loop system where output decreases input signal
- Stress can override → change set-point
- Example: insulin and aldosterone

## b. Circadian Rhythm

- **Diurnal** rhythm: day and night changes
- Example: cortisol rises in morning and drops in late afternoon and at night

## c. Humoral and Neural Control

- **Humoral control**: depend on levels of factors in blood
- Example of neural control: adrenaline secretion controlled by sympathetic nervous system

## d. Pituitary Control

- **Anterior pituitary** controlled by humoral factors secreted by hypothalamus in portal vein
- **Posterior pituitary** controlled by neural inputs from hypothalamus

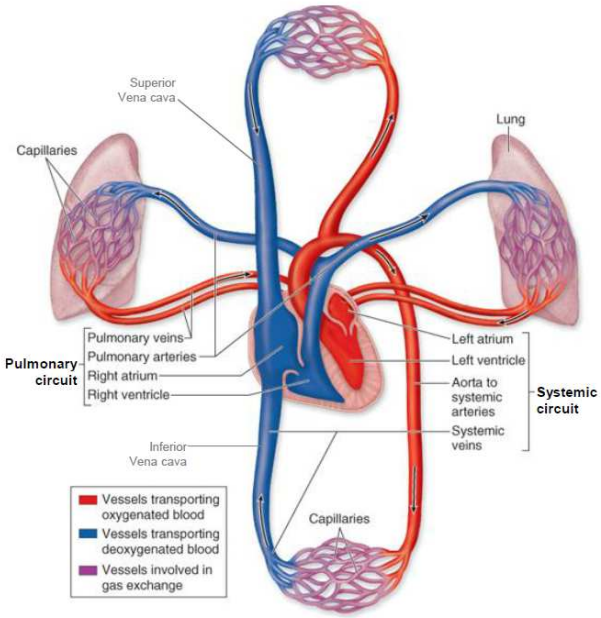
# B. Endocrine Disorders

- Excess secretion often due to secretion by tumours (eg. adrenal tumours secreting cortisol → Cushing's syndrome)
- Deficiency in secretion may be due to destruction of secretion tissues by auto-antibodies (eg. **diabetes mellitus**: loss of β cells secreting insulin)
- Outcome depends on extent of excess/deficiency and compensatory mechanisms
    - **Acromegaly**: excessive GH secretion from a tumor but will not cause **hyperglycaemia** due to insulin control

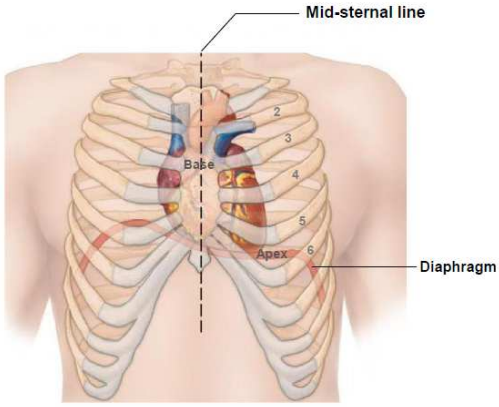
# L39 Structural Organization of the Cardiovascular System

## A. Cardiovascular System

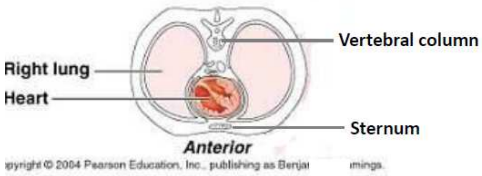
- Consists of the **heart** and **vessels** (arteries, veins, capillaries)
- Function: supplying $O_2$ and nutrients; removing wastes
- **Pulmonary circuit** carries deoxygenated blood to the lungs
- **Systemic circuit** carries oxygenated blood to tissues
- Three-layered wall in heart:
  - **Endocardium** (endothelium)
  - **Myocardium** (cardiac muscles)
  - **Epicardium** (visceral pericardium i.e. c.t.)
- Three-layered wall in blood vessels:
  - **Tunica intima** (endothelium)
  - **Tunica media** (smooth muscles)
  - **Tunica adventitia** (c.t.)



# B. Heart

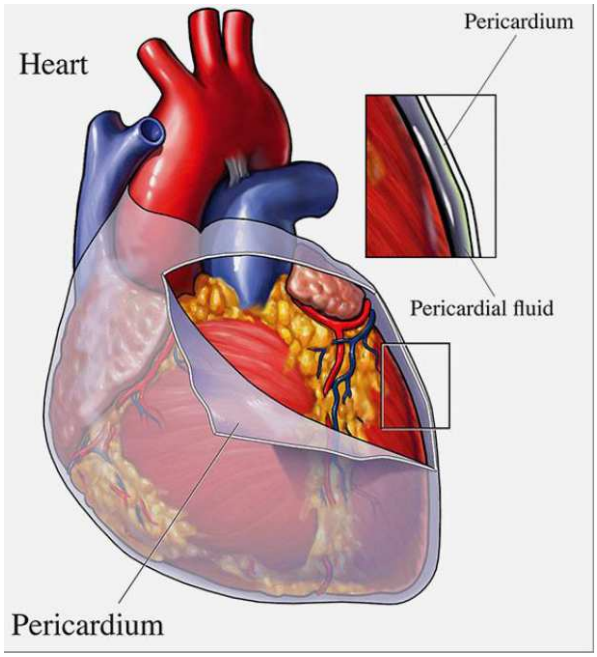



- Location:
  - Anterior to **vertebral column**, posterior to **sternum**
  - Left of midline
  - Deep to 2nd – 5th intercostal spaces
  - Superior surface of diaphragm
- Shape: like a blunt pyramid, with an **apex** and **base**
- Size: approx. ~ size of fist
- Functions:
  - **Generating blood pressure**: required for blood flow through blood vessels
  - **Routing blood**: two pumps, moving blood through pulmonary and systemic circulations
  - **Regulating blood supply**: adjusts blood flow by changing rate and force of heart contractions as needed



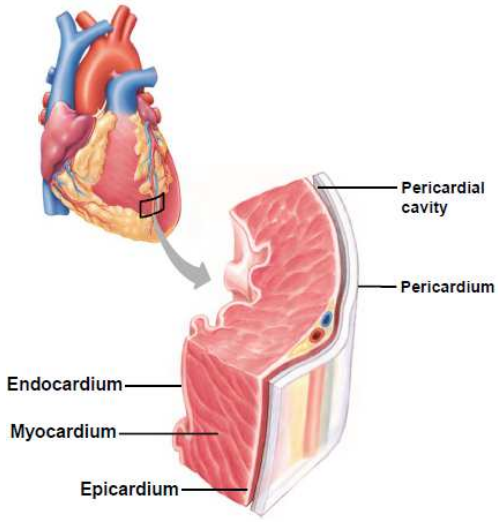

# 1. Pericardium

- A double-layered fibrous sac enclosing the heart
- Keeps the heart contained and protected within the chest wall
- Made up of two layers:
  - **Fibrous pericardium** (outer): tough c.t.
  - **Visceral pericardium** (inner, = **epicardium**): more delicate layer that surrounds the heart
- **Pericardial cavity** between the two layers with serous **pericardial fluid** to act as lubricant



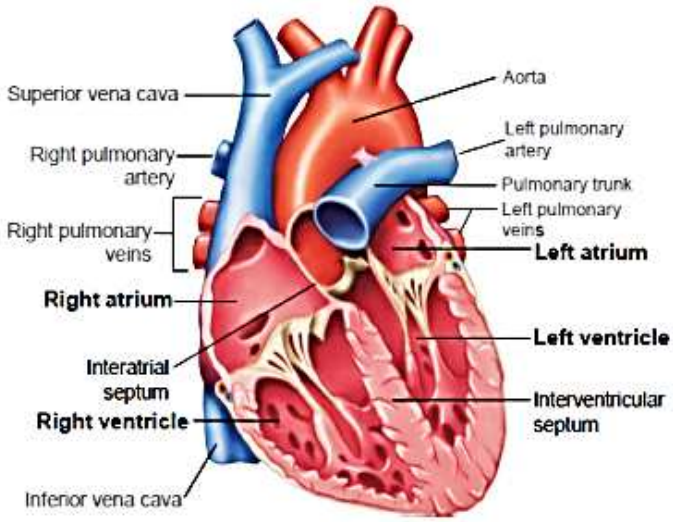
# 2. Heart Wall

- Three layers:
  - **Epicardium**: made up of c.t., = visceral pericardium
  - **Myocardium**: consists of **cardiac muscles** and is the thickest layer
  - **Endocardium**: lined with endothelial cells and is continuous with blood vessel endothelium
- Ventricular wall much thicker than the right ventricle




# 3. Heart Chambers

- Heart has four internal chambers
- Two **atria** (*sing.* **atrium**):
  - Located at the top
  - Receive blood returning to the heart
- Two **ventricles**:
  - Located at the bottom
  - Pump blood to the body
- A **septum** to divide atria and ventricles on each side
- **Right heart** receives deoxygenated blood from two **vena cavae** (superior for heart, chest and arms; inferior for others) and pumps blood into **pulmonary circulation** via **pulmonary trunk**




- **Left heart** receives oxygenated blood from **pulmonary veins** and pumps blood into the **systemic circulation** via **aorta**

# 4. Heart Valves

## a. Atrioventricular (AV) Valves

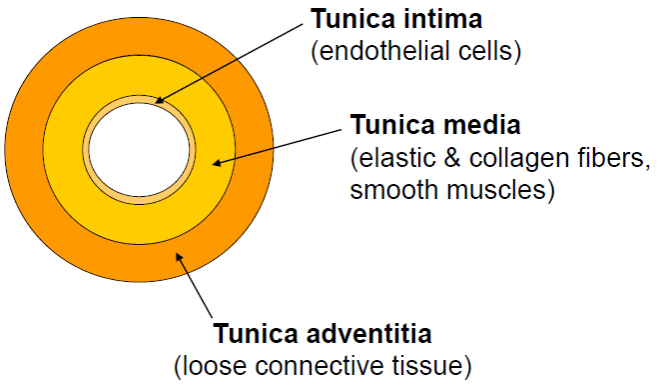
- **Atrioventricular (AV) valve** located between atrium and ventricles to ensure unidirectional flow of blood
  - **Right A-V valve (tricuspid valve)**
  - **Left A-V valve (bicuspid valve)**
- Cusps of valves are attached to **chordae tendinae** which are in turn attached to **papillary muscles** in ventricles
  - **Papillary muscles** contract during ventricle systole → **chordae tendinae** become taut → prevent overturning of A-V valve → maintain unidirectional flow of blood

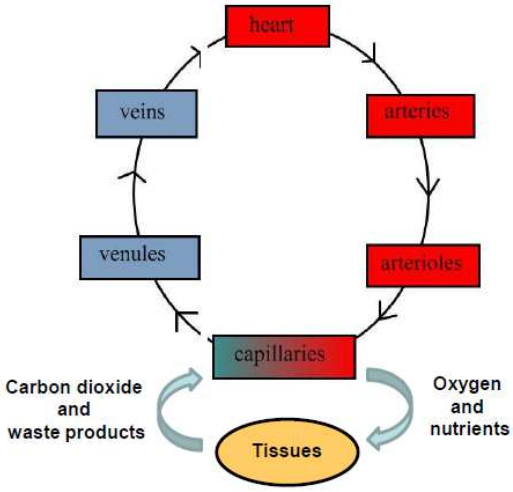
## b. Semilunar Valves

- Three half-moon shaped cusps attached between great vessels and ventricles
- **Pulmonary valve**:
  - At the base of **pulmonary trunk**
  - Prevent backflow of blood into right ventricle from the pulmonary artery
- **Aortic valve**:
  - At the base of **aorta**
  - Prevents backflow of blood into left ventricle from the aorta

# C. Vascular System

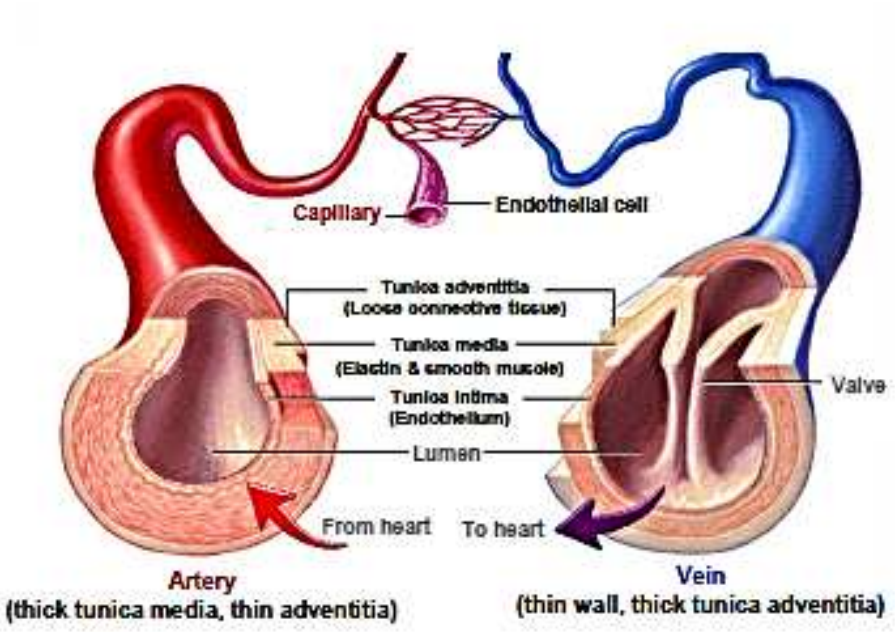
- System of transport formed by blood vessels
- Functions:
  - Carries blood to exchange nutrients, waste products and gases with tissues
  - Helps regulate blood pressure
  - Directs blood low to tissues
- Anatomy:

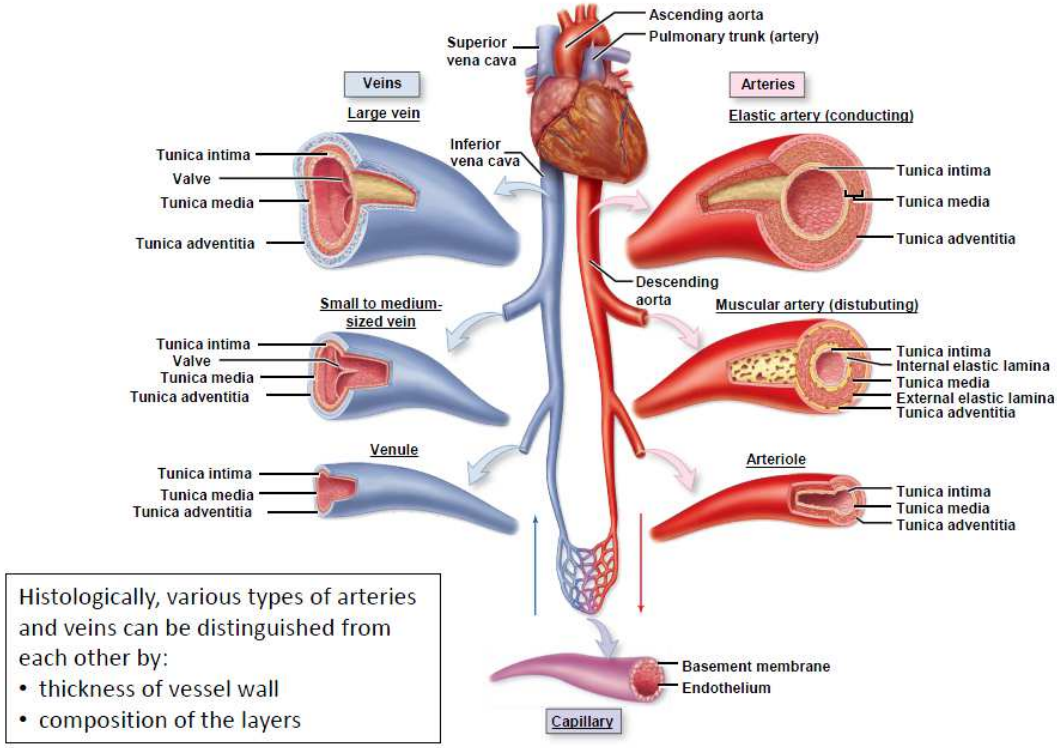



*Vessels differ in size in terms of thickness of **tunica media**, other layers ~ the same

# 1. Artery

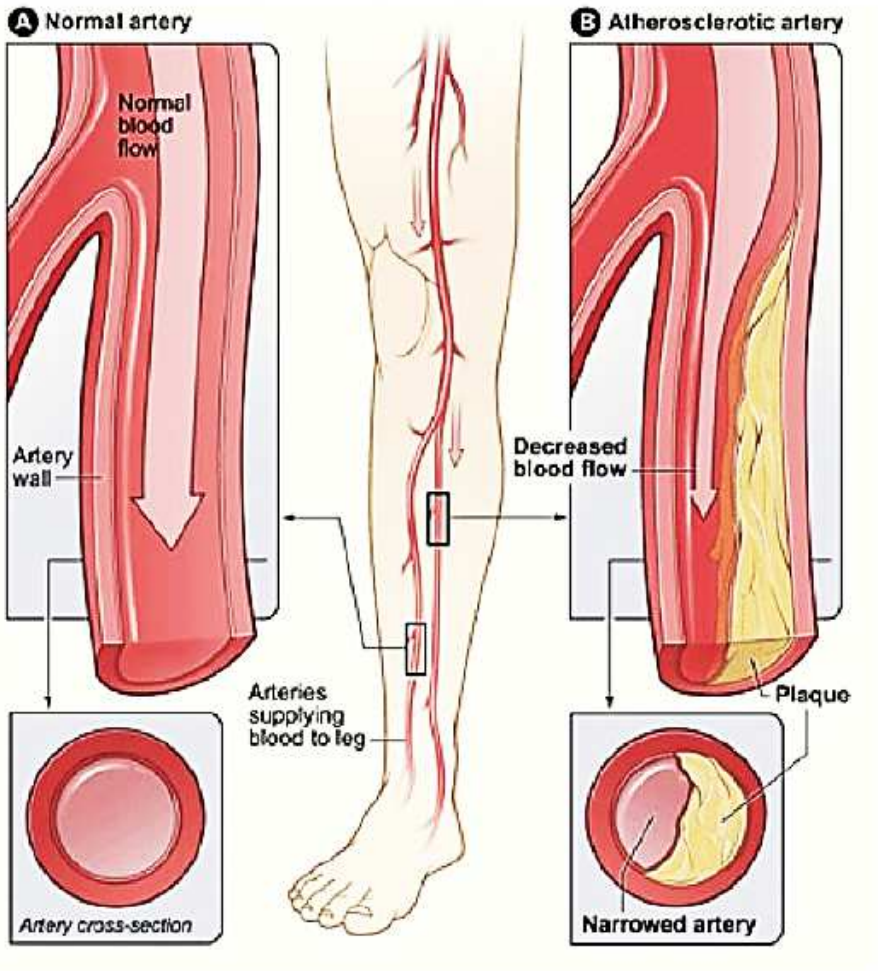



Histologically, various types of arteries and veins can be distinguished from each other by:
- thickness of vessel wall
- composition of the layers

- Help transport blood away from heart to other parts of body
- Has thick muscular wall (**tunica media**) and smaller internal lumen
- Has more elastic fibres
- **Pulse**: rhythmic expansion and contraction of an artery due to heart beat
- Contains blood under high pressure

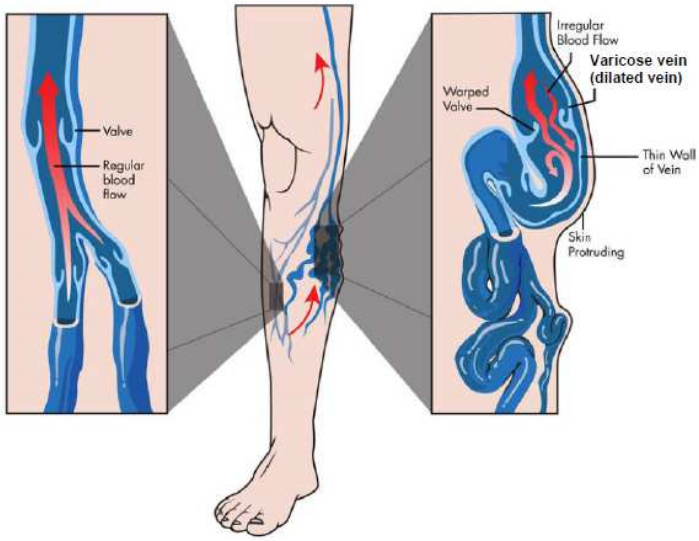
- **Large elastic (conducting) artery**:
  - Thick-walled with large diameter
  - Tunica media has many elastic fibres and little smooth muscle
- **Medium Muscular (distributing) artery**:
  - Thick-walled with smaller diameter
  - Tunica media has abundant smooth muscles and some elastic fibres
- **Arterioles**:
  - Smallest arteries
  - Tunica media consists of one or two layers of smooth muscle cells and a few elastic fibres
- Arterial diseases:
  - **Arteriosclerosis**: general term for degenerative changes in arteries making them elastic
  - **Atherosclerosis**: deposition of lipid plaque on walls
  - **Vasculitis**: blood vessel inflammation
  - **Aneurysm**: dilation (bulge) in wall of blood vesssels



# 2. Vein

- Help transport blood to the heart from other parts of body
- Has thinner wall and larger internal lumen
- Contains much less elastic fibres and smooth muscle
- Contains blood under low pressure
- Has valves to prevent backflow of blood
- Larger veins have all three layers

## a. Varicose Veins



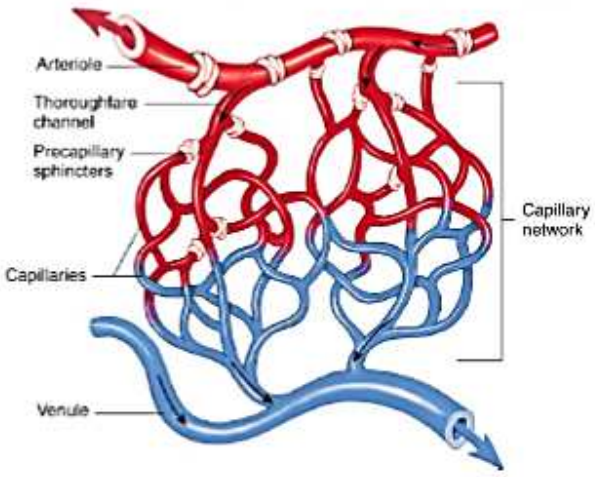

- Enlarged, twisted veins
- Improper functioning of valves → blood accumulate → enlarged and tortuous veins → symptoms eg. leg swelling
- Common in superficial veins of leg
- Could lead to **thrombophlebitis**: vein inflammation related to a **thrombus** (blood clot)
- Risk factors: hereditary, pregnancy, obesity, menopause, aging, standing for a long time

*Comparison between arteries and veins:

| **Arteries** | **Veins** |
|---|---|
| Carrying blood at high pressure | Carrying blood at very low pressure |
| Thick wall | Thin wall |
| Smooth muscle and/or elastic fibers/ lamellae predominate over collagen fibers in tunica media, elastic fibres highly developed | Collagen fibers are relatively abundant among the smooth muscles in the tunica media |
| Smooth muscles and other components are arranged circularly in tunica media – allows change in diameter to regulate blood pressure and blood flow | Collagen fibers and other components arranged longitudinally (prevent excess stretching of vessel wall) |
| No valves | Valves present; to prevent backflow |

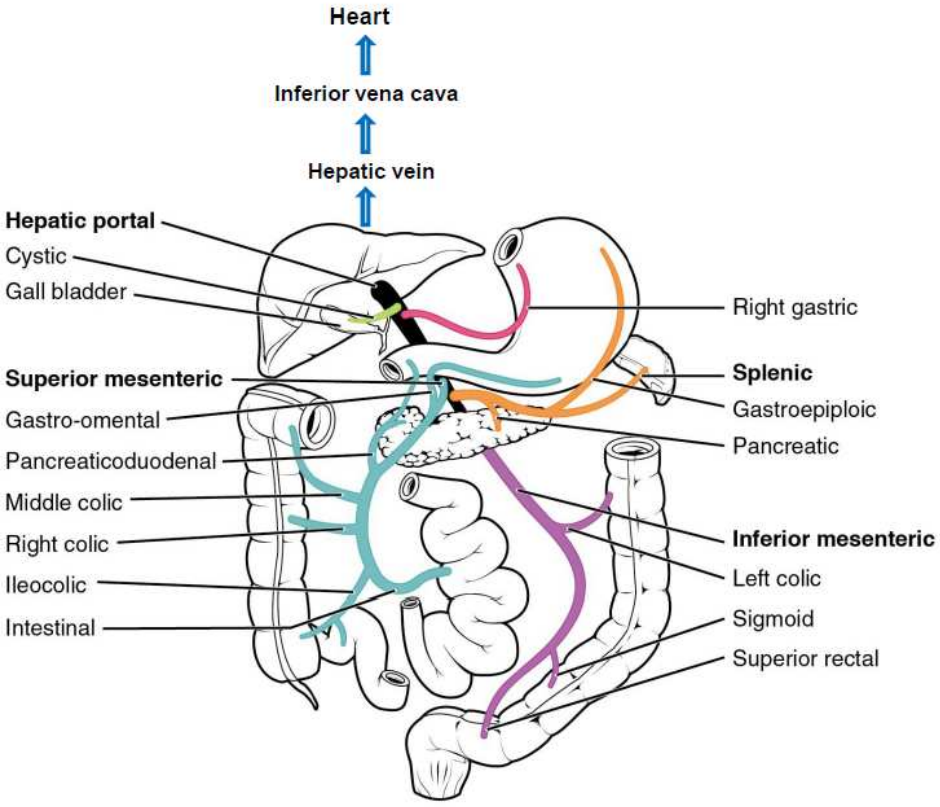
# 3. Capillaries

- Smallest blood vessels connecting arteries and veins
- Wall consists of a single layer of **endothelial cells** (to facilitate diffusion
- Average diameter ~ 8μm (~the same as that of RBCs)
- **Thoroughfare channels (shunt vessels)** carries blood from arterioles to venules rapidly
- **Precapillary sphincters** regulate flow of blood into capillaries




# 4. Circulatory Routes

- Normal route: heart → arteries → arterioles → capillaries → venules → veins → heart (passes through only one network of capillaries)
- **Portal system**: blood flows through two consecutive capillary network
  - Between GI tract to liver
  - Between hypothalamus and anterior pituitary
- Hepatic portal system:

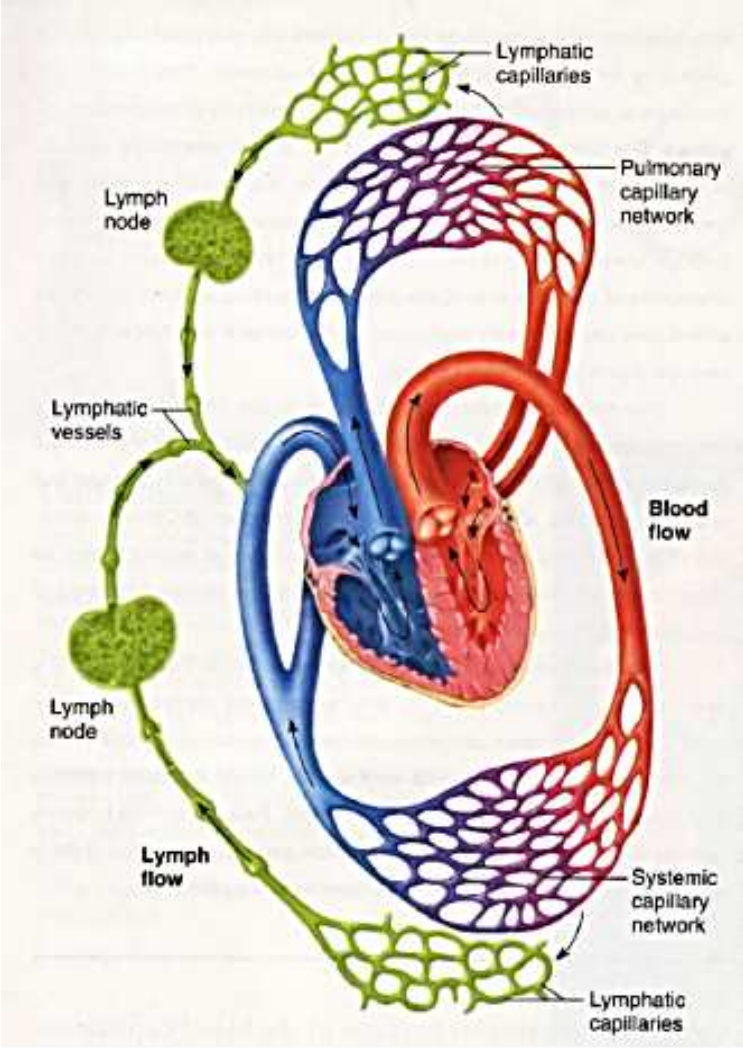


## a. Anastomoses

- **Anastomosis** (*pl.* anastomoses): the point where two blood vessels merge
- **Arteriovenous anastomosis (shunt)**: artery flows directly into vein bypassing capillaries
- **Venous anastomosis**: one vein empties directly into another
  - Most common
  - As a result vein blockage is less serious than an arterial blockage
- **Arterial anastomosis**: two arteries merge
  - Provides collateral routes of blood supply to a tissue
  - Around joints of the limbs

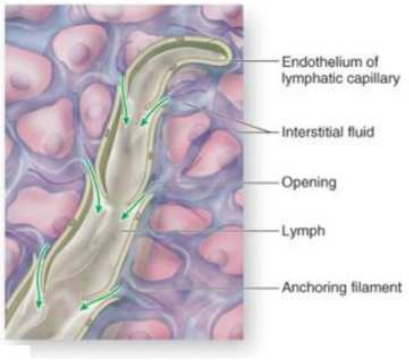
# D. Lymphatic System

- Collects and carries lymph (tissue fluid) from interstitial spaces of tissues and returns to the bloodstream

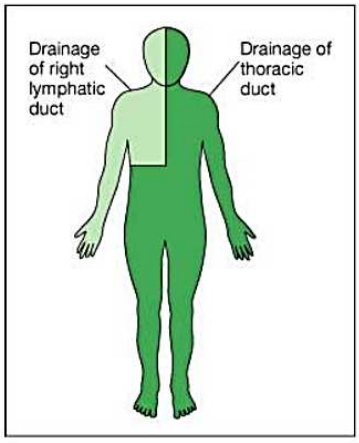


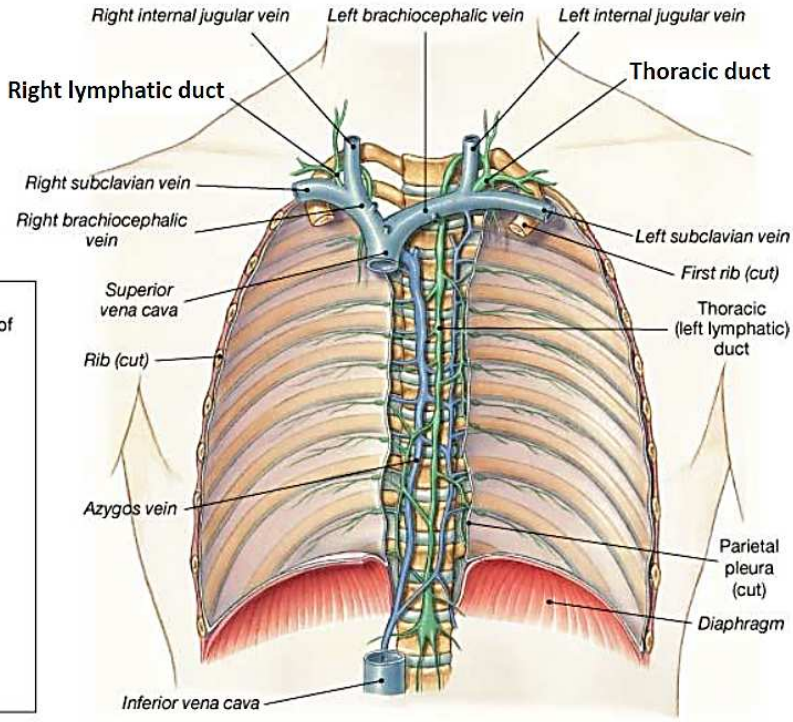
# 1. Lymphatic Vessels

- Flow: lymph capillaries → lymph collecting vessels → lymph trunks → lymph ducts (right lymphatic and thoracic ducts) → large veins
- Blind-ended vessels located in spaces between cells
- Larger than blood vessels and very irregularly shaped
- Regulation of flow: valves, muscle pump, respiratory pump (negative pressure in thoracic cavity)




- Endothelial cells not joined (allow entry of fluid) but overlap to form mini-valves
- Incomplete or absence of basal lamina
- **Thoracic duct** and **right lymphatic duct** collects lymph from all lymph vessels in the body



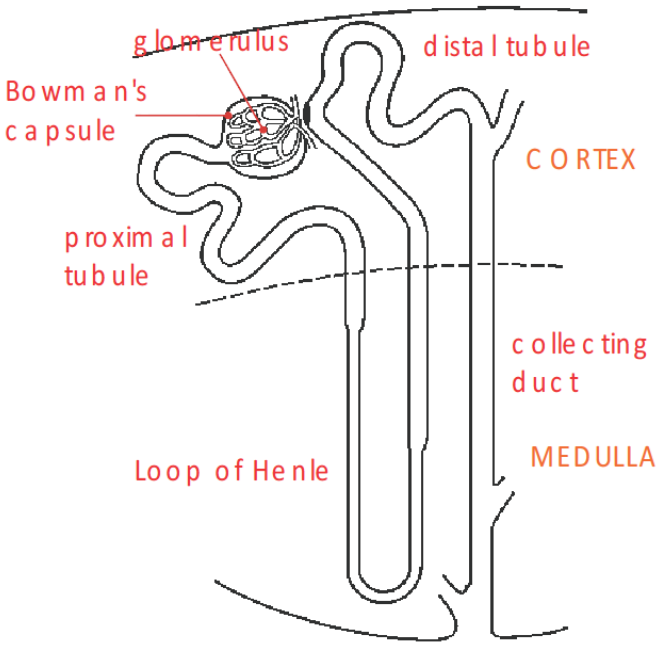
# L40 Introduction to Kidney Function

## A. Urinary Tract

- **Kidneys**: urine formation
- **Ureters**: transport urine to bladder
- **Bladder**: storage of urine
- **Urethra**: route for urine to be expelled from the body

## B. Kidneys

- Functions:
  - Formation of urine
  - Excretion of wastes (eg ammonia, urea)
  - Homeostasis, by regulation of body water, blood pressure (by urine volume), electrolytes and acid/base balance (by urine composition)
  - Hormone secretion (eg erythropoietin, renin)
- **Nephron**: functional unit (~1.3M per kidney)
  - **Bowman's capsule**
  - **Proximal convoluted tubule**
  - **Loop of Henlé**
  - **Distal convoluted tubule**
  - **Collecting duct**
  - **Ureters**



# 1. Renal Process Overview

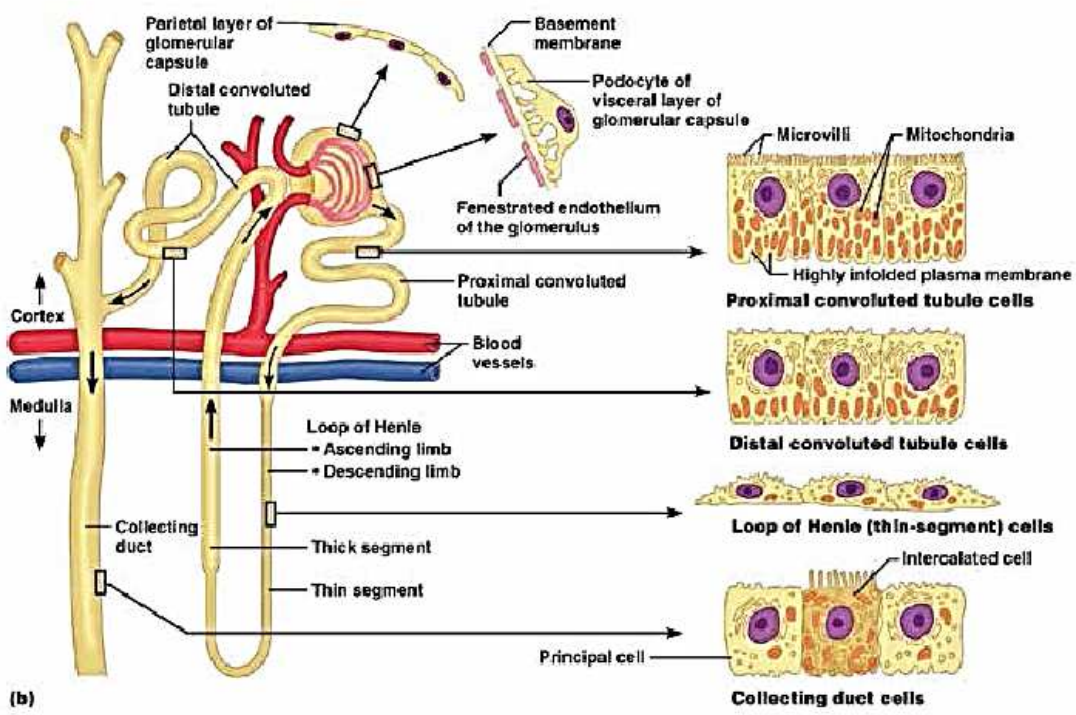
1) **Glomerular filtration**: **ultrafiltrate** of plasma is formed at glomerulus/Bowman's capsule:
   - □ Water and dissolved small molecules filtered
   - □ Cells and plasma protein not filtered
   - □ **Glomerular filtration rate (GFR)**: indicator of renal function (125mL/min or 180L/day)
2) As filtrate moves through tubules of kidney, its volume is reduced by water reabsorption and its composition is altered by reabsorption of substances from it or secretion of substances into it:
   - □ **Proximal tubule**: 70% of filtrate reabsorbed
   - □ **Loop of Henlé**: creates high salt conc. by active transport
   - □ **Distal tubule**: further secretion/reabsorption
   - □ **Collecting duct**: water reabsorption, control of osmolarity of urine;
   - □ As filtrate moves through the nephron:
     - → 179/180L of filtered water is reabsorbed
     - → Most of important electrolytes are reabsorbed
     - → Excretory products are secreted into the fluid and to be carried out from the body
3) Fluid that remains after passing through collecting duct is **urine**;
4) Urine passes down ureter to the bladder for storage;
5) Urine in bladder expelled from body at intervals by process of **micturition** (urination).

# 2. Glomerulus

- Consists of a dense network of capillaries surrounded by **Bowman's capsule** (origin of nephron)
- Note unusual arrangement of blood vessels in kidney: 2 capillary beds in series (glomerular and **peritubular**)
- **Afferent arteriole** and **efferent arteriole** lead into and out of the glomerular capillary bed
  - Each afferent arteriole forms 1 glomerulus
  - Afferent arteriole divides into multiple capillary branches → a 'tuft' (clump) of vessels → large surface area
  - BP gradient forces water from blood into Bowman's capsule (through pores in the wall)
  - Diameter of afferent arteriole is larger than efferent arteriole → high pressure → glomerular filtration

# 3. Renal Tubule

- Tubule walls consist of a single layer of ‘tight’ epithelial cells → minimal barrier to transport and control of transport processes



## a. Proximal Convoluted Tubule

- Composed of mitochondria-rich simple cuboidal epithelium
- Presence of **microvilli**
- **Iso-osmotic reabsorption** of ~70% of filtered fluid:
  - 2/3 of filtered water
  - 2/3 of $Na^+$, $Cl^-$, $K^+$
  - Majority of filtered Glc, AAs
- Fluid leaving proximal tubule is still iso-osmotic to plasma
- **Active reabsorption of $Na^+$** (out of renal tubule cells) drives:
  - Water reabsorption (by osmotic gradient, through aquaporin)
  - $Cl^-$ (by electrochemical gradient, transcellular or paracellular)
  - AAs, Glc, $P_i$ (by co-transport i.e. through protein carriers driven by $Na^+$ gradient)
- **Active reabsorption of $K^+$** (into renal tubule cells)
  - Can diffuse from tubular cell to ECF but most stays intracellularly due to regulated $Na^+/K^+$/ATPase

## b. Loop of Henlé

- Wall composed of simple squamous epithelium (thin limbs) and mitochondria-rich simple cuboidal epithelium (thick limb)
- Composed of **thin descending**, **thin ascending** and **thick ascending limbs**
- At **thin descending limb**,
  - Tubule is highly permeable to water but not very permeable to ion
  - Osmolarity increase in interstitum from outer medulla to inner medulla
  - Osmolarity of fluid lower than interstitial fluid → water leaves tubule → osmolarity rises
- At **thin ascending limb**, tubule is impermeable to water and ions (except $Na^+$ and $Cl^-$)
- At **thick ascending limb**,
  - $Na^+$, $K^+$ and $Cl^-$ is pumped out from thick ascending limb by active transport (help creates high osmolarity in interstitum of medulla)
  - Tubule impermeable to water → osmolarity drops
  - Fluid leaving loop of Henlé is **hypotonic** to plasma

## c. Distal Convoluted Tubule

- Lined by simple cuboidal epithelium but without brush border (microvilli)
- Contains **juxtaglomerular apparatus**:
  - Mechanism regulating GFR and renin secretion based on $[Na^+]$ in distal tubule
  - Excess $Na^+$ ultrafiltration $\rightarrow$ $[Na^+]\uparrow$ in distal tubule $\rightarrow$ GFR $\downarrow$, renin $\downarrow$ $\rightarrow$ body $Na^+$ and water conserved
- ~5% of water reabsorbed
- Further $Na^+$ reabsorption and $K^+$ secretion depending on hormonal control (esp in late distal tubule and collecting duct)
- **Aldosterone** secreted when blood volume $\downarrow$ or $K^+$ $\uparrow$
  - Stimulates active transport of $Na^+$ out of and $K^+$ into renal tubule cells at basolateral membrane $\rightarrow$ $Na^+$ reabsorption and $K^+$ excretion
  - $H_2O$ and $Cl^-$ follows reabsorbed $Na^+$ ($\because$ $Na^+/K^+$/ATP-ase transports 3 $Na^+$ out of and 2 $K^+$ into cell $\rightarrow$ net electrochemical and osmotic gradient)
- Without aldosterone,
  - Any $K^+$ remaining is reabsorbed
  - With most staying intracellular or moving out to be taken up by other cells $\rightarrow$ very low conc. in interstitial space since most $K^+$ comes from food
- **Atrial natriuretic peptide (ANP)** has exactly opposite effect on distal tubule and collecting duct: $\downarrow$ $Na^+$, $H_2O$ reabsorption

## d. Collecting Duct

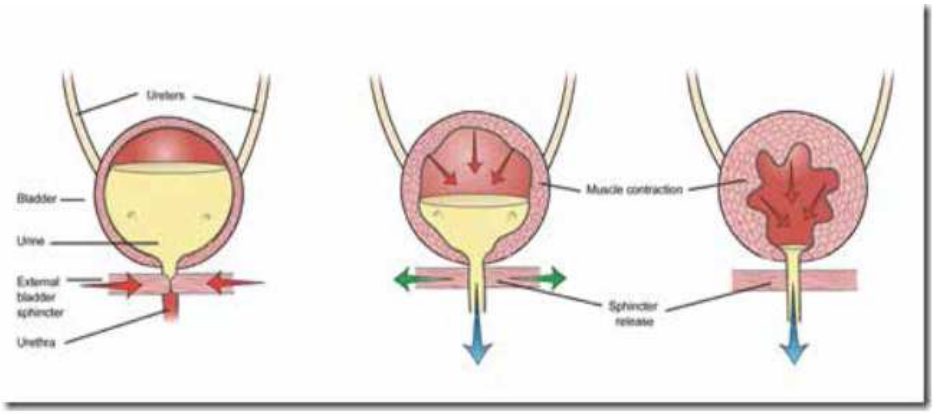
- Lined by simple cuboidal epithelium but grow progressively taller $\rightarrow$ simple columnar epithelium
- Contains two types of cells: **intercalated cells** (controls pH) and **principal cells** (controls $H_2O/Na^+/K^+$ reabsorption)
- Also affected by **aldosterone** level
- Initial portion acts similarly with distal convoluted tubules
- Collecting duct then dips into **medulla** $\rightarrow$ $\uparrow$ osmolarity in interstitial fluid $\rightarrow$ water reabsorption by osmosis
- Permeability to water controlled by ADH via expression of **aquaporin** pores $\rightarrow$ resulting urine may either be hypertonic or hypotonic to plasma

# 4. Ureters

- All collecting ducts empty into renal **pelvis**
- Urine flows down **ureters** from **pelvis** to **bladder**
- Ureters made of smooth muscles → peristaltic waves propel urine down ureters

## a. Micturition (urination)

- Urine flows into bladder, which becomes filled
- Smooth muscle in bladder wall relaxed → bladder pressure only increases a little during filling
- External sphincter muscle prevents urine from leaking out of bladder
- During micturition, sphincter relaxes and bladder contracts → urine expelled
- Micturition an involuntary reflex in infants but becomes voluntary reflex in adults




Storage phase:
- Bladder relaxed
- Sphincter contracted

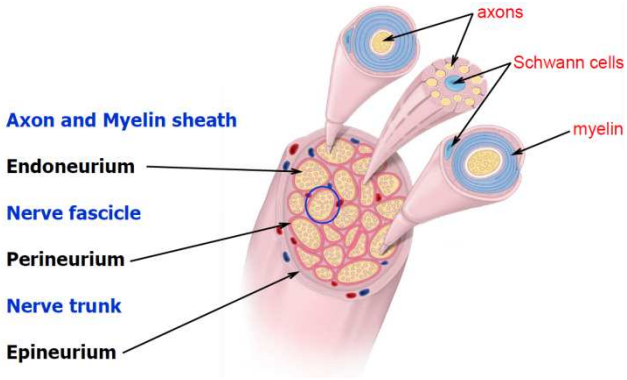
Micturition:
- Sphincter relaxes
- Bladder contracts

Urine is voided

# L41 Neural Architecture

## A. Overview on Nervous System

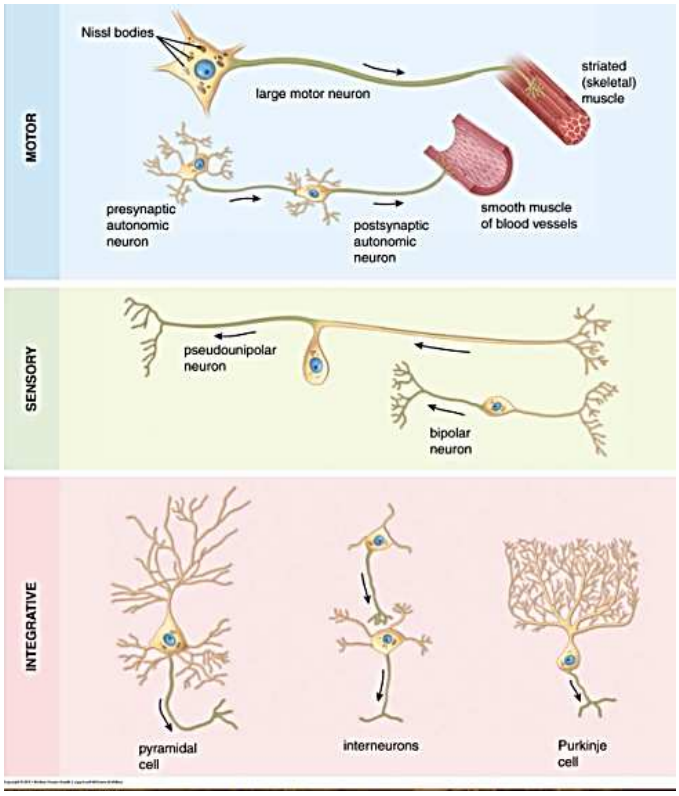
- Cell types:
  - Neurones: structural and functional unit, cannot divide
  - Glial cells: supporting cells, form myelin sheath, can divide throughout adult life
- **Central nervous system (CNS)**: brain + spinal cord (criteria: enclosed by skeleton)
- **Peripheral nervous system (PNS)**: nerve fibres and nerve ganglia outside brain and spinal cord
- **Gray matter**: cell bodies of neurones
- **White matter**: axons of neurones + glial cells




## B. Cells in Nervous System

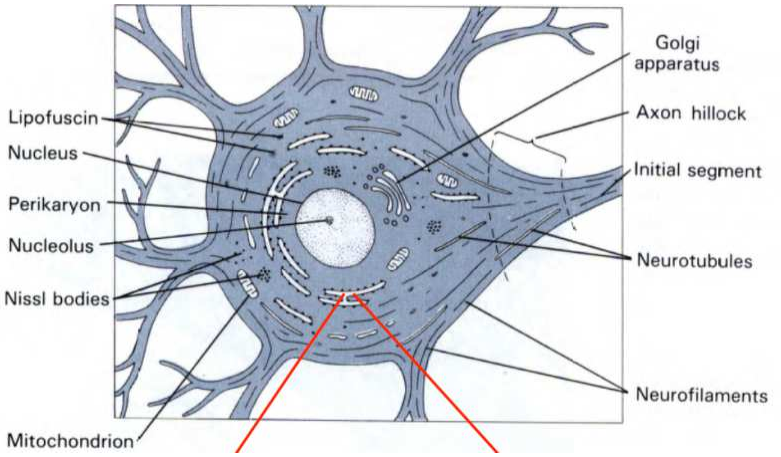
### 1. Neurones

- Classification based on morphology: pseudo-unipolar, bipolar, multipolar
- Classification based on functions: sensory, inter, motor



## a. Soma

- **Soma**: cell body
- Nucleus and cytoplasm
- RER visible as **Nissl bodies** under light microscope
- SER, golgi, mitochondria
- Vesicles containing neurotransmitters or other secretory substances
- **Neurofilaments** (intermediate filaments, for structural support; note exceptional length of axon) and microtubules




## b. Dendrites

- **Dendrites**: fibre leading to **soma**
- Normally unmyelinated
- Usually multiple, branching short extensions of cytoplasm of soma
- Contain virtually all the cytoplasmic organelles found in soma
- Receive impulses from other cells via **synapses**

## c. Axon

- **Axon**: fibre coming out from **soma**
- A single, often long, extension of a specialized type of cytoplasm (**axoplasm**)
- May branch at distal end
- May be myelinated or unmyelinated
- Lacks Golgi, RER, free ribosomes and mRNA (others all present)
- **Axon hillock**: conical transitional zone between soma and axon (with no Nissl bodies)
- Electrical stimulation of soma is propagated along axon to synaptic terminal
- **Antrograde transport**: transport of substances along axon (eg neurotransmitters packaged in Golgi and antrograde transported to axon terminal)
- **Retrograde transport**: transport of substances against direction of axon (eg membrane recycled, virus)
- **Boutons**: swellings of axons, typically sites where synapses occur
  - **Boutons en passant**: along the length
  - **Bouton terminal**: at the end of axon

## d. Synapse

- **Synapse**: junctional specialization for communication between two neurones
- Consists of presynaptic membrane of one neurone in close apposition to postsynaptic membrane of another neurone
- Classification:
  - Based on morphology: axosomatic, axodendritic, axoaxonic
  - Based on function: chemical synapses
- **Synaptic cleft**: space between two neurones
- Presynaptic terminal has vesicles containing neurotransmitters while postsynaptic terminal does not
- Some presynaptic terminals end on effector organs (eg muscles, gland) instead of another neurone

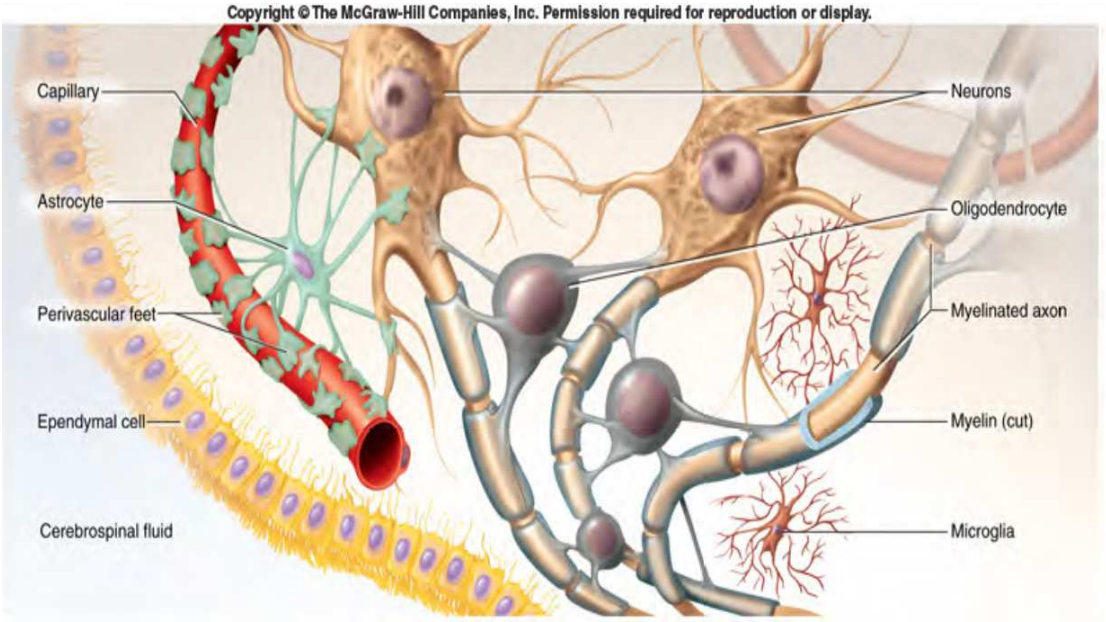
## e. Nerve Endings

- **Motor end-plates and neuromuscular junction**:
  - Ends of spinal motor neurones located in muscles
  - Axon terminals contain vesicles of acetylcholine
  - Synaptic cleft is localized between axon and sarcolemma
- **Sensory nerve endings**:
  - Located in sin, muscle, tendons, etc
  - Responsible for afferent sensory inputs related to touch, pain, temperature, pressure, …
  - Examples: **Pacinian corpuscles** (pressure), **Meissner corpuscle** (touch), free nerve endings (pain), muscle spindles (reflexes)

*Note there are only three types of terminal structures for a neurone:

- Sensory ending
- Synaptic structure with neurone
- Synaptic structure with motor structure

# 2. Glial Cells




## a. Astrocytes

- Largest of the three types of glia
- Irregularly shaped soma
- Many branching processes
- Two types:
  - **Fibrous astrocyte**:
    - → Found mainly in white matter
    - → Has long, usually unbranched processes
  - **Protoplasmic astrocyte**:
    - → Found mainly in gray matter
    - → Has shorter, thicker, highly branched processes
- Function:
  - Keep extracellular $K^+$ low
  - Provision of nutrients
  - Phagocytose neuronal debris and fill in space to form glial scar after injury
  - **Astrogliosis**: proliferation of astrocytes in event of trauma, infection, ischemia, stroke and A-I response
  - Processes cover surface of capillaries within CNS → structural basis of **blood-brain barrier (BBB)**

### i. Blood-brain Barrier (BBB)

- Separate ECF in CNS from blood to protect brain from neurotoxins and bacteria
- Formed from (1) endothelial cells (2) basal lamina (3) astrocyte process
- Tightly packed cell → bacteria and some toxins cannot pass → brain protected

## b. Myelin-forming Cells

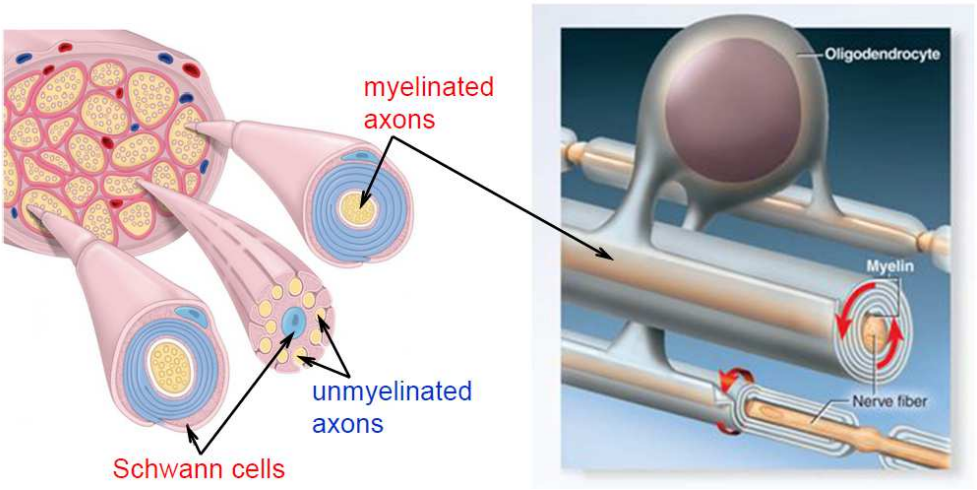
- Myelin formed by **oligodendrocytes** in CNS: one cell forms myelin of many neurones
- **Schwann cell** in PNS: one cell only form myelin on one neuron
  - Retain channel for damaged axon → regeneration of axon in PNS

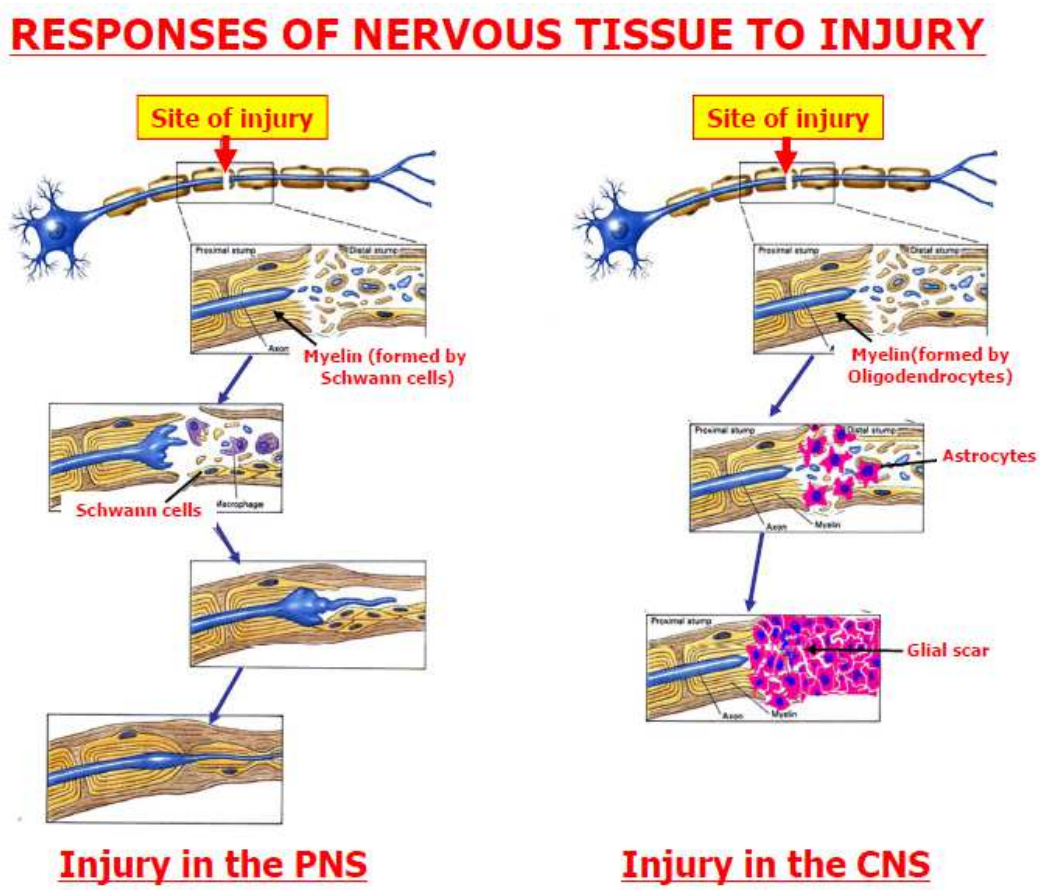
### i. Myelination

- Morphology very similar in PNS and CNS
- Myelin sheath interrupted at regular intervals by **nodes of Ranvier**
- **Internodal segment**: length of myelin sheath between 2 nodes of Ranvier
- One internodal segment is myelinated by one process of an **oligodendrocytes** in CNS or a single **Schwann cell** in PNS
- Function:
  - Greatly accelerates transmission of action potential along axon
  - Provides mechanical and physiological protection for axon
  - Track for axon regeneration in PNS

**Schwann cells**
**Myelin-forming cells of PNS**

**Oligodendrocytes**
**Myelin-forming cells in CNS**






## c. Microglia

- Resident **macrophages** of CNS
- Immunological function: phagocytose and kills plaque, damaged neurone, pathogens
- Injury → microglia cover neuronal soma → microglia proliferation and activation (↑ in no. of processes)

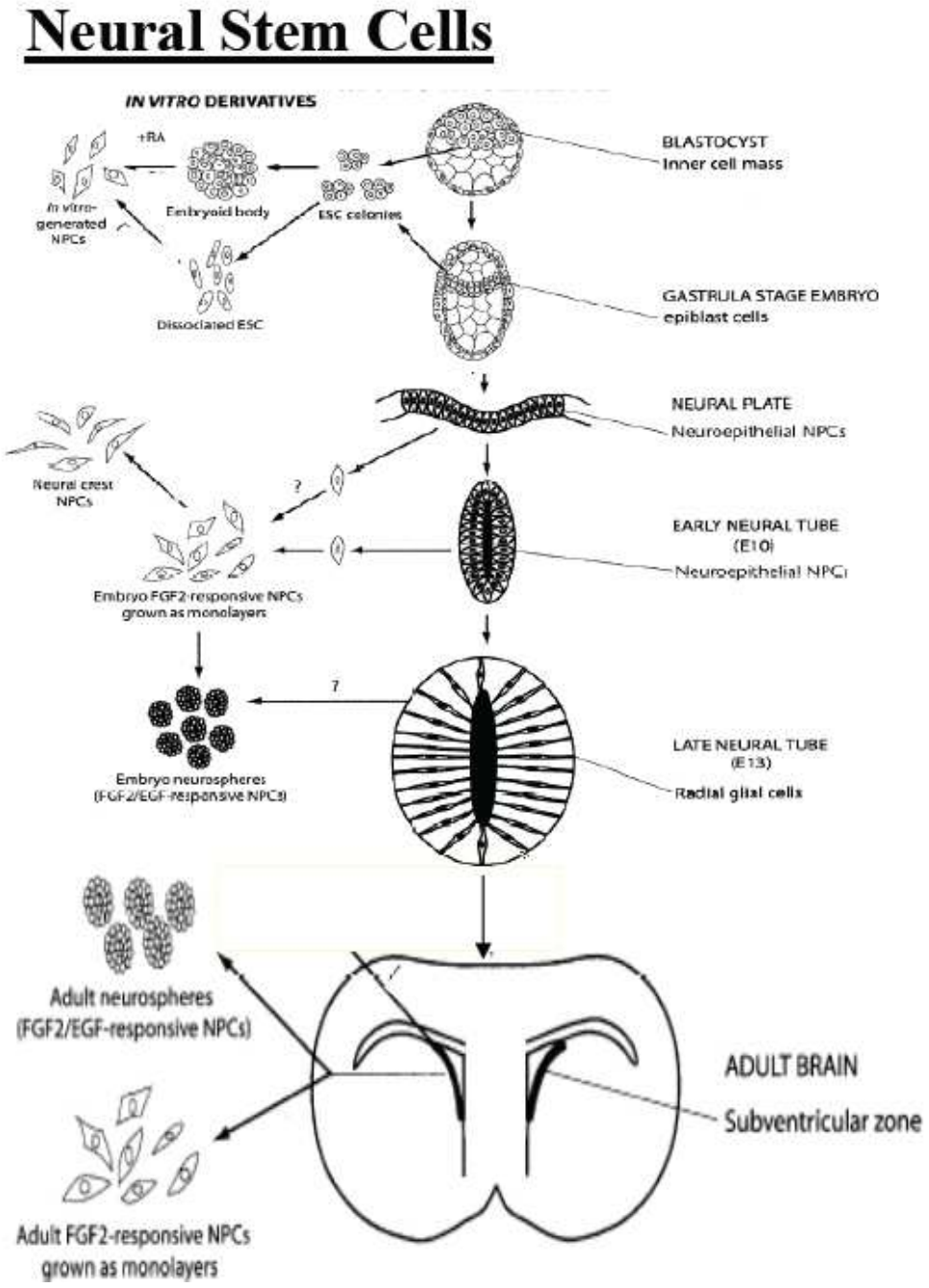
## d. Ependymal Cells

- Epithelial cells that line cavities with cerebrospinal fluid in CNS
- Secretes CSF

## e. Perineuronal Satellite Cells

- Cells located around soma of PNS neurones
- Functions: supply nutrients and structural

3. Neural Stem Cells




- Adult neural stem cells are probably located in **subventricular zone**

# L42 Functional Organization of the

# Cardiovascular System

## A. Cardiovascular System

- Heart, blood vessels, lymphatic vessels
- Heart pumps blood into arteries
- Arteries branch into smaller and smaller arteries → supply blood to all parts of body
- Capillaries allow materials to exchange between blood and tissue
- Veins return blood to heart
- Lymphatic vessels: a separate system of vessels that return excess fluid from tissues to blood vessels
- Function: homeostasis
  - By delivery of $O_2$, nutrients, hormones and heat to tissues and removal of metabolic waste and excess heat from tissues
- Requires energy to **drive flow** and **overcome friction between blood and blood vessels**

# B. Heart

- Two separate pumps:
  - Right heart → pulmonary circulation (25/10 mmHg)
  - Left heart → systemic circulation (120/80 mmHg)
- Heart provides energy to blood to drive flow and overcome friction
  - Chemical energy (ATP) in heart cells is converted to mechanical energy i.e. kinetic energy (velocity) and potential energy (pressure)
- Ventricles: for pumping action of heart
  - Thicker muscular walls to generate powerful contraction
  - Ejects blood at high pressure and high velocity
- Valves: guard entrance and exit to each ventricle to prevent backflow of blood
  - A-V valve between atrium and ventricle (L: bicuspid/mitral; R: tricuspid):
    - → Ventricle relaxed → blood flows from atrium to ventricle → opens A-V valve
    - → Ventricle contract → high ventricular pressure pushes valve **leaflets** across opening → A-V valve closed
    - → **Chordae tendinae** prevents valve from inverting
    - → A-V valve also provides **electrical insulation** between A/V → only point of contact is A-V node → sequential contraction
  - Semilunar valves at base of artery:
    - → Pockets of c.t. in arterial wall
    - → Blood flows out of ventricle → flattens pocket → blood outflow unimpeded
    - → Ventricle relaxes → arterial pressure > ventricular pressure → backflow of blood fills pockets → valve closed → prevents backflow of blood
- Atria: receive and store venous return
  - Venous return to heart continuous but ventricular entry can only occur when ventricle is relaxed (0.5 out of 0.8s in heart cycle)
  - Ventricles contract → venous blood accumulates in atria → flows passively into ventricles when A-V valves open
  - Atria contraction → only 20% of ventricular filling
- Pericardium: tough, secretes lubrication and prevents overstretch (eg by sudden filling of blood when upside down)

# C. Blood Vessels

- Aorta → large arteries → smaller arteries → arterioles → capillaries → venules → small veins → large veins → vena cavae

| Vessels | Structural specialization | Functions |
|---|---|---|
| Aorta, large elastic arteries | Large diameter, thick walls, large proportion of elastin | Distribution, **pressure storage**, conversion of pulsatile cardiac output to continuous flow |
| Small muscular arteries and arterioles | Thick walls, smooth muscle arranged spirally or circularly in walls | Pre-capillary resistance, active control of distribution of cardiac output |
| Capillaries | Very thin walls | Exchange of materials between blood and tissues |
| Venules and small veins | Thin wall, large proportion of smooth muscle | Post-capillary resistance (help regulate capillary pressure), volume reservoir (easily stretched walls: small pressure ↑ → large volume ↑ i.e. compliance → prepare for loss of blood) |
| Large veins and vena cavae | Very thin wall, large diameter (→ ↓ resistance), large proportion of smooth muscle in walls | Volume reservoir, return of blood to heart with minimal energy consumption |

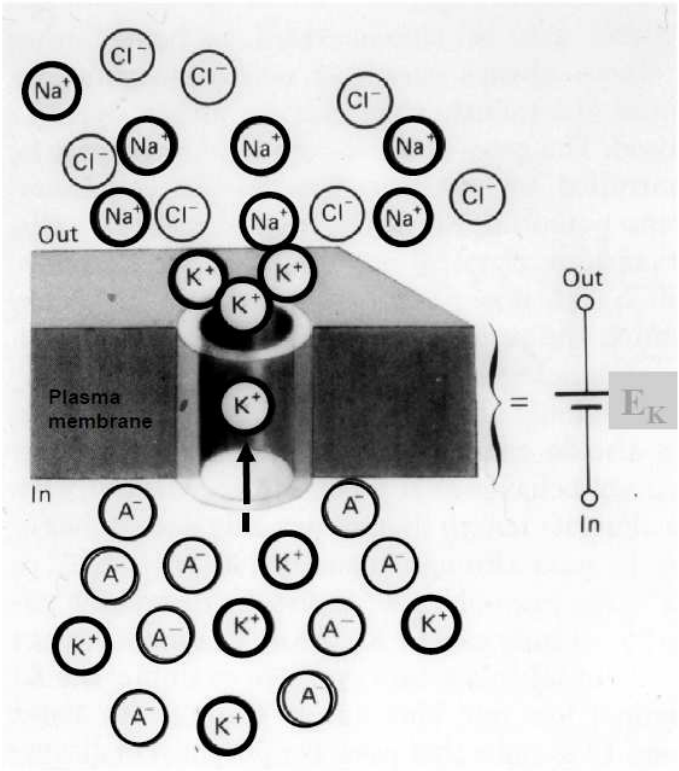
# L43 Membrane Excitability

## A. Trans-membrane Ion Channels

- Note there are two types of channels
  - Non-gated channels
  - Gated channels (esp note **voltage-gated channel**: open only when membrane potential reaches a certain value)

## B. Resting Membrane Potential

- Concentration gradient of major ions: high $[K^+]_{int}$ and high $[Na^+]_{ext}$
- Selective permeability of membrane: more permeable to $K^+$ than $Na^+$ at resting stage ($P_K >> P_{Na}$), impermeable to large anions
- **Equilibrium potential**: p.d. at which conc. gradient of an ion and electric potential gradient balances out and there is no net flow of ions
  - Ion flow along concentration gradient via non-gated channels impeded by electrochemical equilibrium
  - Dependent on specific conc. gradient of that particular ion $\propto \ln([X^+]_{ext}/[X^+]_{int})$
  - If $E > E_x \rightarrow$ net outflux of $X^+$



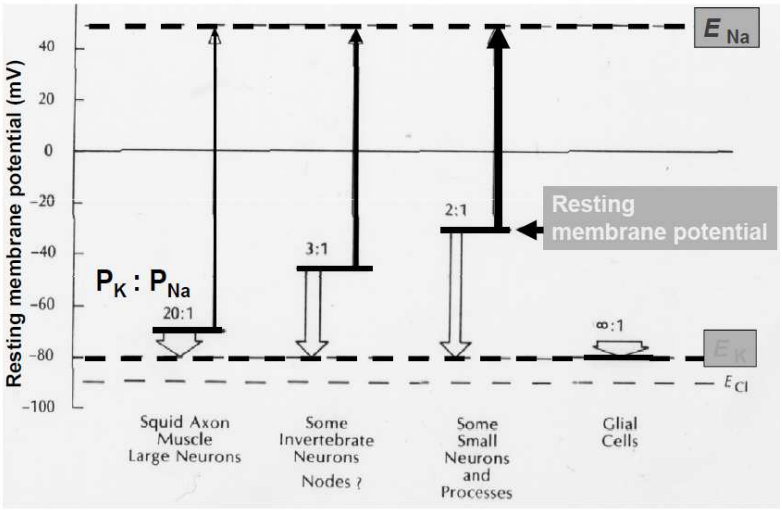

***Hypothetical consideration***

**Assuming the cell is permeable only to $K^+$, it will be in a state of Electrochemical Equilibrium at rest.**

**Concentration gradient pushes $K^+$ out**

**Electrical potential gradient pushes $K^+$ in**

- **Resting membrane potential** is summation of equilibrium potentials of all ions
  - Negative inside relative to outside of cell
  - Magnitude is characteristic of each cell type (ranges from -50mV to -90mV)
- Resting potential dependent on relative permeability of each ions: example of $Na^+/K^+$
  - **Permeability ratio ($P_K$:$P_{Na}$)**: movement of $K^+$ per movement of $Na^+$ allowed by the membrane
  - Permeability ratio dictates resting membrane potential
  - Note $E_{Na}$ = +80mV, $E_K$ = -80mV; but resting membrane potential at negative ∵ $P_K$ (permeability) >> $P_{Na}$

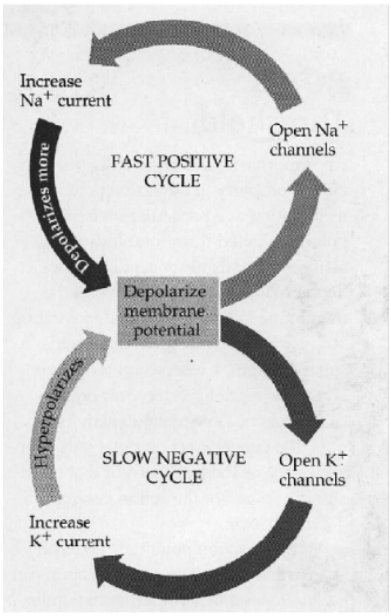



- If only non-gated channels → passive $K^+$ outflux, $Na^+$ influx (without any dissipation of electrochemical gradient)
  - Ionic gradient maintained by $Na^+/K^+$/ATP pump:
    - → ATP-dependent process
    - → Active $Na^+$ outflux coupled by $K^+$ influx at a ratio of 3:2 (varies between cells)

# C. Action Potential

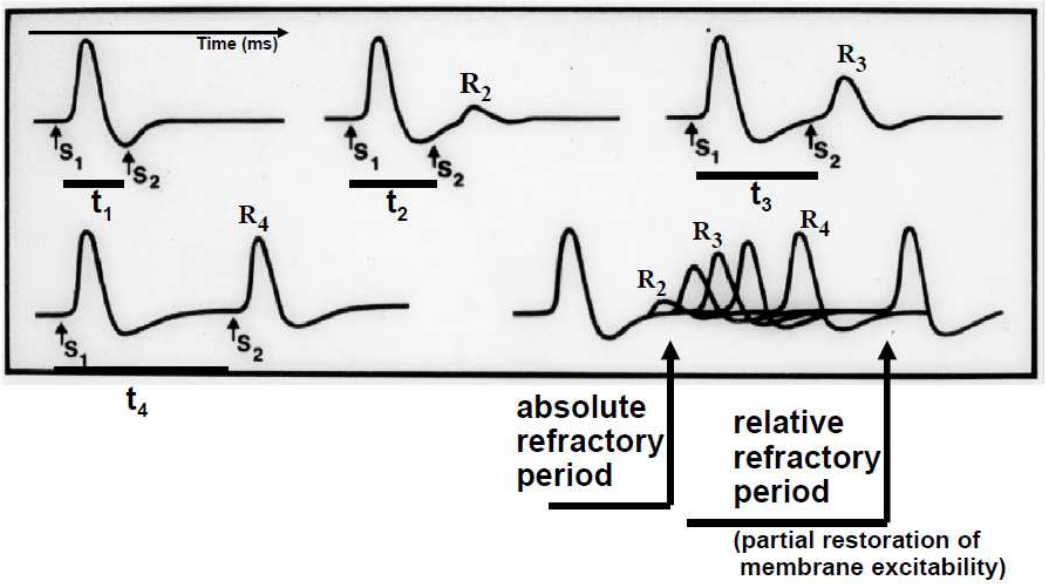
- Basis of signal processing in neurones and muscle cells
- An all-or-none phenomenon
- Time course: 2-4 ms in neurones, 10ms in skeletal muscles, >200 ms in cardiac muscles
- Sequential events:
  - Depolarization to threshold
  - Overshoot
  - Repolarization
- When threshold potential is reached in depolarization due to stimulus, two processes occur simultaneously:

1) **Depolarization**: Beyond threshold triggers self-reinforcing regenerative $Na^+$ influx (due to opening of voltage-gated $Na^+$ channels) [faster process];
2) **Repolarization**: Increase in $K^+$ permeability (due to opening of voltage-gated $K^+$ channels) leading to an increase in $K^+$ outflux [slower process].

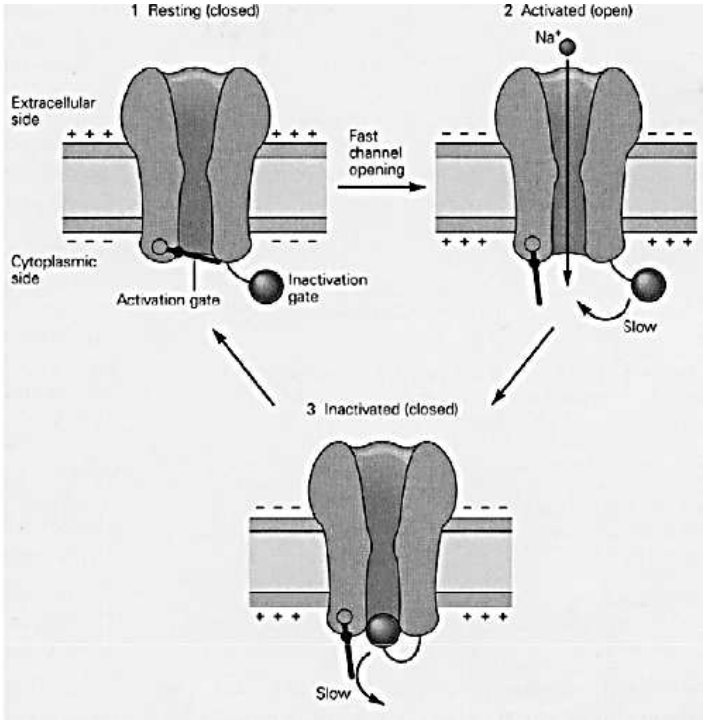



- First (1) dominates when E↑ → E ↑ rapidly due to positive feedback
- Then effect of (2) gradually overtakes as E continue to increase → E ↓ slowly due to negative feedback
- Subsequent metabolic process ($Na^+/K^+$ pump) restores ion content to initial levels
- Experimental evidence from:
  - **Patch Clamp technique**: measures ionic current of individual channels
  - Use of specific channel blocker/antagonists ($TEA^+$ inhibitor to $K^+$ channel, TTX inhibitor to $Na^+$ channel)

# D. Refractory Period




- Period in which it is harder (or even impossible) for new action potentials to propagate
- $Na^+$ channel: dual-gated, one activation gate and another inactivation gate
- $K^+$ channel: one-gated, one activation gate
- **Absolute refractory period**: $Na^+$ channel is inactivated (by another inactivation gate) a short period after action potential → complete inexcitability




- **Relative refractory period**: $K^+$ channels are not closed yet → hyperpolarization → harder for initiation of new action potential

# E. $Ca^{2+}$ and Membrane Excitability

- Participation of $Ca^{2+}$ helps rhythmic contractions in Purkinje cells in cardiac muscles
- $E_{Ca} \fallingdotseq +120mV$, $Ca^{2+}$ channels open even slower than $K^+$ channels $\rightarrow$ $Ca^{2+}$ influx occurs after $Na^+$ influx $\rightarrow$ **lengthens absolute refractory period** $\rightarrow$ maintain cardiac rhythm $\rightarrow$ prevent **arrhythmia** (prevent new heartbeat from forming before the previous one ended)

# F. Clinical Applications

- Synchronous potential change of neurone group(s) of muscle cells can be measured on scalp or body surface (i.e. extracellular measurement) as:
  - Electroencephalogram (EEG)
  - Brainstem Auditory Evoked Response (BAER)
  - Electrocardiogram (ECG)
- Measureable because of **loop ion flows** around action potential

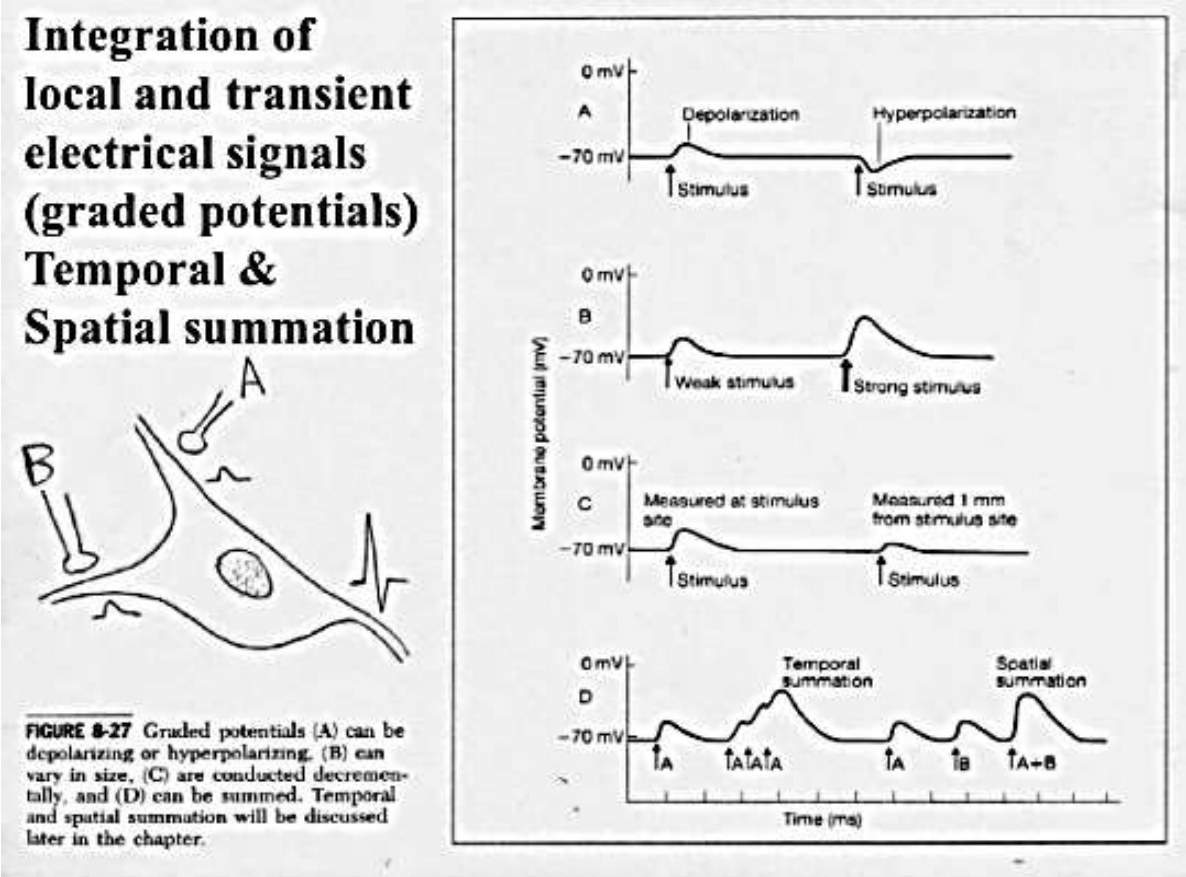
# L44 Transmission of Nerve Signals

## A. Neurones

- **Excitable cell** that generates action potential
  - **Dendrites**: graded potentials integrated and transmitted towards soma
  - **Soma**: cell surface for integration of electrical signals
  - **Axon hillock**: dense with voltage-gated sodium channels and **low threshold** favors the generation of action potential
  - **Initial segment**: starting of axonal fibre
  - **Axon**: where action potentials are transmitted away from soma
  - **Axon terminals**: where synapses are formed with postsynaptic cell
- Electrical signals spread in all directions but propagate in one direction:
  - Dendrites → cell body (hillock)
    - → By passive membrane properties (graded potentials)
    - → 'Analog' signal (with magnitude)
  - Axon hillock → axon terminals (synapses)
    - → Active ionic channels activities (action potential)
    - → 'Digital' signal (1 or 0)
  - Subject to **temporal** and **spatial degradation**
- Synaptic transmission: presynaptic → postsynaptic neurone

# B. Passive Membrane Properties

- **Membrane resistance ($R_m$)**: resistance across the membrane
  - Inversely proportional to membrane permeability to ions
  - Membrane more permeable to $K^+$ than to $Na^+$ at resting state ∵ non-gated $K^+$ channels present
- **Membrane capacitance ($C_m$)**: excess of opposite charges stored on either side of membrane
  - Charges can accumulate due to insulating lipid bilayer present
- **Axial Resistance ($R_a$)**: resistance of the axon (against ion flow)
  - Reduces with ↑ axon diameter
- **Time constant of charging/discharging** = $R_m C_m$
  - Indicates how fast cell membrane can be charged and discharged
  - ↑ time constant → ↑ time for $V_m$ to respond to depolarizing or hyperpolarizing current (charging) and for repolarization of membrane (discharging)
  - Physiological signification: temporal summation → more prominent in cells with high time constants
- **Length constant** = $\sqrt{\frac{R_m}{R_a}}$
  - Indicates how far away the local mV change can spread along membrane
  - Indicative on spread and integration of electrical signals (with spatial summation)
  - Cells with high length constant → less decay of magnitude of local electrical signals spread over a distance

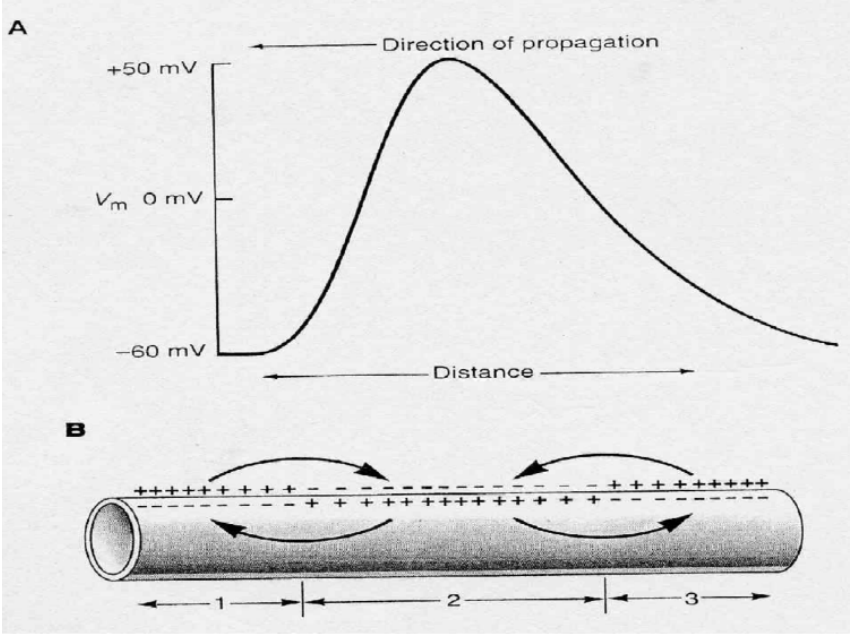



# C. Graded Potentials and Action Potential

- **Graded potentials:** transient in nature
  - Potential decays rapidly in both time (time constant) and space (distance constant)
  - Polarity can either be positive or negative
  - Passive event as a function of the current, reflects mainly biophysical properties of membrane
  - Change in membrane potential $\Delta V_m \propto$ amount × polarity of current (given $R_m$ is fixed or stable)
- **Action potential**: driven by activities of voltage-gated channels
  - All-or-none, stereotyped features
  - Refractory period following gating properties
  - Dependent on presence (and proper functioning of $Na^+$ channels
- **Threshold potential**: membrane potential at which membrane triggers regenerative cycle for generation of an action potential
  - Action potential is fired when a graded potential depolarizes membrane to above the threshold
  - Achieved through spatial and temporal summation

# D. Conduction of Action Potentials

- Local (circular) current flow triggered by an action potential allows travelling of electrical signal along membrane with generation of new action potentials
  - These current loops can be detected by ECG etc.




# 1. Generation

- **Fast gating** of voltage-gated $Na^+$ channels:
  - Activating m gate opens and allows $Na^+$ ions flow in for **rapid depolarization**
  - Inactivating h gate closes rapidly for repolarization
- **Slow gating** of voltage-gated $K^+$ channels:
  - Activating n gate opens slowly
  - $K^+$ ions flow out for rapid **repolarization** and subsequently hyperpolarization

# 2. Propagation

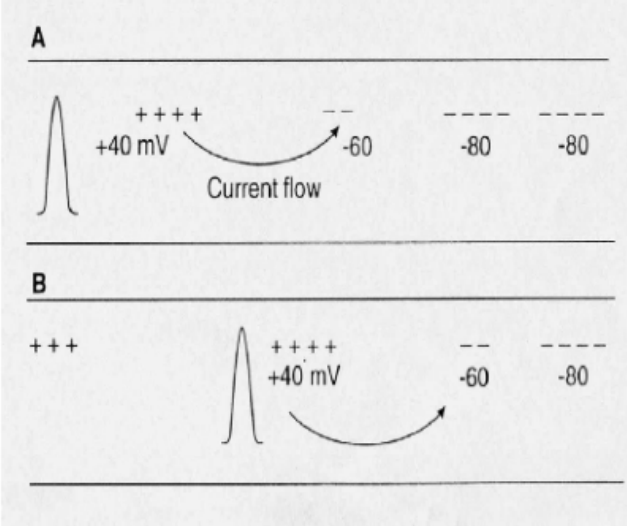
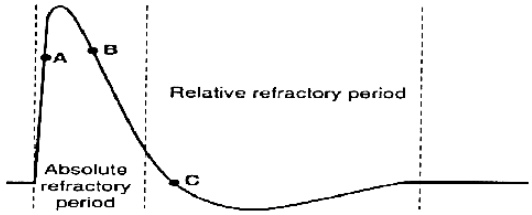



**FIGURE 2-7.** (*A*) The intracellular positive potential (+40 mV) produced during the overshoot of the action potential causes current to flow toward the negative, resting portion of the axon. The flow of current acts as a stimulus that depolarizes the axon toward threshold. (*B*) When threshold is achieved, an action potential is elicited and the entire process is repeated, causing propagation of the action potential along the axon.

- Entry of $Na^+$ during action potential causes:
  - Depolarization of membrane potential ($V_m$)
  - Electrical attraction and diffusion along interior side of membrane → depolarize adjacent membrane areas → reach threshold → new action potential generated



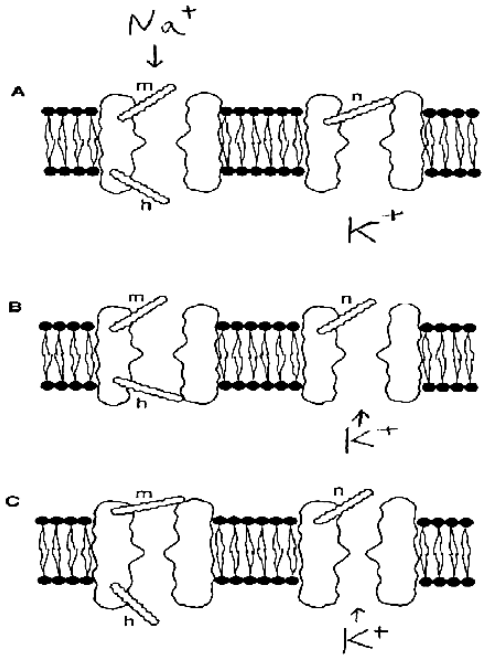




**FIGURE 2-6.** Diagram illustrating how the position of the $Na^+$ and $K^+$ gates changes during the action potential. (*A*) Both the m and h gates are opened during the upstroke of the action potential, allowing $Na^+$ to flow into the cell. (*B*) The closing of the h gates (inactivation) stops the flow of $Na^+$ into the cell. The opening of the n gates allows $K^+$ to flow out of the cell and initiates downstroke. (*C*) During the undershoot, the n gates are open, the m gates are closed, and the h gates are open. The high $K^+$ conductance causes the cell to hyperpolarize.

# 3. Unidirectionality

- Facilitated by the **refractory period**
- **Absolute refractory period**:
  - All activating m gate of $Na^+$ channels are open and inactivating h gate is closed
  - No further depolarization can be activated
  - K channel at opening status → repolarization
  - Threshold potential = ∞
- **Relative refractory period**:
  - Activating m gate of $Na^+$ channel is closed (due to repolarization and hyperpolarization) whereas $K^+$ channels are open
  - Not all $Na^+$ channels are available → higher threshold (decrease to normal)

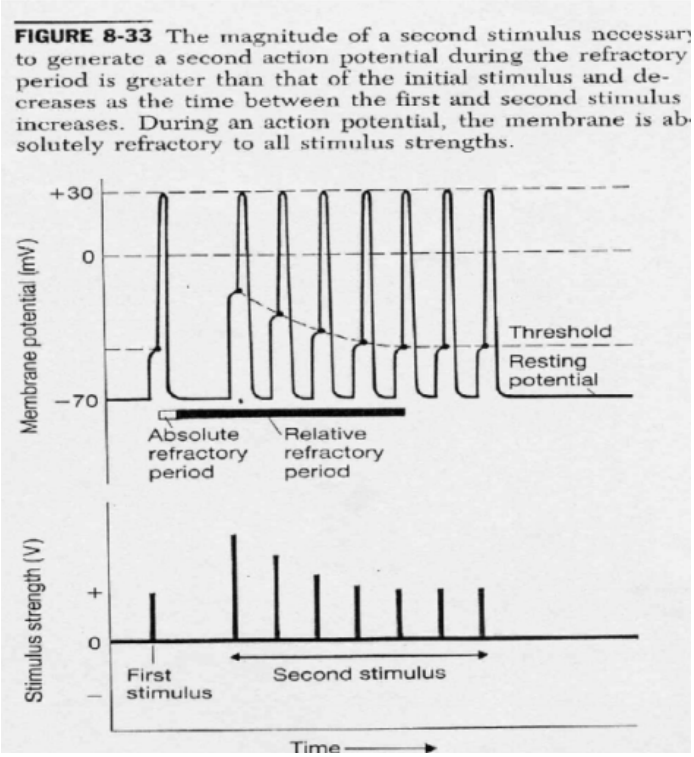


**FIGURE 8-33** The magnitude of a second stimulus necessary to generate a second action potential during the refractory period is greater than that of the initial stimulus and decreases as the time between the first and second stimulus increases. During an action potential, the membrane is absolutely refractory to all stimulus strengths.

# 4. Conduction Velocity

- Enhanced by:
  - Increase in fibre size
  - Myelination

## a. Diameter of Nerve Fibres

- ↑ diameter of nerve fibre → $R_a$ ↓
- Reduction in axial resistance → ions can travel faster within axon → action potential can be propagated at a greater velocity
  - Length constant ↑ → loss in nerve signal reduced
  - Time constant (for conduction along axon, = $C_a$ $R_a$) ↓ → ↓ time needed for charging and discharging next segment in direction of propagation

## b. Myelination: Saltatory Propagation

- **Myelin sheath**: layers of plasma membrane that wraps segments of axon
  - An insulator for plasma membrane of axon fibre
  - ↑ $R_m$ → ↑ length constant
  - ↓ $C_m$ → ↓ time for depolarization spreading along axon
- **Nodes of Ranvier**: area of axon without myelination in between myelinated segments
  - Voltage-gated $Na^+$ channel density relatively high → low threshold potential
- **Saltatory propagation**: increase speed by 'jumping' along axon, also conserves ATP (less is needed for restoration to resting potential)
- Myelination decreases 'leakage' of ions across membrane in myelinated segments → depolarization can only occur at nodes of Ranvier

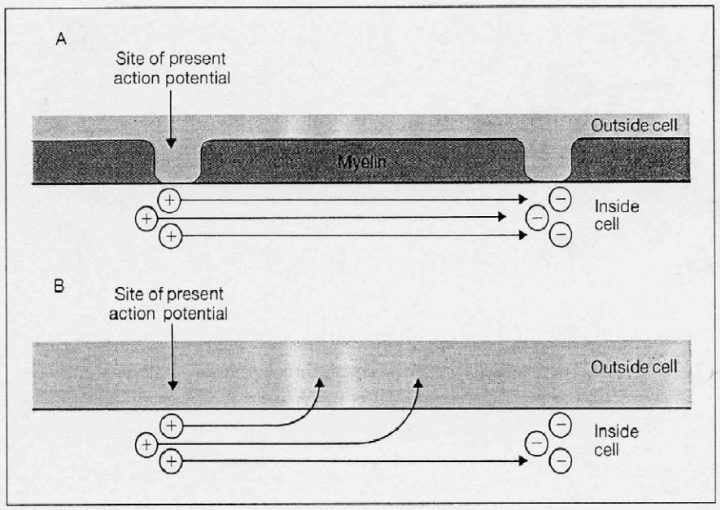



**FIGURE 8-35** Current direction during an action potential in (A) a myelinated and (B) an unmyelinated axon.

# E. Synaptic Transmission

- **Synapse**: a junction that allows transmission of signal between excitable tissues
  - **Electrical synapse**: gap junction (connexon channels) allowing direct flow of current (in the form of ions) from one cell to another
  - **Chemical synapse**: synaptic events require release of neurotransmitters

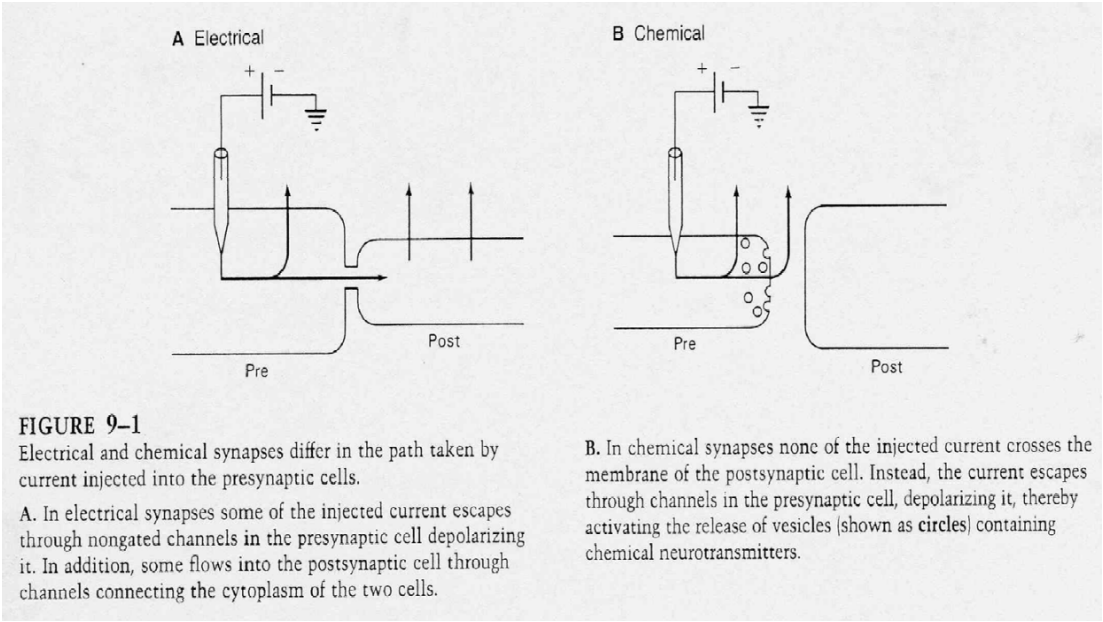



FIGURE 9–1
Electrical and chemical synapses differ in the path taken by current injected into the presynaptic cells.

A. In electrical synapses some of the injected current escapes through nongated channels in the presynaptic cell depolarizing it. In addition, some flows into the postsynaptic cell through channels connecting the cytoplasm of the two cells.

B. In chemical synapses none of the injected current crosses the membrane of the postsynaptic cell. Instead, the current escapes through channels in the presynaptic cell, depolarizing it, thereby activating the release of vesicles (shown as circles) containing chemical neurotransmitters.

- Presynaptic events:

1) Action potential arrives at synaptic terminal, leading to opening of voltage-dependent calcium channels;
2) Influx of extracellular $Ca^{2+}$ into the terminal, triggering signal transduction pathway causing neurotransmitter vesicles to move towards the membrane;
3) Fusion of synaptic vesicles with membrane to release neurotransmitters.

- Neurotransmitters then diffuse across **synaptic cleft**
- Postsynaptic events:

1) Binding of neurotransmitters to specific receptor proteins (ligand-gated ion channels);
2) Ligand-gated ion channels open/close to change permeability to some ions (eg nAChR-mediated channel permeable to mainly $Na^+$ and a bit of $K^+$, leading to depolarization of membrane);
3) Post-synaptic potential generated: **excitatory postsynaptic potential (EPSP)** for depolarization and **inhibitory postsynaptic potential (IPSP)** for hyperpolarization;
4) Integration of temporal summation and spatial summation of EPSP and IPSP at hillock determines whether an action potential is generated for propagation in post-synaptic neurone.

- Neurotransmitters are then degraded by enzymes located in the synaptic cleft

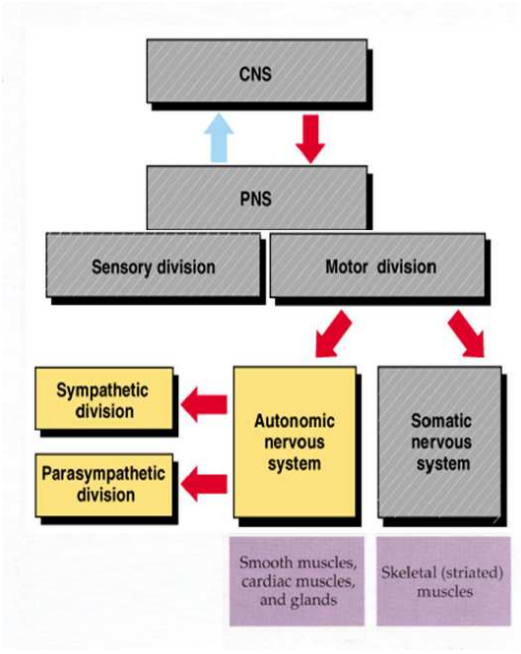
# L45 Functional Organization of the Brain

## A. Brain

- Parts of brain:
  - **Cerebral cortex** (of cerebrum): cognition, perception, voluntary movement
  - **Limbic system**: emotion, memory
  - **Brainstem**: housekeeping
  - **Cerebellum**: motor coordination

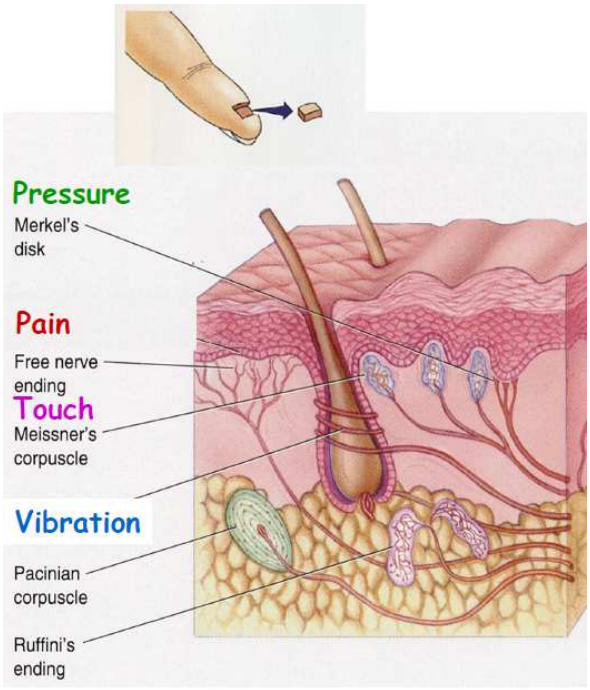
## B. Nervous System Divisions

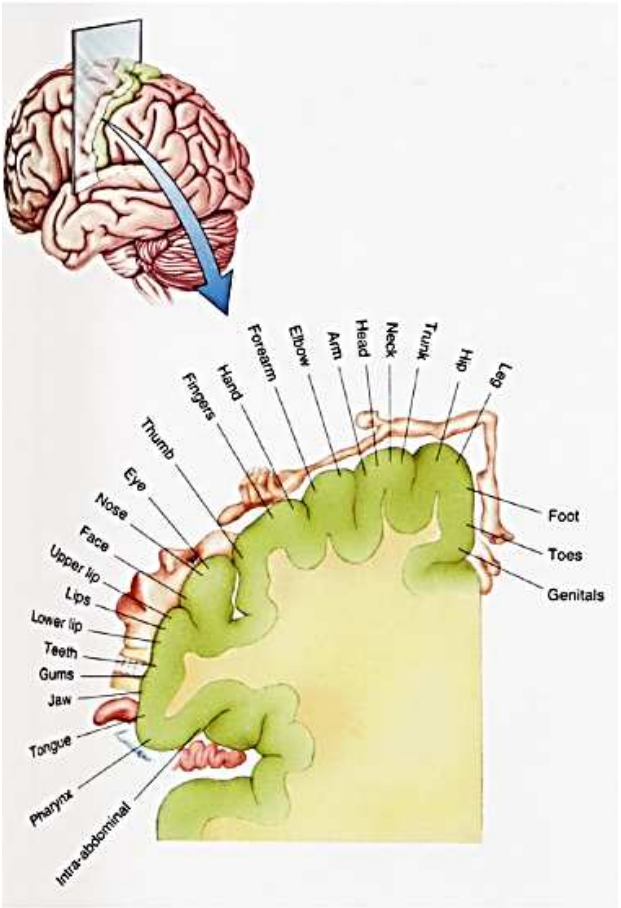
- CNS/PNS
- Sensory/motor divisions
- Autonomic/somatic nervous systems
- Sympathetic/parasympathetic divisions



# 1. Sensory Division

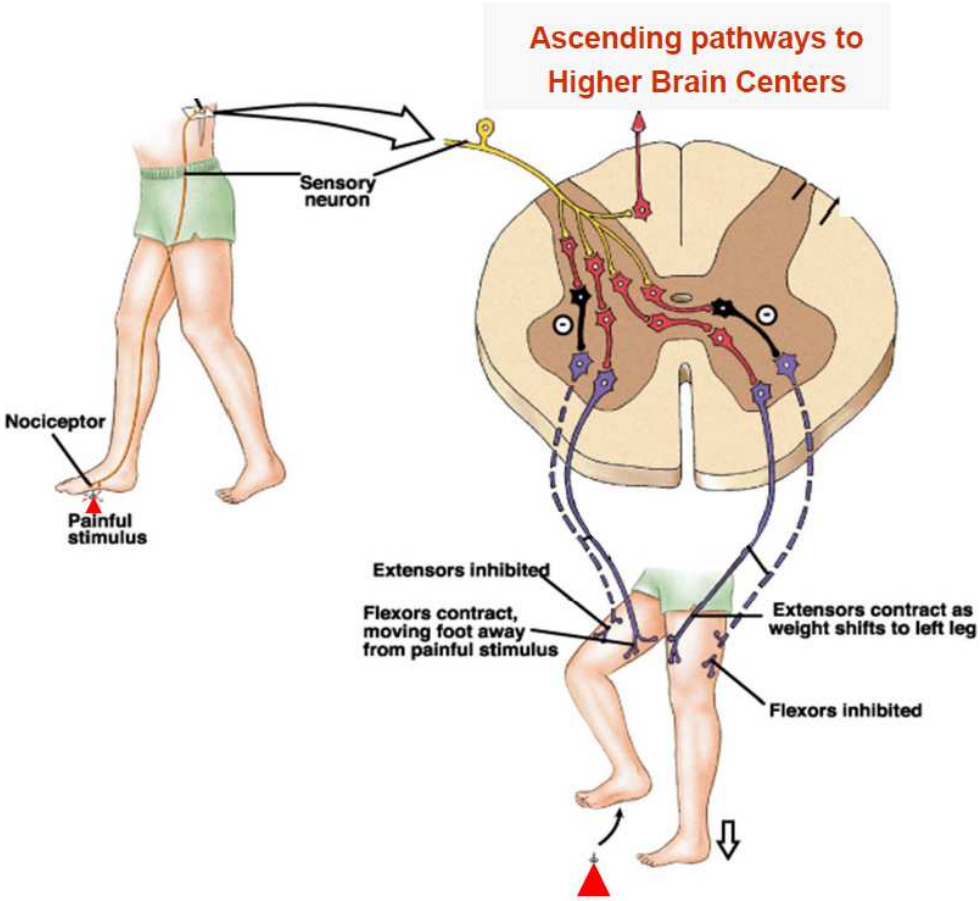
- **Special senses**:
  - **Vision** by eyes
  - **Hearing** by ears (cochlea)
  - **Balance** by ears (semi-lunar canals)
  - **Taste** by tongue
  - **Smell** by nose (olfactory epithelium)
- **Somatic sensation**:
  - Touch by **Meissner's corpuscle**
  - Temperature by hypothalamus and skin thermoreceptors
  - Pain by **free nerve endings**
  - Vibration by **Pacinian corpuscle**
  - Pressure by **Merkel's disk**
  - Skin stretch by **Ruffini's ending**
  - Body position
- Cross projection: left cerebrum controls right body and vice versa
- Note neural pathway for discriminative touch, vibration and positional sense is different from that for temperature and pain
- Different positions of skin have different densities of sensory receptors
- **Topographic projection**: different parts of sensory cortex responsible for different sensory surfaces



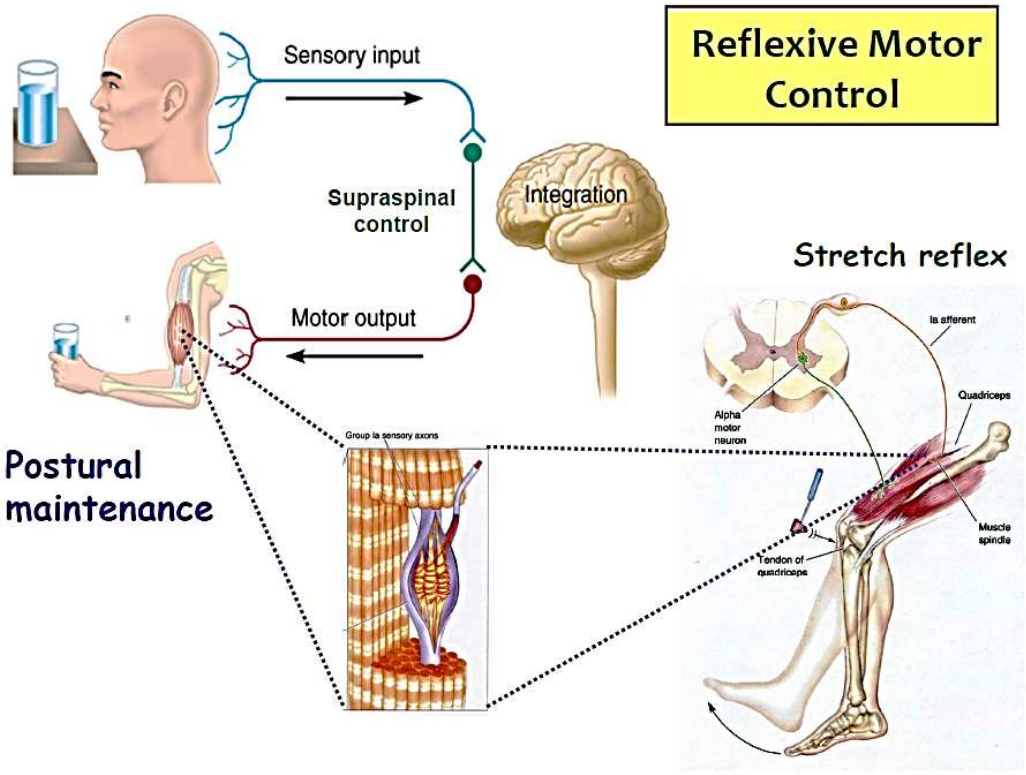



# 2. Motor Division

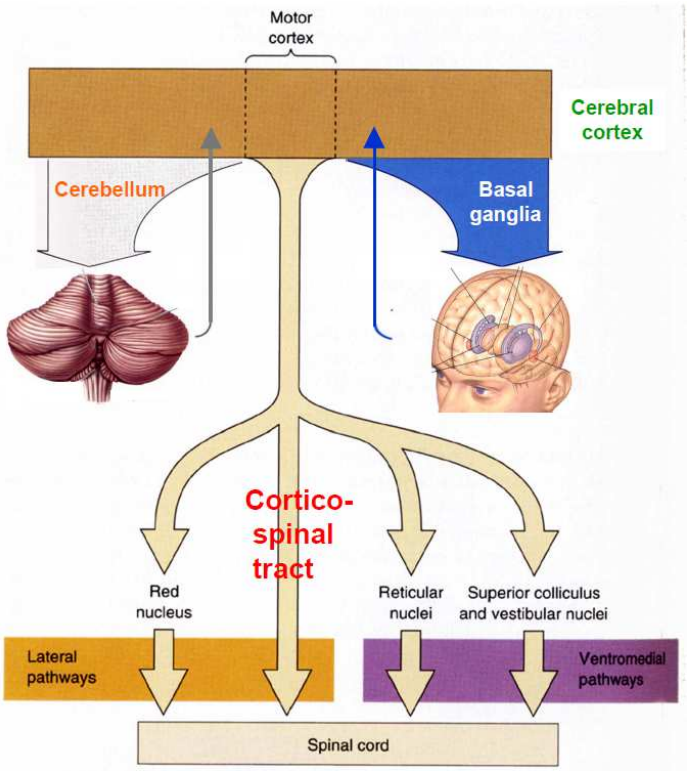
- **Pain withdrawal reflex**:



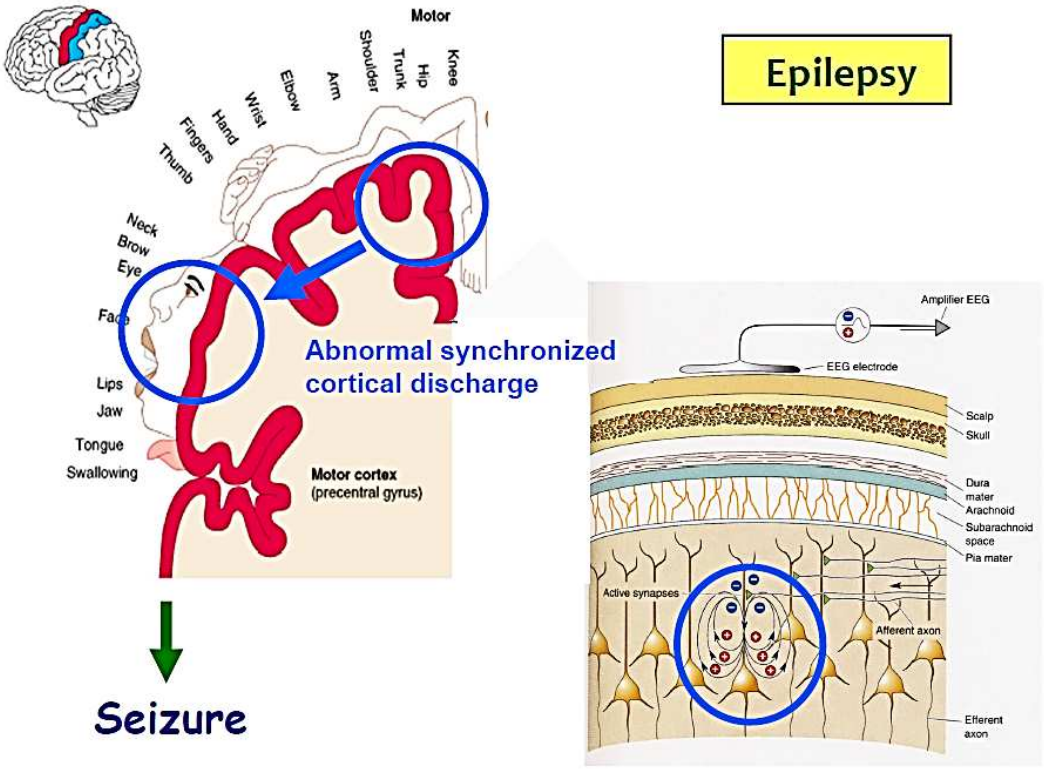
- Reflexive motor control: stretch (knee-jerk) reflex and postural maintenance:




- Voluntary motor control: cerebellum, motor cortex and basal ganglia interact and produces nerve signals via spinal cord to effectors



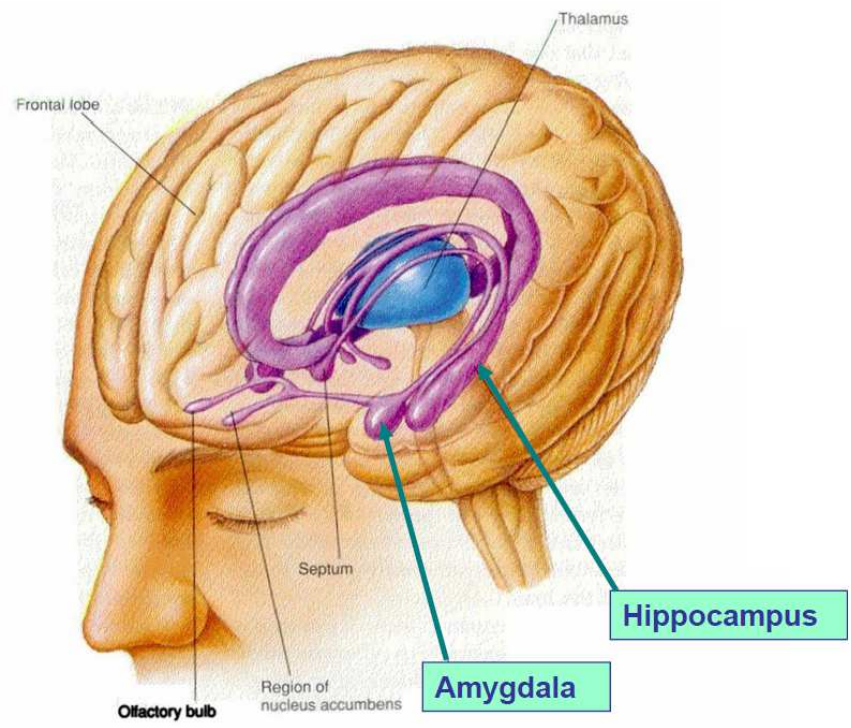
- Abnormality: **epilepsy**
  - Normally an excitatory neurone cannot fire easily after firing de to presence of inhibitory neurones
  - Mechanism fails → groups of neurones fire in abnormal, excessive and synchronized manner → epileptic seizure



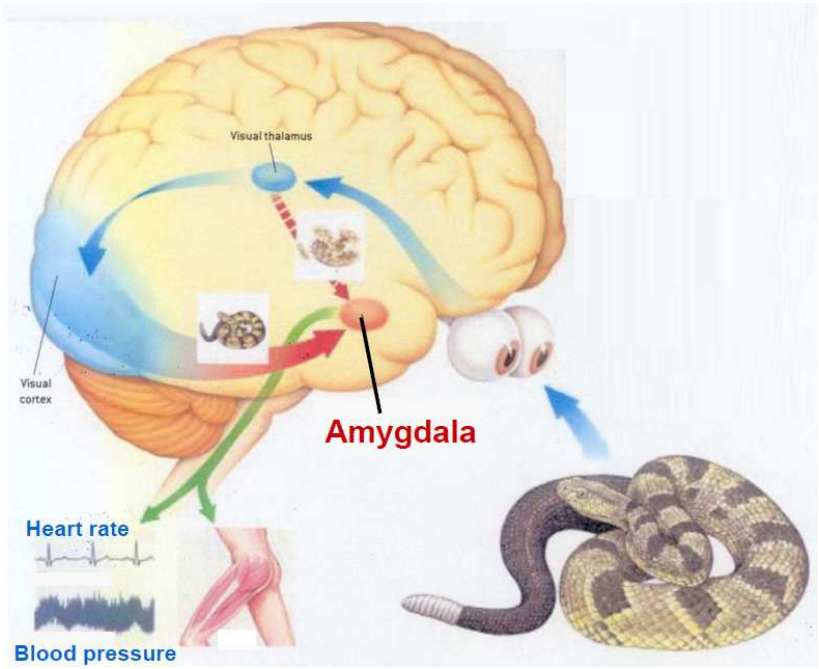

- Abnormality: **Parkinson's disease**
  - **Substantia nigra** (part of midbrain responsible of inhibition of motor systems) cell death → dopamine-releasing cell activity ↓
  - Dopamine ↓ → inhibition on motor system ↓ (∵ dopamine responsible for inhibition) → ↑ effort for movement etc
- Abnormality: **frontal lobotomy** (frontal lobe removed due to surgery)
  - Cannot concentrate
  - Ill-tempered
  - Loss of emotional thought
  - Difficulty in planning
  - Personality changes
  - Lowered moral standards

# 3. Limbic System

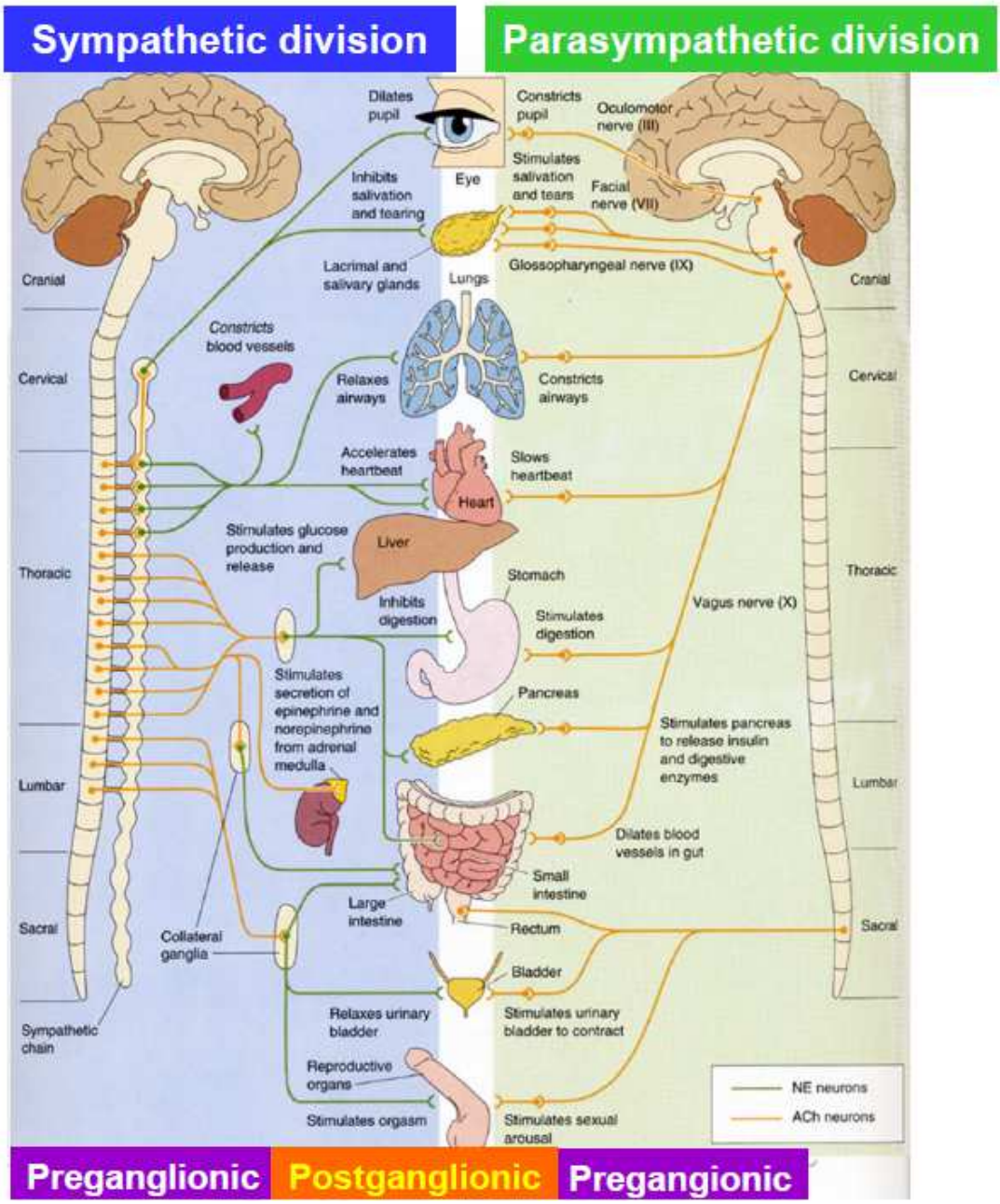
- Composed of **amygdala**, **hippocampus** and many other structures around the **thalamus**
  - **Amygdala**: memory, decision-making, emotional reactions
  - **Hippocampus**: memory, navigation
- Function: learning and memory, sleep and wakefulness, emotions



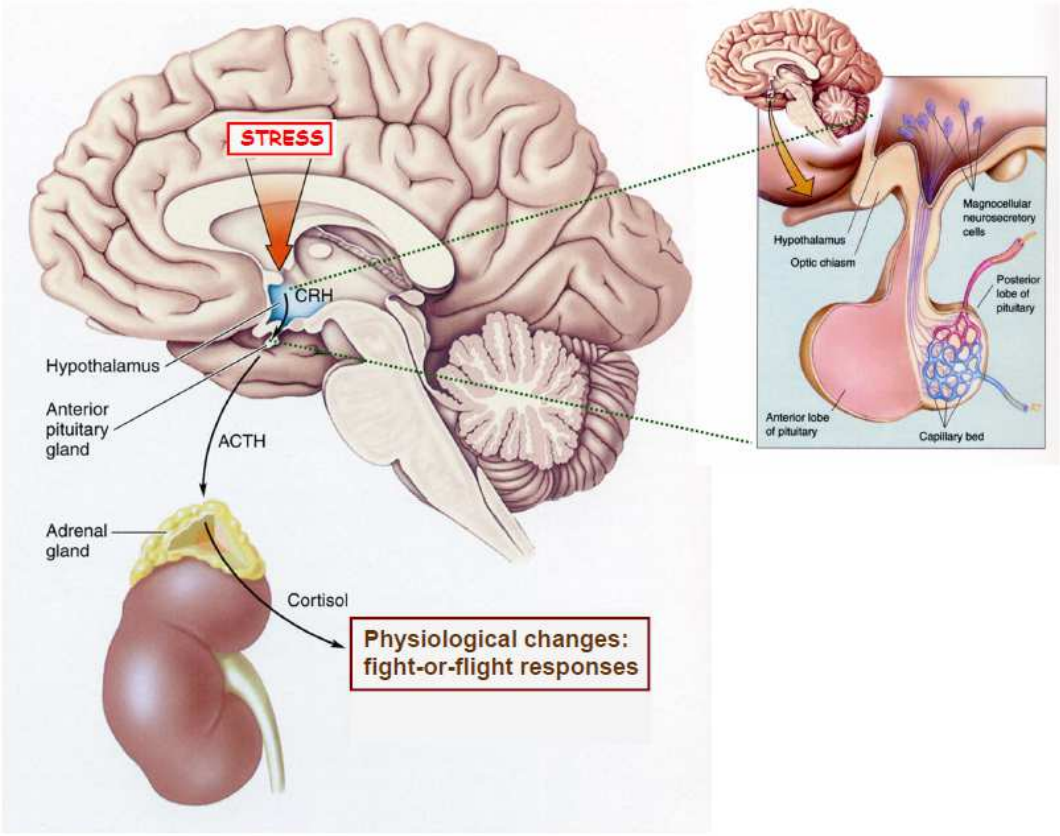

- **Fear response**: amygdala stores emotional experiences → trigger fear response



# 4. Autonomic Nervous System



- Endocrine control:
  - Example: control of cortisol release

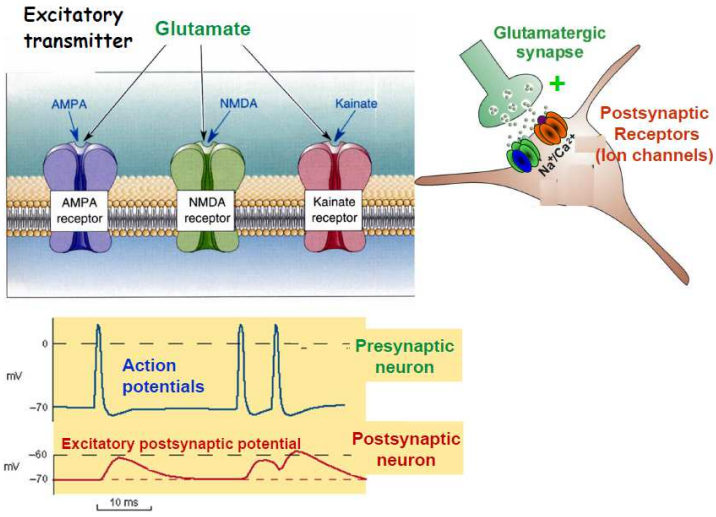


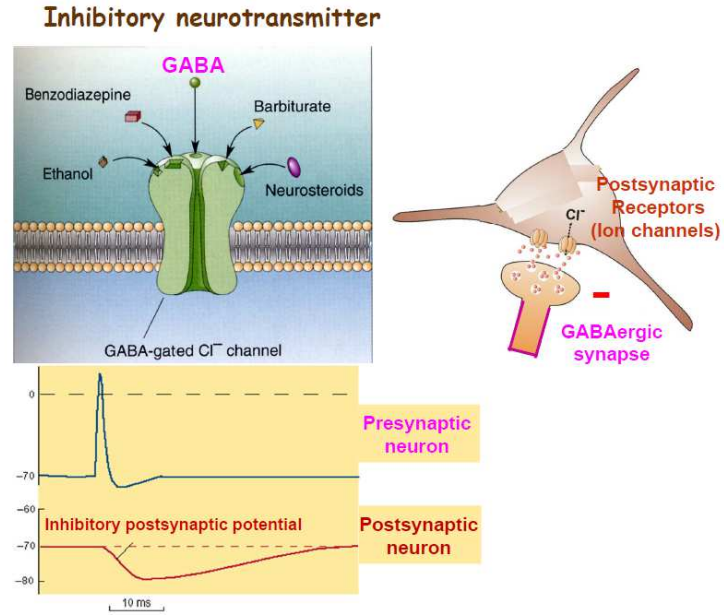

Hypothalamic-pituitary-adrenal (HPA) axis

# C. Inhibitory and Excitatory Synapses

- Neurotransmitters can either be:
  - Excitatory: ↑ chance of action potential (by glutamate-gated $Na^+$ and $Ca^{2+}$ channels)
  - Inhibitory: ↓ chance of action potential (by GABA-gated $Cl^-$ (or $K^+$) channels)

    → ∵ $E_{Cl} \leq$ resting potential → ↑ $P_{Cl}$ causes $V_m$ to drop




- Disorder: 'angel dust', a recreational dissociative drug (PCP), block glutamate-coupled ion NMDA channels → behaviour mimic schizophrenia
- Disorder: **Alzheimer's Disease**: shrinkage of hippocampus resulted in impairment of learning and memory

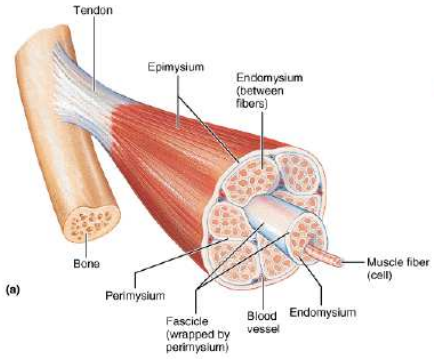
# L46 Excitation and Contraction of

# Muscles

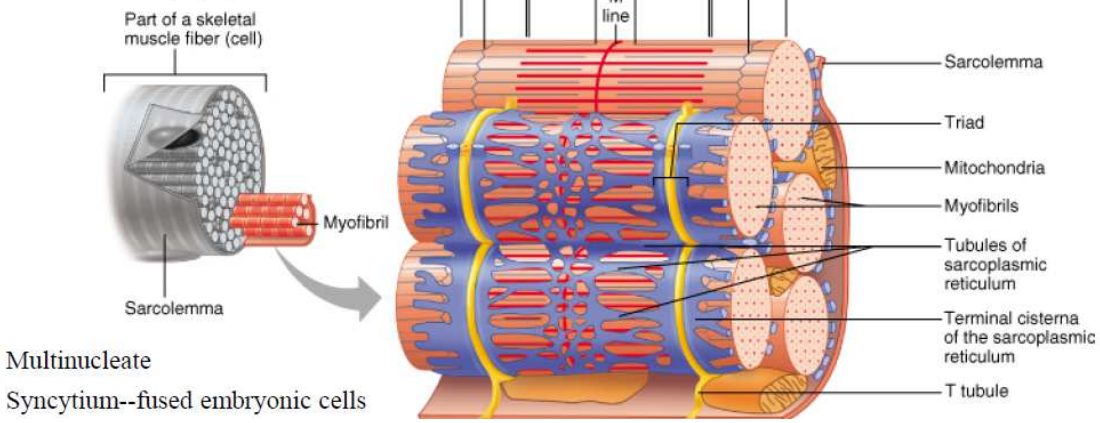
## A. Muscle Overview

- Three types: skeletal, cardiac, smooth
  - Differs in structure, location, function, means of activation
- Muscle contraction depends on two kinds of myofilaments: actin and myosin
- Muscle terminology: pay attention to myo-, mys-, sarco-
- **Skeletal muscle tissue**: attach to and cover bony skeleton
  - Has obvious stripes (**striations**)
  - Controlled voluntarily
  - Contracts rapidly but tires easily
  - Is responsible for overall body motility
- **Cardiac muscle tissue**: occurs only in heart
  - Striated like skeletal muscles but not voluntary
  - Contracts at a fairly steady rate set by heart's pacemaker
  - Neural controls allow heart to respond to changes in bodily needs
- **Smooth muscle tissue**: found in walls of hollow visceral organs, eg. stomach, urinary bladder, respiratory passages
  - Forces food and other substances through internal body channels
  - Not striated and not voluntary
- Functional characteristics:
  - Excitability: ability to receive and respond to stimuli
  - Contractility: ability to shorten forcibly
  - Extensibility: ability to be stretched or extended
  - Elasticity: ability to recoil and resume the original resting length

# B. Skeletal Muscles

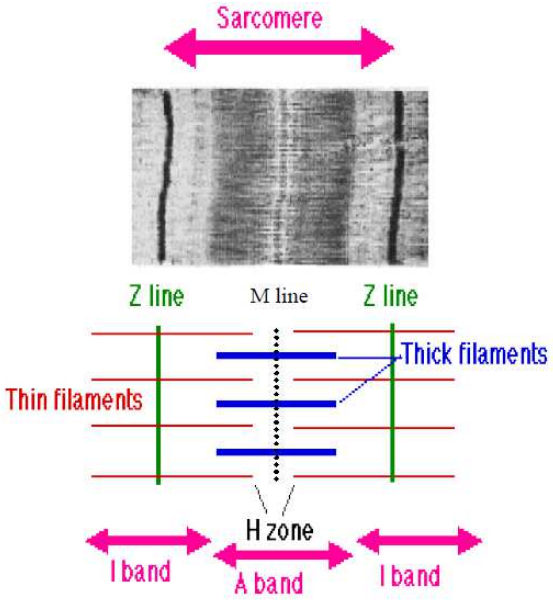


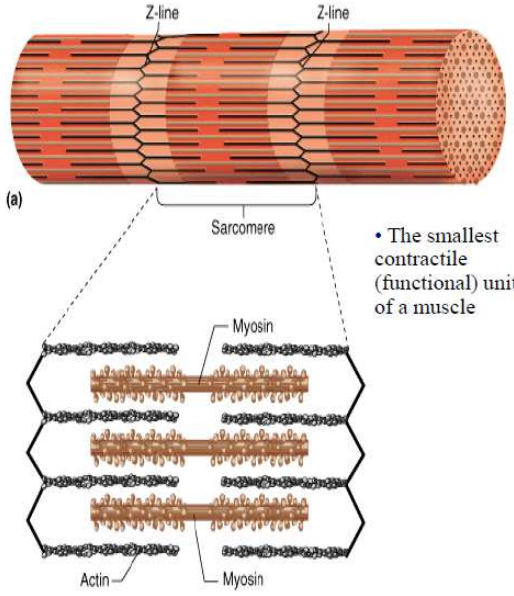

- Myofibrils = Thick + Thin filaments




Multinucleate

Syncytium--fused embryonic cells



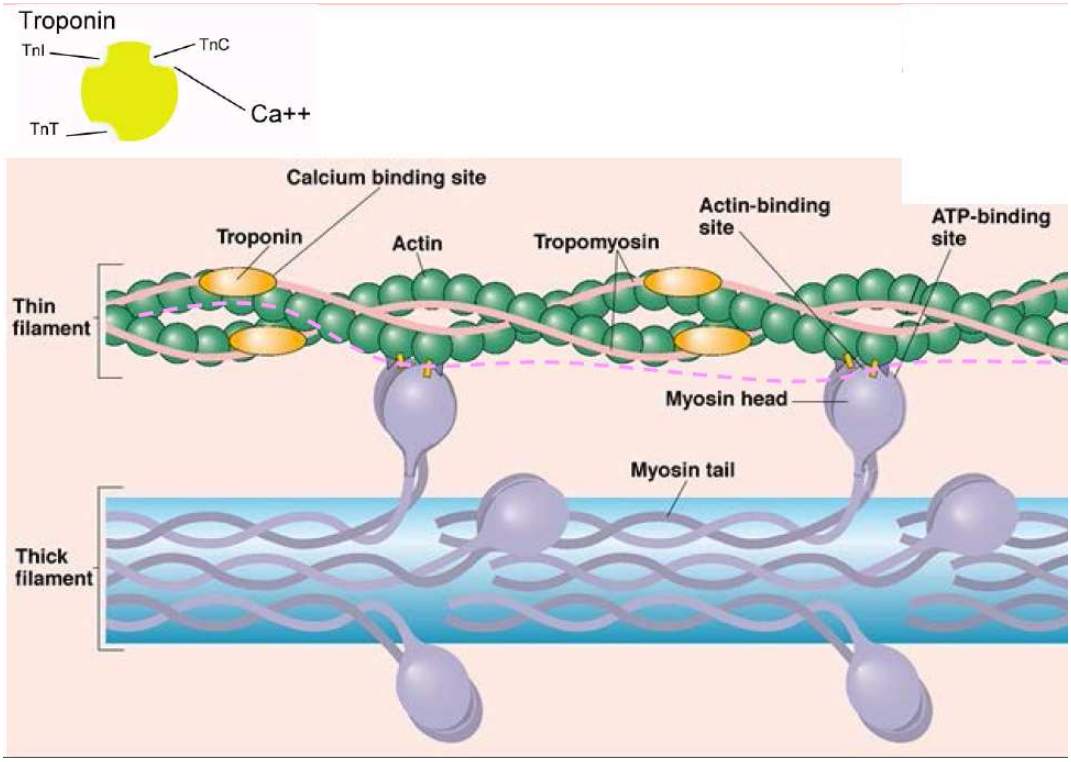

- The smallest contractile (functional) unit of a muscle

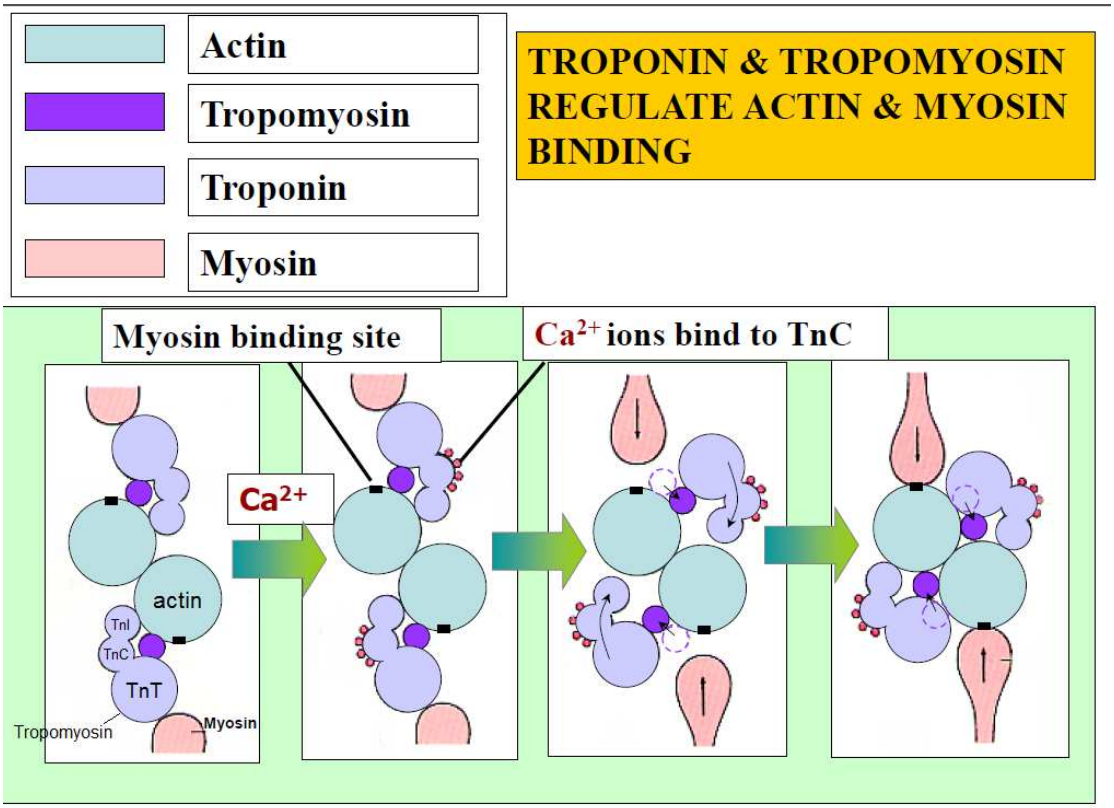
Muscle cells (fibers) composed of myofibrils, each of which contains myofilaments. The sarcomere lies between two Z-lines.

# 1. Sarcomere

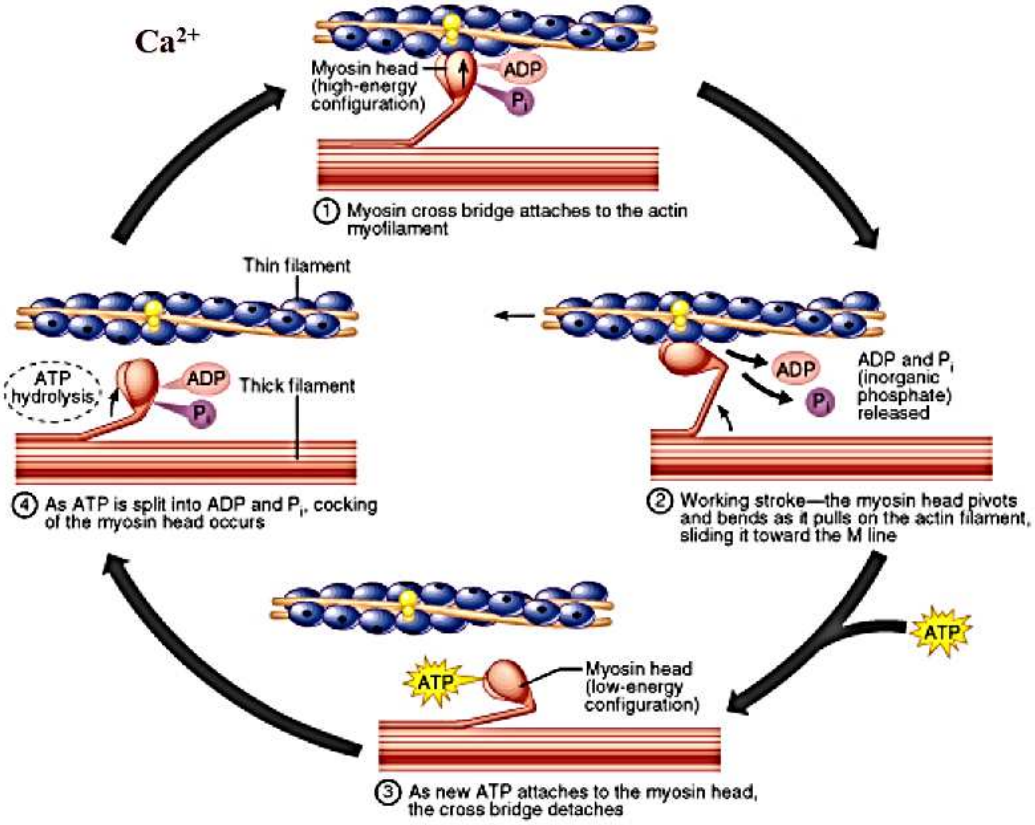
- **Sarcomere**: smallest contractile (functional) unit of a muscle
- The region of a myofibril between two successive Z discs
- Composed of myofilaments made up of contractile proteins
  - Myofilaments are of two types – thick and thin

# C. Skeletal Muscle Contraction Mechanism



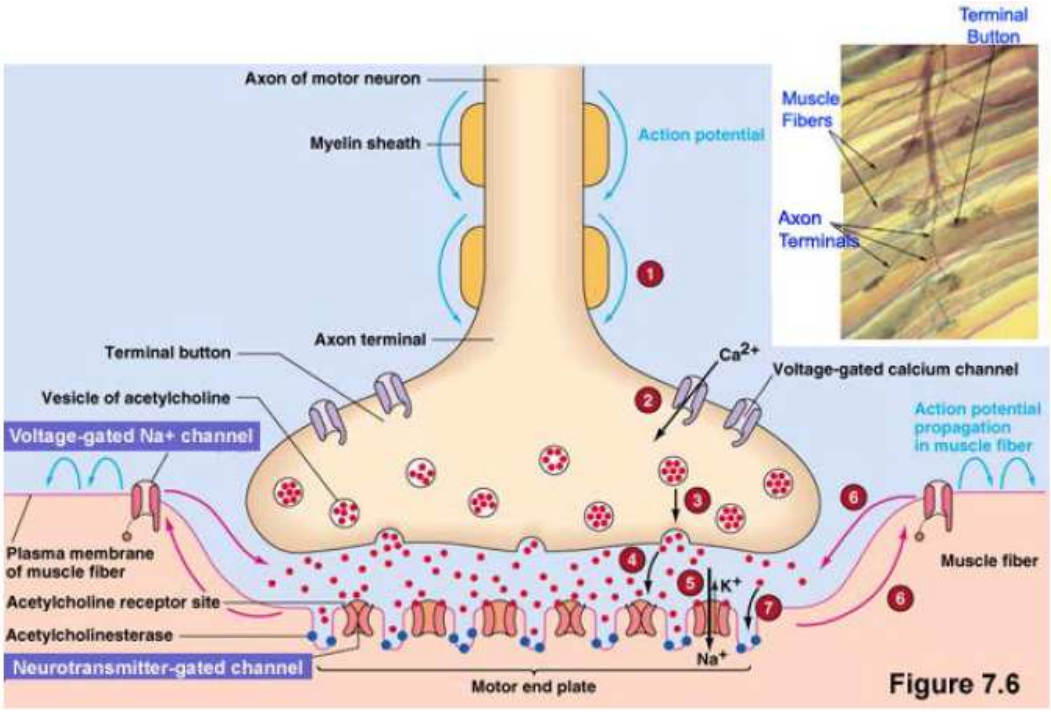
- Thin filament composed of **F-actin**, **tropomyosin** and **troponin**:
  - **F-actin** polymerized from G-actin
  - **Troponin** has $Ca^{2+}$ binding site (TnC) that triggers exposure of myosin-binding site on actin from tropomyosin
  - **Tropomyosin** is a long chain protein that is responsible for covering the myosin binding site on actin
- After $Ca^{2+}$ binding, troponin moves away from myosin binding site and resultant myosin binding leads to a sequence of events that causes sliding of myofilaments
  - **Cross-bridge attachment**: myosin cross-bridge attaches to actin filament
  - **Working (power) stroke**: myosin head pivots and pulls actin filament towards M line (middle of H band)
  - **Cross-bridge detachment**: ATP attachment to myosin head and crossbridge detaches
  - **'Cocking' of myosin head**: energy from hydrolysis of ATP cocks myosin head into high energy state



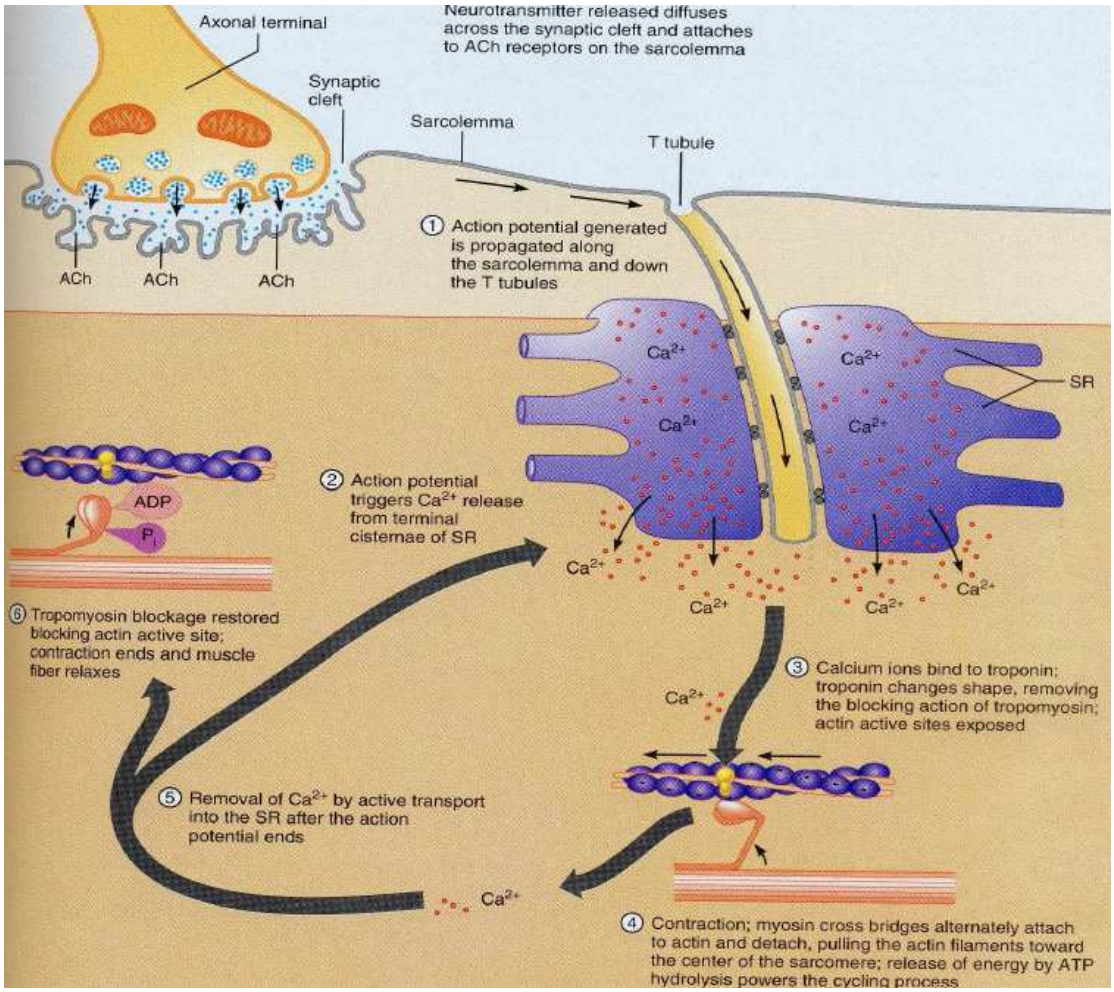

- Role of ATP:
  - Provides energy for cross-bridge movement
  - Breaks link between actin and myosin
- Resulting sliding between actin and myosin causes contraction of skeletal muscle fibres

# D. Excitation-Contraction Coupling

- Prerequisites of contraction:
  - Stimulation by a nerve ending
  - Propagation of an electric current along its sarcolemma
  - Have a rise in intracellular $Ca^{2+}$ levels to trigger contraction
- **Motor unit**: a single motor neurone and muscle fibres connected to it as a unit
- **Neuromuscular junction (NMJ)**: site where motor neurone meets muscle fibre (separated by **neuromuscular cleft**)
- **Motor end plate**: pocket formed around motor neurone by sarcolemma

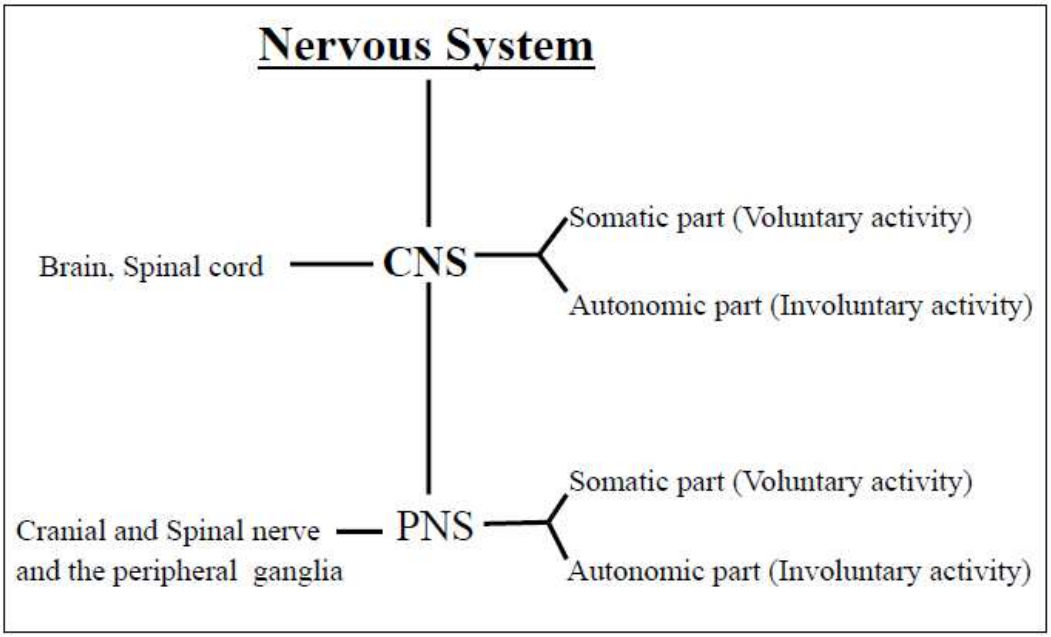



1) Action potential arrives at terminal button of axon;
2) Voltage-gated $Ca^{2+}$ channels open and $Ca^{2+}$ flows into axon terminal;
3) Vesicles of acetylcholine (ACh) move towards synaptic cleft and is released;
4) ACh diffuses across synaptic cleft and combine with AChRs to trigger AChR-mediated ion channels;
5) Action potential propagate along sarcolemma into muscle fibre interior via T-tubule;
6) Action potential passed to sarcoplasmic reticulum, triggering release of $Ca^{2+}$ into cytosol via voltage-gated $Ca^{2+}$ channels;
7) Intracellular $Ca^{2+}$ level rises, causing $Ca^{2+}$ binding with troponin and thus change in position in tropomyosin;
8) Active sites on actin exposed, permitting cross-bridge formation and thus muscle contraction;
9) $Ca^{2+}$ pumped back to SR by $Ca^{2+}$ reuptake pump.




*Death → no ATP → $Ca^{2+}$ cannot be pumped back into SR → actin-myosin complex cannot be split → development of **rigor mortis**, persisting until actin and myosin are broken down by decay process

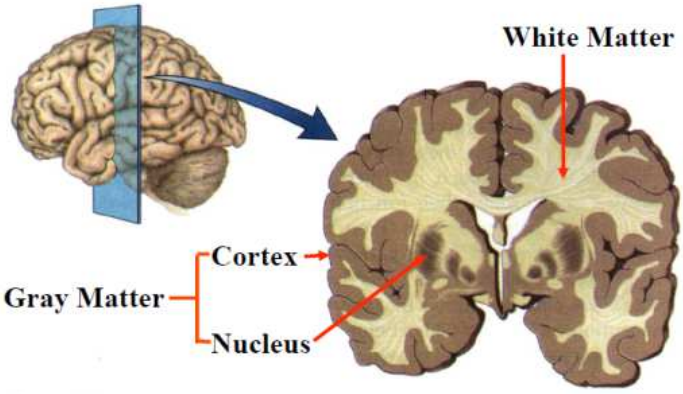
# L47 Structural Organization of the Nervous System



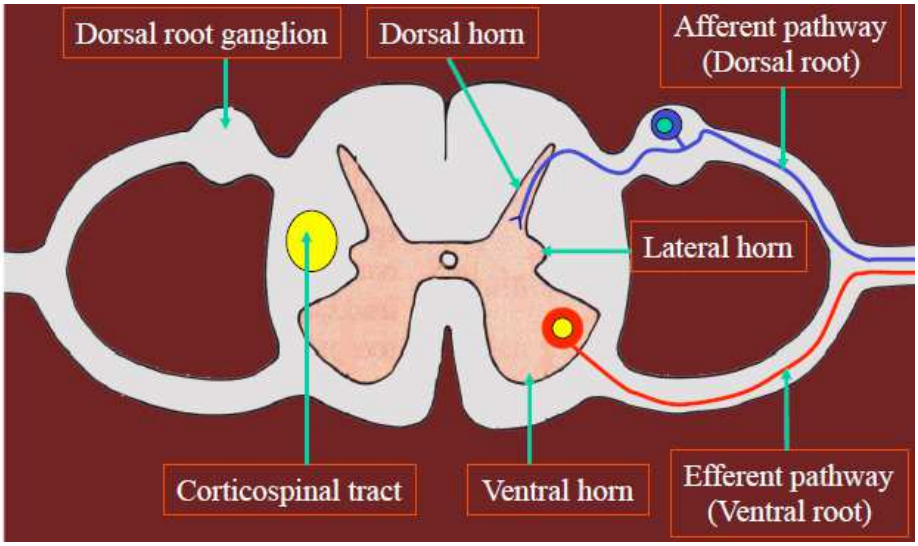

*Peripheral ganglia: clusters of neurone soma outside CNS (eg dorsal root ganglia, cranial nerve ganglia, autonomic ganglia)

# A. Terminology

- **Gray matter**: parts that contain nerve soma which have a gray colour in fresh sample
- **White matter**: parts that contain nerve fibres (axons) which have a white glistening colour in fresh sample

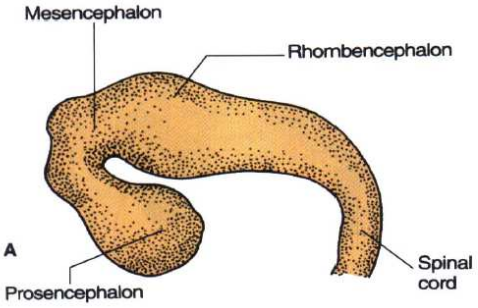


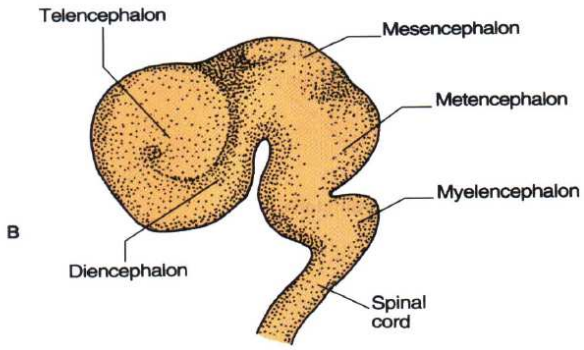

- **Cortex**: superficial coat of gray matter in cerebral and cerebellar hemispheres
- **Nucleus**: group of nerve cell bodies in other parts, usually in deeper parts of the brain
- **Horns and columns**: group of nerve cell bodies in spinal cord (such as ventral horn and column)
- **Ganglion**: accumulation of nerve soma outside CNS (i.e. in PNS)
- **Tract**: a collection of nerve fibres with a common origin and termination (such a corticospinal tract, spinothalamic tract etc)
- **Efferent pathway**: away from region under consideration (usually away from CNS)
- **Afferent pathway**: towards the region under consideration (usually towards CNS)

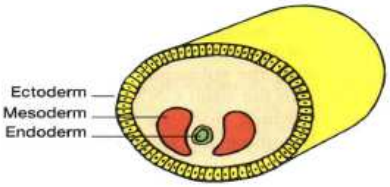


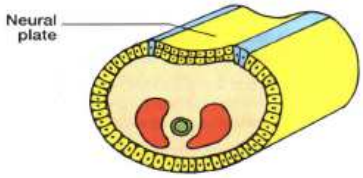
# B. Development of Nervous System

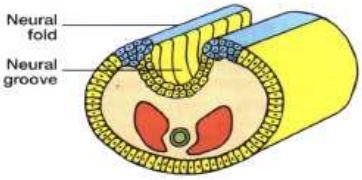
- Ectoderm → neural plate → neural groove, neural fold (form CNS), neural crest (form peripheral ganglia) → neural tube → brain and spinal cord

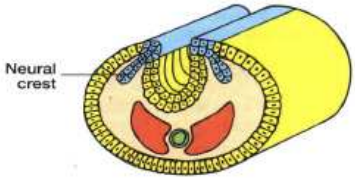


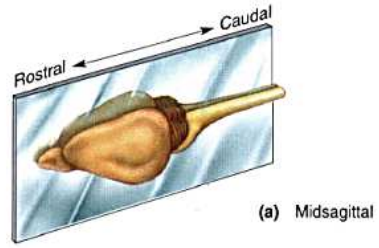


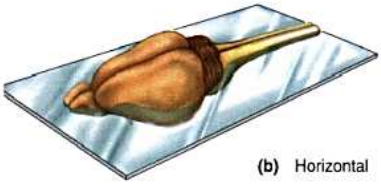
# C. Central Nervous System

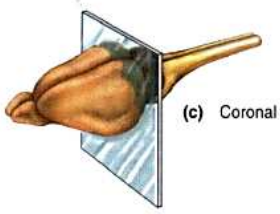
## 1. Brain

### a. Anatomical Cut Planes

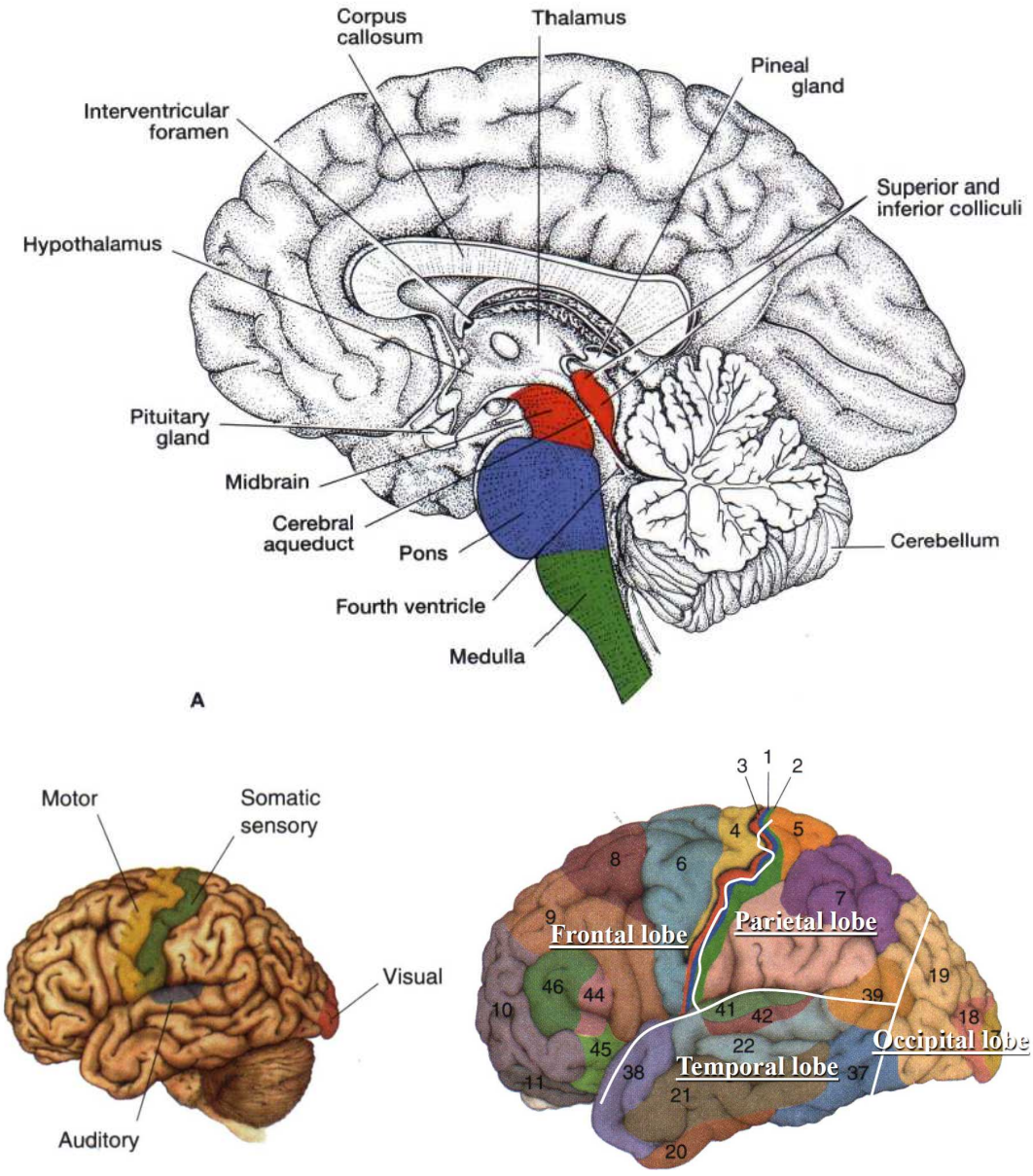
- **Sagittal**: cut parallel to long axis of brain, through only one half of brain or along midline (~hotdog)
- **Horizontal**: cut parallel to long axis of brain, through both right and left halves of brain (~hamburger)
- **Coronal**: cut perpendicular to long axis of brain (~loaf of bread)



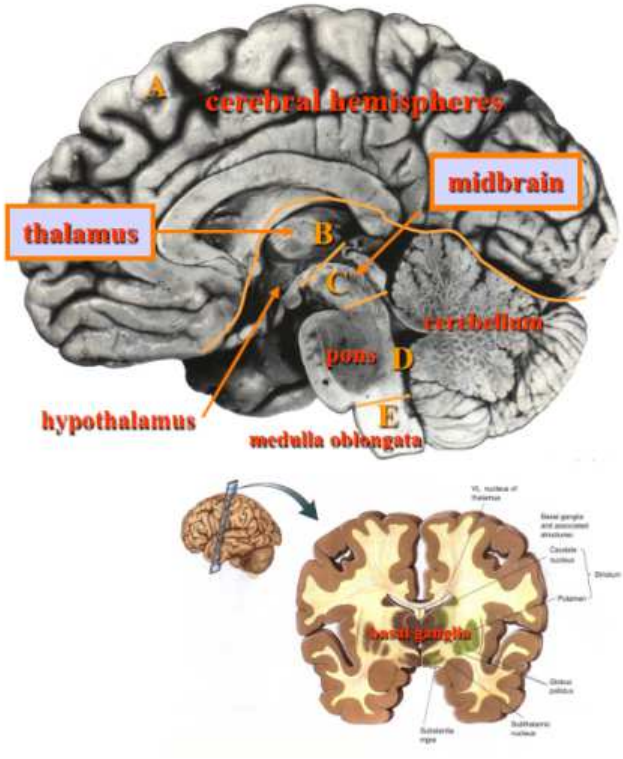



## b. Division of Brain

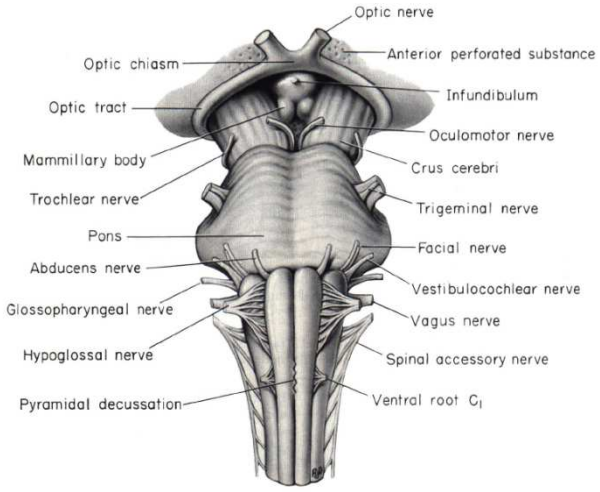


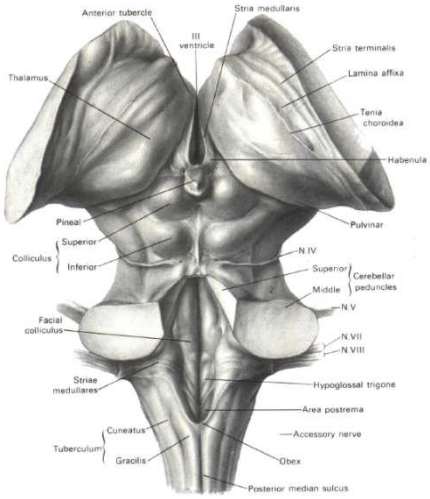
- **Telencephalon (A)**:
  - Two **cerebral hemispheres** (thinking, sensory, behavior, thinking, emotion…)
  - Two pairs of **basal ganglia** (caudate and lentiform nuclei, for motor functions)
- **Diencephalon (B)**:
  - **Thalamus** (mainly sensory)
  - **Hypothalamus** (autonomic nervous system)
- **Mesencephalon (C)**: **midbrain**
- **Metencephalon (D)**:
  - **Cerebellum**: control and adjustment of movement
  - **Pons**: connection between cerebral and cerebellar cortex
- **Myelencephalon (E)**: **medulla oblongata**



## c. Brain stem

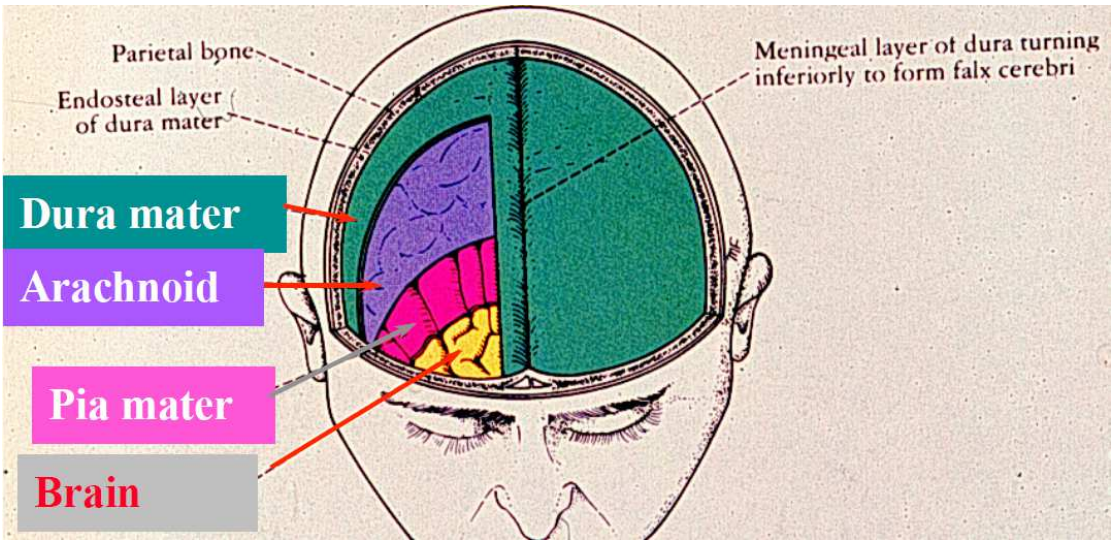
- Consists of **midbrain**, **pons** and **medulla oblongata**
- Functions:
  - All ascending and descending pathways pass through brain stem
  - Many important life centers (eg heartbeat, breath, BP…) are located in brain stem
  - Nuclei of most cranial nerves are located in brain stem



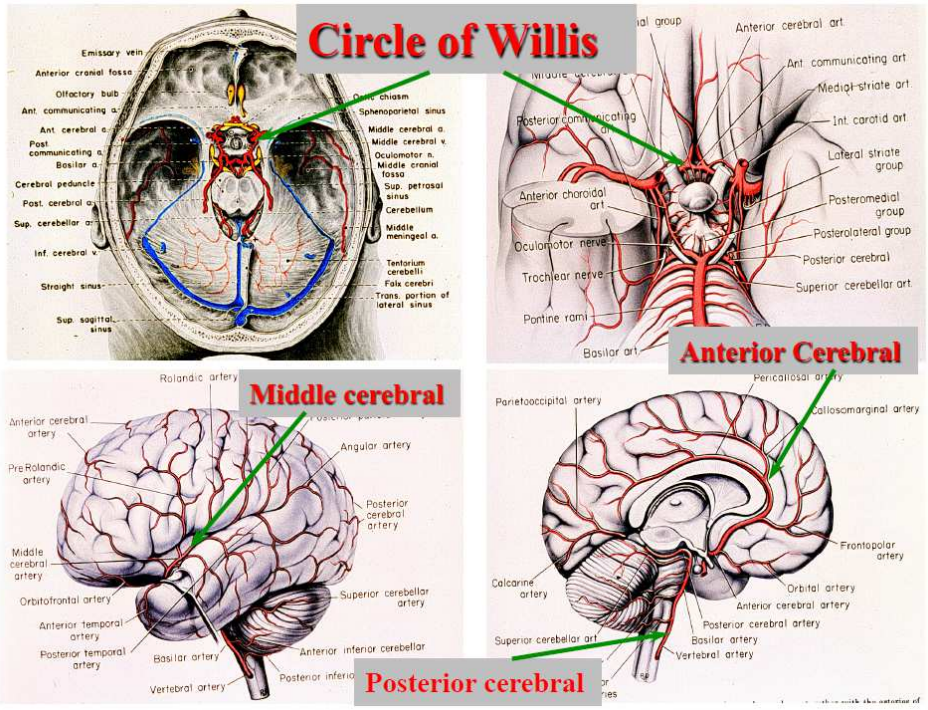

## d. Meninges

- Three membrane covering whole CNS: **dura mater** (outer), **arachnoid** (middle), **pia mater** (inner)



## e. Blood Supply to Brain

- **Circle of Willis**: circulatory anastomosis supplying the brain
- Cerebrum supplied by three major arteries: **anterior cerebral**, **middle cerebral** and **posterior cerebral**




## f. Cerebrospinal Fluid (CSF) Circulation

***Circulation of CSF***

**Lateral ventricle**

(Interventicular Foramen) ↓

**Third ventricle**

(Cerebral aqueduct) ↓

**Fourth ventricle**

(Lateral Foramina) ↓ (Median Foramen)

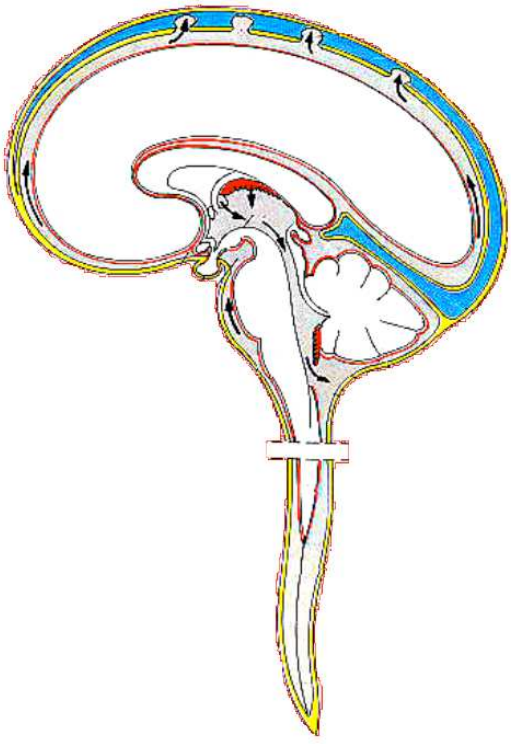
**Cerebellomedullary cistern**

↓

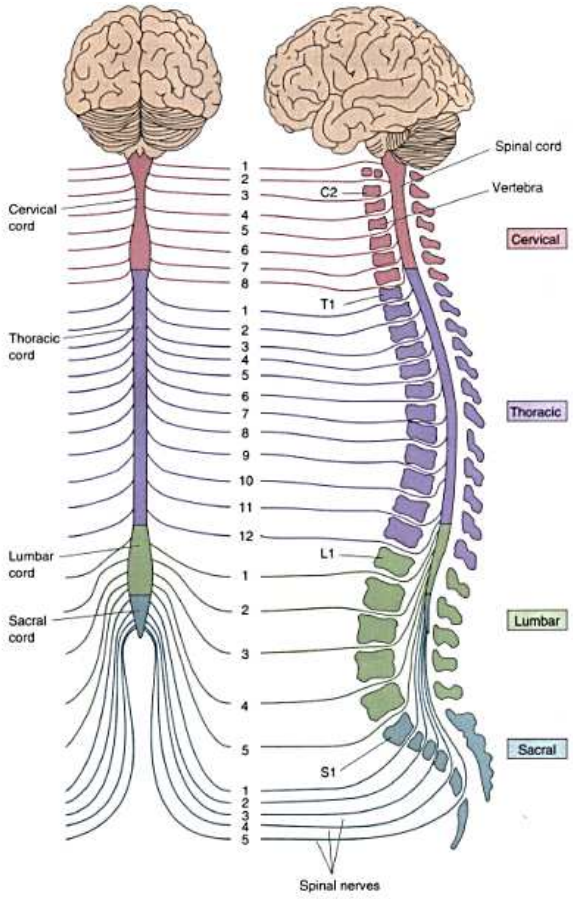
**Subarachnoid space**

(Arachnoid granulation) ↓

**Superior sagittal sinus**



# 3. Spinal Cord and Spinal Nerves




- Spinal nerves:
  - **Vertebral column (26)**:
    - → **Cervical (C1-C7)**
    - → **Thoracic (T1-T12)**
    - → **Lumbar (L1-L5)**
    - → **Sacral (fused, S1-S5)**
    - → **Coccygeal (fused)**
  - **Spinal nerves (31):**
    - → **C1-C8**
    - → **T1-T12**
    - → **L1-L5**
    - → **S1-S5**
    - → **Coccygeal**
  - Note C1 spinal nerve is above C1 vertebra → 8 cervical nerves
- **Gray matter**: dorsal (sensory), lateral (autonomic) and ventral (motor) horns
- **White matter**: dorsal, lateral, ventral funiculus; ascending, descending and intersegmental pathways

# D. Peripheral Nervous System

- **Cranial nerves** (12 pairs)
- **Spinal nerves** (31 pairs)
- **Autonomic nervous system**: sympathetic and parasympathetic nervous systems
- **Cranial** and **spinal ganglia**

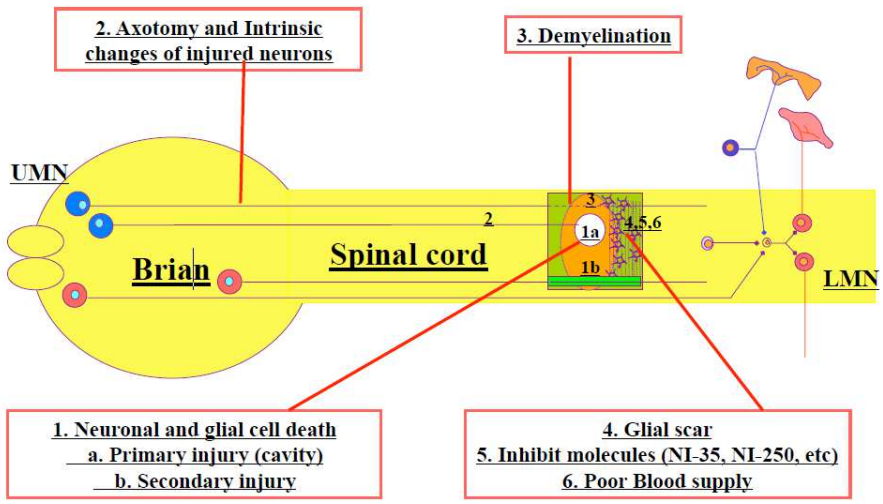
*Communications within nervous system

- **Cellular level**: synapse
- **Within same region**: interneurons, short communicating tracts
- **Between different regions**: long projecting fibre tracts (ascending/descending pathways)
- **Bundles of nerve fibres in CNS**: tract, fasciculus, peduncle, brachium, commissure, funiculus
- **Bundles of nerve fibres in PNS**: nerve, root, trunk, ramus

**Clinical considerations

- Glia continue to divide through lifetime → major source of cerebral tumors
- Axon injury → degeneration in PNS and regeneration in PNS

**Pathological changes following spinal cord injury (SCI)**

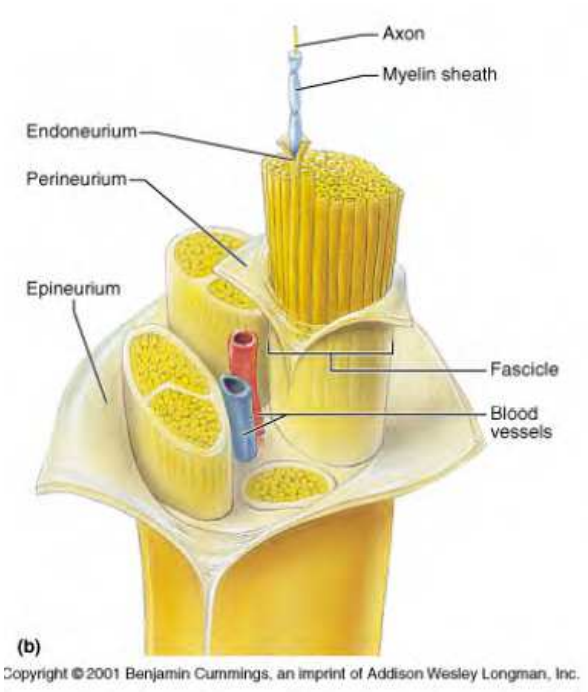


# L48 Peripheral Nervous System (PNS)

## A. Peripheral Nervous System Overview

- **Peripheral nervous system**: part of the nervous system that is NOT enclosed by skeleton
- Boundary: at **base of spinal roots**
- Components:
  - By location: cranial nerves, spinal nerves, autonomic nervous system
  - By function: somatic motor system, somatic sensory system, autonomic nervous system

## 1. Peripheral Nerves





- **Epineurium**: dense fibrous connective tissues enclosing entire nerve
- **Perineurium**: moderately dense fibrous c.t. surrounding fascicles of axons mking up a nerve
- **Endoneurium**: delicate, loose c.t. surrounding individual axons and their Schwann cells
- Note that even in one fascicle there can be bot motor and sensory neurone
- Neurones contributing to the peripheral nerves are partly contained within CNS

## 2. Peripheral Nerve Ganglia

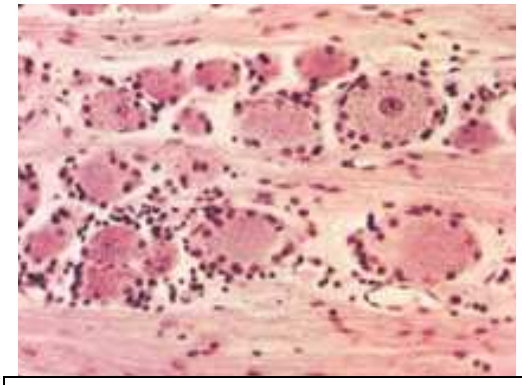
### a. Sensory Ganglia

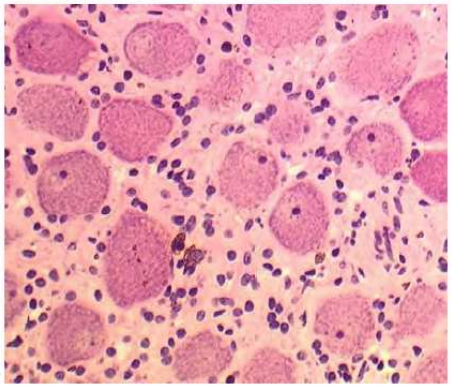
- **Sensory ganglia**: pseudo-unipolar neurones surrounded by a layer of satellite cells
- Two types:
  - Cranial ganglia associated with cranial nerves
  - Spinal ganglia associated with dorsal roots of spinal nerves
  - Receive afferent impulses going to CNS

## b. Autonomic Ganglia

- **Autonomic ganglia**: multipolar neurones surrounded by a layer of satellite cells
- Two types:
  - Sympathetic: located in sympathetic trunk
  - Parasympathetic: located within innervated organs

*Difference between sympathetic ganglion and sensory ganglion in photomicrographs:

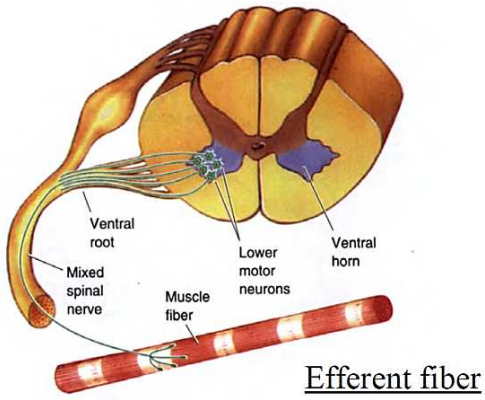




| Sensory Ganglion | Sympathetic Ganglion |
|---|---|
| 1) With fibre traps;<br>2) More satellite cells;<br>3) Cells of different size. | 1) Without fibre traps;<br>2) Less satellite cells;<br>3) Cells of different sizes |

# 3. Somatic Motor System

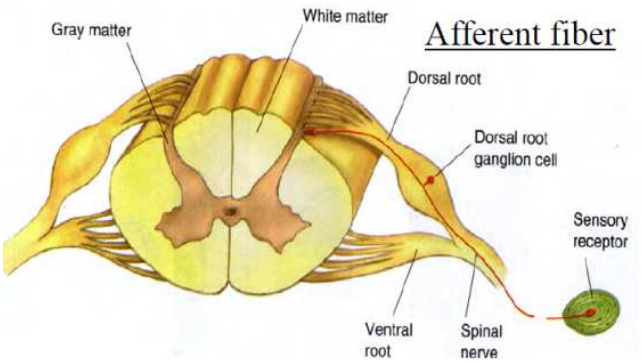
- Cell bodies of motor system located in CNS
- Axons organized into nerve bundle and located in PNS
- Terminals located in skeletal muscles to form motor end plate




Efferent fiber

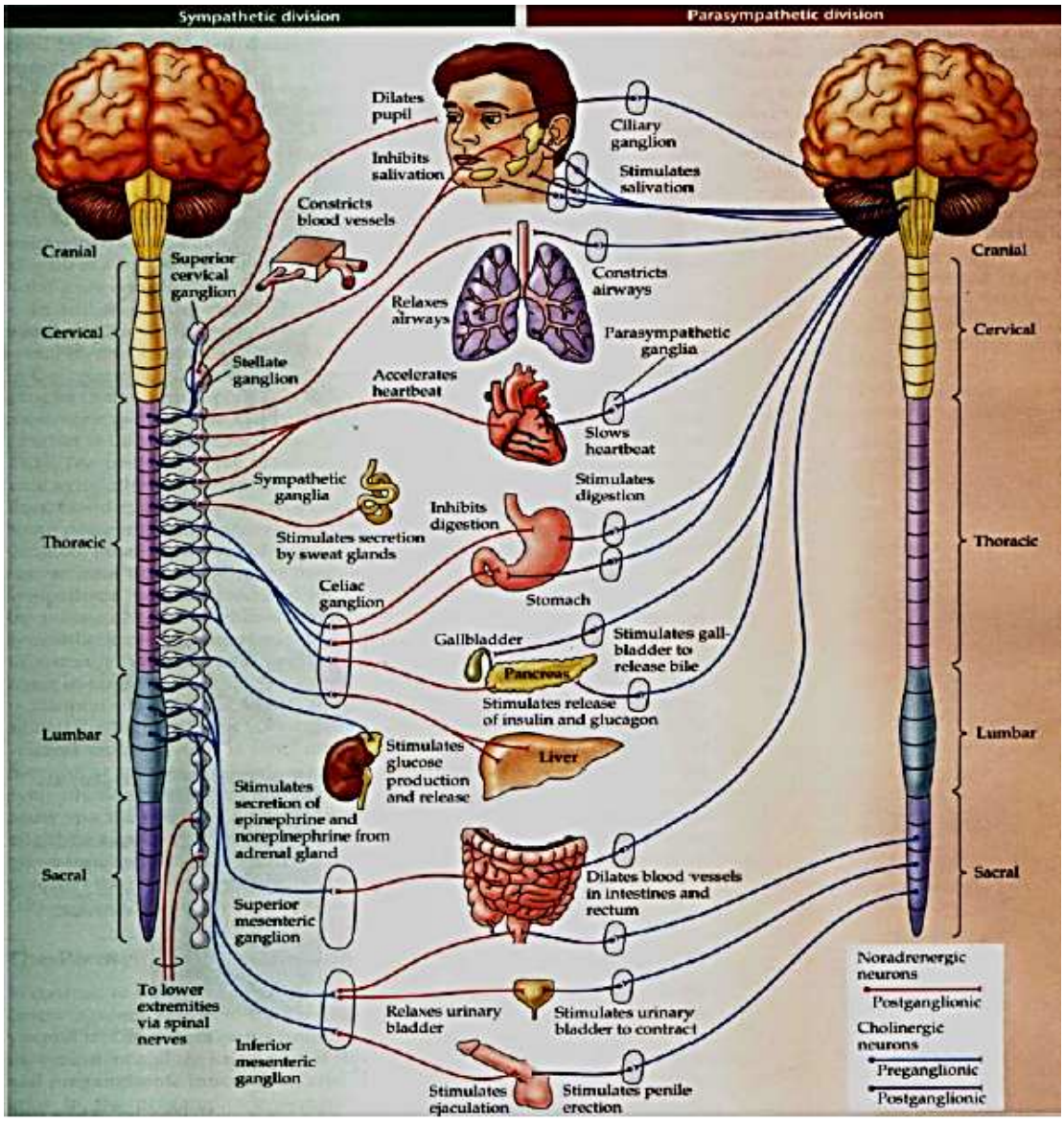
# 4. Somatic Sensory System

- Cell bodies of sensory system located in PNS (ganglia eg dorsal root ganglia)
- Axons usually divided into branches:
  - One branch connects with peripheral organs → sensory endings
  - One projects to CNS and terminates within CNS




Afferent fiber

# 5. Autonomic Nervous System




# B. Cranial Nerves

- Formed from neurones of which the soma is within the brain
- **12 pairs** of cranial nerves:
- Note: CN II (optic nerve) considered as an extension of the brain (myelin formed by oligodendrocytes) → not part of PNS

# C. Spinal Nerves

- Formed from axons from neurones in spinal cord and dorsal root ganglia
- **31 pairs** of spinal nerves:
  - **8 cervical**
  - **12 thoracic**
  - **5 lumbar**
  - **5 sacral**
  - **1 coccygeal**
- Divided into five clusters:
  - **Cervical plexus (C1-C4)** – upper neck
  - **Brachial plexus (C5-T1)** – lower neck + shoulder
  - **Thoracic nerves (T2-T12)** – chest (do not form a plexus)
  - **Lumbar plexus (L1-L4)** – abdomen
  - **Sacral plexus (L4-S3/4)** – hip

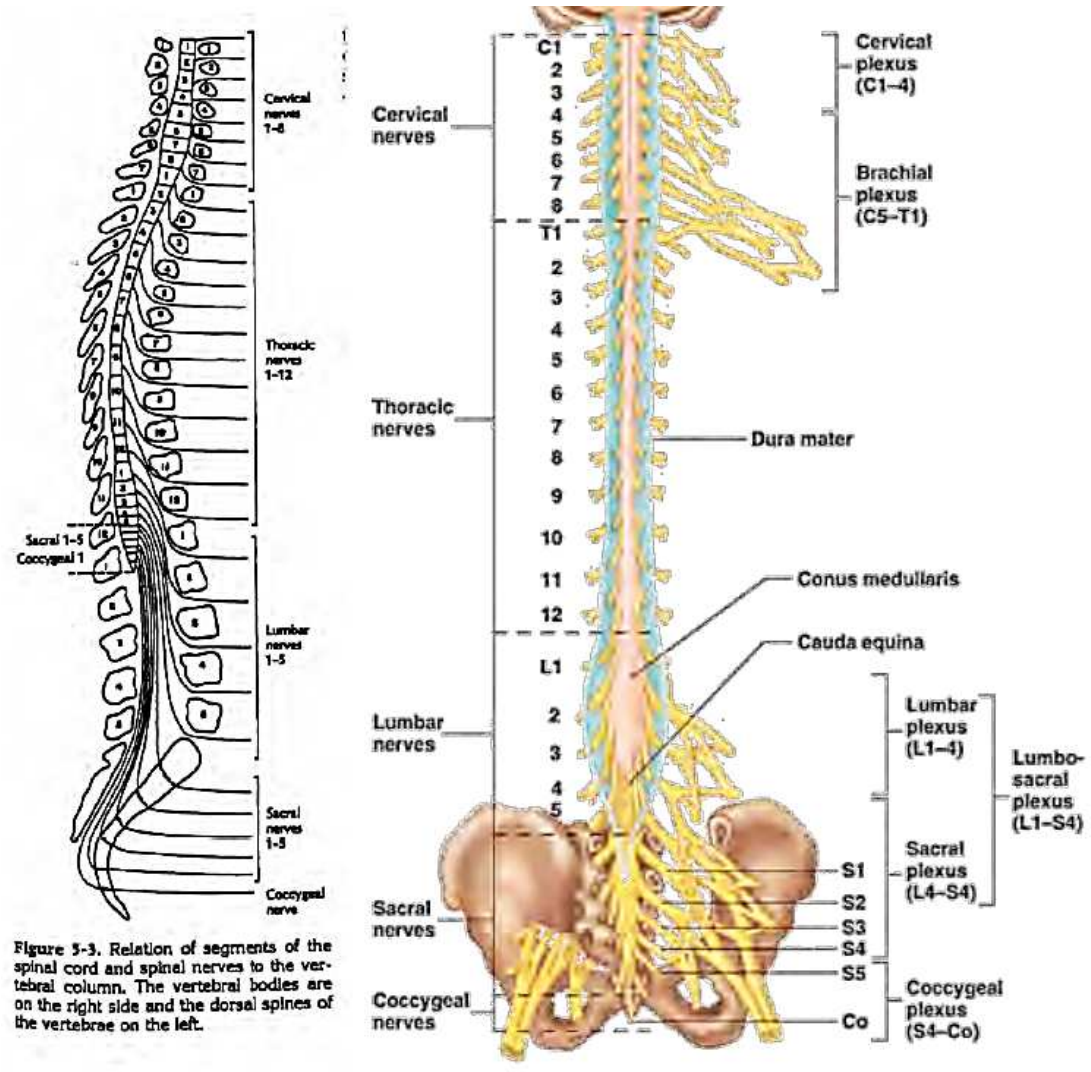
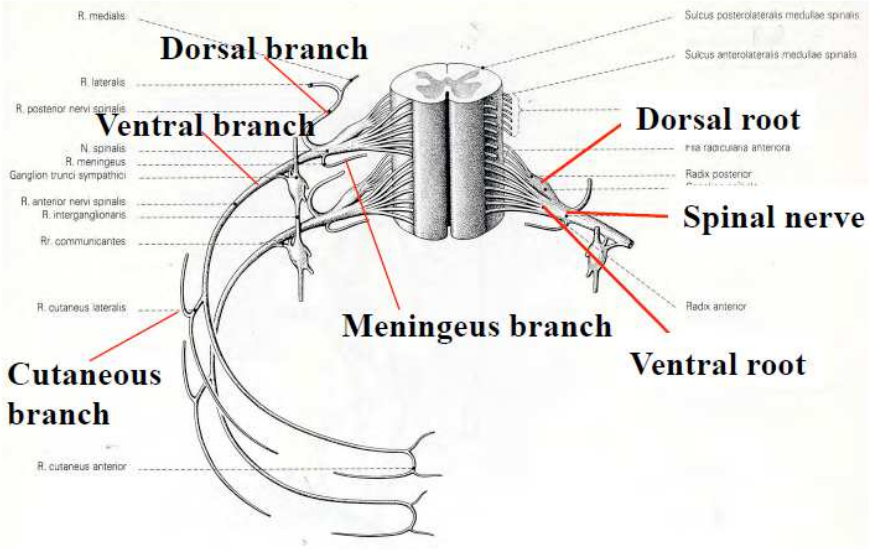



Figure 5-3. Relation of segments of the spinal cord and spinal nerves to the vertebral column. The vertebral bodies are on the right side and the dorsal spines of the vertebrae on the left.

# 1. Branching of Spinal Nerves

- Using thoracic nerves as an example:

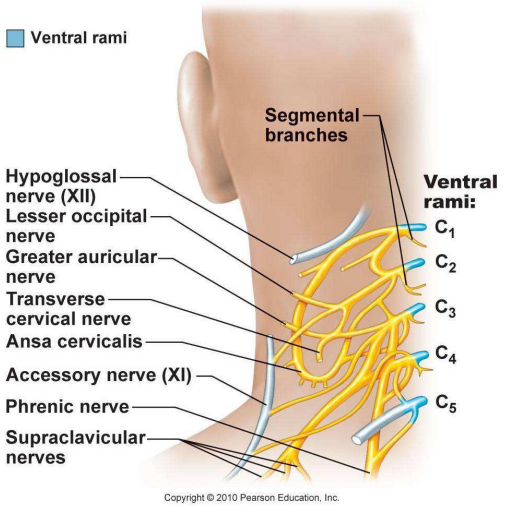



- **Dorsal branch** (mixed) innervates back of the body
- **Ventral branch** (mixed) innervate rib region
- **Cutaneous branch** (sensory) innervate skin
- **Meningeal branch** innervate area around spinal cord

*Esp note difference between dorsal/ventral branch and dorsal/ventral roots: former is mixed but latter corresponds to sensory/motor neurones only

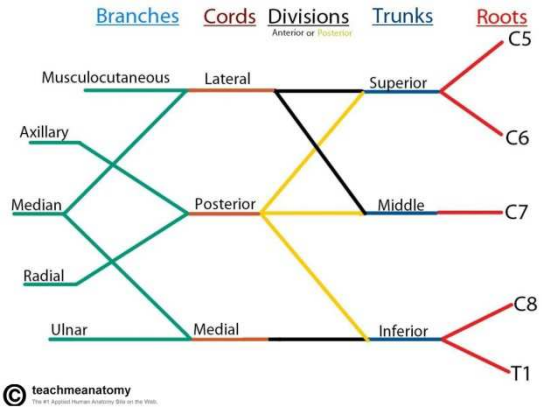
## 2. Cervical Plexus

- C1-C4
- Innervates superficial neck structures, skin of neck, posterior portion of head
- **Phrenic nerve** from C3-C5 innervates diaphragm

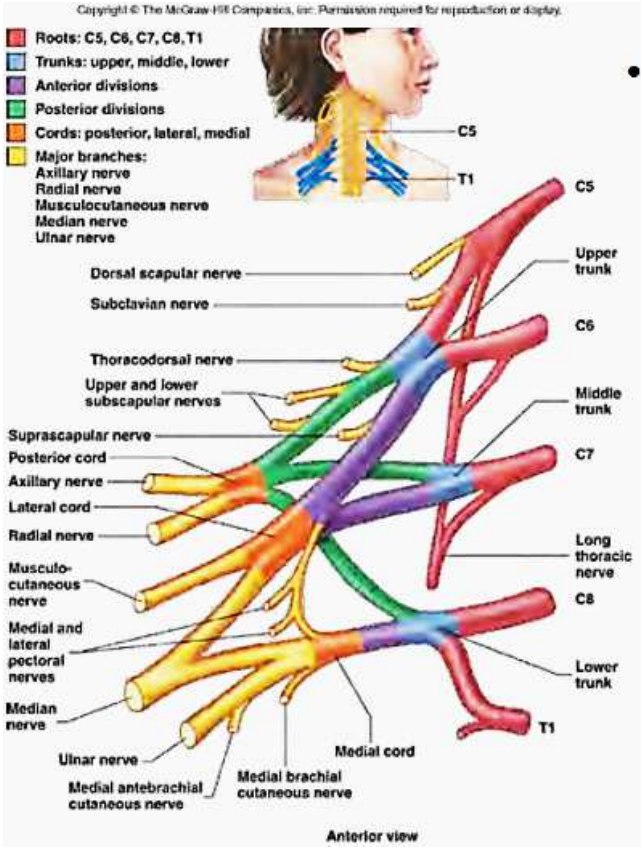



## 3. Brachial Plexus

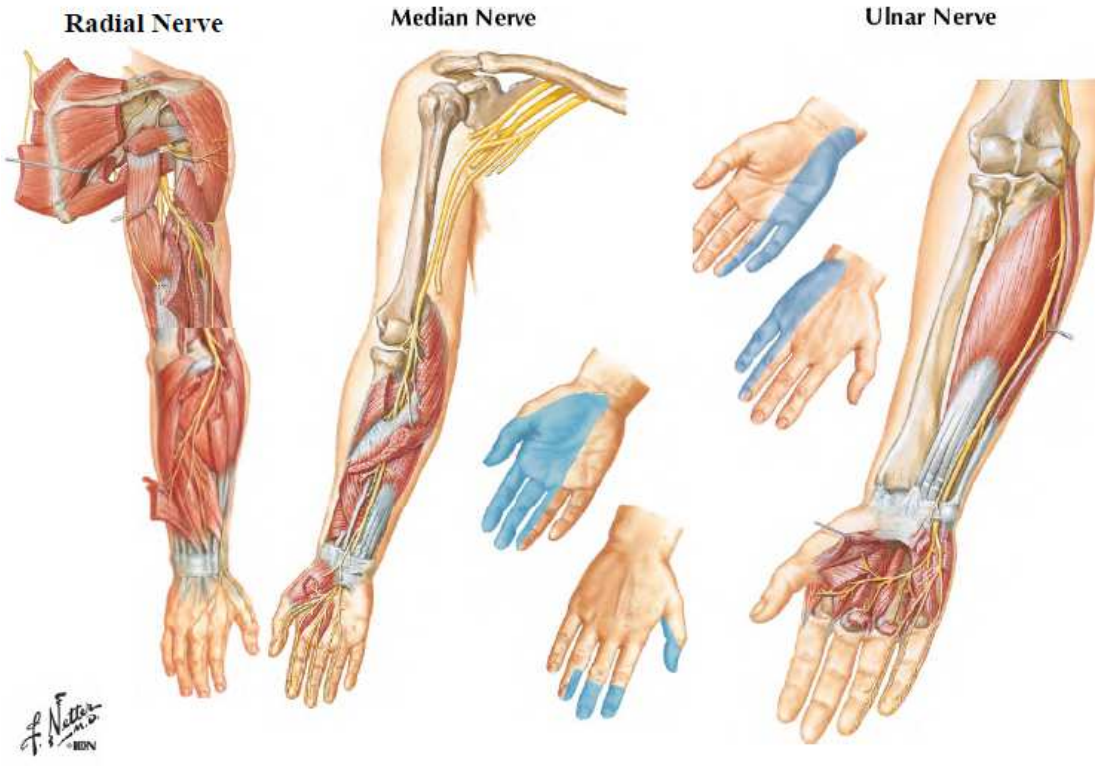
- C5-T1
- Five ventral **rami** (nerve branches) form three **trunks** that separate into six **divisions** then form cords that give rise to five major nerves: (axillary, radial, musculocutaneous, ulnar, median)
- Other smaller nerves (pectoral, long thoracic, thoracodorsal, subscapular, suprascapular) also formed



- 5 spinal segments, 5 times of reorganizations (root, trunk, division, cord, branch), 5 major branches

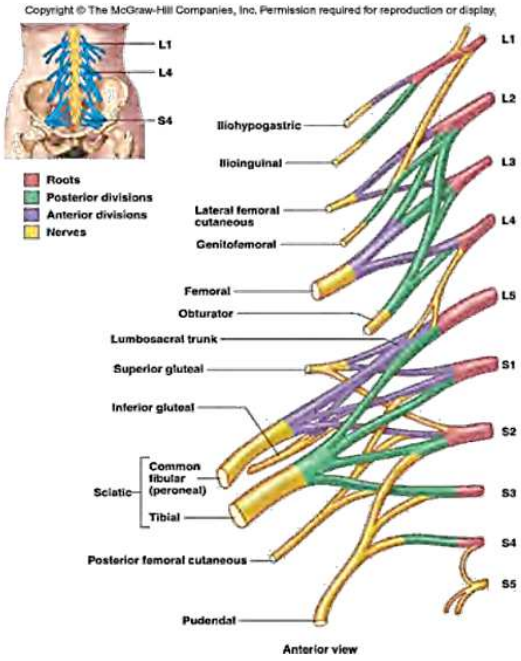



- Radial, median and ulnar nerves innervate different regions of arms



# 4. Lumbosacral Plexus

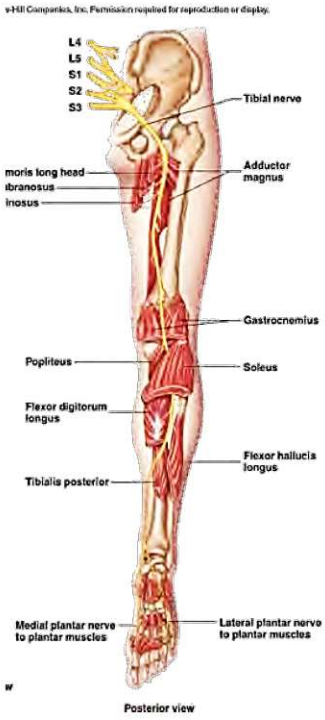
- **Lumbar plexus** from ventral rami of L1-L4
- **Sacral plexus** from ventral rami of L4-S3/4
- Usually considered together due to close relationship
- Four major nerves exit and enter lower limb: **obturator**, **femoral**, **tibial**, **common fibular (peroneal)** (collectively known with tibial as **sciatic nerve**)



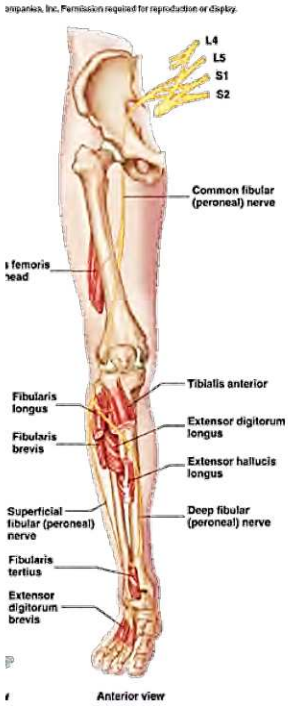

## a. Sciatic Nerve

- Tibial and common fibular nerves are collectively known as **sciatic nerve**

**Tibial**




**Common fibular**

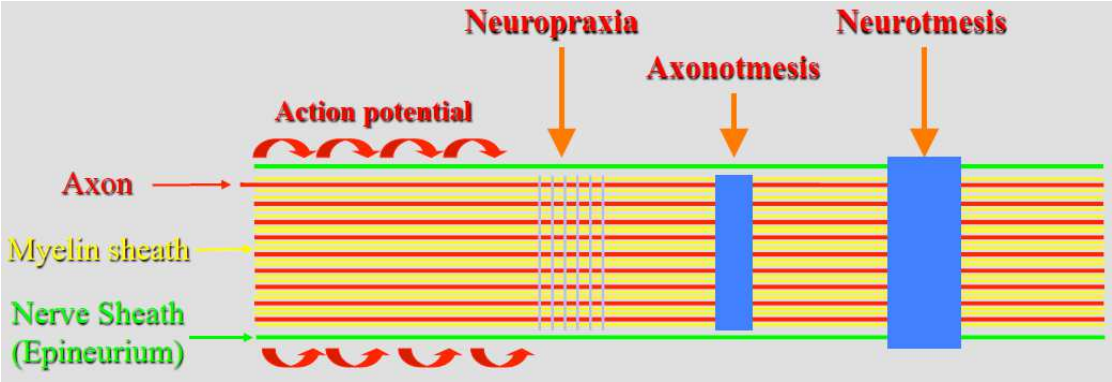


# D. Disorder and Injury of PNS

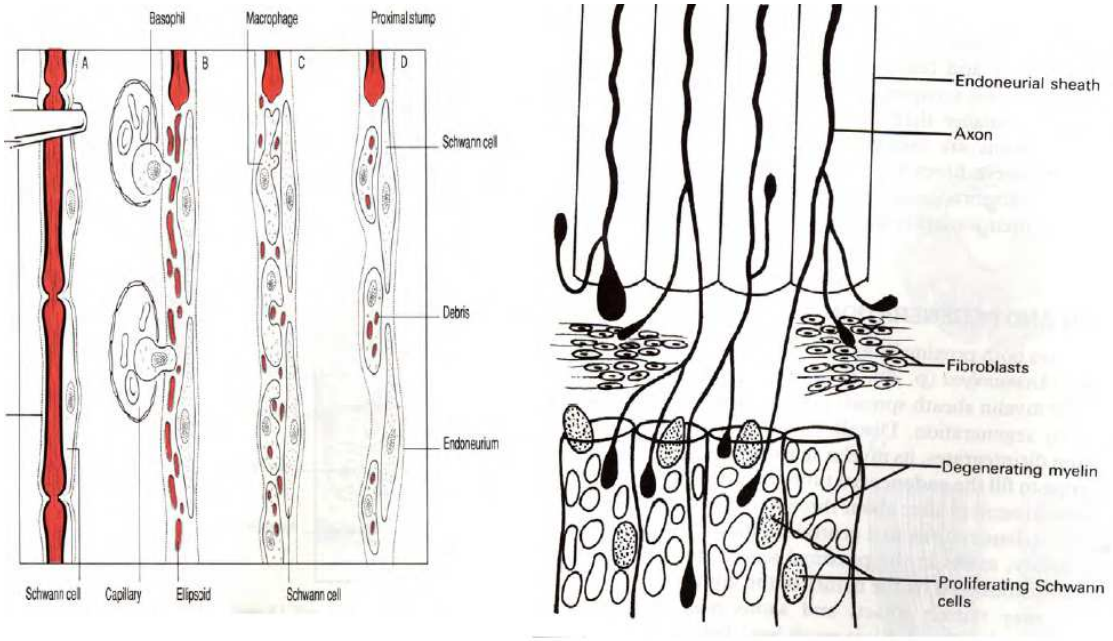
- **Neuropathy**: functional disturbances and pathological changes in peripheral nervous system (eg damage to neurones and their myelin sheath
- **Neuritis**: inflammation of PNS
- **Injury**: injury to axons or soma of neurones
- **Regeneration**: peripheral nerves are capable of regeneration undersome circumstances

## 1. Seddon's Classification of Peripheral Nerve Injuries

- **Neuropraxia**: injury without any anatomical discontinuity but resulting in functional disruption
- **Axonotmesis**: microscopic division of nerve fibres (axons) without obvious discontinuity of nerve sheath
- **Neurotmesis**: complete anatomic division of nerve fibres with obvious discontinuity of nerve sheath



# 2. Regeneration of Peripheral Nerves after Injury

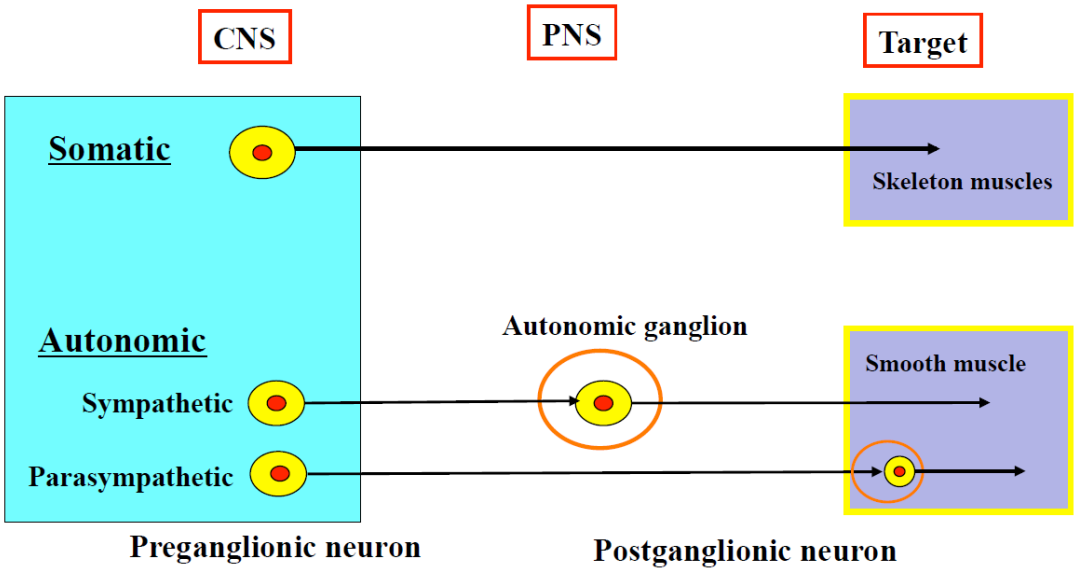



- Three criteria of revival of motor function after peripheral nerve injury:
  - **Neurone can survive**: if injury is too close to CNS the whole neurone may die
  - **Regeneration of axon**: in some cases the motor neurone may fail to regenerate axons
  - **Reinnervation of muscles and functional recovery**: possibility of muscle and neural atrophy after loss of innervation for a period of time

# L49 Autonomic Nervous System

## A. Autonomic Nervous System Overview

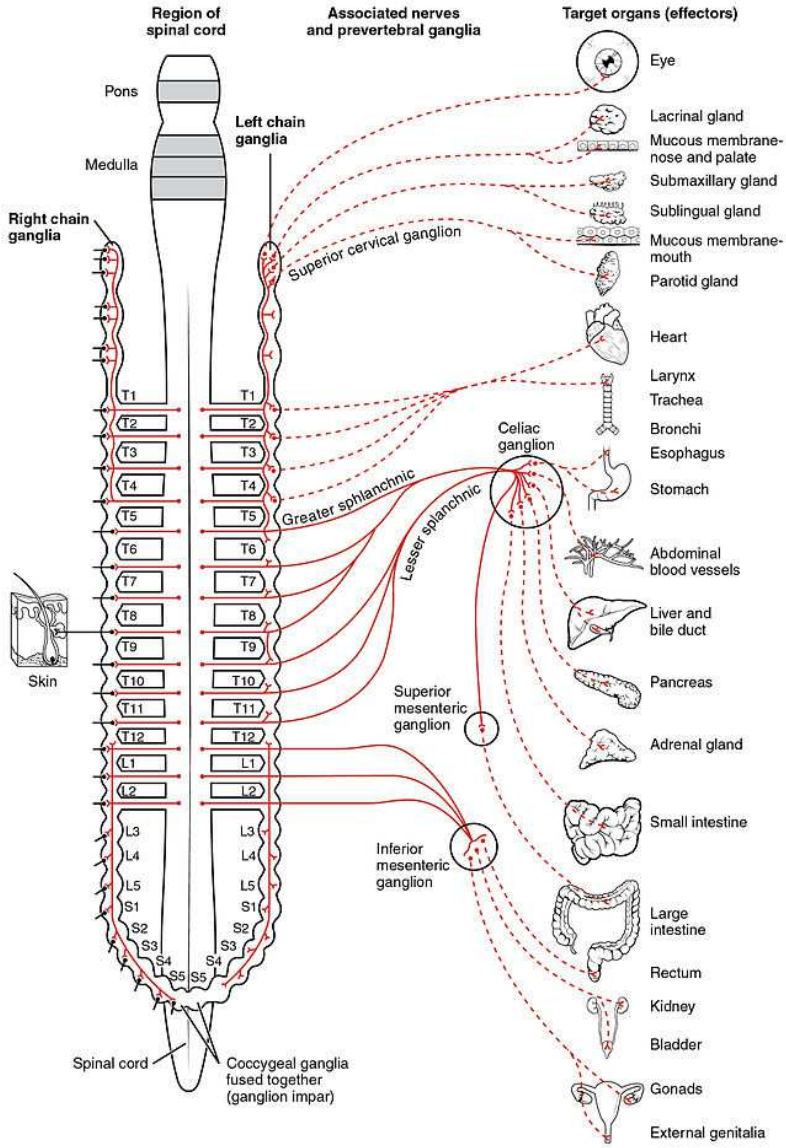
- Axons usually form plexus and terminate within innervated organs
- Cell bodies usually located in **autonomic ganglia**:
  - Autonomic ganglia of PN at innervated organ (**terminal ganglion**)
  - Autonomic ganglia of SN in PNS (**prevertebral ganglion**) or sympathetic trunk (**paravertebral ganglion**)
- Efferent pathway consists of **preganglionic neurone** and **postganglionic neurone**:



# B. Divisions of Autonomic Nervous System

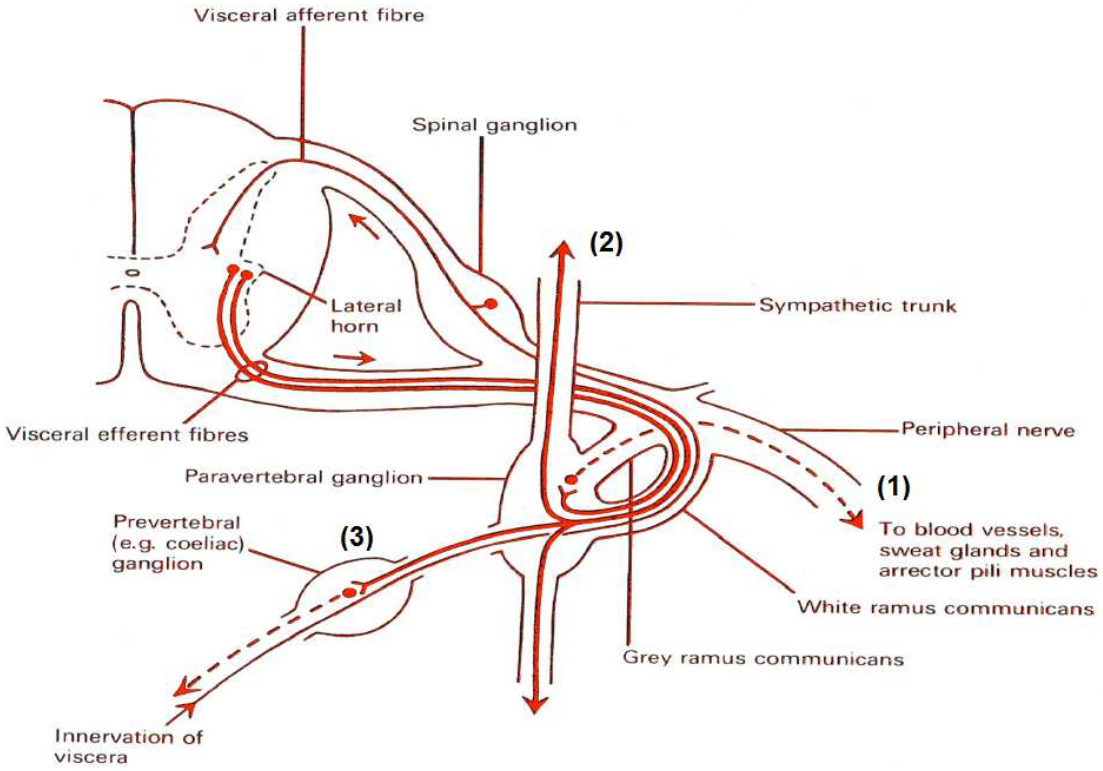
- Autonomic nervous system consists of **sympathetic (SN)** and **parasympathetic nervous systems (PN)**
- Centre of SN located in **lateral horn** of T1-L3 spinal cord
- Centre of PN located in brain stem and S2-S4 spinal cord
- Higher center of autonomic system located in hypothalamus
- Different neurotransmitters used for the two synapses of efferent pathways in PN and SN:
  - SN: nAChR (nicotinic cholinergic), NE (norepinephrine, adrenergic)
  - SN (sweat): nAChR, mAChR (muscarinic cholinergic)
  - PN: nAChR, mAChR

# 1. Sympathetic Nervous System (SN)




- Cell bodies of preganglionic neurones of SN located in **intermediolateral cell column** in **lateral horn** of spinal cord T1-L3
- Axons exists via **ventral roots** and **spinal nerves** and reach paravertebral ganglia of **sympathetic trunk**

- **Sympathetic trunk**: a series of paravertebral ganglia joined together by nerve fibres
  - Extend from base of skull to coccyx on ventrolateral side of vertebral column




- Three possibilities of connections for presynaptic fibre upon reaching sympathetic trunk (via **white connecting ramus**):

1) Establish synaptic contacts with postganglionic neurones at level of entrance (and leave via **grey connecting ramus**);
2) May pass up and down in sympathetic trunk before establishing synaptic contacts with postganglionic neurones at different levels of sympathetic trunk;
3) May pass through the ganglion and synapse in one of prevertebral ganglia (celiac, superior mesenteric, inferior mesenteric).

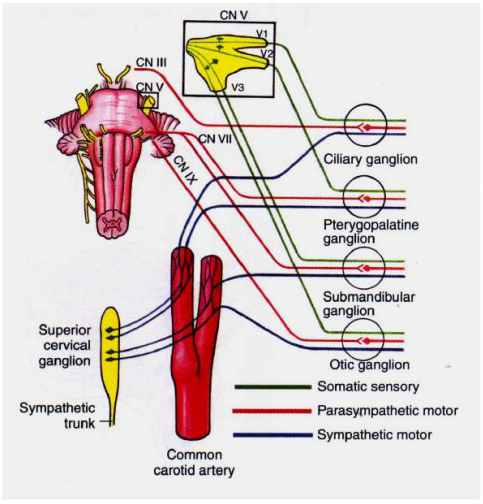
- **White connecting ramus** (only from T1-L3): connection between spinal nerve and sympathetic trunk
  - Contains both **preganglionic fibres** and **visceral efferent fibres**
- **Grey communicating ramus** (found along entire trunk): **unmyelinated** connection between spinal nerve and sympathetic trunk
  - Contains **postganglionic fibres** returning to spinal nerve from sympathetic trunk
- **Plexus**: postganglionic fibres from paravertebral and prevertebral ganglia join arteries as plexuses of nerve fibres to different internal organs

# 2. Parasympathetic Nervous System (PN)

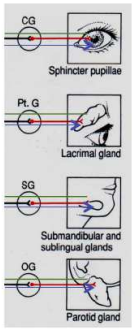
- Made up of cranial nerves and spinal nerves:
- Cranial nerves:
  - **Oculomotor nerve (CN III)** → ciliary muscle and sphincter pupillae
  - **Facial nerve (CN VII)** → submandibular and sublingual gland
  - **Glossopharyngeal nerve (CN IX)** → parotid gland
  - **Vagus nerve (CN X)** → the principal nerve of PN, innervates rest of body

**Somatic nervous system (Afferent fibers)**

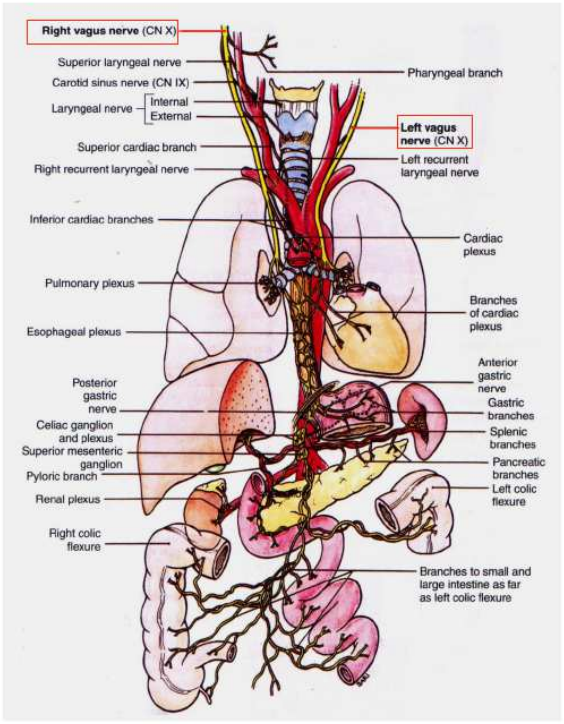
**Sympathetic nervous system**




**Parasympathetic nervous system (cranial nerves III, VII, and IX)**

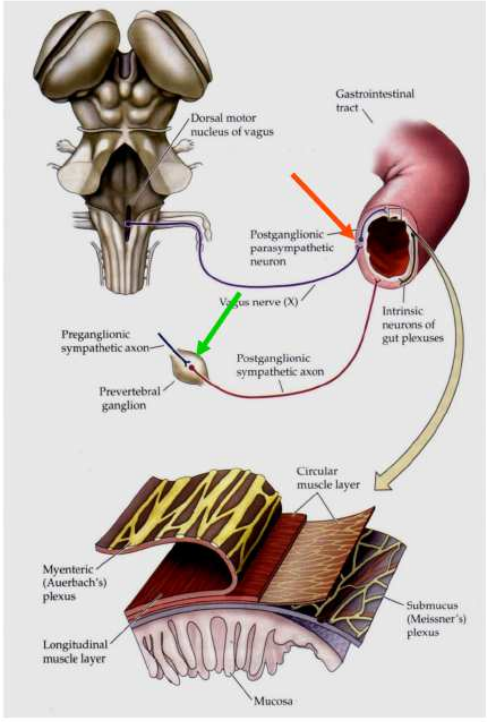



**Parasympathetic nervous system (cranial nerve X)**

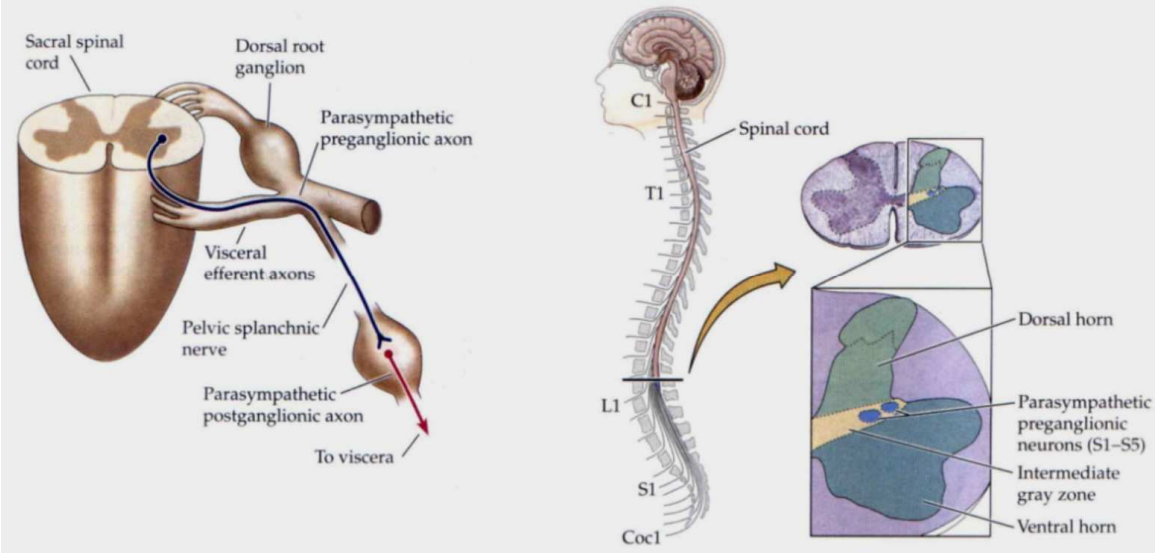



**Sympathetic ganglion**

**Parasympathetic ganglion**



- Spinal nerves: **sacral spinal cord (S2-S4)**
  - Cell bodies of preganglionic neurones located in **intermediolateral cell column** of S2-S4 spinal cord
  - Postganglionic neurones located close to peripheral organs (descending and sigmoid colon, rectum, bladder, genitalia)




# C. Functions of Autonomic Nervous System

- SN and PN generally have opposing actions
- SN mediates response of body to stress: speed up heart rate, increases BP, mobilizes body's energy stores for emergency and prepare for action (i.e. **fight or flight**)
- PN acts to conserve body's resource and restore homeostasis: slows heart, reduces BP and prepare body for relaxation or rest (i.e. **sleep, sex, sandwich**)

*Note: In sex, SN responsible for **orgasm** but PN responsible for **sexual stimulation**