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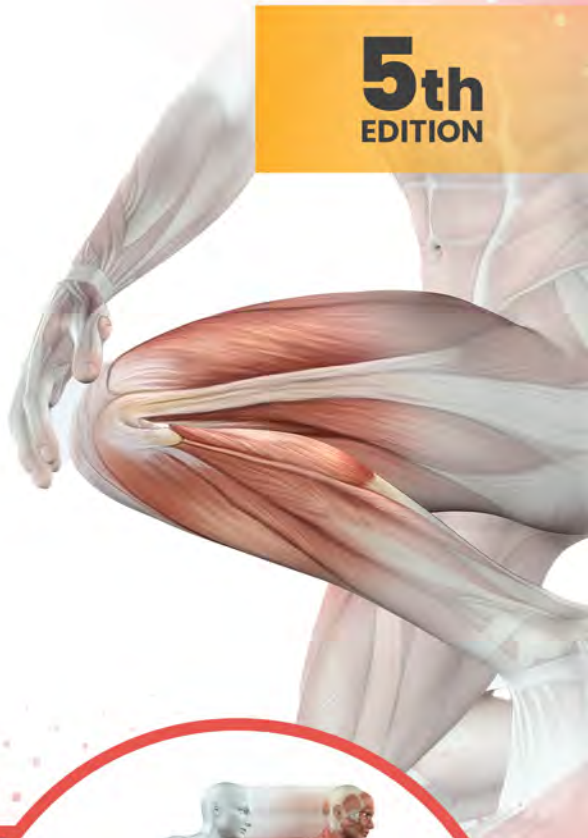
Physiology

5th EDITION

As per the New Pattern Exams (NEXT) with many Clinical Case-Based Questions

References and Updates from Ganong 26/e, Guyton 14/e, Harrison 21/e, Katzung 14/e



Papers/Questions Covered

- INI-CET - 2022 – 2020
- Recent Qs (Jan) 2022 – 2012
- AIIMS June 2020 – 2010
- Expected Clinical Case-Based Qs
- CBME-Based Subjective Qs with Chapter Reference

- Written and Compiled by a Leading Faculty and Subject Expert of Physiology
- Enriched with Recent/Latest Updates

Includes

1500+	100+	100+	500+
MCQs of Recent Exams	CBQs	IBQs	Illustrations/Images

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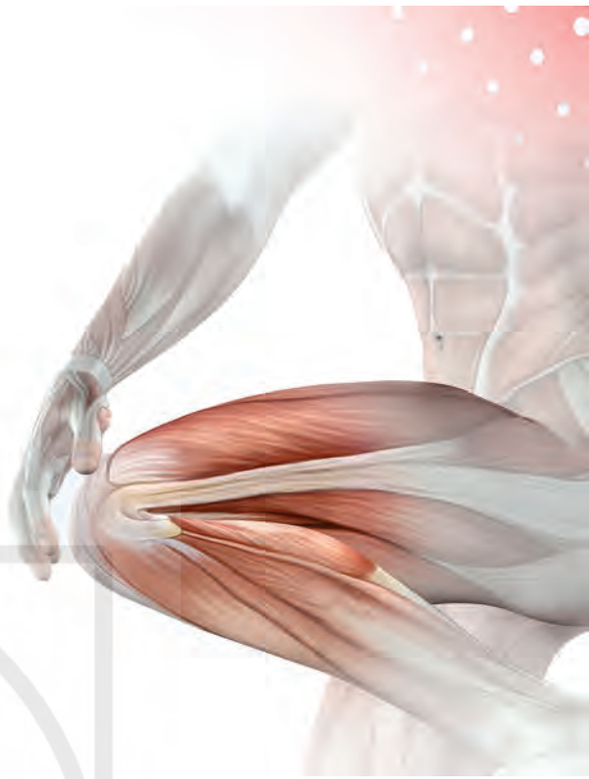

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Preface

Dear Students,

Gone are those days when you used to get repeated topics and your PG seat was secured. Now the time has changed in such a way that one needs to be thoroughly updated in all the topics as well as it is necessary to interrelate and integrate the information with other medical subjects to keep your preparation at par. Keeping in mind the need of the students and the necessary changes that are required in the present scenario, I have written this book covering all the major aspects of physiology and have integrated that information with other medical subjects.

Cardinal concepts of physiology are explained in simple and easy-to-understand language. At the end of every physiology topic, **clinical information** regarding the topic is highlighted in **separate boxes** so that in short term one can use the information to solve PGMEE MCQs and in long term, it helps in understanding the disease process and to effectively treat various diseases. Information repeatedly asked in PGMEE is given in **High Yield boxes**. For easy memorization, Mnemonics are given with the complex concepts. At the end of the book, the important topics that have been repeatedly asked in the PGMEE exams have been given separately in point-wise manner for the last-minute revision. A thorough reading of the book helps the students understand all the other relevant information related to other PGMEE subjects.

Finally, I wish, "This book would be the first book that all PG aspirants must read during their PG preparation and this book would be the last choice to revise before they appear for PGMEE."

Grasp the CRISP dear PG aspirants. Happy reading!

S Krishna Kumar
Email: tallboykk@gmail.com

Contents

CBME-Based Subjective Questions with Chapter References*

Competencies	Subjective Questions	For Answer Refer to Chapter
	General Physiology	
PY1.1	Describe the structure and functions of a mammalian cell	Chapter 2
PY1.2	Describe and discuss the principles of homeostasis	Chapter 1
PY1.3	Describe intercellular communication	Chapter 2
PY1.4	Describe apoptosis – programmed cell death	Chapter 2
PY1.5	Describe and discuss transport mechanisms across cell membranes	Chapter 1
PY1.6	Describe the fluid compartments of the body, its ionic composition and measurements	Chapter 1
PY1.7	Describe the concept of pH and Buffer systems in the body	Chapter 11
PY1.8	Describe and discuss the molecular basis of resting membrane potential and action potential in excitable tissue	Chapter 2
PY1.9	Demonstrate the ability to describe and discuss the methods used to demonstrate the functions of the cells and their products, their communications and applications in Clinical care and research.	Chapter 2
	Hematology	
PY2.1	Describe the composition and functions of blood components	Chapter 6
PY2.2	Discuss the origin, forms, variations and functions of plasma proteins	Chapter 6
PY2.3	Describe and discuss the synthesis and functions of hemoglobin and explain its breakdown. Describe variants of hemoglobin	Chapter 6
PY2.4	Describe RBC formation (erythropoiesis and its regulation) and its functions	Chapter 6
PY2.5	Describe different types of anemias and Jaundice	Chapter 6
PY2.6	Describe WBC formation (granulopoiesis) and its regulation	Chapter 6
PY2.7	Describe the formation of platelets, functions and variations.	Chapter 6
PY2.8	Describe the physiological basis of hemostasis and, anticoagulants. Describe bleeding and clotting disorders (Hemophilia, purpura)	Chapter 6
PY2.9	Describe different blood groups and discuss the clinical importance of blood grouping, blood banking and transfusion	Chapter 6
PY2.10	Define and classify different types of immunity. Describe the development of immunity and its regulation	Chapter 6
PY2.11	Estimate Hb, RBC, TLC, RBC indices, DLC, Blood groups, BT/CT	Chapter 6
PY2.12	Describe test for ESR, Osmotic fragility, Hematocrit. Note the findings and interpret the test results etc.	Chapter 6
PY2.13	Describe steps for reticulocyte and platelet count	Chapter 6
	Nerve and Muscle Physiology	
PY3.1	Describe the structure and functions of a neuron and neuroglia; Discuss Nerve Growth Factor and other growth factors/cytokines	Chapter 5
PY3.2	Describe the types, functions and properties of nerve fibers	Chapter 3
PY3.3	Describe the degeneration and regeneration in peripheral nerves	Chapter 3
PY3.4	Describe the structure of neuro-muscular junction and transmission of impulses	Chapter 4
PY3.5	Discuss the action of neuro-muscular blocking agents	Chapter 4
PY3.6	Describe the pathophysiology of Myasthenia gravis	Chapter 4
PY3.7	Describe the different types of muscle fibres and their structure	Chapter 4
PY3.8	Describe action potential and its properties in different muscle types (skeletal and smooth)	Chapter 4

**Important competency-based topics covered*

Contd...

1

CHAPTER

GENERAL PHYSIOLOGY

HOMEOSTASIS

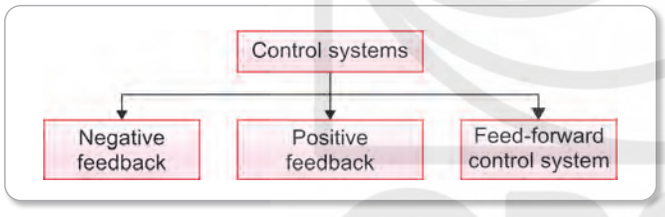
- Imagine what happens to our blood glucose levels after food intake. It rises but not indefinitely. It is immediately sensed by beta cells of pancreas and insulin is released, which brings back blood glucose to near normal levels. The concept here is **CONSTANCY**.
- All our body parameters have to be maintained at **NEAR NORMAL** levels. This concept of **CONSTANCY** is called **HOMEOSTASIS**. The term was coined long ago by **WALTER CANNON.**

Now what maintains it? Well yes, we have **control systems**.

CONTROL SYSTEMS

Negative Feedback

- In this type of control system, an **INCREASED** level of a particular parameter is immediately followed by its **DECREASE**.
- The classical example is blood pressure (BP) regulation by **BAROREFLEX.**
- Baroreceptors sense the increase in BP as they are **STRETCH RECEPTORS**. Once they sense it, impulse is sent to medulla, which to decreases the BP immediately as a part of the reflex, called baroreflex.
- The degree of effectiveness with which a control system maintains constant conditions is determined by the **GAIN** of the negative feedback.



Let us consider this example to understand the concept of GAIN recently tested in AIIMS exam.

A person is doing treadmill running. His systolic blood pressure rises to 180 mm Hg. On stopping the exercise, his systolic BP falls to 150 mm Hg immediately. What is the **GAIN** of this control system?

The formula for calculating gain is,

$$\text{Gain} = \frac{\text{Correction}}{\text{Error}}$$

Correction = 180 mm Hg – 150 mm Hg = 30 mm Hg
Error remaining = 150 mm Hg – 120 mm Hg = 30 mm Hg (120 mm Hg is the normal intended systolic BP)

So, Gain = 30/30 = 1

- Any system that leaves error is not 100% effective in preventing change. Imagine what would happen if the denominator becomes zero? The ratio becomes infinity. Such a principle is called **INFINITE FEEDBACK GAIN PRINCIPLE**.
- Another good example for negative feedback control system is **ENDOCRINE HORMONE REGULATION**. Remember Dexamethasone suppression test in Cushing's syndrome. Cortisol inhibits adrenocorticotropic hormone (ACTH). Thyroid hormones inhibit thyroid stimulating hormone (TSH) from anterior pituitary.

REMEMBER

KIDNEY displays infinite feedback gain principle in regulation of BP, which means it won't leave any error during correction of BP. It brings BP back to the exact previous value.

Positive Feedback

- **Most control systems operate by negative feedback and not positive feedback**.
- Imagine a person experiencing HEMORRHAGIC SHOCK. The amount of blood in the body is decreased to such a low level that enough blood is not available for the heart to pump effectively. This scenario results in weakening of the heart, leading to further diminished pumping, and a further decrease in coronary blood flow. This causes more weakness of the heart; the cycle repeats itself again and again, until death occurs.
- Positive feedback, once started, enhances or amplifies its effect on its own. That is why positive feedback is also called VICIOUS CYCLE. Shock is one example of positive feedback.

At times, positive feedback can be useful and the examples where it is useful were plenty of times asked in PGMEE.

Luteinizing Hormone (LH) Surge

- We discussed before that all endocrine hormone regulations falls under negative feedback. Remember "EXCEPTIONS are always the MCQs"… "What's UNIQUE what's DIFFERENT are always the MCQs"
- Only time where the endocrine hormone regulation comes under a positive feedback is LH surge and the hormone responsible is ESTROGEN.
- Exactly 24–36 hours before ovulation, estrogen increases the levels of LH and hence, it is considered as an example of positive feedback. **Remember LH surge is increasing levels of LH**. At one point, LH reaches its peak value, which is called LH PEAK and it happens 8–12 hours before ovulation.

REMEMBER

LH surge occurs 24–36 hours before ovulation. LH peak occurs 8 – 12 hours before ovulation

Entry of Calcium into Sarcoplasmic Reticulum of Muscle

- Another example for positive feedback is seen in muscle.
- Sarcoplasmic reticulum (SR) is the storehouse of calcium. This SR has a channel protein, which takes up calcium and is called Sarcoplasmic Reticulum Calcium ATPase (SERCA) pump. Once small amount of calcium enters SR using SERCA, it increases more calcium influx. and that's why it is considered positive feedback. **This phenomenon is entirely responsible for MUSCLE RELAXATION**.

- Also remember SR has a calcium channel which releases calcium called RYANODINE RECEPTOR and this channel protein is involved in MUSCLE CONTRACTION.

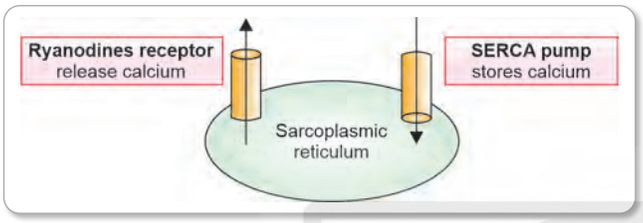


Fig. 1: SERCA Pump

Parturition

- Once labor is initiated, the uterine contractions dilate the cervix, which in turn sets up signals in afferent nerves that increases OXYTOCIN secretion.
- **The plasma oxytocin levels rise and cause further uterine contraction ultimately leading to the delivery of the fetus. The name of this positive feedback reflex seen during parturition is called FERGUSON's REFLEX.**

High Yield Point

Ferguson's reflex – positive feedback reflex seen during parturition because of oxytocin

Action Potential

- Opening of sodium channels during depolarization phase of action potential increases sodium influx leading to a sharp overshoot.
- The name of this positive feedback cycle is called **HODGKIN's CYCLE**.

Blood Coagulation

- Blood coagulation process is also called **COAGULATION CASCADE**.
- The word cascade simply means **AMPLIFICATION** of subsequent steps.
- When a blood vessel is ruptured, *clotting factors* are activated. Once activated, these factors activate remaining clotting factors ultimately leading to blood coagulation.

Mnemonic

Summary of the examples of positive feedback can be easily remembered with this mnemonic CCLASP.

- **C**lotting
- **L**H surge
- **S**hock
- **C**alcium entry into SR
- **A**ction potential
- **P**arturition

Feed-Forward Control

- Remember, in positive and negative feedback, we need a stimulus to get a response.
- However, there is a control system in our body in which no stimulus is required, yet the system ANTICIPATES and makes corrective changes. Such a system is called **Feed forward or Anticipatory or Adaptive Control.**

Examples of Feed-Forward Control

- **Cephalic phase of gastric secretion:** Just thinking about food increases gastric acid production.
- Thinking about exercise itself increases heart rate (anticipatory tachycardia) and respiratory rate.
- Role of cerebellum in motor coordination.
- When the temperature in skin falls, hypothalamus anticipates core internal body temperature is going to fall and send impulses to prevent core temperature from falling. Shivering is one important mechanism to generate heat when exposed to cold environment.

BODY FLUIDS

In a 70 kg adult man, body composition is as follows:

Component	Percentage of Body Weight (%)
Water	60
Protein	18
Fat	15
Minerals	7

So, maximum percentage contribution is always water. Now let's see how this water is distributed.

<table>
<tr><th colspan="3">Total Body Water (TBW) (60% of body weight), 42 liters</th></tr>
<tr><th>Intracellular Fluid</th><th colspan="2">Extracellular Fluid</th></tr>
<tr><td rowspan="2">2/3rd of TBW i.e., 40% body weight (28 liters)</td><td colspan="2">1/3rd of TBW, i.e., 20% body weight (14 liters)</td></tr>
<tr><td>Interstitial Fluid</td><td>Plasma</td></tr>
<tr><td></td><td>75% or 3/4th of ECF or 15% of body weight (10.5 liters)</td><td>25% or 1/4th of ECF Or 5% of body weight (3.5 liters)</td></tr>
</table>

Measurements of Body Fluid Volumes

The principle employed for this is called **INDICATOR DILUTION PRINCIPLE.**

Requirements

- We need a specific indicator.
- Amount of indicator injected must be known.
- Concentration of the indicator must be known.

The formula is,

$$\text{Amount} = \text{Concentration} \times \text{Volume}$$

We are interested in volume. So,

$$\text{Volume} = \text{Amount}/\text{Concentration}$$

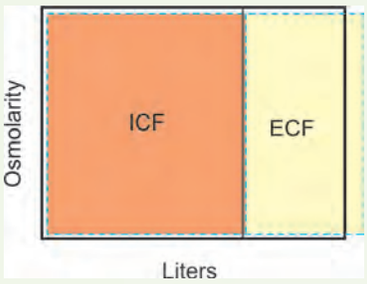


Fig. 5: Addition of Isotonic Fluid

Loss of Isotonic Fluid – Diarrhea

- ECF volume decreases, but no change occurs in the osmolarity of ECF or ICF.
- Plasma protein concentration and hematocrit increase.
- Arterial blood pressure decreases because ECF volume decreases.

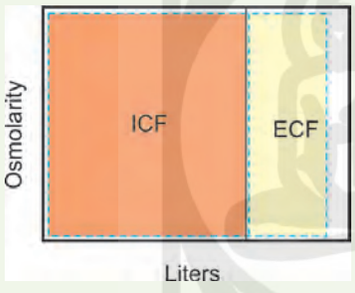


Fig. 6: Loss of Isotonic Fluid

Excessive Intake of NaCl

- The osmolarity of ECF increases because osmoles (NaCl) have been added to the ECF.
- Water shifts from ICF to ECF. As a result of this shift, **ICF osmolarity increases** until it equals that of ECF.
- As a result of the shift of water out of the cells, **ECF volume increases** and **ICF volume decreases.**

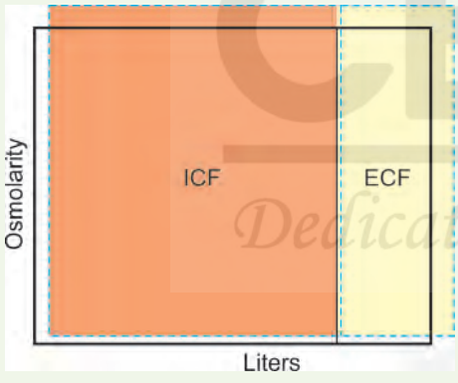


Fig. 7: Excessive Intake of NaCl

Addison's Disease – Loss of NaCl

- The osmolarity of ECF decreases. As a result of the lack of aldosterone, more NaCl is excreted by the kidney.
- ECF volume decreases because water shifts into the cells. As a result of this shift, **ICF osmolarity decreases** until it equals ECF osmolarity, and **ICF volume increases.**
- Plasma protein concentration and hematocrit increases because of the decrease in ECF volume.
- Arterial blood pressure decreases.

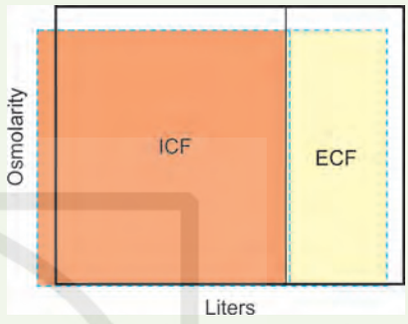


Fig. 8: **Addison's Disease – Loss of NaCl**

Diabetes Insipidus, Sweating in Hot Environment – Loss of Water

- The osmolarity of ECF increases because sweat is hyposmotic (relatively more water than salt is lost).
- ECF volume decreases because of the loss of volume in the sweat.
- Water shifts out of ICF; as a result of the shift, **ICF osmolarity increases** until it is equal to ECF osmolarity, and **ICF volume decreases.**

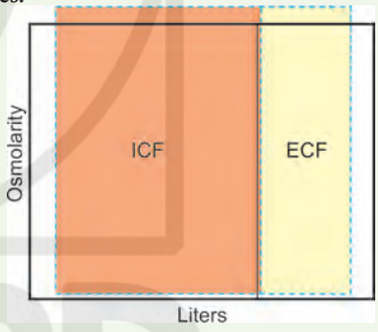


Fig. 9: Diabetes Insipidus

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)—Gain of Water

- The osmolarity of ECF decreases because excess water is retained.
- ECF volume increases because of the water retention.
- Water shifts into the cells; as a result of this shift, **ICF osmolarity decreases** until it equals ECF osmolarity, and **ICF volume increases.**

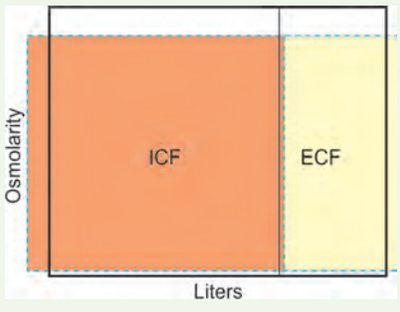


Fig. 10: SIADH

Clinical importance

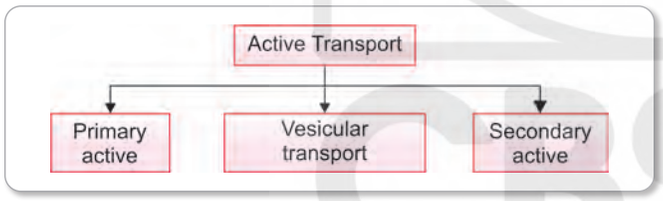
Clinical Example	ECF Volume	ICF Volume	ECF Osmolarity	ICF Osmolarity
Gain of isotonic NaCl-Saline infusion	Increase	No change	No change	No change
Loss of isotonic NaCl-Diarrhea	Decrease	No change	No change	No change
Excess intake of NaCl-Hypertension	Increase	Decrease	Increase	Increase
Loss of NaCl-Addison's disease	Decrease	Increase	Decrease	Decrease
Loss of water-Sweating	Decrease	Decrease	Increase	Increase
Gain of water-SIADH	Increase	Increase	Decrease	Decrease

Active Transport

Active transport processes utilize energy by hydrolysis of ATP (Universal energy currency of the cell).

Primary Active Transport

- In primary active transport, the energy is derived directly from breakdown of ATP.
- One of these ATPases is **sodium–potassium adenosine triphosphatase (Na^+, K^+ ATPase),** which is also known as the **Na^+, K^+ pump.**
- **Other examples are:**
  - H^+ K^+ ATPases in the gastric mucosa and the renal tubules.
  - Ca^{2+} ATPase pumps Ca^{2+} out of cells.
  - H^+ ATPases acidify many intracellular organelles, namely lysosomes.



Sodium Potassium ATPase Pump

- Na^+ K^+ pump uses the energy to move 3 sodium ions from inside to outside of the cell and moves 2 potassium ions from outside to inside.
- The coupling ratio is 3 : 2.
- It is an electrogenic pump which means it moves three positive charges out of the cell for each two that it moves in.
- It has 2 subunits and both the subunits are different. That is why it is called a **HETERODIMER**.
- The two subunits are α and β.
  - α subunits has intracellular and extracellular binding sites.
  - The intracellular portion of the α subunit has a Na^+- binding site **(1)**, a phosphorylation site **(4)**, and an ATP-binding site **(5)**.
- The extracellular portion has a K^+-binding site **(2)** and an ouabain-binding site **(3).**
- The β subunit is a glycoprotein, which has three extracellular glycosylation sites.

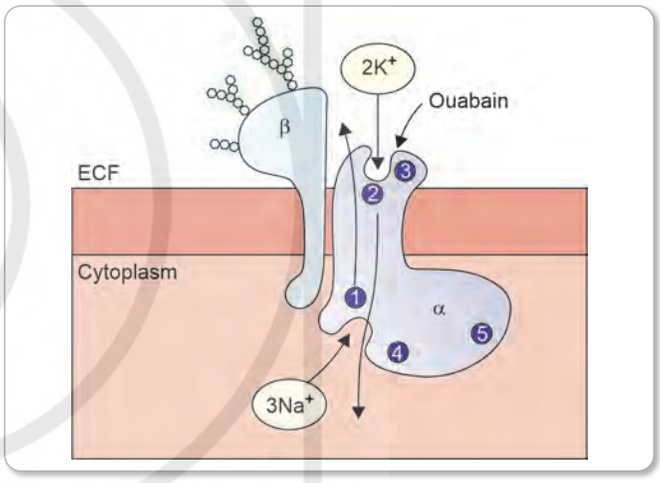


Fig. 1: Sodium Potassium ATPase Pump

Regulation of Na^+ and K^+ Pump

- Active transport of Na^+ and K^+ is one of the major energy using processes in the body.
- On an average, it accounts for about 24% of the energy utilized by cells, and in neurons it accounts for 70%.
- The major hormone, which maintains basal metabolic rate is **Thyroid hormone,** which does this function primarily by increasing the activity of Na^+ K^+ pump.
- **Aldosterone** increases Na^+ K^+ pump activity. Remember aldosterone is a steroid hormone with receptor in the nucleus. Few steroid hormones are recently found out to be having receptor in the cell membrane. This action of aldosterone, which increases Na^+ K^+ pump activity is its cell membrane receptor action.
- **Insulin** increases Na^+ K^+ pump activity.
- **Dopamine** in the kidney **inhibits** the pump by phosphorylating it, causing a natriuresis.
- Cardiac glycosides namely **ouabain, digoxin inhibit** the pump to enhance myocardial contractility. **Istaroxime** is an investigational steroid derivative that increases contractility by inhibiting Na^+/K^+-ATPase (like cardiac glycosides), but in addition appears to facilitate sequestration of Ca^{2+} by the sarcoplasmic reticulum.

Clinical Case-Based Questions

1. **A 59-year-old female is admitted to burns center following water heater blast at home. Loss of plasma volume is suspected. Which of the following indicator is useful to estimate plasma volume?**
   a. Inulin b. Mannitol
   c. Tritium d. Radiolabelled albumin
2. **A 49-year-old male who is a chronic alcoholic had a massive episode of hematemesis and got admitted in emergency care. His blood pressure is 70/50 mm Hg. Which of the following feedback mechanism operates during progressive stage of shock?**
   a. Negative feedback b. Feed Forward mechanism
   c. Positive feedback d. Anticipatory control
3. **A 50-year-old male complains of abdominal pain and got admitted. He is a known case of arthritic joint pain and taking NSAIDs for last one year. Pantoprazole is prescribed for his condition. This drug targets which transport process?**
   a. Simple diffusion b. Primary active transport
   c. Facilitated diffusion d. Secondary active transport
4. **A 60-year-old female presents with progressive dysphagia for the past 6 months. She had difficulty in swallowing solid foods. She also had loss of appetite and loss of weight. BOTOX injection administered for her treatment. This agent inhibits which transport process?**
   a. Transcytosis
   b. Endocytosis
   c. Pinocytosis
   d. Exocytosis
5. **A 12-year-old boy presented with an incidental finding of high blood glucose levels during routine screening. He was on Growth hormone treatment for the past few weeks. Intravenous insulin is administered for his treatment. Insulin moves glucose into cells by?**
   a. Simple diffusion
   b. Facilitated diffusion
   c. Exocytosis
   d. Endocytosis

Answers to Clinical Case-Based Questions

1. Ans. (d) Radiolabelled albumin

- Burns is usually associated with significant plasma loss
- Plasma volume is usually estimated by Evans blue dye, Radiolabelled albumin
- Plasma volume can also be calculated using the formula: Plasma Volume = Blood volume (1- Hematocrit)

2. Ans. (c) Positive Feedback

- Positive feedback is also called VICIOUS CYCLE
- During hemorrhagic shock, loss of blood flow to heart weakens cardiac muscle and progressive decrease in cardiac contraction.
- The cycle repeats itself again and again until death occurs, an example of positive feedback

3. Ans. (b) Primary active transport

- NSAIDs are known to cause peptic ulcer as side effect
- In gastric parietal cells, there is H^+ ATPase which is considered to be the proton pump and it is an example of primary active transport
- Other examples of primary active transport are Na K ATPase and Calcium ATPase
- Pantoprazole is a proton pump inhibitor

4. Ans. (d) Exocytosis

- Botulinum toxin is useful in treatment of Achalasia cardia
- It inhibits the release of acetylcholine by cleaving the SNARE proteins involved in its exocytosis
- Achalasia cardia is treated with Injections of botulinum toxin (Botox) directly into the Lower Esophageal Sphincter (LES) - blocks acetylcholine release that prevents smooth muscle contraction – leading to relaxation of LES

5. Ans. (b) Facilitated diffusion

- Growth Hormone is HYPERGLYCEMIC and DIABETOGENIC
- Insulin moves glucose into insulin sensitive cells like heart, skeletal muscle, adipose tissue using Glucose transporter GLUT-4
- GLUT-4 is an example of facilitated diffusion

Multiple Choice Questions

Homeostasis and Body Fluids

1. **Blood pressure regulation by baroreceptors is an example of:** *(Recent Question 2022)*
   a. Feed forward
   b. Positive feedback
   c. Negative feedback
   d. Adaptive control regulation
2. **A body fluid sample is being studied and has Na 10 mEq/L, K 140 mEq/L, CI 4 mEq/L. Identify the fluid compartment.** *(Recent Question 2021)*
   a. Interstitial b. ICF
   c. ECF d. Plasma
3. **A 30-year-old man weighing 70 kg had a sodium level of 120 meq/L. Calculate the sodium deficit.** *(Recent Question 2021)*
   a. 280 b. 480
   c. 840 d. 1400
4. **I-125 labelled albumin is used for measurement of:** *(AIIMS May 2019)*
   a. Plasma volume
   b. Interstitial fluid volume
   c. ICF
   d. ECF
5. **Which of the following is an example of feed forward mechanism?** *(AIIMS May 2019)*
   a. Increased blood pressure during supine posture
   b. Salivation on smelling food
   c. Shivering on exposure to cold environment
   d. None of the above
6. **You are an intern and want to determine the quantity of IV fluids needed for a patient. How much amount of transient loss/insensible loss per day would you account for in your calculations?** *(AIIMS Nov 2019)*
   a. 150–200 mL/day b. 200–350 mL/day
   c. 350–400 mL/day d. 500–600 mL/day
7. **A man weighing 60 kg has 45% hematocrit. What will be his plasma volume?**
   a. 2640 mL b. 3080 mL
   c. 3850 mL d. 3300 mL
8. **A muscular man weighing 70 kg has hematocrit of 45%, what would be his plasma volume:**
   a. 2310 mL b. 2695 mL
   c. 3080 mL d. 2890 mL
9. **Feed forward control system is employed during the regulation of:**
   a. Blood volume b. pH
   c. Temperature d. Blood pressure
10. **A man weighing 70 kg has a hematocrit of 45%. What would be his approximate plasma volume?**
    a. 2310 mL b. 2695 mL
    c. 2890 mL d. 3080 mL
11. **Which of the following is not mediated through negative feedback mechanism?**
    a. BP regulation b. Growth hormone release
    c. Thrombus formation d. ACTH release
12. **On changing position from lying down to standing, there is a drop in 10 mm of Hg in BP. Immediately he recovered by 8 mm Hg leaving behind 2 mm Hg. The gain for baroreceptor system for the control of BP is:**
    a. 2 b. 4
    c. 8 d. 10
13. **Total body water is:** *(Recent Question 2013)*
    a. 40% of body weight b. 20% of body weight
    c. 10% of body weight d. 60% of body weight
14. **Volume of ICF in body:** *(Recent Question 2012)*
    a. 0.2 × body weight b. 0.4 × body weight
    c. 0.6 × body weight d. 0.8 × body weight
15. **ECF is how much part of total body water?** *(Recent Question 2014)*
    a. One-third b. Half
    c. Two-third d. None
16. **ICF is:** *(Recent Question 2012)*
    a. 14 L b. 20% of body weight
    c. 28 L d. 33% of body weight
17. **Volume of interstitial fluid in a normal adult:** *(Recent Question 2015)*
    a. 5 L b. 10 L
    c. 15 L d. 20 L
18. **10 g mannitol was injected out of which 10% is excreted. After equilibrium, plasma conc. of mannitol is 50 mg/mL. Calculate ECF volume:**
    a. 10 L b. 18 L
    c. 42 L d. 52 L
19. **False about total body water (TBW):** *(Recent Question 2015)*
    a. ICF is 2/3rd of TBW
    b. In newborn TBW is 60% body weight
    c. Premature newborns have more TBW
    d. In adults, TBW is 60% of body weight
20. **Interstitial fluid volume can be determined by:**
    a. Radioactive iodine and radiolabeled water
    b. Radioactive water and radiolabeled albumin
    c. Radioactive sodium and radiolabeled water
    d. Radioactive sodium and radiolabeled albumin
21. **Plasma volume is measured by:** *(Recent Question 2015)*
    a. Inulin b. Evans blue
    c. Mannitol d. D_2O
22. **Most accurate measurement of extracellular fluid volume (ECF) can be done by using:** *(Recent Question 2012-13)*
    a. Sucrose
    b. Mannitol
    c. Inulin
    d. Aminopyrine
23. **Isotope used to measure RBC volume is:** *(Recent Question 2015)*
    a. Cr5l b. H3
    c. D_2O d. I^{135}
24. **All are seen more in ECF; Except:** *(Recent Question 2015)*
    a. Na^+ b. Cl^-
    c. Mg^{++} d. HCO_3^-

Homeostasis and Body Fluid

1. Ans. (c) Negative feedback

- Blood pressure regulation by baroreflex is a classical example of negative feedback
- Increase in BP is followed by a quick fall in BP

2. Ans. (b) ICF

Compartment	Major cation	Major anion
ECF	Sodium (Na^+)	Chloride (Cl^-)
ICF	Potassium (K^+)	Phosphates (PO_4^{2-})

3. Ans. (c) 840

- Sodium Deficit = 0.6 * Body weight* (Desired sodium – Actual sodium)
- Sodium Deficit = 0.6 * 70* (140–120) = 840

4. Ans. (a) Plasma volume

(Ref: Ganong 25th ed p.309)

Volume	Indicators
Total Body Water	Deuterium (most commonly used) Tritium Antipyrine
Extracellular fluid	Inulin (Gold standard substance) Sucrose Mannitol Sodium Thiosulphate
Plasma volume	Evans blue dye, ^{125}I-albumin
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume **= plasma volume/ (1– hematocrit)**
Interstitial fluid	Calculated as extracellular fluid volume – plasma volume
Intracellular fluid	Calculated as total body water – extracellular fluid volume

5. Ans. (c) Shivering on exposure to cold environment

(Ref: UMP, 4th ed RL Bijlani p.12)

- Feed forward control is also called anticipatory control
- Here body anticipates the change and employs corrective measures accordingly
- When the temperature in skin falls, hypothalamus anticipates core internal body temperature is going to fall and send impulses to prevent core temperature from falling
- Shivering is one important mechanism to generate heat when exposed to cold environment

6. Ans. (d) 500-600 mL/day

(Ref: Ganong 25th ed p. 4)

- Insensible water loss is the water loss that occurs through respiratory system, skin and feces
- It usually amounts to 500–600 mL/day

7. Ans. (a) 2640 mL

(Ref: Ganong 25th ed p. 3)

- Normal blood volume is 8% of body weight. So here it is 4.8 L
- Plasma volume = Blood volume (1-Hematocrit)
- Plasma volume = 4.8 (1–0.45) = 2640 mL

8. Ans. (c) 3080 mL

(Ref: Ganong 25th ed/p.3)

- Blood volume = plasma volume/(1 - hematocrit)
- So, Plasma volume = Blood volume * (1- hematocrit)
- Normal blood volume is 8 % of body weight. For 70 kg male it is 5.6 L
- Plasma volume = 5.6* (1 – 0.45)
- So, Plasma volume = 3080 mL

9. Ans. (c) Temperature

(Ref: UMP, 4th ed/RL Bijlani p.12)

- There is a control system in our body when no stimulus is required but still the system ANTICIPATES and makes corrective changes. Such a system is called Feed forward or Anticipatory or Adaptive Control

Examples of feed forward control

- Temperature control – Thermoregulatory responses are initiated by hypothalamus BEFORE the changes in environmental temperature have succeeded in changing the body's core body temperature
- Cephalic phase of gastric secretion- Just thinking about food increases gastric acid production
- Thinking about exercise itself increases heart rate and respiratory rate
- Role of cerebellum in motor coordination

10. Ans. (d) 3080 mL

(Ref: Ganong Review of medical physiology, 21st ed p.2)

- 8% of body weight is blood volume
- So, here for 70 kg man, Blood volume is 5.6 liters (70*8/100)
- Blood Volume = Plasma volume/1-hematocrit
- So, Plasma volume = Blood volume*(1-hematocrit)
- Here, Plasma volume = 5.6*(1-0.45) = 3080 mL

11. Ans. (c) Thrombus formation

(Ref: Guyton, 13th ed/p.7)

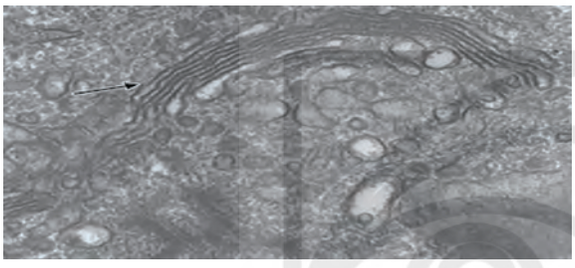
- Thrombus formation is an example of positive feedback
- Negative feedback - an INCREASED level of that particular parameter is immediately followed by a DECREASE
- Examples of negative feedback are:
  - Blood pressure regulation by **Baroreflex**
  - **Endocrine Hormone Regulation.**

"Characteristics and clinical importance of phospholipids"

Phospholipids	Membrane Asymmetry (Seen outside or inside)	Characteristics and Clinical Importance
Phosphatidylcholine (Lecithin)	Outside	• Most abundant phospholipids of the cell membrane • Especially seen in pulmonary surfactant (Dipalmitoyl lecithin) • Useful in assessment of fetal lung maturity – Amniotic fluid lecithin/sphingomyelin (L/S) ratio • (L/S) ratio ≥2 indicates lung maturity
Phosphatidylserine (PS)	Inside	• Exposure of PS to the outer surface of cell membrane – an important "eat me" signal for **apoptosis** • Annexin A5 assay is used to detect cells that have expressed PS on the outer cell surface. This assay distinguish viable cells from apoptotic cells • This inside to outside shift of PS is done by an enzyme called **Scramblase** • In platelets, outside exposure of PS serves as a procoagulant surface, which enhances blood clotting • Decreased scramblase activity leads to **Scott syndrome,** an inherited hemorrhagic disorder due to lack of PS exposure outside in platelets
Phosphatidylinositol	Inside	• Phosphatidylinositol is the precursor of second messenger IP_3 and DAG • Anchors certain membrane proteins called glycosylphosphatidylinositol (GPI) anchored proteins
Sphingomyelin	Outside	• Abundant in specialized areas of membrane called **Lipid rafts** • Lipid of myelin sheath – main insulator which fastens nerve conduction velocity • Deficiency of the enzyme **sphingomyelinase** leads to **Niemann-Pick disease** characterized by enlarged liver and spleen, mental retardation and fatal in early life • Red blood cells with increased sphingomyelin content in their outer side of cell membrane becomes **acanthocytes –** seen in **abetalipoproteinemia**
Cardiolipin (phosphatidylglycerol)	Inside	• "Signature phospholipid of mitochondria" • Abundant in inner mitochondrial membrane • Cardiolipin is involved in all the major functions of mitochondria namely ATP synthesis, Apoptosis • **Barth syndrome:** ▪ The enzyme involved in metabolism of cardiolipin is **Tafazzin.** ▪ If the gene encoding tafazzin is mutated, it leads to Barth syndrome characterized by dilated cardiomyopathy, skeletal muscle weakness, growth retardation and neutropenia ▪ It is an X linked recessive condition that affects only male • **Anti-cardiolipin antibodies:** ▪ Responsible for recurrent arterial or venous thrombosis, spontaneous abortion in **antiphospholipid antibody syndrome** ▪ Detected in serodiagnostic flocculation test for **syphilis** referred to as the **VDRL** (Venereal Disease Research Laboratory) test

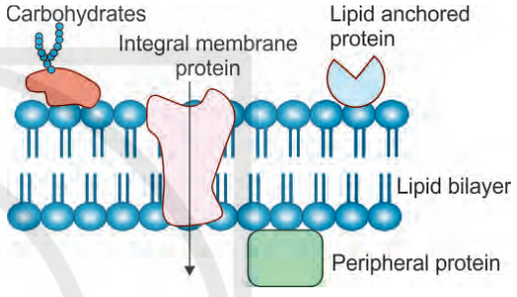
Image-Based Questions

1. In the electron micrographic picture given below, identify the organ marked with the arrow:



a. Cis golgi complex
b. Trans golgi complex
c. Smooth endoplasmic reticulum
d. Medial golgi complex

2. Component of cell membrane (inside red box) shown in this picture is:



a. Cholesterol
b. Phospholipid
c. Stearic acid
d. Palmitic acid

Answers to Image-Based Questions

1. Ans. (a) Cis golgi complex

(Ref: Ganong, 25th ed/p.44)

- Golgi has cis end and trans end.
- Cis end is the receiving end for synthesized proteins from endoplasmic reticulum.
- Once processed in Golgi, protein is stored in vesicles and delivered out through trans end.

2. Ans. (b) Phospholipid

(Ref: Ganong, 25th ed/p.35)

- Phospholipids are amphipathic.
- They are the most abundant lipids in cell membrane.

Clinical Case-Based Questions

1. **A 20-year-old female presents with bleeding episodes of unknown cause. She had normal coagulation profiles but abnormal platelet aggregation. Provisional diagnosis of Scott syndrome is made. This syndrome is because of defect in:**
   a. Scramblase b. Acid Lipase
   c. Trypsin d. Carboxy peptidase
2. **A 59-year-old male presents with fatigue and breathlessness. Lab investigation reveals anemia, thrombocytopenia and hyperbilirubinemia. Flow cytometry assay of CD 55 and CD 59 were performed. This disease affects which class of proteins in cell membrane?**
   a. Integral proteins b. Peripheral proteins
   c. Transmembrane proteins d. GPI anchored proteins
3. **A 55-year male admitted for work up of stroke like symptoms and convulsions. Patients' venous lactate levels were elevated. He is a known case of Type II diabetes mellitus. This disease affects:**
   a. Cell membrane
   b. Rough endoplasmic reticulum
   c. Lysosomes
   d. Mitochondria
4. **A 10-month-old baby presents with developmental delay and coarse facial features. Foamy cytoplasmic cell infiltrations are noted in the lung. Genetic testing reveals the diagnosis of I cell disease. This disease is due to deficiency of:**
   a. Phospholipase A2
   b. Protein Kinase G
   c. Phosphotransferase
   d. Chymotrypsin
5. **A 32-year-old male presents with acute pain in multiple joints. He had a history of gouty arthritis with frequent attacks in the past 5 years. Colchicine is prescribed for his condition. This drug targets:**
   a. Microtubules
   b. Microfilaments
   c. Intermediate filaments
   d. Tonofilaments

Answers to Clinical Case-Based Questions

1. Ans. (a) Scramblase

- In platelets, outside exposure of Phosphatidyl Serine (PS) serves as a procoagulant surface which enhances blood clotting
- Decreased scramblase activity leads to **Scott syndrome**, an inherited hemorrhagic disorder due to lack of PS exposure outside in platelets

2. Ans. (d) GPI anchored proteins

- Lipid-anchored proteins attached to the external surface of the plasma membrane are covalently linked to glycosylphosphatidylinositol (GPI)
- They are also called GPI anchored proteins.
- Examples of such proteins are CD 55 and CD 59
- Lack of CD 55 and CD 59 leads to **Paroxysmal Nocturnal Hemoglobinuria(PNH)**

3. Ans. (d) Mitochondria

- MELAS stands for Mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes
- May present only as diabetes mellitus
- It is a mitochondrial disorder
- The organs particularly affected are the ones with high metabolic requirements

4. Ans. (c) Phosphotransferase

- The enzyme of Golgi apparatus which adds Mannose 6 phosphate is called phosphotransferase
- Proteins with Mannose 6 phosphate tagging will be delivered to lysosomes
- Deficiency of phosphotransferase leads to a disease called **I cell disease**

5. Ans. (a) Microtubules

- **Colchicine** inhibits the function of microtubules by depolymerizing them
- This action inhibits the movement of neutrophils and suppresses inflammation
- This drug is useful in treatment of Gouty arthritis

3

CHAPTER

PHYSIOLOGY OF NERVE FIBERS

Absolute Refractory Period

- Corresponding to the period from the time the firing level is reached until repolarization is about one-third complete.
- No stimulus, no matter how strong, will not excite the nerve during absolute refractory period.

Relative Refractory Period

- Begins from the remaining part of repolarization to the end of action potential.
- Stronger than normal stimulus (suprathreshold stimulus) produces action potential in relative refractory period.

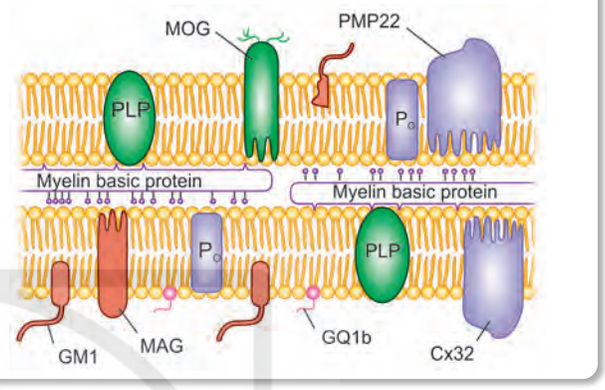
Effects of the ionic concentration changes on membrane potential

Effect	Consequences
Hyponatremia	• Has no effect on resting membrane potential. • Mainly it **decreases the size** of action potential because sodium ions are responsible for the upstroke phase of action potential.
Hyperkalemia	• Have major effects on resting membrane potential. • If extracellular K^+ ions are more, they hamper the normal diffusion of K^+ from inside to outside of cell. So, more of K^+ tends to stay inside the cell. • Since K^+ is a positively charged ion it moves the resting potential closer to the threshold for eliciting an action potential, thus the neuron becomes **more excitable.**
Hypokalemia	• If extracellular K^+ ions are less, they make the gradient more favorable for K^+ to diffuse out of the cell. • Since more K^+ ions are leaving the cell, the membrane potential is reduced and the neuron is **hyperpolarized.**
Hypocalcemia	• Calcium ions are membrane stabilizers. • A decrease in extracellular Ca^{2+} concentration increases the excitability of nerve by decreasing the amount of depolarization necessary to produce the action potential. **Hyperexcitability** is seen.
Hypercalcemia	• An increase in extracellular Ca^{2+} concentration can stabilize the membrane by **decreasing excitability**.

Conduction of Action Potential in Nerve Fibers

- This property is primarily determined by the presence or absence of **Myelin**.
- Nerve fibers can be myelinated or unmyelinated. Myelinated nerve fibers conduct the impulse fast and unmyelinated nerve fibers conduct the impulse slowly.

The molecular architecture of myelin sheath



MYELIN

- Myelin insulates nerve fibers and fastens conduction of impulses.
- Myelin speeds impulse conduction by permitting action potentials to jump between naked regions of axons called nodes of Ranvier. Such a type of nerve conduction is called **Saltatory conduction.**
- Myelin is a lipid protein complex.
- Myelinated nerve membrane is unique in that it is the only membrane where lipid content is more (80%) as compared to proteins (20%).

Clinical importance of myelin proteins

Myelin Proteins	Clinical Importance
CNS specific Myelin Proteins	
Myelin Basic Protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG)	• Autoantibodies are directed against these proteins in a demyelinating disorder **multiple sclerosis**
Proteolipid Protein (PLP)	• Mutations in **Proteolipid Protein (PLP)** causes **Pelizaeus-Merzbacher disease-** an-linked recessive demyelinating disorder characterized by spasticity, seizures and dementia
Peripheral Nervous System Specific Myelin Proteins	
P Zero protein (P_0)	• Mutation in **P Zero protein (P_0)** leads to a sensory neuropathy Charcot-Marie-Tooth disease (CMT) type 1B
Peripheral myelin protein 22 (PMP22)	• Mutations in **PMP22** leads to, ▪ **Charcot-Marie-Tooth disease (CMT) type 1A** ▪ **Hereditary liability to pressure palsies -** an autosomal dominant disorder characterized by pressure-related mononeuropathies

Contd...

Myelin Proteins	Clinical Importance
Myelin Proteins Common to Both CNS and PNS	
Myelin ganglioside GQ1b	• Mutations in GQ1b leads to **Fisher variant of Guillain-Barre Syndrome (GBS)** characterized by demyelination, ataxia, ophthalmoplegia, areflexia and anti-GQ1b antibodies
Myelin-Associated Glycoprotein (MAG)	• Affected in peripheral neuropathies associated with monoclonal gammopathies

REMEMBER

- Myelin is formed by oligodendrocytes in central nervous system.
- Myelin is formed by Schwann cells in peripheral nervous system.

- Oligodendrocyte can myelinate multiple neurons at a time but Schwann cell can myelinate only one neuron at a time.
- Myelin is present throughout the nerve fibers except at Nodes of Ranvier.

REMEMBER

Myelin Figures

- Seen in ischemic cell injury. They are the degenerating cell membrane accumulating in cytoplasm or extracellular.

Luxol Fast Blue

- This is a special stain for staining myelin sheath. This stain has high affinity for phospholipids of myelin sheath.

FACTORS AFFECTING NERVE CONDUCTION VELOCITY

- Important factors that determine the velocity of propagation of action potentials are:
  - Axon diameter
  - Myelination
  - Temperature
- Axon diameter
  - Increases in axon diameter increase conduction velocity by decreasing the longitudinal resistance so that local currents can spread further.
- Myelination
  - Myelinated fibers have high conduction velocity because myelination reduces membrane capacitance.
- Temperature
  - Decrease in temperature decreases nerve conduction velocity.
  - In low temperatures, the amount of current required to generate an action potential increases.

CLASSIFICATION OF NERVE FIBERS

- Erlanger and Gasser classified nerve fibers into three types as: A, B and C based on their diameter, degree of myelination and conduction velocities. The classification is for both sensory and motor nerve fibers. The classification is as follows:

Fiber Type	Myelin Present or Absent	Diameter (μm)	Conduction Velocity (m/s)	Functions
A α	Myelinated	12–20 **(Largest)**	70–120 **(Highest)**	Proprioception; somatic motor
A β	Myelinated	5–12	30–70	Touch, pressure
A γ	Myelinated	3–6	15–30	Motor to muscle spindles
A δ	Myelinated	2–5	12–30	Pain, temperature
B	Myelinated	<3	3–15	Preganglionic autonomic
C, dorsal root	Unmyelinated	0.4–1.2 **(Smallest)**	0.5–2 **(Lowest)**	Pain, temperature
C, Sympathetic	Unmyelinated	0.3–1.3	0.7–2.3	Postganglionic sympathetic

- There is a classification by name Lloyd classification only for sensory nerve fibers. It is as follows:

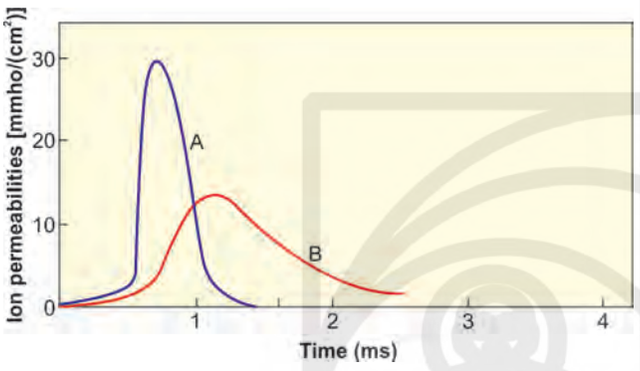
Number	Origin	Fiber Type
Ia	Muscle spindle, annulo spiral ending	A α
Ib	Golgi tendon organ	A α
II	Muscle spindle, flower spray ending, touch pressure	A β
III	Pain and cold receptors	A δ
IV	Pain and temperature receptors	C

Relative Susceptibility of Mammalian A, B, and C Nerve Fibers to Conduction Block Produced by Various Agents

Susceptibility to	Most Susceptible	Intermediate	Least Susceptible
Hypoxia	B	A	C
Pressure	A	B	C
Local anesthetics	A	B	C

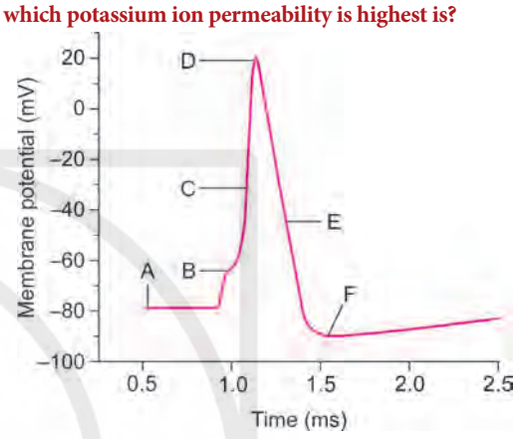
Image-Based Questions

1. Identify the ions based on conductance graph of a neuron shown below:



a. Na, k
b. K, Na
c. Na, Ca
d. Ca, Na

2. In this diagram depicting nerve action potential, point at which potassium ion permeability is highest is?



a. Point A
b. Point B
c. Point D
d. Point F

Answers to Image-Based Questions

1. Ans. (a) Na, k

(Ref: Ganong's Review of Medical Physiology, 25th ed., ch-4, p.91)

- During depolarization- Sodium ion current rises
- Later during repolarization – potassium ion current rises

2. Ans. (d) Point F

(Ref: Ganong, 25th ed/p.90)

- During the action potential, potassium ion permeability is highest during the hyperpolarization phase which is point F in the diagram
- Also note that point C is rapid depolarization phase where sodium ion permeability is highest. Exactly at point D, membrane potential approaches sodium ion's equilibrium potential and depolarization phase comes to an end

Clinical Case-Based Questions

1. **A 40-year-old female was rushed to the emergency department with an episode of convulsions at home. She is a known case of generalized tonic clonic seizure and was on phenobarbital therapy. This drug influences which phase of neuronal action potential?**
   a. Depolarization b. Repolarization
   c. Hyperpolarization d. Latent period
2. **A 59-year-old male was found unconscious in the road side and admitted to emergency medical services. ECG shows ventricular tachycardia at a rate of 140. His potassium level is 8.7 mmol/L. High extracellular potassium makes the membrane?**
   a. More excitable b. Less excitable
   c. Hyperpolarization d. Doesn't affect excitability
3. **A 55-year female admitted with complaints of palpitation, tremor, and weight loss and numbness. Trousseau and Chvostek signs were positive. Blood chemistry showed low serum corrected calcium level (7.3 mg/dL). A decrease in extracellular calcium?**
   a. Decreases the excitability of nerve
   b. Increases the excitability of nerve
   c. No change in excitability
   d. Increases the threshold to fire action potential
4. **A 25-year-old female presents with difficulty in reading, clumsiness using her arms while driving and fatigue. MRI study revealed demyelination in major brain areas. Which of the following cells are involved in this disease process?**
   a. Astrocytes
   b. Microglia
   c. Oligodendrocytes
   d. Chandler cells
5. **A 20-year-old male while practising long jump had a cut in his forearm because of spikes in his shoes during jumping. Suturing was done using local anesthetic lignocaine. This drug blocks which channels?**
   a. Calcium channels
   b. Potassium channels
   c. Chloride channels
   d. Sodium channels

Answers to Clinical Case-Based Questions

1. Ans. (c) Hyperpolarization

- GABA is the major inhibitory amino acid neurotransmitter of brain.
- It produces inhibition by causing hyperpolarization
- GABA agonist like phenobarbital is useful in management of epilepsy

2. Ans. (a) More excitable

- If extracellular K^+ ions are more, they hamper the normal diffusion of K^+ from inside to outside of cell. So, more of K^+ tend to stay inside the cell
- Potassium ions are positive and the inside of cell is depolarized and it makes the membrane more excitable and more prone to arrythmia

3. Ans. (b) Increases the excitability of nerve

- Calcium ions are membrane stabilizers
- Low calcium levels lead to opening of sodium channels more frequently
- This increases the frequency of action potential firing leading to HYPEREXCITABILITY

4. Ans. (c) Oligodendrocytes

- Autoantibodies are directed against proteins like myelin basic protein, myelin oligodendrocyte glycoprotein in a demyelinating disorder multiple sclerosis
- This disorder is characterized by decrease in nerve conduction velocity
- OLIGODENDROCYTES are the major cells that are involved in myelination in CNS

5. Ans. (d) Sodium channels

- A delta and C fibers are involved in pain transmission
- This transmission pathway involves voltage-gated sodium channels
- Local anesthetic agents, like lignocaine blocks such sodium channels

Clinical importance of neuromuscular junction

Neuromuscular Junction in Microbiology

Botulinum Toxin

- *C. botulinum* inhibits the release of acetylcholine by cleaving the SNARE proteins involved in its exocytosis.
- Botulinum toxin has been "weaponized" by governments and terrorist organizations-Bioterrorism.
- The toxins are of seven types (A, B, C, D, E, F, and G).
- Toxins A and E cleave SNAP-25.
- Toxins B, D, F and G cleave Synaptobrevin.
- Toxin C cleaves Syntaxin.
- Since acetylcholine is not released from nerve terminals, the effect seen is flaccid paralysis.
- Since botulinum toxin inhibits the release of acetylcholine, it is useful in conditions characterized by excessive muscle contraction. It is available in the form of BOTOX.

Neuromuscular Junction in Forensic Medicine

Organophosphate Poisoning

- They are acetylcholineesterase inhibitors. They amplify all actions of acetylcholine.
- They are highly effective as insecticides. The agents are **parathion, malathion**.
- They are well absorbed from the skin, lung, gut, and conjunctiva.
- Central nervous system toxicity is an important component of poisoning with these agents
- Organophosphate poisoning is usually treated with muscarinic antagonist atropine and choline esterase activator namely pralidoxime.
- Tabun, sarin, soman are the acetylcholine esterase inhibitors used as nerve agents during war fares.

Neuromuscular Junction and Diseases

Myasthenia Gravis (MG)	Lambert Eaton Myasthenia Syndrome (LEMS)
• An autoimmune disease due to auto-antibodies directed against nicotinic acetylcholine receptors (AChRs). It is a post synaptic disorder • Due to antibody mediated destruction of receptors, there is decrease in number of AChRs • The cardinal features are weakness and fatigability of muscles but deep tendon reflexes are preserved • The amount of ACh released per impulse normally declines on repeated activity. It is the reason behind **decremental response** seen in repeated nerve stimulation in myasthenia gravis called **myasthenic fatigue** • The protein responsible for clustering of AChRs is called **muscle-specific kinase (MuSK)**. Anti-MuSK antibody occurs in about 40% of patients without AChR antibody • Another protein called **low-density lipoprotein receptor related protein 4 (lrp4)** is also involved in clustering of AChRs. Antibodies against lrp4 are also seen in myasthenia gravis • Thymus appears to play role in generation of these auto antibodies. Thymectomy offers long-term benefits in patients affected by myasthenia gravis • Medical management includes anticholinesterase drugs namely pyridostigmine and immunosuppressive agents like glucocorticoids, azathioprine, cyclosporine, and rituximab are also useful	• LEMS is a presynaptic disorder involving • LEMS is caused by autoantibodies directed against P/Q-type calcium channels at the motor nerve terminals • It is distinguished from myasthenia gravis by two important reasons. One, LEMS has depressed or absent reflexes and two, high frequency repetitive nerve stimulation causes incremental response in LEMS. • Many patients with LEMS have an associated malignancy, most commonly small-cell carcinoma of the lung • Treatment involves pyridostigmine and 3,4-Diaminopyridine (3,4-DAP). This drug 3,4-DAP acts by blocking potassium channels which results in prolonged depolarization of the motor nerve terminals and thus enhances ACh release

Calcium Ions – Couples Excitation to Contraction

- Calcium ions are responsible for muscle contraction.
- Calcium ion movement in skeletal muscle is regulated by a structure in muscle called **sarcotubular system.**
- Sarcotubular system has two tubules namely T tubule and L tubule.

- T tubules are present in the sarcolemma (plasma membrane of muscle) and L tubules are the sarcoplasmic reticulum (smooth endoplasmic reticulum of muscle) which stores and release calcium called terminal cisterns located at the junction of A and I band.
- One T tubule is surrounded by two L tubules. This classical arrangement is called **Triad** in skeletal muscle.
- T tubules have a calcium channel called **dihydropyridine receptors (DHPR).** In response to muscle depolarization, DHPR acts as voltage sensors and makes physical interaction with another calcium channel present in sarcoplasmic reticulum called **ryanodine receptor (RyR)**.

High Yield Points

- T tubules - **Dihydropyridine receptors (DHPR)**
- Sarcoplasmic reticulum - **Ryanodine receptor (RyR)**

- **This physical interaction between dihydropyridine receptors and ryanodine receptor (RyR) releases calcium from sarcoplasmic reticulum which causes muscle contraction**.

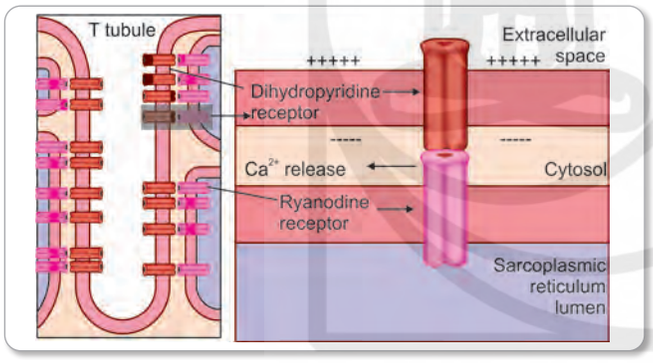


Fig. 3: Process of muscle contraction

Muscle calcium channels and their importance

Dihydropyridine Receptors (DHPR)	Ryanodine Receptor (RyR)
• Certain drugs namely amlodipine, nifedipine and nicardipine are DHPR calcium channel blockers are used to treat hypertension	• **Malignant hyperthermia:** • An autosomal dominant disease due to mutations in ryanodine receptor • This mutation releases excess calcium from sarcoplasmic reticulum leading to excessive muscle contraction and increased body temperature • The disease is usually treated using ryanodine receptor blocker **dantrolene** • The disease is usually triggered by neuromuscular blocking drug succinylcholine

Skeletal Muscle–the Contraction Part

- Once calcium ions are released from sarcoplasmic reticulum, they immediately bind with the troponin subunit troponin C.
- At rest, myosin binding site in actin is covered by troponin I and troponin. Also at rest, the myosin head contains tightly bound adenosine phosphate (ADP).
- Binding of calcium with troponin C causes a conformational change by removing troponin I and troponin T and exposes the myosin binding site in actin.
- Now myosin is free to interact with actin forming cross bridges.
- Upon formation of the cross-bridge, ADP is released, causing a conformational change in the myosin head that moves the thin filament relative to the thick filament, comprising the cross-bridge "power stroke". This sliding of microfilaments is the basis of **sliding filament theory** of muscle contraction.
- After a power stroke, ATP binds to the myosin head. Whenever ATP binds to myosin head, it gets detached from actin.
- Myosin head has ATPase activity which hydrolyses the ATP to ADP and inorganic phosphate.
- Now the myosin head with ADP starts the next cycle.
- As long as Ca^{2+} remains elevated and sufficient ATP is available, this cycle repeats.

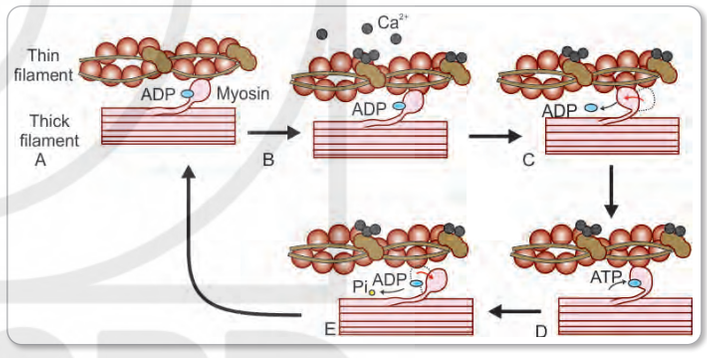
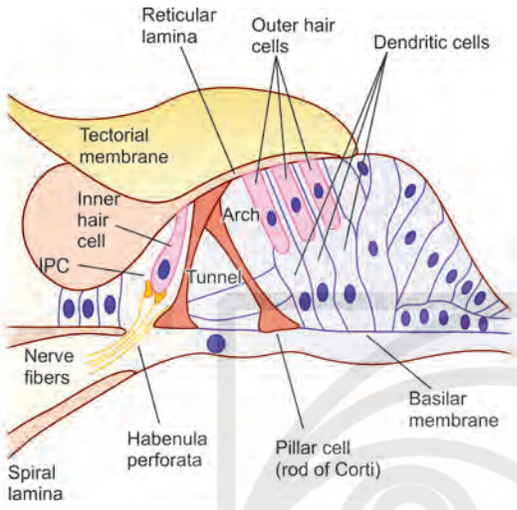


Fig. 4: Sliding filament theory

Rigor mortis

- When ATP is not available, myosin **heads continue binding with the active sites of actin proteins via** adenosine diphosphate **(ADP), and the muscle is unable to relax. Such sustained contraction is seen after death of an individual**.
- Also called postmortem stiffening or cadaveric rigidity.
- Rigor Mortis mostly helps to know the time since death. In general it is apparent in about 1–2 hours after death, gets well-established in the entire body in about 9–12 hours. It is maintained for about 12 hours and then gradually passes off in the same order as it appeared.
- According to **Nysten's rule,** "Cadaveric rigidity affects successively the masticatory muscles, those of the face and neck, those of the trunk and arms, and finally those of the lower limbs".
- **The disappearance of rigor follows** the same fashion as its appearance.



Organ of Corti:

- Contains the receptors for hearing -Hair cells.
- The hair cells are arranged in four rows: *three rows of outer hair cells which are 20,000 in number and one row of inner hair cells which are 3,500 in number).*
- Spiral ganglion contains the cell bodies of the sensory neurons that innervate these hair cells.
- 95% of these sensory neurons innervate the inner hair cells; only 5–10% innervate the outer hair cells.
- Most importantly, outer hair cells receive more of efferent from central areas concerned with hearing.

Role of Basilar Membrane in Hearing Process–The Frequency Analyzer

- Sound waves produce vibrations of the basilar membrane.
- The basilar membrane is thin at the apex of the cochlea but thicker and tauter toward the base.
- **High-frequency sounds** vibrates basilar membrane best near the base of the cochlea, while **low-frequency sounds** vibrates basilar membrane best near the apex of the cochlea–This aspect of basilar membrane gives it the name "**The frequency analyzer".**
- This gives the appearance of a **traveling wave** in basilar membrane–This theory is called **traveling wave theory of von Békésy.**

Role of Hair Cells in Inner Ear

- Hair cells are the sensory receptors of hearing.
- The resting membrane potential of the hair cells is about –60 mV.
- Hair cells have a motor protein namely **prestin.**
- Hair cells have a common structure–The tallest hair cell is called Kinocilium and the progressively shorter hair cells are called Stereocilia.
- These hair cells are connected together by **tip links** which has **mechanically sensitive cation channels.**
- When the entire hair cells bend toward the tallest one, these channels open leading to influx of potassium (mainly). This causes depolarization and activation. Hair cells in inner ear are unique in the sense that their depolarization is due to potassium ion.
- When all the hair cells bend away from the tallest one, these channels close leading to inhibition.

Hair Cells in Inner Ear–Clinical Importance

Drugs that cause color vision abnormalities:

Hair Cells and Pharmacology Drugs That Cause Ototoxicity	
Drug	**Mechanism of Ototoxicity**
Aminoglycoside antibiotics: Neomycin, kanamycin and amikacin	Disruption of protein synthesis in hair cells
Loop diuretics: Ethacrynic acid, furosemide	Changes permeability of hair cells
Anti-cancer drugs - Cisplatin, carboplatin	Disrupts hair cells metabolism
Aspirin	Damages outer hair cells
Quinine	Damages outer hair cells

Hair cells and ENT

Electrocochleography

- It is the technique of recording electrical potentials generated in the inner ear.
- The potential recorded is called cochlear microphonics.

Cochlear Microphonics

- It is the alternating current potential produced mainly by outer hair cells.
- Produced due to acoustic stimulation of basilar membrane leading to flow of potassium ions through hair cells.
- It is absent in the part of cochlea where outer hair cells are damaged.

Otoacoustic Emissions (OAEs)

- Related to the amplification function of the cochlea.
- Mainly generated by outer hair cells whose function is to amplify sound vibrations entering the inner ear from the middle ear.
- First demonstrated experimentally by David Kemp. Also called Kemp waves.
- They can be spontaneous or evoked.
- Otoacoustic Emissions (OAE) testing is the simple, non-invasive test for hearing defects in newborn babies and in children.

Mnemonic

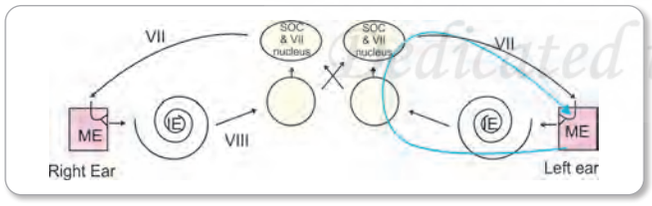
"Auditory pathway can be easily remembered with the help of a very familiar mnemonic E COLI MA"

Structure	Characteristics
Eighth nerve	• Carries the afferent auditory information
Cochlear nuclei	• 95% of fibers in cochlear nuclei are myelinated fibers that receive input from inner hair cells • Small number (5%) of unmyelinated fibers receives input from outer hair cells
Superior **O**livary nucleus	• Receives information from both the ears (bilateral) • Helps in localization of sound and the direction from which the sound comes • Also send efferent to outer hair cells in the form of **olivocochlear bundle** modulates the sensitivity of these hair cells and blocks background noise
Lateral lemniscus	• Projects auditory information to inferior colliculus
Inferior colliculus	• All auditory pathways ascending through the brain stem converge in inferior colliculi • Helps in localization of sound and the direction from which the sound comes
Medial geniculate body	• Thalamic nuclei for hearing • Projects to auditory cortex
Auditory cortex	• Location - superior temporal gyrus of the temporal lobe • Also called **Heschl gyrus** • Tonotopic organization - low tones are represented anterolaterally and high tones posteromedially • **Planum temporale**–Part of auditory cortex involved in language related auditory processing. It is larger in the left hemisphere

Protection of Ear from Damage Induced by Loud Sounds

Stapedial Reflex

- Afferent–VIII cranial nerve.
- Center–Superior olivary complex.
- Efferent–VII cranial nerve.
- To protect the cochlea from damaging vibrations.
- To mask low-frequency sounds.
- Reduce the intensity of lower-frequency sound transmission by 30–40 decibels.
- Because of contraction of the tensor tympani and stapedius muscles.
- Also called tympanic reflex or attenuation reflex.
- Reaction time is 40–160 ms.



Balance (Equilibrium)

Balance is maintained by **vestibular apparatus** that includes two important structures in inner ear namely,

- Semicircular canals.
- Otolith organs namely **saccule** and **utricle**.

Semicircular Canals

- **Mainly respond to head rotation**.
- These superior, lateral and posterior semicircular canals are perpendicular to each other - oriented in the three planes of space.
- Contain the receptor Hair cells located in **crista ampullaris** which are innervated by vestibular division of the eighth cranial nerve.
- Surrounded by gelatinous partition called **cupula**.

Otolith Organs

- **Mainly respond to changes in gravity and head tilt**.
- Are saccule and utricle.
- The sensory epithelium of these organs is called the **macula,** which are innervated by vestibular division of the eighth cranial nerve.
- Here hair cells are embedded in crystals of calcium carbonate called the otoliths.

Central Vestibular Pathways

- The cell bodies of the neurons supplying the cristae and maculae on each side are located in the vestibular Nuclei which have four parts.

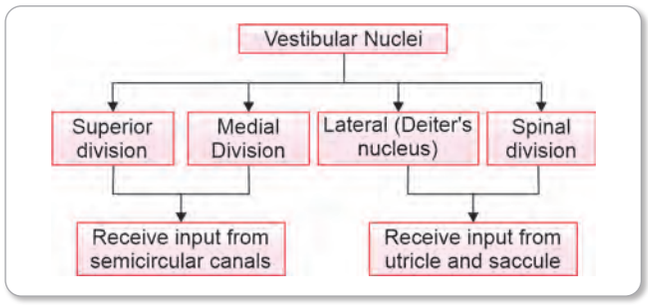


Fig. 10: Vestibular nuclei

Sign	Upper Motor Neuron	Lower Motor Neuron
Atrophy	None	Severe
Fasciculations	None	Common
Tone	Spastic	Decreased
Distribution of weakness	Pyramidal/regional	Distal/segmental
Muscle stretch reflexes	Hyperactive	Hypoactive/absent
Babinski sign	Present	Absent

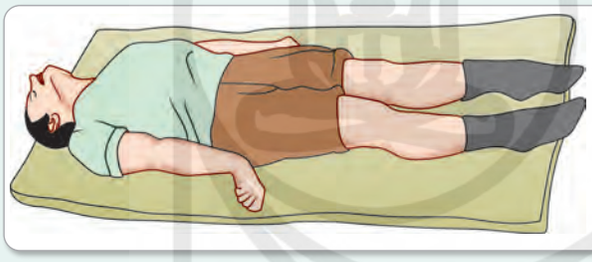
- Now, let's disturb the hierarchy. Let's see what will happen if there is lesion in the control centers.

Decerebration and decortication

Decerebration

- **Meaning:** A complete transection of the brain stem between the superior and inferior colliculi
- **Effect:** Brain stem pathways beginto function independently. They are no longer under cortical control

Decerebrate rigidity



In decerebrate rigidity,

- Lower extremities are extended
- Toes pointed inward
- Upper extremity is extended
- Fingers flexed and the forearms pronated
- Neck and head are extended.

Lessons learnt from decerebration:

- After decerebration, influence of corticospinal and rubrospinal tract on lower brain stem pathways is lost
- Hyperactivity in extensor muscles - mainly due to excitatory reticulospinal pathway

What activates this reticulospinal pathway?

- Dorsal sensory roots from muscle spindles activate reticulospinal pathway
- In turn, reticulospinal pathway activates gamma motor neurons leading to facilitation of stretch reflex and decerebrate rigidity
- Cortical motor areas inhibit stretch reflex. Once their influence is lost in decerebration, there is facilitation of stretch reflex
- Proof - removal of dorsal roots to a limb immediately eliminates the hyperactivity of extensor muscles

What will happen when anterior lobe of the cerebellum is removed in a decerebrate animal?

- There is exaggeration of extensor muscle hyperactivity. This is called **decerebellate rigidity**.
- Removal of dorsal roots to a limb **does not** eliminate the hyperactivity of extensor muscles here.
- Activation of α-motor neurons is the major reason for rigidity in decerebellate rigidity.

In essence,

- **Decerebrate rigidity** is due to exaggerated gamma motor neuron discharge. It is because of this, decerebrate rigidity is also called gamma rigidity.
- **Decerebellate rigidity** is due to exaggerated alpha motor neuron discharge. It is because of this, decerebrate rigidity is also called alpha rigidity.

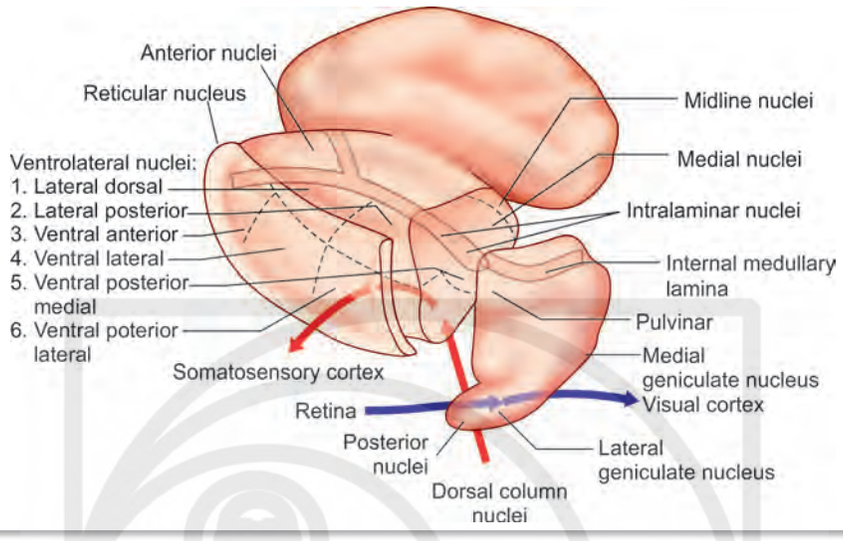
Clinical conditions causing decerebrate rigidity posturing in humans

- Coma due to **uncal herniation** because of space-occupying lesions from large tumors, hemorrhages, strokes, or abscesses in the cerebral hemisphere.

Decortication

- **Meaning** - Removal of the cerebral cortex.
- **Effect** - Influence of corticospinal tract on lower brain stem motor pathways is lost.

Contd...

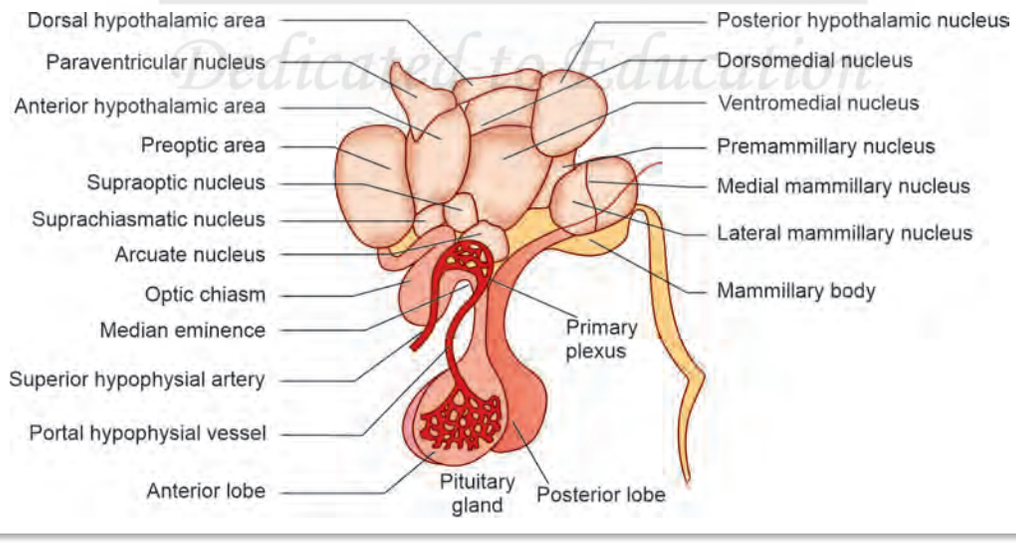


Thalamic Nuclei	Function
Lateral geniculate bodies	• Concerned with vision
Medial geniculate bodies	• Concerned with hearing
Ventral posterior lateral (VPL) and ventral posteromedial nuclei (VPM)	• Transmit somatosensory information to sensory cortex
Ventral anterior and ventral lateral nuclei	• Concerned with motor functions • Receive input from basal ganglia and cerebellum • Project to the motor cortex
Anterior nuclei	• Forms part of papez circuit concerned with learning and memory
Midline and intralaminar nuclei	• Nonspecific thalamic nuclei having widespread projections
Dorsomedial thalamic nucleus	• Concerned with olfaction (smell)

- All the thalamic nuclei mentioned above are excitatory that use glutamate as neurotransmitter
- All the thalamic nuclei ultimately project to Layer 4 of cerebral cortex
- Thalamic reticular nuclei:
  - Exceptional thalamic nuclei in a way that it is the only inhibitory nuclei of thalamus that use GABA as neurotransmitter
  - It is also the only nuclei that do not project outside thalamus. It is a local processing nuclei

HYPOTHALAMUS

- It is the principal autonomic center of the brain. Also called "head ganglion of autonomic nervous system".
- Mainly concerned with maintenance of homeostasis through its control of visceral functions and endocrine functions.



Clinical Case-Based Questions

1. **A 45-year-old female admitted with acute confusional state and right-sided hemiparesis. Brain CT shows right-sided temporal mass and obstructing hydrocephalus. Biopsy confirmed the diagnosis of pilocytic astrocytoma. Elongated, eosinophilic, irregular structures that occur within astrocytic processes in this disorder is called as?**
   a. Alzheimer's type II astrocytes
   b. Corpora amylacea
   c. Rosenthal fibers
   d. Negri Bodies
2. **A 32-year-old female presented with a two-month history of progressive rhinorrhoea from the right nostril. She had a history of headaches, which aggravated by bending over, but never with any associated fever. Identifying the fluid as cerebrospinal fluid involves estimation of:**
   a. Glucose
   b. Chloride
   c. Osmolarity
   d. Beta 2 transferrin
3. **A 22-year-old man was brought into the emergency room with a stab wound on the right side of the neck. He complained of right lower leg weakness and difficulty in right hand grasping. He is conscious. Neurological examination showed loss of touch sensation on the right side. Which of the following senses will be lost in the contralateral side?**
   a. Proprioception
   b. Vibration
   c. Pain
   d. Visual loss
4. **A 27-year-old woman was admitted to the neurological clinic with gait disturbance past 6 months. She also had intentional tremor and dysmetria and abnormal finger to finger test. Which is the only excitatory cell present in the brain part affected in this condition?**
   a. Purkinje cells
   b. Granule cell
   c. Golgi cell
   d. Stellate cell
5. **A 75-year-old female patient with a history of hypertension, hypercholesterolemia and depression was admitted for acute anterograde amnesia. Neuropsychological evaluation revealed severe damage of episodic memory. MRI of brain will reveal ischaemia of which of the following brain region in this individual?**
   a. Cerebellum
   b. Basal ganglia
   c. Medulla oblongata
   d. Hippocampus

Answers to Clinical Case-Based Questions

1. Ans. (c) Rosenthal fibers

- Rosenthal fibers are found in regions of long-standing gliosis
- Are thick and elongated, eosinophilic, irregular structures that occur within astrocytic processes containing ubiquitin and heat shock proteins
- Seen in pilocytic astrocytoma and Alexander disease

2. Ans. (d) Beta 2 transferrin

- β2-transferrin is a product of neuraminidase activity is very specific for CSF.
- It is found only in CSF
- Leakage of clear CSF fluid from the nose is called CSF Rhinorrhoea and involves estimation of β2-transferrin

3. Ans. (c) Pain

- Brown-Sequard syndrome occurs when trauma such as bullet or a stab wound leading to hemisection of spinal cord
- Patient usually presents with Ipsilateral loss of joint position and vibratory sense (posterior column), contralateral loss of pain and temperature sense (spinothalamic tract), ipsilateral weakness (corticospinal tract) below the lesion

4. Ans. (b) Granule cell

- Granule cells are the only excitatory cells of cerebellum
- They use Glutamate as neurotransmitter
- They form parallel fibers in cerebellum

5. Ans. (d) Hippocampus

- Hippocampus is involved in conversion of short-term memory to long-term memory
- Affected individuals with hippocampal lesion have Anterograde amnesia–cannot form long-term memories
- **Sommer sector lesion involves hippocampus and it leads to profound memory loss**

Multiple Choice Questions

Neurons and Glial Cells

1. Slowest conducting fiber is: *(Recent Question 2019)*
a. Somatic motors
b. Proprioceptive
c. Postganglionic autonomic
d. Preganglionic autonomic

2. Node of Ranvier is seen in: *(Recent Question 2012)*
a. Cell body
b. Dendrites
c. Axons
d. Terminal boutons

3. In a neuron, graded electrogenesis occurs at: *(Recent Question 2012)*
a. Soma- dendritic zone
b. Initial segment
c. Axon
d. Nerve ending

4. Initiation of impulse starts in: *(Recent Question 2014)*
a. Axon
b. Axon hillock + initial segment
c. Cell body
d. Dendritic tree

5. Myelination in peripheral nervous system is done by: *(Recent Question 2015)*
a. Astrocytes
b. Oligodendrocytes
c. Ependymal cells
d. Schwann cells

6. True about Schwann cell: *(Recent Question 2015)*
a. Part of central nervous system
b. Present only in myelinated nerve fibers
c. Form myelin sheath
d. Derived from surface ectoderm

7. Orthodromic conduction is: *(Recent Question 2012)*
a. An axon can conduct impulse in one direction only
b. An axon can conduct impulse in both direction
c. The jumping of depolarization from node to node
d. The print at which a runaway spike potential

8. Pseudounipolar cells: *(Recent Question 2012)*
a. Sympathetic ganglia
b. Parasympathetic
c. Cranial nerve ganglion
d. Dorsal root ganglion

9. Neurons in sympathetic ganglia are: *(Recent Question 2012)*
a. Unipolar
b. Bipolar
c. Pseudounipolar
d. Multipolar

10. Nissl bodies in neurons are: *(Recent Question 2013)*
a. Golgi apparatus
b. Endoplasmic reticulum
c. Mitochondria
d. Lysosome

11. Nissl's bodies located intracytoplasmic are in? *(Recent Question 2012)*
a. Perikaryon of neuron
b. Smooth muscle
c. Skeletal muscle
d. Cardiac muscle

12. Axonal transport is: *(Recent Question 2012)*
a. Antegrade
b. Retrograde
c. Antegrade and retrograde
d. None

13. Thickening of axon leads to: *(Recent Question 2012)*
a. Increased speed of conduction
b. Decreased speed of conduction
c. Increased absolute refractory period
d. Unmyelination

14. Phagocytosis in the CNS is done by: *(Recent Question 2012)*
a. Astrocytes
b. Schwann cells
c. Microglia
d. Oligocytes

15. Function of microglia in CNS: *(Recent Question 2012)*
a. Phagocytosis
b. Myelin synthesis
c. Fibrosis
d. Blood brain barrier

16. In brain, which cells convert glutamate to glutamine? *(Recent Question 2013)*
a. Oligodendrocytes
b. Astrocytes
c. Ependymal cells
d. Microglia

Synapse

17. Release of synaptic vesicles from the presynaptic terminals is inhibited by:
a. Preventing depolarization of nerve terminal
b. Inhibition of conduction of nerve impulse
c. Prevention of Ca^{2+} influx
d. Prevention of Na^{+} influx

18. Slow IPSP in autonomic ganglia is generated by:
a. Nicotinic cholinergic
b. Muscarinic cholinergic
c. Dopamine
d. GnRH
e. Adrenaline

19. Simulation of postganglion sympathetic neurons leads to:
a. Fast EPSP
b. Slow EPSP
c. Fast IPSP
d. Slow IPSP
e. Very slow EPSP

20. Impulses which inhibit postsynaptic neuron itself:
a. Renshaw cell inhibition *(Recent Question 2015)*
b. Presynaptic inhibition
c. Direct inhibition
d. Indirect inhibition

21. Renshaw cell inhibition is:
a. Feedback facilitation
b. Feed forward inhibition
c. Direct inhibition
d. Feedback inhibition

22. Presynaptic facilitation is caused by:
a. Prolonged opening of calcium channels
b. Prolonged opening of chloride channels
c. Prolonged opening of potassium channels
d. Prolonged opening of sodium channels

23. Feed forward inhibition is seen in:
a. Medulla
b. Cerebellum
c. Basal ganglia
d. Hypothalamus

Neurotransmitters

24. Neurotransmitter released by inner hair cells during depolarisation is:
a. Glutamate
b. Glycine
c. Acetylcholine
d. GABA

Answers with Explanations

Neurons and Glial Cells

1. Ans. (c) Postganglionic autonomic

(Ref: Ganong, 25th ed/p.94)

C, dorsal root	Unmy-elinated	0.4-1.2 **(Smallest)**	0.5-2 **(lowest)**	Pain, temperature
C, Sympa-thetic	Unmy-elinated	0.3-1.3	0.7-2.3	Postganglionic sympathetic

2. Ans. (c) Axons

(Ref: Ganong, 25th ed/p.85)

- The area where myelin sheath is absent in an axon has **Nodes of Ranvier**

3. Ans. (a) Soma- dendritic zone

(Ref: Ganong, 25th ed/p.86)

- Local changes in the membrane potential of soma and dendrites are called graded potentials
- They summate to generate an action potential at the axon hillock

4. Ans. (b) Axon hillock + initial segment

(Ref: Ganong, 25th ed/p.86)

5. Ans. (d) Schwann cells

(Ref: Ganong, 25th ed/p.86)

- Myelin is formed by oligodendrocytes in central nervous system and Schwann cells in the peripheral nervous system

6. Ans. (c) Form myelin sheath

(Ref: Ganong, 25th ed/p.85)

- Oligodendrocyte can myelinate multiple neurons at a time but Schwann cell can myelinate only one neuron at a time

7. Ans. (a) An axon can conduct impulse in one direction only

(Ref: Ganong, 25th ed/p.86)

- Under normal physiological condition, impulses are conducted in one direction only from cell body through the axon to the nerve endings–Orthodromic conduction

8. Ans. (d) Dorsal root ganglion

(Ref: Ganong, 25th ed/p.86)

Pseudo-unipolar neuron	• Are variants of bipolar cells in which one ends goes to the spinal cord and the other end goes to peripheral skin • Example- Dorsal root ganglion cell
Multipolar neuron	• Have single axon and many dendrites • They are the most common type of neuron in the human nervous system • Example- spinal motor neuron, Purkinje cells of cerebellum, sympathetic ganglia

9. Ans. (d) Multipolar

(Ref: Ganong, 25th ed/p.86)

10. Ans. (b) Endoplasmic reticulum

(Ref: Ganong, 25th ed/p.86)

- Rough endoplasmic reticulum of neurons is called Nissl bodies
- They are present in cell body or soma
- They are mainly concerned with protein synthesis

11. Ans. (a) Perikaryon of neuron

(Ref: Ganong, 25th ed/p.85)

12. Ans. (c) Antegrade and retrograde

(Ref: Ganong, 25th ed/p.86)

- Neurotransmitters are synthesized in neuron's cell body. They have to be transported in vesicles to the synaptic endings. If the direction of movement is from cell body to axon ending, it is called **Anterograde (or) forward axonal transport**. It uses the **microtubule kinesin**
- Once the neurotransmitters are released from synaptic endings, the empty vesicles recycle back to cell body to replenish neurotransmitters. If the direction of movement is from axon ending to cell body, it is called **Retrograde (or) reverse axonal transport**. It uses the **microtubule Dynein**

13. Ans. (a) Increased speed of conduction

(Ref: Ganong, 25th ed/p.87)

Factors affecting nerve conduction velocity

- Important factors that determine the velocity of propagation of action potentials are:
  - Axon diameter
  - Myelination
  - Temperature
- Axon diameter
  - Increases in axon diameter increase conduction velocity by decreasing the longitudinal resistance so that local currents can spread further
- Myelination
  - Myelinated fibers have high conduction velocity because myelination reduces membrane capacitance
- Temperature
  - Decrease in temperature decreases nerve conduction velocity
  - In low temperatures, the amount of current required to generate an action potential increases

Conduction Rate (m/s) in Cardiac Tissue	
SA node	0.05
Atrial pathways	1
AV node	0.05 (Lowest)
Bundle of His	1
Purkinje fibers	4 (Highest)
Ventricular muscle	1

Drugs that Modify Cardiac Conduction Velocity – Dromotropic Agents

Positive Dromotropic Agents

- They increases cardiac conduction velocity
- Examples are:
  - Circulating catecholamines
  - β adrenoceptor agonists (β1)
  - Muscarinic receptor antagonists (M2)

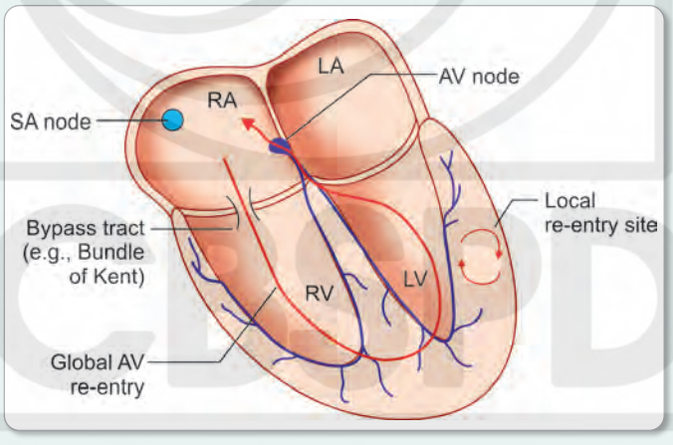
Negative Dromotropic Agents

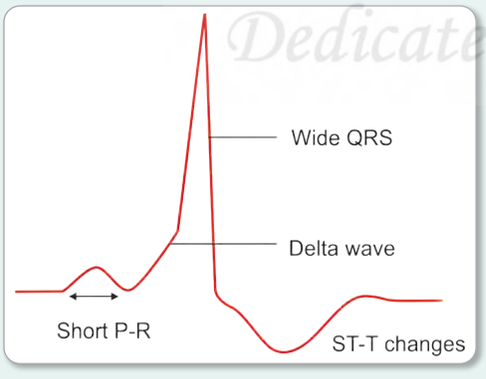
- They decrease cardiac conduction velocity. Useful as ventricular rate control agents.
- **Examples are:**
  - Parasympathetic vagal stimulation
  - Acetylcholine
  - Digoxin (parasympathomimetic action)
  - β blockers
  - Verapamil

IMPULSE CONDUCTION THROUGH ACCESSORY PATHWAYS

- This commonly leads to "re-entry" and premature activation of the ventricles, an important mechanism for arrhythmia development

Wolff-Parkinson-White (WPW) Syndrome





- WPW is characterized by Paroxysmal supraventricular tachycardia
- The accessory pathway that connects atrium to ventricle is called bundle of Kent
- **Delta wave:** Initial portion of the QRS complex with a slow upstroke is seen in ECG

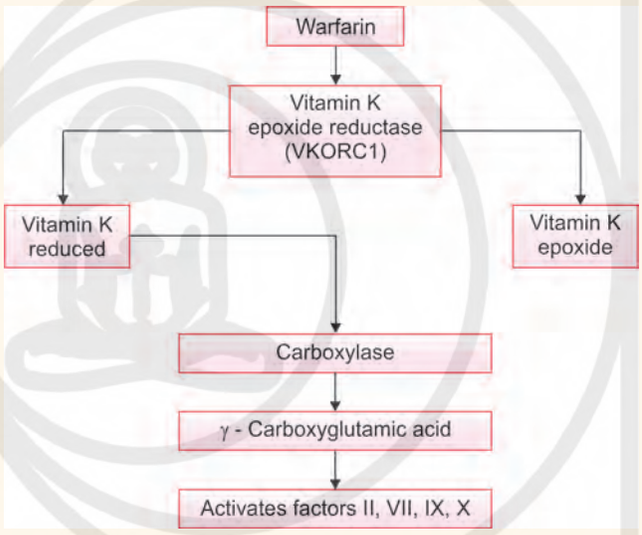
Indirect Thrombin Inhibitor Drugs

- **These drugs acts mainly through Antithrombin III mediated inhibition of thrombin. They are:**
  - Unfractionated heparin (UFH) or high-molecular-weight (HMW) heparin
  - Low-molecular-weight (LMW) heparin- Enoxaparin, Dalteparin, Tinzaparin
  - Fondaparinux - synthetic pentasaccharide
- Most common side effect of these drugs is bleeding. This is usually prevented by administration of heparin antagonist drug **protamine sulfate**

Anticoagulant drugs that target Vitamin K

- Vitamin K is required for the activation of clotting factors namely II, VII, IX, X

Vitamin K Cycle



- **Coumarin anticoagulants are the antagonists of vitamin K. They are:**
  - Warfarin – acts by inhibiting Vitamin K Epoxide reductase (VKORC1)
  - Dicumarol
  - Phenindione

Anticoagulant Agents that Target Calcium

- Remember calcium ion is the clotting factor IV
- Calcium chelating agents acts by removing calcium which is essential for coagulation. They are:
  - Ethylenediaminetetraacetic acid (EDTA)
  - Trisodium citrate

New Oral Anticoagulant Drugs

Oral Direct Factor XA Inhibitors

- Rivaroxaban
- Apixaban
- Edoxaban

Fibrinolytic (Thrombolytic) Drugs

- These are the drugs that lyses clot. They are commonly used in treatment of myocardial infarction. The Drugs are:
  - Streptokinase
  - Urokinase
  - Recombinant human tissue plasminogen activators (t-PAs)
    - Alteplase
    - Reteplase
    - Tenecteplase

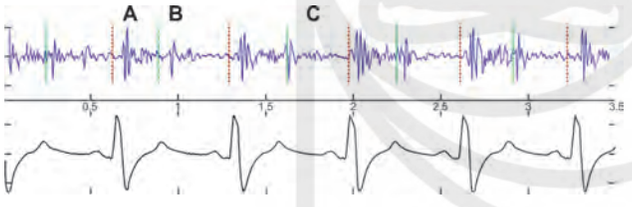
Contd...

Image-Based Questions

1. Below are two vessels shown. Assuming the pressure along both the vessels is the same and both of them follow linear flow pattern. What will be the amount of blood flow in A compared to B? *(AIIMS May 2017)*

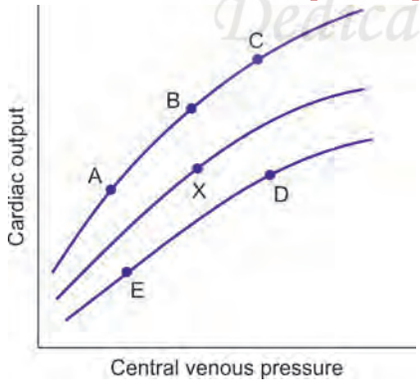
a. 32 times
b. 16 times
c. 8 times
d. 4 times

2. Below is the picture of phonocardiogram and chest lead ECG, which of the following marked areas point to the second heart sound?



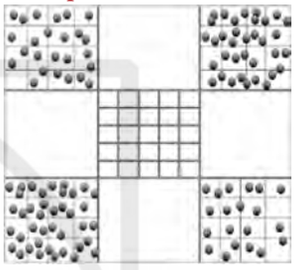
a. A
b. B
c. Not adequate information provided
d. C

3. In this graph regarding starling curves, mild hemorrhage will cause stroke volume to shift from point X to point?



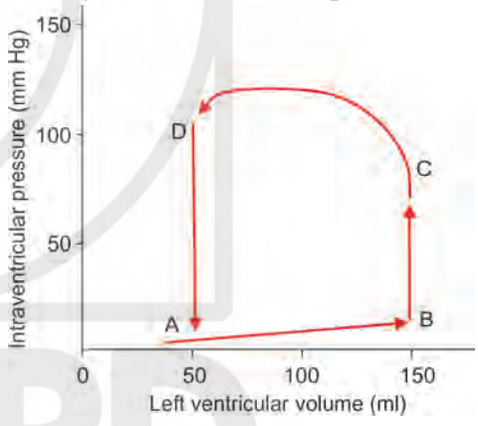
a. Point A
b. Point B
c. Point C
d. Point E

4. The following image is taken from a Neubauer chamber after charging of fluid. If the dilution factor is 20, what is the total cell count per cu.mm?



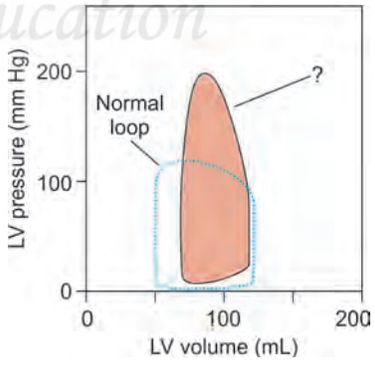
a. 6000
b. 3000
c. 7000
d. 11000

5. Calculate ejection fraction from the picture below.



a. 30%
b. 50%
c. 60%
d. 66%

6. Pressure volume loop is shifted to left side in:



a. Aortic regurgitation
b. Mitral regurgitation
c. Aortic stenosis
d. Congestive cardiac failure

Answers to Image-Based Questions

1. Ans. (c) 8 times

Ref: Ganong, 25th ed/p.573

Blood flow (F) inside vessel depends on:

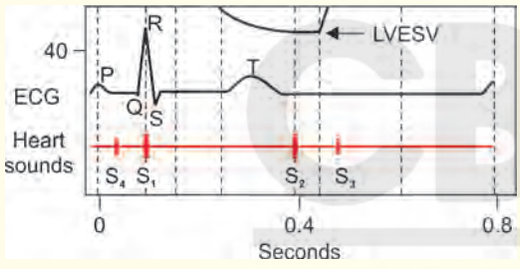
- Pressure difference (P_A - P_B) – directly related
- Viscosity of the fluid (η) – inversely related
  - Viscosity is a measure of a fluid's resistance to flow
  - A fluid with low viscosity flows easily. Such fluids are called **Newtonian fluid**. Example is water
  - A fluid with high viscosity flows resists motion. Such fluids are called Non-newtonian fluid. Example is blood
  - **Fahraeus-Lindqvist effect:** This effect is seen mainly in capillaries where RBCs flow in the center which leaves cell free plasma near the vessel wall. So, the viscosity change per unit change in hematocrit is much less in capillaries
- Radius of the vessel (r^4) – directly related
- Length of the vessel (L) – inversely related
- Interrelation of these factors are expressed in **Poiseuille-Hagen formula** which is:

$$F = (P_A - P_B) * \pi r^4/8 \eta L$$

  - Since, length is doubled and diameter is doubled in vessel A, its flow will be:
    $F = 2^4/2 = 16/2 = 8$ times

2. Ans. (b) B

Ref: Ganong, 25th ed/p.542



S1	Peak of R wave
S2	End of T wave
S3	Rapid filling phase
S4	End of P wave

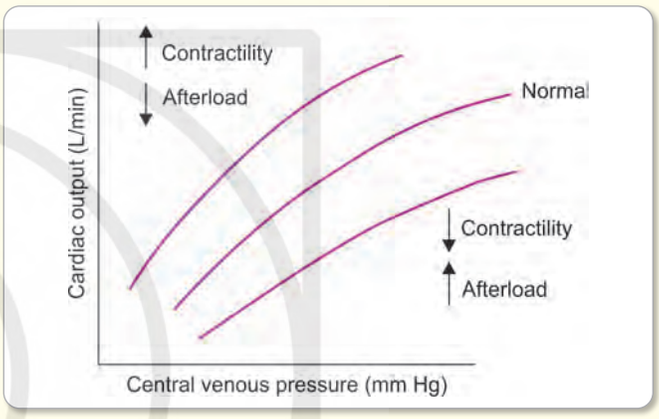
3. Ans. (a) Point A

Ref: Guyton 13th ed.p.119

- Understanding Starling curve

Concept:

- Starling's law of the heart states that increasing preload increases the force of contraction
- Starling's curve is the plot of this preload Vs force of contraction
- So, X axis is preload and Y axis is force of contraction
- Representatives for preload – X axis can be end-diastolic volume or central venous pressure
- Representatives for force of contraction – Y axis can be stroke volume or cardiac output



- Starling curve shifts up and to the left means increase in contractility and decrease in afterload
- Starling curve shifts down and to the right means decrease in contractility and increase in afterload

Regarding this question,

- Point marked X is the normal curve
- Mild hemorrhage can lead to decrease in preload (venous return)
- A major Compensatory mechanism for Mild hemorrhage is sympathetic activation which causes increase in cardiac contractility and heart rate. So, the answer lies in upper curve
- Same cardiac output is achieved in spite of decrease in preload but by increase in cardiac contractility. So, the stroke volume (cardiac output) shifts to point A

4. Ans. (a) 6000

(Ref: GK pal, textbook of practical physiology, 2nd ed/p.55)

How to approach any question on Neubauer chamber?

- Very simple. Simply count the number of cells in the respective squares
- For WBC count – 4 corner square cells counted and added
- For RBC count – among the center 25 small squares, upper right, upper left, lower right, lower left and center squares are counted and added
- Remember the multiplication factor:
  - For WBC count – multiply by 50
  - For RBC count – multiply by 10000

Here in this question, total numbers of WBCs are 120. So, the answer is 120 × 50 = 6000

5. Ans. (d) 66%

(Ref: Ganong, 25th ed/p.540)

- In the graph, end diastolic volume (EDV) = 150 mL

Clinical Case-Based Questions

1. **A 38-year-old male was admitted with a history of worsening breathlessness and palpitations. His ECG revealed a ventricular rate of 170 beats/min. Ivabradine treatment started for his condition. This drug acts by blocking:**
   a. Calcium channels b. Potassium channels
   c. Funny current channels d. Chloride channels
2. **A 32-year-old female admitted with exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, abdominal distension and lower limb edema. Her transthoracic echo revealed severe stenotic tricuspid valve. Which of the following changes in JVP is seen in this condition?**
   a. Absent a wave b. Tall v wave
   c. Prominent y descent d. Large a wave
3. **A 72-year-old man who is undergoing dialysis treatment for his end stage renal disease complains of fatigue, breathlessness and generalized weakness. His hemoglobin level is 7 g/dL. Which of the following drug is most useful in this clinical setting?**
   a. Nifedipine
   b. Paracetamol
   c. Recombinant erythropoietin
   d. Losartan
4. **A 68-year-old female was admitted due to pain and swelling of the right upper limb swelling. She also had chest pain on exertion. Her coronary angiography showed obstructions of 90% in the left coronary and circumflex arteries. The peak left coronary flow occurs during:**
   a. Rapid ejection phase
   b. Isovolumic contraction
   c. Slow ejection phase
   d. Isovolumic relaxation
5. **A 75-year-old male patient admitted with two-month history of shortness of breath, tiredness, and leg swelling. He also reported general weakness and decreased libido. His transthoracic echo revealed dilated right and left ventricles. When the radius of a heart chamber is increased, a greater tension (more work) must be developed in the heart to produce any given pressure. This is according to:**
   a. Frank Starling law
   b. Laplace law
   c. Fick's law
   d. Marey's law

Answers to Clinical Case-Based Questions

1. Ans. (c) Funny current channels

- Ivabradine is useful to reduce heart rate in sinus tachycardia
- It blocks funny current channels in SA node
- Ivabradine is also useful in treatment of angina and heart failure

2. Ans. (d) Large a wave

- a wave is due to right atrial contraction (atrial systole)
- In tricuspid stenosis, right atrium is contracting against stenosed tricuspid valve. So, large a wave is seen
- Large a wave can also be seen in pulmonic stenosis and right atrial myxoma

3. Ans. (c) Recombinant erythropoietin

- Kidney is the major source of erythropoietin.
- 85% of the erythropoietin comes from peritubular capillary bed cells of the kidneys
- Recombinant human erythropoietin (rHuEPO) drugs are commonly used in treatment of Anemia secondary to chronic kidney disease

4. Ans. (d) Isovolumic relaxation

- Normal Coronary blood flow: 60–80 mL/100 gm/min or 250 mL/min viz, 5% of resting cardiac output
- The peak left coronary flow occurs at the end of isovolumetric relaxation (Diastole)

5. Ans. (b) Laplace law

- Laplace law states that tension in the wall of a cylinder (T) is equal to the product of the transmural pressure (P) and the radius (r) divided by the wall thickness (w)
- T = Pr/w
- When the radius of a heart chamber is increased, a greater tension (more work) must be developed in the heart to produce any given pressure according to Laplace law

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About the Author

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