Multiple-Choice Questions in Medical Physiology

For Postgraduate Medical Entrance Examinations
Revised 2014

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Written and published by E.S.Prakash.

Disclaimer: Science and medicine constantly change and while I have tried to check information presented here with sources known to be reliable, I cannot guarantee that this book is error free. I encourage you to crosscheck information contained herein with other sources. This book is not written to be used to directly guide the care of patients. Therefore, I cannot accept any responsibility for any consequences that may arise from the use of information contained here in the care of patients. *– E.S.Prakash*

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Frequently used abbreviations
aka – also known as
BP – blood pressure
CSF – cerebrospinal fluid
ECF – extracellular fluid
Hb – hemoglobin
Hct – hematocrit
ICF – intracellular fluid
ISF – interstitial fluid
MAP – mean systemic arterial pressure
MCQ – multiple-choice question
PCV – packed cell volume
RBC – red blood cell
SVR – systemic vascular resistance
T/F – True or false
TPR – total peripheral resistance (aka. Systemic vascular resistance)
WBC – white blood cell
WNL – within normal limits

2 minutes please

Think of this book as a tool to help you assess how well you have learnt medical physiology. It has been written primarily for use in revision courses for doctors who are preparing for competitive postgraduate medical entrance examinations in India, but undergraduate medical students and postgraduate physiology students, may also find this helpful. The intent here is to use multiple-choice questions (MCQ) as a means to help the reader revise key facts, test understanding of concepts and the ability to apply them.

Many questions that I have seen appear on entrance examinations test conceptual understanding and meaningful learning. However, depending on the exam, some test knowledge of facts that are not of significance to a practicing primary care physician, and an undesirable backwash effect of this is it tends to encourage rote learning over indepth learning of important concepts. In writing this book, I have focused on the immediate *'learning needs'* of the target audience, which is to be successful on these exams.

I've frequently included questions solely for learning and systematic revision of certain topics. Thus, not all questions are written to be equivalent in standard to questions commonly appearing in entrance examinations. That being said, the difficulty level of questions varies from one exam to another with some predominantly testing recall of facts whereas others test knowledge and understanding and the ability to apply concepts and solve problems. Just to be clear, no attempt is made here to be comprehensive. Summaries of certain topics can be found at the start of each section. I'd suggest giving the summaries a quick read before doing questions and explanations (for questions) that may be found in summaries upfront are not repeated.

As MCQs with multiple correct answers enable more material to be revised with fewer questions, I have also frequently used such questions; this helps us get into and sustain the important habit of carefully reading all options in a question. Furthermore, some entrance exams use the *multiple true-false* type of MCQ, so some practice with this type of question is needed.

For the purpose of preparing and revising for PG entrance examinations, I recommend: ***Ganong's Review of Medical Physiology* by Barrett et al,** published by Mc Graw Hill, 2012.

I continue to revise and publish *Multiple-Choice Questions in Medical Physiology* on a regular basis, and I welcome suggestions from readers for improving it. If you spot an error, please let me know. If any corrections are needed, I'll post them on my website at **http://esprakash.wordpress.com/mcqmedphy/** as soon as they are identified.

This book is dedicated to the memory of Dr. William F. Ganong.

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GENERAL PHYSIOLOGY

Body composition:
Body mass = fat mass + lean body mass.

The water content of lean body mass (fat-free mass) is relatively constant and is about 70 ml/100 g. For example, in a healthy adult male weighing 70 kg and whose total body water is measured to be 42 L (= 42 kg), lean body mass = 42 / 0.7 = 60 kg, and fat mass is 10 kg. Body fat % = 10/70 × 100 = 14%. Fat is relatively anhydrous. Body fat percentage is greater in women compared to men.

Body Fluid Compartments:
Typical values in a healthy adult male weighing 70 kg are as given below:

Compartment	Volume	Marker
Total body water	42 L	D_2O
ICF	28 L	-
ECF	14 L	Sucrose
Interstitial fluid	10.5 L	-
Plasma	3.5 L	Evans blue Radioiodinated albumin

Intravenously administered sucrose distributes throughout ECF ('sucrose space') and it does not enter cells. ECF volume in a 70-kg healthy adult is about 14 L (20% of body weight). The volume of interstitial fluid is about 10.5 L (75% of ECF volume) and plasma volume is about 3.5L (25% of ECF volume). Heavy water distributes throughout body water. Inulin and mannitol distribute exclusively in the ECF. Evans blue dye stays in the plasma, and radioiodinated albumin has also been used to estimate plasma volume.

Calculating Serum Osmolality:
Serum osmolality is calculated in mosm/L as equal to:

$$2 [Na^+] + [glucose] / 18 + [BUN] / 2.8,$$

where serum Na is expressed in mmol/L and serum glucose and serum urea nitrogen are expressed in mg/dL.

Blood urea vs. blood (serum) urea nitrogen:
The formula of urea is NH_2CONH_2
Molar mass of urea is 60 g; each molecule of urea has 2 nitrogen atoms.
The mass of nitrogen in urea is $2 \times 14 = 28$ g
Thus, a urea concentration of 60 mg/dL corresponds to a [BUN] of 28 mg/dL.

Normally, the osmolality of serum or plasma is chiefly due to Na and its accompanying anions Cl and HCO_3. We multiply Na by 2 to account for obligate anions accompanying Na. Normally, serum osmolality ranges from 280–295 mOsm/Kg H_2O. The osmolality of body fluids can also be directly measured using the freezing point depression method.

The concentration of sodium in ECF is quantitatively the most important determinant of plasma osmolality.

Relationship between blood volume and plasma volume:

Blood volume
    = plasma volume × [100 / (100–Hct)]

The relationship between blood flow and plasma flow through an organ is similar.

For example, renal blood flow
    = renal plasma flow × [100 / (100–Hct)]

ICF is much more acidic than ECF. For example, in muscle cells the pH is typically about 6.8. Steady state osmolality (i.e., concentration of osmotically active particles) of all body fluid compartments must be the same. The fact that, in a healthy adult, ICF volume is twice as large as ECF volume indicates that the absolute number of osmoles is much greater in the ICF.

What is osmosis?
Osmosis is the movement of water across a semipermeable membrane permeable to water but not to solutes, from a solution with lower concentration of osmoles to a solution with a higher concentration of osmoles. This continues until *osmotic equilibrium* (i.e., the osmolality of either compartment is equal) is attained.

What is an osmole?
An osmole (effective osmole) is an osmotically active particle; i.e., capable of causing osmosis. Examples include sodium ion, chloride ion, protein anions, and phosphate ion. A solute to which the cell membrane is relatively impermeable will function as an *effective osmole*. For example, in comparison to water, the cell membrane is relatively impermeable to sodium, chloride, mannitol. The amount of ions crossing the cell membrane through channels and transporters is much smaller relative to the magnitude of osmotically driven water fluxes.

What is an *ineffective osmole*?
If the cell membrane is significantly permeable to a solute (for example, urea), the substance will move across the membrane until its concentration is exactly the same on both sides of the membrane. In such an instance, osmosis (net movement of water) does not occur. However, urea does function as an effective osmole in the renal medullary interstitium because the permeability of the inner medullary collecting ducts to urea is mediated by urea transporters dependent upon stimulation by antidiuretic hormone.

Effective osmolality of plasma: Since urea equilibrates across the cell membrane in the steady state, an increase in serum urea nitrogen does not cause cellular dehydration. **The effective osmolality** of plasma (in mOsm/L) is estimated as $2\,[Na^+] + [glucose] / 18$ where Na is in mmol/L and glucose is expressed in mg/dL.

Osmotic pressure is the pressure required to stop water flux (osmosis) across a semipermeable membrane.

Osmotic pressure $P = CRT$ (Van't Hoff equation), where,
C is concentration of osmoles; R is a constant, and T is temperature in Kelvin

In the steady state, the osmolality of all body fluids is identical; that is, osmotic pressure gradient across the plasma membranes of cells in the steady state is zero.

Osmolality is a *colligative property* that depends upon the number of solute particles, and not the size of the particles. As an example, the contribution of 1 Na ion and 1 albumin molecule toward the osmolality of plasma is the same. Since the molar concentration of proteins in plasma is very low (60 g/L) compared to that of Na (140 mM) and Cl (100 mM), plasma proteins contribute very little to the osmolality of plasma compared to Na and its accompanying ions.

Colloid osmotic pressure of plasma (oncotic pressure): While proteins are present in plasma at a concentration of 60-80 g/L, they are not normally present in significant concentrations in the interstitium. Thus, the osmotic pressure of plasma proteins (called *colloid osmotic pressure* or *oncotic pressure*) is much greater than the osmotic pressure of proteins in the interstitium. This oncotic pressure gradient across the capillary restrains fluid filtration and favors reabsorption of fluid into the capillary.

Hemolysis begins when normocytes are placed in 0.5% NaCl and is complete in 0.3% NaCl. In contrast, when RBCs are placed in hypertonic saline, they lose water and diminish in size.

Why is 0.9% NaCl called an isotonic solution?
0.9% (precisely 0.85%) NaCl has the same osmolality as normal human plasma (about 290 mOsm/kg H_2O, see the calculation below). When it is infused into an individual with an ECF osmolality of 290 mOsm/kg H_2O, it does not cause any change in the *steady state* volume of red blood cells or other cells – it is an *isotonic* solution. Tonicity of a solution refers to the effect of a solution on the osmolality of normal human plasma in the steady state,

Calculate the osmolality of 0.85% NaCl.
0.85% NaCl contains 0.85 g of NaCl per deciliter of the solution = 8.5 g/ L of the solution
Molar mass of NaCl = 58.5 g; 1 mol of NaCl contains 58.5 g of NaCl
8.5 g corresponds 8.5/58.5 mol = 0.145 mol = 145 mmol/L
Each Na in this solution is accompanied by 1 chloride ion. Therefore, the total concentration of

osmoles (osmotically active particles) = 2 × 145 = 290 mOsm/L

Changes in body fluid volumes: The term dehydration is used by some to refer to states in which intracellular volume is reduced in addition to extracellular volume. Some authors however classify dehydration as isoosmotic, hyperosmotic and hypo-osmotic implying their definition of dehydration to be a reduction in ECF volume or total body water (see below). Some use the term hypovolemia to refer to a reduction in blood volume whereas some use the term hypovolemia to refer to ECF volume contraction; one can easily avoid confusion by referring directly to the compartment in question – example, reduction in blood volume, reduction in plasma volume etc. Blood volume is more critically regulated than ECF volume.

Classification of dehydration*:

Type	Example of a cause
Isosmotic	Blood loss
Hyperosmotic	Deficiency of ADH
Hypoosmotic	Adrenocortical insufficiency

*Overhydration is classified likewise.

Changes in ICF volume in various types of dehydration:

Type	ECF volume	ICF volume
Isosmotic	Decreases	No change
Hyperosmotic	Decreases	Decreases
Hypoosmotic	Decreases	Increases

Is 5% dextrose isotonic or hypotonic?
Molar mass of dextrose (D-glucose, $C_6H_{12}O_6$) is 180 g
5% solution contains 50 grams of dextrose per liter of the solution
50g = 50/180 mol = 0.277 mol = 277 mmol = 277 mOsm/L ~ 270–280 mOsm/kg H_2O

As 5% dextrose has approximately the same osmolality as normal human plasma, it is an isosmotic solution. However, when dextrose is infused, it is metabolized and the net effect (over a period of time, especially when large volumes are infused) is that of adding water to plasma. This "excess" water can enter cells. That is, 5% dextrose is **hypotonic** because it dilutes plasma in

the steady state, and it is of value in replenishing ICF volume in intracellular dehydration.

The difference between osmolality and tonicity: While osmolality refers to the concentration of osmotically active particles in a liter of a solution, *tonicity* of a solution refers to the effect of an administered solution on the steady state osmolality of normal human plasma.

In well hydrated individuals, the hypo-osmolality that occurs when hypotonic dextrose solutions are infused is sensed by osmoreceptors in the anterior hypothalamus and secretion of antidiuretic hormone is promptly inhibited to excrete 'excess' water.

Classification of mechanism of transport across cell membranes:

Mechanism	Examples
Simple diffusion	Diffusion of oxygen, carbon dioxide, anesthetic gases, nitric oxide through lipid layer
Facilitated diffusion	Glucose entry into cells through GLUT 1-5; passage of ions through ion channels*
Primary active transport	Na-K ATPase, H-K ATPase, Ca-ATPase, H-ATPase
Secondary active transport	Na-glucose cotransporter (SGLT), Na-amino acid cotransport, Na-H exchanger, Na-Ca exchanger

Notes on Transport across Cell Membrane:

Simple diffusion, by definition, is diffusion occurring through the lipid bilayer. **Facilitated diffusion** occurs through protein molecules in the cell membrane (ion channels or transport proteins). Some authors consider ion flux through ion channels also as an instance of "simple diffusion" – this distinction is a matter of taste.

By definition, a **primary active transport** process is driven by hydrolysis of ATP.

Na-K ATPase:
- It is a primary active transport process.
- It is ubiquitous i.e., present in all cells.
- The pump is present in the cell membrane.

- It pumps 3 Na ions out of the cell and 2 K ions into the cell. Thus it makes the inside of the cell negative with respect to exterior; i.e. it contributes to a small extent (about 4 mV) to the genesis of RMP.
- It plays an important role in maintaining cell volume. If the pump is inhibited as can happen when ATP is limiting, intracellular Na increases also increasing the size of cells.
- Digoxin, a cardiac glycoside, inhibits this pump. Inhibition of the pump leads to an increase in intracellular sodium. Since cytosolic Ca is extruded from cardiomyocytes in part by the Na-Ca exchanger (NCX) on the cell membrane, the consequence of inhibition of Na-K ATPase with therapeutic doses of digoxin in heart failure is an increase in cytosolic calcium and augmentation of the force of contraction of cardiac muscle cells.
- About 70% of the ATP generated in nerve cells is used to energize the Na-K ATPase.

A **secondary active transport** process utilizes an ion gradient as a source of energy rather than ATP. The Na-Glucose cotransporter (SGLT) utilizes the energy of the Na gradient (Na battery) to drive the uphill transport of glucose from ECF to ICF. Note that the species that is actively transported by SGLT is glucose. The Na-amino acid symporter is similar. The term 'secondary' refers to the fact that the energy source (the sodium ion gradient), which drives this process, depends upon normal operation of a primary active transport process – the Na-K pump that generates a Na ion gradient. If the Na-K pump fails due to lack of ATP or any other reason, then, the Na gradient will be gradually reduced and all secondary active transport processes powered by the Na gradient will also be affected.

Nomenclature of transporters based on the direction of movement and the number of species of transported. *Note*: this is **not** a classification of *mechanism* of transport.

Name	Definition	Example
Uniport	1 species transported	Ca-ATPase, GLUT*
Symport (also cotransport)	2 species transported in the same	Na-glucose cotransport, Na-K-2Cl

Name	Definition	Example
	direction	cotransport
Antiport (also countertransport)	2 species transported in opposite directions	Na-K ATPase, Na-H exchanger, Cl-HCO₃ exchanger.

*GLUT – glucose transporter

Carrier mediated transport – this term refers to transport processes in which the transport species physically attaches to a carrier molecule, and is *carried* by it. Carrier mediated transport processes can be active or passive. Na-K ATPase (an active transport process) and glucose transport via GLUT (a passive transport process) are both examples of carrier-mediated transport.

Different authors use the word *transport* in this context differently. Some do not use the word transport to refer to ion movement through ion channels; for them transport entails physical attachment of the transported species to the transporter molecule.

Other modes of transport: Exocytosis, endocytosis, transcytosis (vesicular transport). Exocytosis is triggered by a rise in intracellular calcium. Proteins injected into the circulation often have been endocytosed into vesicles by endothelial cells to be exocytosed as vesicles into the interstitium. This process called transcytosis or vesicular transport requires an input of free energy.

Types of intercellular communication:

Type	Mediators
Neurocrine	Neurotransmitters acting across synapses
Endocrine	Hormones acting on target cells located at distant sites
Paracrine	Hormones acting locally without entering the general circulation
Gap junctions	Cells are electrically coupled by gap junctions which allow passage of ions and small molecules
Juxtacrine	Cells linked to adjacent cells through cell adhesion molecules and cell adhesion molecule receptors in extracellular matrix

Components of signal transduction pathways and their functions:

Components	Functions
Hormone / neurotransmitter	Signal
Receptor	Recognizes the signal
Signal coupling proteins	Coupling ligand binding to intracellular signaling
Second messengers	Intracellular molecules that amplify extracellular hormonal (first messenger) signals several fold
Effector molecules	Enzymes, channels, transporters, that mediate the physiologic effects of the hormone

Signal transduction cascades and second messengers:

Signal transduction cascades	Second messenger(s)
Adenylate cyclase cascade	cAMP
Phosphatidyl inositol pathway	Inositol trisphosphate (IP_3), DAG, and Ca
Guanylyl cyclase	cGMP
Hormones acting on intracellular receptors	Hormone-receptor complex

Drugs / toxins used in G-protein research:

Drug/toxin	Mechanism of action
Cholera toxin	ADP-ribosylation of α subunit of Gs, activation of adenylate cyclase
Pertussis toxin	Inhibition of α subunit of Gi
Forskolin	Directly activates adenylate cyclase

Notes on G-proteins:
1. They have 3 subunits (α, β, γ);
2. Each subunit is distinct (heterotrimeric)
3. They are guanylyl nucleotide (GTP / GDP) binding proteins
4. The α subunit has inherent GTPase activity
5. The β and γ subunits are coupled to effectors molecules like adenylyl cyclase, ion channels.
6. G proteins couple hormone binding to the receptor to an intracellular signaling pathway. In essence, they are signal coupling proteins.

7. Hormone receptors that are coupled to G-proteins are called G-protein coupled receptors (GPCR)
8. GPCR have seven transmembrane domains; thus they are often called seven-helix receptors or serpentine receptors. Most peptide hormones, catecholamines, histamine and serotonin signal through GPCRs. In contrast, steroid hormones, thyroid hormones and retinoic acid act primarily upon cytsolic and nuclear receptors.
9. There are several types of G proteins:
10. Gs is stimulatory G protein, and it activates adenylyl cyclase;
11. Gi is inhibitory G protein and it inhibits adenylyl cyclase;
12. Activation of Gq leads to activation of the membrane bound enzyme phospholipase C, and the generation of inositol trisphosphate and diacylglycerol.
13. Other families of proteins such as *ras* resemble G-proteins in structure and function.
14. Mutations in G proteins are implicated in the development of cancer, and account for a variety of endocrine diseases.

Some Notes on Acid-Base Concepts:
pH = - log [H] in moles/liter
Suppose [H] = 100 nM, pH = - log [10^{-7}]
= - 7 [-1] = 7

pH	Hydrogen ion concentration corresponding to this pH
7	100 nM
6	1000 nM
5	10000 nM
4	100000 nM

H ion concentration is expressed using logarithms; however, the linear scale is easier on the eye and more informative in my opinion for clinical use. A unit change in pH say from 6 to 7 represents a ten-fold change in H ion concentration. The table above is meant to emphasize this.

pH of various body fluids:

pH	[H] concentration in *nanomoles per liter*	Compartment / condition
1	100 million	Gastric juice
6.9	120	ICF (muscle); arterial plasma in life

pH	[H] concentration in *nanomoles per liter*	Compartment / condition
		threatening acidosis
7	100	Pure water
7.1	80	Inside RBC
7.33	50	Cerebrospinal fluid
7.4	40	Normal arterial plasma
7.7	20	Severe alkalosis
8	10	Pancreatic juice

The Henderson-Hasselbalch equation reads thus:
$pH = pKa + \log \{[salt] / [acid]\}$

Consider the H_2CO_3-HCO_3 system. The buffer acid is H_2CO_3. The conjugate base is HCO_3.
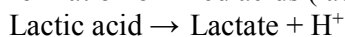
$[H_2CO_3] \rightleftharpoons [H^+] + [HCO_3^-]$

$pH = pK + \log [HCO_3^-] / [H_2CO_3]$

If the buffer acid were half dissociated, i.e., the concentration of acid and the conjugate base are equal, then, [salt] = [acid], and pH would equal pK. A buffer system works best when the pH of the solution is close to the pK value.

What does HCO_3 in ECF buffer?
HCO_3 in ECF combines with H liberated by the formation of fixed acids (lactic acid, ketoacids).
Lactic acid $\rightarrow$ Lactate + H^+
H^+ are buffered by HCO_3 to form H_2CO_3
H_2CO_3 is unstable and it dissociates to form CO_2 + H_2O. CO_2 is volatile. The lungs excrete CO_2.
H^+ formed from lactic acid are eliminated as carbon dioxide, but this entails loss of HCO_3.

In contrast, bicarbonate cannot buffer protons formed from CO_2 (carbonic acid; see the reaction sequence below).

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3$

Thus, protons formed from carbondioxide can be buffered only by hemoglobin or plasma proteins.

The Henderson-Hasselbalch equation may be simplified, omitting logarithms, to read thus:

$[H^+]$ in nM $= \dfrac{24 \times PaCO_2 \text{ (mm Hg)}}{[HCO_3^-] \text{ mM}}$

This is the **modified Henderson's equation**.

Substitute normal values of $PaCO_2$ and plasma HCO_3 and you can easily remember the equation. Normally, $[H^+] = 40$ nmol/L; this corresponds to an arterial plasma pH of 7.4. This is on the left side of the equation.

$40 = 24$ (a constant) $\times 40 / 24$

On the right side, $40 =$ normal $PaCO_2$ and $24 =$ normal plasma HCO_3. The constant 24 has been derived taking into consideration the solubility coefficient of carbon dioxide at body temperature, so that $PaCO_2$ can be substituted in the equation instead of the concentration of carbonic acid.

Questions:
In each of the following questions, select the **single best** response unless instructed otherwise.

1. The water content of lean body mass is about:
A. 30 ml/100 g
B. 50 ml/100 g
C. 70 ml/100 g
D. highly variable

2. Body mass index is calculated as:
A. weight in pounds by height in meters
B. weight in kg by height in meters
C. weight in kg divided by square of height in meter squared
D. weight in kg divided by body surface area

3. The most abundant cation in ICF is
A. Sodium
B. Potassium
C. Magnesium
D. Calcium

4. The most abundant anion in ECF is
A. bicarbonate
B. chloride
C. phosphate
D. protein anion

5. ECF volume is determined by:
A. plasma [Na]
B. plasma protein concentration
C. the amount of sodium in the ECF

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6. The body fluid compartment that contains more osmotically active particles (in relation to other fluid compartments in the same individual) is:
A. intracellular fluid
B. plasma
C. interstitial fluid

7. The following values are obtained on a sample of serum from a child that has clinical evidence of dehydration.
Serum [Na] = 135 mmol/L
Serum [glucose] = 540 mg/dL
Serum [urea nitrogen] = 56 mg/dL

The osmolality of serum is expected to be close to:
A. 290 mOsm/kg H_2O
B. 300 mOsm/kg H_2O
C. 310 mOsm/ kg H_2O
D. 320 mOsm/kg H_2O
E. 330 mOsm/kg H_2O

8. The following values are obtained on a sample of serum from a child that has clinical evidence of dehydration.
Serum [Na] = 130 mmol/L
Serum [glucose] = 540 mg/dL
Serum [urea nitrogen] = 56 mg/dL

Assuming there are no toxins in ECF, the effective serum osmolality is approximately:
A. 290 mOsm/kg H_2O
B. 300 mOsm/kg H_2O
C. 310 mOsm/ kg H_2O
D. 320 mOsm/kg H_2O
E. 330 mOsm/kg H_2O

9. What percentage of osmolality of plasma in a healthy, well hydrated individual is attributable to sodium and its accompanying anions?
A. 30 %
B. 50 %
C. 70 %
D. 90 %

10. Which of the following contributes **least** to the osmolality of plasma?
A. Glucose
B. Proteins
C. Sodium
D. Urea

11. The osmolar concentration of sodium in normal human plasma is approximately:
A. 275 – 295 mOsm/L
B. 135 – 145 mOsm/L
C. 240 – 250 mOsm/L
D. 95 – 110 mOsm/L

12. In the *steady state*, the value of which of the following variables is the same in ICF and ECF?
A. pH
B. Osmolality
C. Concentration of proteins
D. Number of osmoles

13. Which compartment does the term "sucrose space" refer to?
A. Extracellular fluid (ECF)
B. Interstitial fluid (ISF)
C. Intracellular fluid (ICF)
D. Plasma

14. The volume of distribution of intravenously administered sucrose in a healthy well hydrated 70-kg man is about:
A. 3.5 liters
B. 10.5 liters
C. 14 liters
D. 28 liters

15. In a healthy adult, ECF volume constitutes what fraction of body weight?
A. 10%
B. 20%
C. 30%
D. 40%

16. In a healthy adult male weighing 70 kg, the total volume of fluid present in the transcellular compartment does not normally exceed:
A. 1 liter
B. 3 liters
C. 5 liters
D. 7 liters

17. Which of the following markers administered intravenously distributes exclusively in intracellular fluid?

A. Evans blue dye
B. Heavy water
C. Sucrose
D. None of the above

18. Which of the following substances can be used as a marker for the ECF compartment?
A. Nonmetabolizable sugars
B. Glucose
C. Radio-iodinated albumin
D. D_2O

19. Which of the following markers is **incorrectly** matched with its volume of distribution?
A. Antipyrine - total body water
B. Inulin - ECF volume
C. Evans blue - plasma volume
D. I^{125} albumin - blood volume

20. 100 mg of sucrose is injected intravenously into an adult male weighing 70 kg. The plasma concentration of sucrose after mixing is 0.01 mg/ml. If 5 mg of sucrose has been metabolized during this period, the ECF volume in this individual is approximately:
A. 6 liters
B. 9.5 liters
C. 14 liters
D. 17.5 liters

21. A known amount of heavy water and inulin are injected intravenously into a healthy 35 year old male. The volume of distribution of heavy water and inulin were 36 liters and 12 liters respectively. Which of the following estimations is **most likely**?
A. Plasma volume is 6 liters.
B. Interstitial fluid volume is 6 liters.
C. ICF volume is 28 liters.
D. ECF volume is 12 liters.

22. In a healthy adult weighing 70 kg, plasma volume was estimated to be 3000 ml. His hematocrit was 40%. His blood volume is approximately:
A. 5000 ml
B. 5200 ml
C. 5400 ml
D. 5600 ml

23. What fraction of total body potassium is present in plasma?
A. 0.4%
B. 8.2%
C. 12%
D. 88%

24. A substance injected intravenously was found to be distributed through 35% of total body water. Which of the following is **most likely**?
A. It did not pass through blood capillaries.
B. It entered neurons and cerebral ventricles.
C. It did not enter cells.
D. It was excluded from 'third spaces'.

25. Of the following substances, the lipid bilayer per se (i.e., without proteins) is **most permeable** to:
A. sodium ions
B. urea
C. glucose
D. water

26. Red blood cells from a healthy individual were placed in each of the following solutions and observations were made after 1 hour. Cells would have **most likely** have lysed when placed in:
A. 0.3% NaCl
B. 0.9% NaCl
C. 1.2% NaCl

27. Which of the following solutions is hypertonic?
A. 0.9 % NaCl
B. 5% dextrose
C. 20% mannitol
D. Distilled water

28. The volume of RBC placed in a NaCl solution with an osmolality of 280 mOsm/Kg H_2O is 100 femtoliters. What will be the steady state volume when they are placed in a NaCl solution with an osmolality of 350 mOsm/Kg H_2O?
A. 120 fL
B. 80 fL
C. 50 fL
D. Data inadequate

29. ICF volume does **not** change when dehydration is:

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A. isotonic
B. hypertonic
C. hypotonic

30. Two liters of 0.9% NaCl is administered to a 12-year old boy with moderate isotonic dehydration. What is the expected change in ICF volume after NaCl administration?
A. No change
B. Increase by 0.5 liter
C. Increase by 2 liters
D. Decrease by 0.5 liter
E. Decrease by 2 liters

31. ICF volume decreases when dehydration is:
A. isotonic
B. hypertonic
C. hypotonic

32. If the intent is to replenish total body water in a dehydrated individual which of the following should be administered intravenously?
A. 0.9% NaCl
B. 5% dextrose solution
C. Albumin
D. 10% glucose solution
E. Distilled water

33. Cell volume and pressure is mainly dependent upon activity of:
A. Na glucose cotransporter
B. Na-K pump
C. glucose transporter
D. Na-Ca exchanger

34. Which of the following exerts the greatest osmotic effect across capillaries on a mole-mole basis?
A. Sodium
B. Chloride
C. Dextran
D. Hydroxyethyl starch
E. Albumin
F. Fibrinogen

35. The rate of diffusion of a substance across the cell membrane is **inversely** proportional to:
A. concentration gradient for the substance
B. diffusion coefficient
C. surface area available for diffusion

D. thickness of the membrane

36. Which of the following modes of transport across the cell membrane is quantitatively more important for flux of ions?
A. Diffusion
B. Filtration
C. Vesicular transport

37. Amongst plasma proteins, albumin makes the greatest contribution to the colloid osmotic pressure of plasma proteins **because**, relative to most plasma proteins, albumin:
A. is the most abundant plasma protein
B. has the longest half-life
C. has the lowest molar mass
D. exits the capillary fastest

38. Osmotic pressure of crystalloids is not included in the Starling's equation describing fluid exchange across capillaries **because:**
A. they were discovered after Starling described the forces
B. crystalloids carry electric charges
C. crystalloids diffuse freely across the capillary endothelium
D. the quantity of crystalloids in plasma is negligible compared to plasma proteins

39. The term oncotic pressure is applied to osmotic pressure exerted by:
A. albumin and other plasma proteins across the capillary wall
B. crystalloids across the cell membrane
C. hemoglobin across the capillary wall
D. substances such as urea, lactate, glucose across the cell membrane

40. Which of the following is matched **incorrectly?**
A. Microfilaments: actin, myosin
B. Intermediate filaments: vimentin, keratin
C. Microtubules: clathrin
D. Cytoskeleton: spectrin, ankyrin

41. The mitotic spindle is made up of a protein called:
A. tubulin
B. caveolin
C. connexin

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D. annexin

42. The mitochondrial genome is **absent** from:
A. sperm cells
B. ovum
C. mature red blood cells
D. white blood cells

43. Cytosolic calcium concentration in unexcited cells is about:
A. 2.5 mM
B. 10 mM
C. 150 μM
D. 100 nM

44. Most of the calcium in the endoplasmic reticulum is sequestered by:
A. calmodulin
B. caldesmin
C. calbindin
D. calsequestrin

45. Which of the following statements regarding regulation of cell cycle is **incorrect?**
A. This serves to regulate transition of the cell from one phase of the cell cycle to the next.
B. At restriction points, cyclins always promote transition from G0 to S phase.
C. Defects in DNA synthesis normally allow progression from G2 to M phase.
D. Deficiency of p53 allows progression to M phase.

46. Which of the following is an example of primary active transport?
A. Ca extrusion from cells by the Na-Ca exchanger
B. Glucose entry into cells through glucose transporter 2 (GLUT-2)
C. H_2O flux across cell membranes through aquaporins
D. Glucose uptake into intestinal epithelial cells by Na-glucose cotransporter 1 (SGLT-1)
E. Ca sequestration in sarcoplasmic reticulum by Ca-ATPase

47. Sodium-glucose cotransport in the intestine and kidney is an example of:
A. primary active transport
B. secondary active transport

C. facilitated diffusion
D. passive transport

48. Which of the following is / are active transport processes? *(Select all correct answers).*
A. Extrusion of calcium into ECF
B. Efflux of K during repolarization
C. Entry of chloride into neurons
D. Transcytosis (vesicular transport)

49. Which of the following processes is ATP dependent? *(Select all correct answers).*
A. Acidification of lysosomes
B. Actin-myosin cross bridge cycling
C. Exocytosis
D. Micropinocytosis

50. Which of the following transport processes is mediated by a carrier protein in the plasma membrane? *(Select all correct answers).*
A. Glucose uptake through SGLT-1
B. Na influx through Na channels
C. Na-K ATPase
D. Water fluxes through aquaporins

51. Which of the following processes does **not** exhibit 'saturation kinetics'?
A. Facilitated diffusion
B. Na^+-Ca^{2+} exchanger
C. Simple diffusion
D. Na^+ coupled active transport

52. Na-K-2Cl transporter in the apical membrane of the thick ascending limb of the loop of Henle is an example of:
A. primary active transport
B. secondary active transport
C. passive transport
D. countertransport

53. Which of the following is an example of passive transport?
A. Calcium efflux by calcium pump
B. Na-Ca exchanger
C. Potassium efflux through potassium leak channels
D. Calcium sequestration in sarcoplasmic reticulum

54. Which of the following ions is **not** transported across the cell membrane by a primary active transport mechanism?
A. Na
B. Cl
C. K
D. Ca

55. Figures A and B given below depict the relationship between transport rates (in Y-axis, in arbitrary units) and concentration gradients (in X-axis, in arbitrary units) of two substances A and B respectively.
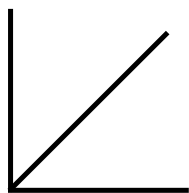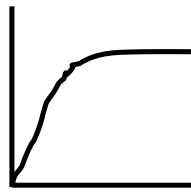

    Fig A   *Fig B*

Which of the following statements is **correct**?
A. B is transported by facilitated diffusion
B. Transport of B is ATP dependent
C. There is a 'transport maximum' for B
D. Substance A would move in one direction only

56. Emiocytosis requires an increase in the intracellular concentration of:
A. Na
B. K
C. Ca
D. Cl

57. How many transmembrane domains do G-protein coupled receptors have?
A. 2
B. 3
C. 7
D. 12

58. How many subunits do G proteins have?
A. One
B. Two
C. Three
D. Four

59. Which G protein activates adenylyl cyclase?

A. Gs
B. Gq
C. Gi
D. Gl

60. Which subunit of G proteins has intrinsic GTPase activity?
A. Alpha
B. Beta
C. Gamma
D. Delta

61. Which of the following hormones does **not** act via a G-protein coupled receptor in the cell membrane?
A. Thyrotropin releasing hormone
B. Angiotensin II
C. Antidiuretic hormone
D. Thyroxine

62. Which toxin inhibits the function of Gi?
A. Cholera toxin
B. Pertussis toxin
C. Forskolin
D. Saxitoxin

63. Which receptor does **not** span the cell membrane seven times?
A. Rhodopsin
B. *Beta*-adrenergic receptor
C. Insulin receptor
D. M_2 receptor

64. The second messengers in the phosphatidyl inositol cascade are:
A. IP3, DAG and calcium
B. protein kinases A (PKA) and C
C. cAMP and cAMP dependent PKA
D. cGMP and calcium

65. Which of the following stimulates the release of calcium from the endoplasmic reticulum?
A. IP3
B. PTH
C. 1, 25 $(OH)_2 D_3$
D. DAG

66. Protein kinase C is activated by:
A. IP_3
B. diacylglycerol (DAG)

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C. cAMP
D. guanylyl cyclase

67. Which of the following is **not** a second messenger in a signal transduction pathway?
A. cAMP
B. Guanylyl cyclase
C. Inositol trisphosphate
D. Diacyclglycerol
E. Steroid hormone – receptor complex

68. The smooth muscle relaxing effects of endothelium derived relaxing factor nitric oxide are mediated by an increase in intracellular level of:
A. cAMP
B. cGMP
C. calcium
D. endothelin

69. Which of the following hormones or growth factors does **not** signal via receptor tyrosine kinases?
A. Insulin
B. ANP
C. Epidermal growth factor
D. Platelet derived growth factor

70. Guanylyl cyclases are activated by:
A. CO, NO and ANP
B. NO, ANP and ET1
C. AII, NO and ANP
D. ANP, ET1 and AII

71. Which of the following hormone(s) mediate(s) its effects by activating nuclear / cytosolic receptors? *(Select all correct answers).*
A. Thyroxine
B. Retinoic acid
C. Estradiol
D. Progesterone
E. Aldosterone
F. Cortisol
G. 1, 25 $(OH)_2$ D3

72. Which intercellular junctions directly allow the passage of small molecules and ions between the cytosol of one cell and its neighbor without movement into interstitial fluid?
A. Gap junctions
B. Focal adhesions

C. Zonula occludens
D. Desmosomes

73. Gap junctions are made up of a protein called:
A. connexin
B. clathrin
C. cadherin
D. calcineurin

74. Connexins do **not** allow the passage of:
A. polypeptides
B. Na ions
C. Ca ions
D. inositol trisphosphate
E. amino acids

75. The philosophy that all vital mechanisms are directed toward maintaining constancy of composition of the internal environment and that this is necessary for the sustenance of life was first propounded by:
A. Claude Bernard
B. Walter B Cannon
C. William Harvey
D. Alan Hodgkin

76. The term 'homeostasis' was coined by:
A. Claude Bernard
B. Walter B Cannon
C. Homer Smith
D. William Harvey

77. The core body temperature of an experimental animal is raised from 98ºF to 106ºF by passive heating. Eventually, it dropped to 99ºF. What is the gain of the temperature regulation system in this instance?
A. Zero
B. One
C. -7
D. Infinity

78. Which of the following statements about negative feedback control systems is **incorrect**?
A. Output is one of the inputs to the system.
B. It is based on a 'set-point' for the controlled variable.
C. The system corrects "errors".

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D. The 'set point' of the system cannot be changed by inputs other than the controlled variable.

79. The SI unit of pressure is:
A. mm Hg
B. cm H_2O
C. Pascal
D. Torr

80. The diameter of a red blood cell is approximately:
A. 7×10^{-3} m
B. 7×10^{-6} m
C. 7×10^{-9} m
D. 7×10^{-10} m

81. The volume of a red blood cell is approximately:
A. 8×10^{-10} liter
B. 80 cubic microliter
C. 85 microns
D. 90 femtoliter

82. Which of the following quantities is dimensionless?
A. Specific gravity of plasma
B. Osmolality of urine
C. Resistance to air flow
D. Ejection fraction
E. Filtration fraction
F. Diffusion coefficient

83. If an individual is breathing 15 times per minute, respiratory frequency is approximately:
A. 0.1 Hz
B. 0.15 Hz
C. 0.2 Hz
D. 0.25 Hz
E. 0.3 Hz

84. If intracellular and extracellular calcium are 2 millimoles per liter and 100 nanomoles per liter, the ratio of intracellular and extracellular calcium is approximately:
A. 200
B. 2000
C. 20000
D. 200000

85. The mass of 1 mole of potassium is 39 g. If the potassium chloride concentration of a solution is 39 mg %, the concentration of potassium in this solution is closest to:
A. 1 mmol/L
B. 3.9 mmol/L
C. 10 mmol/L
D. 100 mmol/L

86. If the pH of a urine sample is 5.4, and the pH of arterial plasma is 7.4, the ratio of concentration of hydrogen ions in the urine sample and plasma is approximately:
A. 0.8
B. 2
C. 10
D. 100

87. What is the ratio of the concentration of hydrogen ions in gastric juice (pH 1.4) and arterial plasma (pH 7.4)?
A. 10^3
B. 10^4
C. 10^5
D. 10^6

88. The $[H^+]$ of arterial plasma is normally about:
A. 20 nmol/L
B. 30 nmol/L
C. 40 nmol/L
D. 50 nmol/L

89. In each of the options below, $[H^+]$ is expressed in nanomoles/L, $PaCO_2$ is in mm Hg and $[HCO_3]$ in mmol/L. Which of the following is **true**?
A. $PaCO_2 = [H^+] \times [HCO_3]$
B. $[H^+] = 24\,[PaCO_2] / [HCO_3]$

90. Normally, the ratio of $PaCO_2$ and plasma HCO_3 is:
A. 1.2
B. 1.4
C. 1.6
D. 1.8

91. The Henderson-Hasselbalch equation states that when a buffer acid is half dissociated the pH of the solution is equal to:
A. pKa
B. 7.0

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C. 2 pKa

D. 0.5 pKa

92. A buffer is most effective when the pH of the solution is close to:

A. 0.5 pKa

B. pKa

C. 2 pKa

93. The most abundant protein in mammalian cells is:

A. actin

B. collagen

C. titin

D. dystrophin

94. The diameter of which of the following cytoskeletal components is the **least**?

A. Microfilaments

B. Intermediate filaments

C. Microtubules

95. Which of the following is an example of a ligand-gated ion channel?

A. Nicotinic Ach receptor (nAchR)

B. *Beta*-2 adrenergic receptor

C. 5 HT receptor

D. Histamine 2 receptor

96. Which of the following is an example of juxtacrine communication?

A. Cell-cell anchors caused by interactions between TGF and TGF receptors on adjacent cells

B. Passage of ions and small molecules between the cytosols of adjacent cells through connexons.

C. Attachment of cell membrane to basal lamina via integrins.

97. We speak of second messengers in signal transduction pathways. In the case of epinephrine acting on beta-1 adrenergic receptors in the SA node, the first messenger is:

A. epinephrine

B. *beta*-1 adrenergic receptor

C. the alpha subunit of Gs protein

D. adenylyl cyclase

98. Activation of which of the following enzymes leads to formation of diacylglycerol and inositol 1,4,5 trisphosphate?

A. Cyclooxygenase

B. Hormone sensitive lipase

C. Lipocortin

D. Phospholipase A_2

E. Phospholipase C

99. Which of the following is **not** known to act via a G-protein coupled receptor in target cell membranes?

A. Acetylcholine

B. Aldosterone

C. Epinephrine

D. Histamine

100. Dimerization of which of the following hormone receptors is essential for signaling?

A. Acetylcholine receptor

B. *Beta-2* adrenergic receptor

C. Growth hormone receptor

D. Histamine receptor

Answers: General Physiology

1C	2C	3B	4B	5C
6A	7D	8A	9D	10B
11B	12B	13A	14C	15B
16A	17D	18A	19D	20B
21D	22A	23A	24C	25D
26A	27C	28B	29A	30A
31B	32B	33B	34E	35D
36A	37A	38C	39A	40C
41A	42AC	43D	44D	45BC
46E	47B	48AD	49all	50AC
51C	52B	53C	54B	55C
56C	57C	58C	59A	60A
61D	62B	63C	64A	65A
66B	67B	68B	69B	70A
71all	72A	73A	74A	75A
76B	77C	78D	79C	80B
81D	82ADE	83D	84C	85C
86D	87D	88C	89B	90C
91A	92B	93A	94A	95A
96A	97A	98E	99B	100C

Explanations:

1. See the note on body composition on *page 4*.

5. Children and adults have the same concentration of sodium in plasma. Yet their ECF volumes are greatly different. Thus, ECF volume is proportional to the amount of sodium contained in ECF, not the concentration of this ion.

6. The concept is the same as that in *Question 5.* ICF contains more osmoles than ECF because it is the larger of the two compartments.

7. Formula for calculating serum osmolality is on *page 4.*

8. Effective osmolality of plasma is defined on *page 5.*

10. Osmolality of a solution depends upon the number of osmoles per unit volume of the solution. 1 Na ion and 1 albumin molecule exert the same osmotic effect. The concentration of Na in plasma is 140 mmol/L. The concentration of albumin in plasma is much less. Thus, the contribution of proteins to the osmolality of plasma is negligible. This is why they are not included in the equation used to calculate serum osmolality.

11. The osmolality of normal human plasma is approximately 275-295 mOsm/L, but the question is about the osmolar concentration of sodium which is 135-145 mOsm/L.

18. Examples of substances that distribute exclusively in the ECF include inulin, mannitol, and sucrose. Isotonic solutions of inulin, mannitol and sucrose can all be used to determine ECF volume. Radioiodinated albumin may be used for estimating plasma volume.

20. Indicator-dilution principle: Volume of distribution (Vd) of the indicator equals the amount injected (A) divided by the concentration (C) in plasma (of the indicator) after mixing.

In the above example,
Vd of sucrose = ECF volume
Amount of sucrose injected iv = 100 mg
Amount metabolized = 5 mg
Amount remaining in ECF = 95 mg
Concentration after mixing = 0.01 mg/ml

Vd of sucrose = 95 mg / 0.01 mg/ml = 9500 ml = 9.5 L

23. TBW = ICF + ECF volumes = 28 + 14 = 42 L
Concentration of potassium in ICF = 140 mM *(K is the major intracellular cation and its typical concentration is worth remembering)*
Concentration of potassium in ECF = 5 mM
Plasma volume = 3.5 L
Volumes of all other fluids combined = 38.5 L
Amount of K in plasma is about 20 mmol.
Amount of K in all other fluids ~ 3980 mmol.
Don't do an actual calculation, you can easily *ballpark* to 0.4% as the correct answer since the choices are sufficiently apart – save time!

24. Volume of distribution of this substance = 30% of total body water (TBW). In a healthy adult male weighing about 70 kg, the volumes of ICF and ECF are 28 and 14 L respectively; i.e., $1/3^{rd}$ of TBW is outside cells. Thus, the substance in question most likely distributed exclusively in ECF.

28. The following mathematical relationship applies to the situation described in the question.
$Pi \times Vi = Pf \times Vf$
Pi and Pf are initial and final osmolalities and Vi and Vf are initial and final volumes respectively
$280 \times 100 = 350 \times Vf$
Vf = 80 femtoliters
Thus, there is a decrease in RBC volume in the steady state when it is placed in hypertonic saline.

29. Isotonic dehydration is the result of proportional loss of NaCl and water (basically a fluid with the composition of plasma minus proteins) from ECF, and there is no change in ECF osmolality. There is thus no drive for movement of water between ICF and ECF, and therefore there is no change in ICF volume. Therapy is aimed at replenishing ECF volume such as with 0.9% NaCl, a solution that is isotonic with normal human plasma. In hypertonic dehydration, steady state ECF osmolality increases; thus, it leads to intracellular dehydration as well. In hypotonic dehydration, steady state osmolality of ECF is decreased and some of this water will enter cells.

32. In the steady state, hypertonic dehydration is associated with a reduction in ECF as well as ICF volume. So therapy must be aimed at replenishing total body water, not merely ECF volume. 5% dextrose solution is iso-osmotic (its osmolality is approximately 280 mOsm/kg H_2O). However, in the steady state, all of the dextrose (D-glucose) is taken up by cells and metabolized, and the net result is the addition of water that distributes in ECF and ICF.

33. By pumping 3 Na ions out of the cell for every 2 K ions pumped into the cell, the Na-K ATPase effectively removes one osmole (and the corresponding water equivalent) from the cell. Thus, inhibition of Na-K pump would cause cells to swell.

34. Starling's law of filtration: Starling described forces that affect fluid flux across capillaries.

Fluid movement = Kf [(Pc + πi) – (Pi + πc)], where,
Kf - capillary filtration coefficient
Pc - hydrostatic pressure in the capillaries
Pi - hydrostatic pressure in the interstitium
πc - capillary colloid osmotic pressure
πi - colloid osmotic pressure in the interstitium

Normally, Pc is the principal force favoring filtration. The osmotic pressure of plasma is normally about 25 mm Hg higher relative to the osmotic pressure of interstitium because 'plasma' proteins (colloids) are limited to plasma; proteins in plasma restrain fluid filtration into the interstitium.

Albumin is quantitatively the most important contributor to the colloid osmotic pressure of plasma. 1 g of albumin in 100 ml of plasma exerts an osmotic effect of 6 mm Hg; the same concentration of globulins exert a pressure of only about 1.5 mm Hg.

35. According to Fick's law of diffusion,
Diffusion rate (J) = DA dc/dx
D - Diffusion coefficient
A- Area available for diffusion
dc - concentration gradient

dx - thickness of membrane

The diffusion coefficient is affected by factors such as temperature, and the permeability of the membrane to the molecule/ion in question. Permeability of a membrane to an ion/molecule is in turn affected by the number of ion channels or transporter molecules available to transport the species in question.

37. Osmotic pressure is simply dependent upon the number of particles and not the mass of a substance. Albumin (or plasma proteins) does not make a significant contribution to the osmolality and osmotic pressure of plasma because they are found in concentrations much lower than Na, Cl – the most effective osmoles in ECF. However, albumin is quantitatively the most important contributor to the colloid osmotic pressure of plasma (oncotic pressure) because it is restricted to plasma and does not exit the capillary as fast. Among plasma proteins, albumin is the most abundant and hence it contributes the most to colloid osmotic pressure of plasma.

38. Crystalloids include NaCl, Ringer's lactate – they diffuse freely across the capillary so they do not cause an osmotic pressure difference across the capillary membrane. In contrast, colloids include large molecular weight substances such as plasma proteins, plasma expanders like dextran, gelatin and hydroxyethyl starch that distribute primarily in plasma and restrain filtration of fluid across capillaries.

39. Actin is present in virtually all cells although most abundant in muscle. Collagen is the most abundant protein in extracellular matrix. Titin is the largest protein in the human body. Dystrophin is a glycoprotein in the muscle cell membrane; it is involved in transmitting the tension generated by shortening of sarcomeres eventually to the tendon.

40. Microtubules have a 9 + 2 fibrillar structure. They are made up of tubulin, dynein, and kinesin. The mitotic spindle is made up of microtubules. Colchicine arrests cells in metaphase by inhibiting polymerization of microtubules.

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42. Mature RBCs do not have mitochondria and exclusively use anaerobic glycolysis to generate ATP. Although sperm cells contain mitochondria, mitochondria from sperm cells do not enter the secondary oocyte during fertilization; i.e., mitochondrial DNA in the zygote is exclusively of maternal origin.

43. ECF $[Ca^{2+}]$ = 2.5 mM
Cytosolic $[Ca^{2+}]$ in unexcited cells = 100 nM
ECF $[Ca^{2+}]$ / cytosolic $[Ca^{2+}]$ = 25000

A transient increase in intracellular calcium is *used* as a signal to activate or inactivate intracellular processes such as exocytosis, muscle contraction. $[Ca^{2+}]i$ is quickly normalized by the sarcoplasmic-endoplasmic reticulum calcium pump (SERCA pump) and a Na-Ca antiporter (also called the Na-Ca exchanger, NCX) in the cell membrane. Sustained increases in intracellular calcium trigger apoptosis, culminating in cell death.

45. Deficiency of the tumor suppressor protein p53 allows entry into M phase and facilitates the growth of tumors, and a number of cancers are associated with deficiency of p53.

48. Proteins are translocated from capillaries into the interstitium by transcytosis (vesicular transport). This involves endocytosis of the protein molecules into vesicles in endothelial cells and exocytosis of these vesicles into the interstitium.

49. All of them are examples of active processes. There are proton translocating ATPases in lysosomes.

50. The term 'carrier-mediated transport' emphasizes the fact that the transported species binds to a transport protein. Glucose *attaches* to the GLUT molecule and a conformational change in GLUT shuttles glucose to the interior of the cell. The transport of Na and K by Na-K ATPase is also an example of carrier-mediated transport because both ions bind to the transporter.

In contrast, aquaporins and ion channels are not carrier proteins; they are channels through which water or the respective ions flow. The ions themselves do not bind to ion channels. This is an example of diffusion facilitated by the presence of proteins in the cell membrane (facilitated diffusion). Some authors also call it "simple diffusion".

54. Chloride transport across the cell membrane occurs by secondary active transport mechanisms or diffusion but not by a primary active transport mechanism.

55. Option C (correct): Substance B uses a saturable transport mechanism. Susbtance B may be transported either by facilitated diffusion (example, GLUT) or active transport (example, Ca ATPase), so *option A* is not a valid inference. Both are like enzyme catalyzed reactions and exhibit saturation kinetics. *Option B* is not necessarily true – GLUT is an example of facilitated diffusion but it does not use ATP. Diffusion rate is proportional to the concentration gradient when other factors affecting diffusion are held constant. *Option D* is incorrect – the diffusing species moves randomly but net diffusion occurs down a concentration gradient.

56. Emiocytosis (exocytosis) of secretory granules requires a rise in intracellular calcium – for example, the release of insulin by B cells of the pancreas involves depolarization of the B cell by closure of K channels followed by influx of calcium through voltage dependent calcium channels. The transient rise in intracellular calcium brings about emiocytosis of granules that contain insulin, proinsulin, C-peptide.

72. Gap junctions (electrical synapses; connexons) are made up of a protein called connexin; these are large diameter channels that allow the passage of ions and other small molecules such as amino acids and glucose. Thus, they electrically couple adjacent cells. They are found in visceral smooth muscle and heart and between some neurons. The ventricle of the heart contracts as one unit because gap junctions electrically couple all muscle fibers in the ventricle. However, connexins do not allow large molecules such as proteins to pass between cells.

73. Clathrin is a protein involved in receptor-mediated endocytosis; it is the protein that coats pits that are the sites of aggregation of cell-surface receptors involved in receptor-mediated endocytosis. Cadherin is a cell adhesion molecule. Calcineurin, like calmodulin, is a calcium binding protein found in cells.

77. Gain of a control system = correction / error. In this example, the correction is 7 degrees i.e. from 106ºF down to 99 ºF, and the error (deviation from the original value of 98ºF in the steady state) is 1ºF. The gain of a 'negative feedback control system'is negative. If the error is zero, gain is infinite. Guyton and colleagues suggested that the renal 'pressure-natriuresis' mechanism for controlling body fluid volumes has infinite gain.

78. Take temperature regulation as an example. The 'central controller' or integrator' of all relevant sensory input is the hypothalamus. The fact that a rise in body temperature leads to a fall in temperature back toward 98.6ºF suggests that temperature is the controlled variable, and this operates as a *negative feedback control system*. This means that there must be a 'sensor' for temperature. The hypothalamus is in fact able to sense core body temperature.

When there is an infection, often the release of cytokines as part of the immunologic response act on the brain to raise the 'set-point' of the temperature regulation system to a higher level so that a higher than normal body temperature is maintained and results in fever. The control system is then said to be 'reset' to a higher operating point. However, once the infection and the immune response resolve and the concentration of cytokines and prostaglandins that reset the temperature set point upward resolve, the set point returns to 98.6ºF indicating that resetting of a control system is not necessarily permanent.

As far as biological systems are concerned, the application of control system theory is a means to share our understanding of how they operate but there is risk of teleologic misconception in using control theory jargon.

85. Concentration of KCl = 39 mg% = 39 mg/dL = 390 mg/L = 0.390 g/L
Molar mass of K = 39 g
1 molar solution of K = 39 g/L
Thus, 0.39 g/L of K = 10 mmol/L of K

90. Normally, $PaCO_2$ = 40 mm Hg, and plasma HCO_3 = 24 mM and $PaCO_2$ / $[HCO_3]$ = 1.6. If this were the case, then the $[H^+]$ of arterial plasma would be equal to 40 nM (corresponding to an arterial pH of 7.4) as predicted by the modified Henderson equation.

96. Ganong, 2012, p. 54

99. Ganong, 2012, p. 59

100. Ganong, 2012, p. 63-64

NERVE, MUSCLE, SYNAPTIC PHYSIOLOGY AND NEUROTRANSMISSION

Resting membrane potential (RMP) refers to the transmembrane potential (i.e., the potential difference across the cell membrane) in the steady (unexcited) state. RMP is present across all cells (see below).

A summary of the genesis of resting membrane potential.
1. The cell membrane is impermeable to organic anions and proteins present in ICF.
2. In neurons for example, in the resting state, the cell membrane is quite permeable to K, (about 50 times more permeable to K than Na). K exits the cell down its concentration gradient, making the inside of the cell negative with respect to exterior.
3. Charge separation occurs across the membrane (a thin capacitor) leaving the inside of the membrane negative with respect to outside.
4. Additionally, the Na-K ATPase mechanism contributes a small extent to making the inside of the cells negative.

Magnitude of RMP in different tissues

Cell / tissue	Magnitude of RMP (inside negative)
Nerve cells	- 70 mV
Skeletal muscle	- 90 mV
GI smooth muscle	Variable; - 40 to - 60 mV
Cardiac muscle	- 90 mV
SA node	- 70 mV
Red blood cells	- 10 mV

The two types of forces tending to drive ion flux across membranes are the electrical and chemical (concentration) gradients. Flux requires the membrane to be permeable to ions.

Equilibrium potential: the membrane potential at which net transmembrane flux of a particular ion is zero because the electrical gradient counterbalances the chemical gradient.

Example, Na flux across the membrane would stop when the membrane potential reaches + 60 mV. The equilibrium potential of an ion is calculated using the Nernst equation.

E_{Na} = - 61 log [Na]i / [Na]o, where i and o refer to intra- and extracellular concentration of the ion in question.

E_{Na} = - 61 log [10/140] = + 61 mV

Similarly, for K:
E_K = - 61 log [K]i / [K]o
Normally, Ki = 140 mM, Ko = 5 mM
E_K = - 90 mV

Equilibrium potentials for various ions across nerve cell membranes:

Ion	ICF (mM)	ECF (mM)	Equilibrium potential (mV)
Na	10	140	+ 60
K	140	5	- 90
Cl	10	120	- 70
Ca	100 nM	2.5	+ 130

Excitability: The response to a 'threshold stimulus' with a propagated action potential.

The physiologic basis of excitability: High potassium permeability at rest (and therefore an RMP in the range of –50 to –90 mV), and presence of voltage gated Na channels are essential. Only nerve, neurons, and the three muscle types (skeletal, cardiac and smooth) are excitable. Other tissues are not.

What is the effect of hyperkalemia on RMP of cardiac muscle cells?
When plasma [K+] = 5 mM, the potassium equilibrium potential of cardiac muscle cells is minus 90 mV inside negative.

When plasma [K+] is raised to 10 mM, or when extracellular potassium in the vicinity of ischemic or injured myocardium increases to 10 mM, the potassium equilibrium potential in that zone becomes

E_K = - 61 log [140/10] = - 70 mV

Thus hyperkalemia makes K_{Eq} less negative.

Since the resting membrane is much more permeable to K relative to Na, RMP is closer to E_K. Thus, hyperkalemia makes RMP less negative; closer to threshold. The SA node has an RMP of -70 mV. In this situation, the injured myocardium would be expected to compete with SA node to pace the heart. This clearly increases the risk of cardiac arrhythmias.

Hypokalemia makes cells less excitable by making RMP more negative.

RMP is measured with microelectrodes, and it is calculated using the Goldman-Hodgkin-Katz equation. The RMP is affected by the conductance of all ions in a resting membrane. This is why RMP differs between tissues (-60 mV in neurons and -90 mV in skeletal muscle).

If the nerve is stimulated with the cathode (using a subthreshold stimulus), it produces small depolarizations (called catelectrotonic potentials). These small depolarizations are *local responses;* i.e. they are not propagated through the nerve fiber. The stimulus that is just adequate to result in a propagated action potential is called ***threshold stimulus.***

The membrane potential at which voltage gated Na-channels open all at once to result in a full fledged action potential is called ***firing level*** or ***threshold level*** and it is about -55 mV in nerve fibers. Within a millisecond of opening, Na channels get deactivated; i.e. close and cannot be opened until the membrane potential comes back down to firing level. On the other hand, voltage gated K channels open allowing rapid efflux of K. This repolarizes the membrane; i.e., brings it back to RMP.

Differences between local responses and action potentials:
Local responses (also called *electrotonic* potentials) may be depolarizing (also called **catelectrotonic** potentials) or hyperpolarizing (also called **anelectrotonic** potentials). Excitatory postsynaptic potentials (EPSP) and miniature motor end plate potentials (MEPP) are examples of catelectrotonic responses. Inhibitory postsynaptic potentials (IPSP) are anelectrotonic

responses. Electrotonic potentials are *graded responses* (i.e. proportional to stimulus intensity) that occur with subthreshold stimuli, and their magnitude is typically a few mV. They undergo spatial and temporal summation. They are not propagated. In contrast, action potentials are propagated responses that occur with "threshold stimuli". They are all-or-none; i.e., they occur with a constant size.

Excitability during various phases of the action potential:
Absolute refractoriness: No matter how strong the stimulus, a nerve (or muscle) is absolutely refractory to stimulation during the action potential until repolarization brings the membrane back to firing level. Within a millisecond of the beginning of the upstroke of the action potential, sodium channels are inactivated.

Relative refractory period: In this period, only a suprathreshold stimulus would trigger an action potential. The reason why a stronger stimulus is required for excitation is because the stimulus has to overwhelm the repolarizing current.

Supernormal phase: a weaker stimulus would trigger an action potential.

Subnormal phase: during afterhyperpolarization, a stronger stimulus would be required to bring the membrane to threshold.

Nerve and muscle may be excited using electrical, chemical or mechanical stimuli. For electrical stimuli, one may speak of the following stimulus parameters.
1. **Intensity:** subthreshold, threshold, suprathreshold
2. **Duration:** typically (in milliseconds)
3. **Frequency:** 1-100 Hz
4. **Rise time:** time in which stimulus intensity rises to its maximum value.

Threshold stimulus: The minimum stimulus intensity that elicits an action potential in an excitable tissue under a given set of conditions.

All-or-none law: If a stimulus is sufficiently intense as to bring the membrane to threshold, the

intensity of the stimulus has no bearing on the size of the action potential.

Physiologic basis of the all-or-none law:
Action potential occurs only when the *firing level (or threshold)* is reached because the voltage-gated sodium channels that allow a massive influx of Na open and cause the upstroke of the action potential occur only at the firing level.

Effect of stimulus intensity on electrical response of nerve and muscle (all-or-nothing):

Stimulus Intensity	*Electrical response in nerve / muscle*
Subthreshold	No action potential
Threshold	Action potential
Suprathreshold	Action potential of the same strength
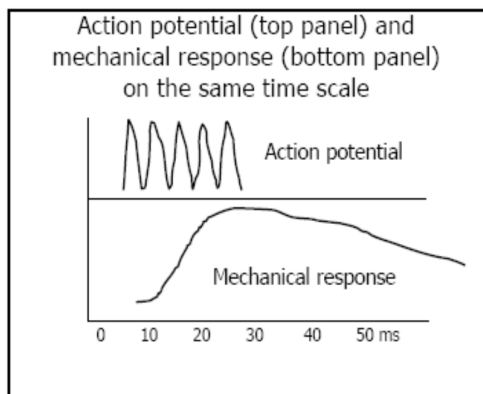
The figure above depicts action potentials in a skeletal muscle fiber (top panel) and mechanical response (bottom panel) on the same time scale in skeletal muscle. Whereas the duration of the action potential is only about 5 ms, the duration of the mechanical response (contraction followed by relaxation) is much longer. Thus, it is possible to summate mechanical responses to successive stimulation of muscle. In cardiac muscle, this is not possible since the duration of absolute refractory period is much longer (about 200 ms at a heart rate of 75 bpm), and therefore relaxation commences before cardiac muscle is reexcitable.

Muscle twitch: A muscle twitch is contraction followed by relaxation occurring in response to a single stimulus.

Twitch duration = contraction time + relaxation time.

Twitch duration is quite variable and skeletal muscle is classified as *fast* or *slow*, depending upon twitch duration and other characteristics. The duration of muscle twitch in fast skeletal muscle fibers could be as short as 10 ms. In contrast, in slow skeletal muscle fibers, twitch duration is typically greater than 100 ms.

In cardiac muscle, when average heart rate is 75 beats per minute, average twitch duration is 800 ms; i.e., cardiac muscle is much slower than slow skeletal muscle. The twitch duration in the smooth muscle of sphincters is longer. Smooth muscle is thus the 'slowest' of the three muscle types.

Tetanizing stimulus frequency: With high frequency stimulation of skeletal muscle, it is possible to summate the effects of multiple stimuli and increase the force of muscle contraction. Tetanus is the most forceful and sustained muscle contraction (i.e. with no relaxation in between). To tetanize skeletal muscle, it must be stimulated at a minimum frequency called the *tetanizing frequency; this* depends on the duration of contraction. The minimum stimulus frequency required for tetanizing the muscle is the reciprocal of the contraction period expressed in seconds.

For example, if the contraction period is 100 ms (i.e., 0.1 s), the tetanizing frequency is 1/0.1 = 10 Hz.
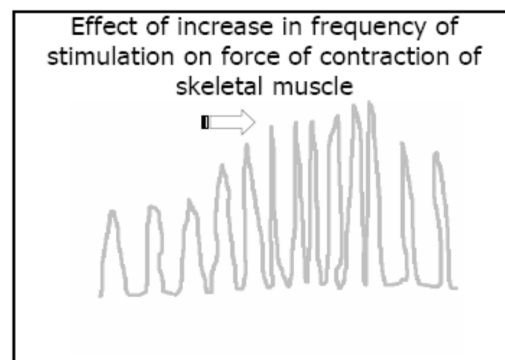
The figure above depicts the effect of an increase in the frequency of contraction of skeletal muscle on force. With increasing frequency of stimulation at a given intensity, the force of successive

contractions increase because of the *beneficial effect* of previous contractions and it is related to increased availablility of intracellular calcium for later contractions. This is called the **staircase phenomenon**, *Treppe* or **Bowditch effect.** With a decrease in frequency of stimulation, a gradual decrease in force of contraction is also observed.

Axoplasmic transport: This refers to transport of molecules in the cytoplasm of the axon. This is not to be confused with conduction of the nerve impulse, which is much faster.

Anterograde transport (i.e., from the cell bodies to axon terminals) is brought about by microtubules (kinesin and several other proteins are involved). **Retrograde transport** involves transport of a substance from nerve terminal toward the cell body. This is also achieved on microtubule tracks in the axoplasm. Viruses, some neurotrophins are taken up and transported this way.

Axoplasmic transport	Speed (mm/day)
Fast anterograde transport	400
Slow anterograde transport	0.5–10
Retrograde transport	200

Questions
Instruction: **Except where indicated, select the single best answer.**

1. Most of the ATP generated in nerve cells is utilized to energize the:
A. Na-Ca exchanger
B. H-ATPase in the cell membrane
C. Na-K ATPase
D. synthesis of proteins

2. Fast anterograde transport occurs at a rate of about:
A. 40 mm/day
B. 400 mm/day
C. 1 mm/day
D. 10 mm/day

3. The largest known axons are found in:
A. humans
B. whales
C. squids
D. ostriches

4. The normal resting cardiac muscle cell is most permeable to:
A. Na
B. K
C. Ca
D. Cl

5. The membrane potential at which net flux of an ion across the membrane is zero is called:
A. resting membrane potential
B. spike potential
C. threshold potential
D. electrotonic potential
E. equilibrium potential of that ion

6. The resting membrane potential of ventricular cardiomyocytes is closest to the equilibrium potential for:
A. sodium
B. chloride
C. potassium
D. calcium

7. The Nernst potential (also called equilibrium potential) is positive for:
A. Na and Cl
B. Na and K
C. Na and Ca
D. K and Cl

8. The equilibrium potential of chloride in mammalian spinal motor neurons is typically about:
A. + 20 mV
B. minus 40 mV (inside negative)
C. minus 70 mV (inside negative)
D. minus 90 mV (inside negative)

9. The resting membrane potential of some neurons is equal to the equilibrium potential of:
A. Na
B. K
C. Cl
D. Ca

10. If intracellular and extracellular potassium concentrations are approximately 140 mmol/L and 14 mmol/L respectively, the equilibrium potential for potassium is approximately:

A. minus 30 mV inside negative
B. minus 60 mV inside negative
C. minus 90 mV inside negative
D. minus 120 mV inside negative

11. Which one of the following increases excitability of cardiac muscle?
A. Increase in ECF $[K^+]$ from 5 to 10 mM
B. Increase in ECF $[K^+]$ from 5 to 70 mM
C. Decrease in ECF $[K^+]$ from 5 to 1.4 mM

12. Hypokalemia would be expected to result in:
A. increased neuronal excitability
B. a more negative RMP
C. no change in RMP
D. a decrease in firing level of neurons

13. The membrane potential of cardiac muscle cells is most affected by even a small change in plasma concentration of:
A. Na
B. K
C. Cl
D. Ca

14. Which of the following would justify excluding sodium conductance from the equation for estimating resting membrane potential in skeletal muscle fibers?
A. Extracellular [Na] is higher than ICF [Na]
B. Na-K pump extrudes 3 Na for 2 K pumped in
C. Negligible Na permeability of the resting membrane
D. Unexcited cells are equally permeable to Na and K

15. Excitability, in neurophysiology, is defined as:
A. presence of a resting membrane potential
B. use of more than 30% of ATP synthesized for powering the Na-K ATPase
C. response to a threshold stimulus with a propagated action potential
D. presence of voltage gated ion channels in a tissue

16. Physiologically, the site of origin in motor neurons of conducted impulses is the:
A. dendritic zone
B. axon hillock
C. node of Ranvier
D. terminal buttons

17. In motor neurons, the portion of the cell with the lowest threshold for the production of a full-fledged action potential is:
A. initial segment
B. soma
C. dendritic zone
D. node of Ranvier

18. In the CNS, the membranes that wrap around myelinated neurons are those of:
A. Schwann cells
B. oligodendroglia
C. endothelial cells
D. astrocytes

19. The number of Na channels per square micrometer of membrane in myelinated mammalian neurons is maximum in the:
A. cell body
B. dendritic zone
C. initial segment
D. node of Ranvier

20. Action potential conduction velocity is influenced by:
A. axon diameter
B. temperature
C. myelination

21. Which one of the following statements about electrotonic potentials is **incorrect?**
A. They are graded responses.
B. They are local (non-propagated) responses.
C. They may be depolarizing or hyperpolarizing.
D. They are produced by a threshold stimulus.

22. A stronger than normal stimulus can cause excitation of nerve or muscle during the:
A. absolute refractory period
B. relative refractory period
C. spike potential
D. overshoot

23. An excitable cell has an RMP of -70 mV and a firing level of - 50 mV. This cell would be inexcitable when its membrane potential is:
A. - 30 mV
B. - 55 mV
C. - 70 mV

D. - 90 mV

24. For the same conditions (as in the above question), the cell would be **most excitable** when its membrane potential is:
A. - 30 mV
B. - 55 mV
C. - 70 mV
D. - 90 mV

25. The duration of action potential in a nerve is typically closest to:
A. 2 ms
B. 20 ms
C. 200 ms
D. 2000 ms

26. Is conduction of nerve impulse in motor axons unidirectional or bidirectional?

27. A traveling nerve impulse does **not** depolarize the area immediately behind it because:
A. it is hyperpolarized
B. the area immediately behind is refractory
C. it is not self-propagating
D. the conduction is always orthodromic

28. The nerve fiber type **most susceptible** to conduction block by pressure is:
A. type A
B. type B
C. type C

29. Which of the following nerve fibers is **most susceptible** to hypoxia?
A. Somatic motor neurons
B. Nociceptive afferents
C. Preganglionic autonomic neurons
D. Fibers transmitting touch sensation

30. Which nerve fiber type is **most susceptible** to conduction block by local anesthetics?
A. Type A
B. Type B
C. Type C

31. In spinal anesthesia, which of the following is lost first?
A. Sympathetic tone
B. Sensation in the lower limbs
C. Motor function

D. Proprioception

32. Nociceptors (nerve endings signaling pain) signal through:
A. Aα fibers
B. Aβ fibers
C. Aγ fibers
D. Aδ fibers
E. C fibers

33. The duration of action potential in a skeletal muscle fiber is typically:
A. 5 ms
B. 25 ms
C. 100 ms
D. 250 ms

34. When heart rate is about 75 beats per minute, the mean duration of action potential in ventricular muscle cells is approximately:
A. 5 ms
B. 25 ms
C. 100 ms
D. 250 ms

35. Though the equilibrium potential of Na is + 60 mV, membrane potential does not reach this value during the overshoot of the action potential because:
A. the concentration gradient of Na is reversed
B. Na channels undergo inactivation in 1 ms
C. voltage gated K channels open when membrane potential reaches 0 mV
D. the membrane is impermeable to Na

36. In skeletal muscle, thin filaments do **not** contain:
A. actin
B. myosin
C. troponin
D. tropomyosin

37. Actin is tethered to Z-lines in the sarcomere by:
A. actinin
B. titin
C. nebulin
D. dystrophin

38. Ryanodine receptor is located in the:

A. sarcolemma
B. T-tubule
C. terminal cisterns of sarcoplasmic reticulum
D. cytosol

39. The ATPase activity of which of the following proteins is altered to regulate skeletal muscle contraction?
A. Actin
B. Myosin
C. Troponin
D. Tropomyosin

40. The major source of calcium for contraction of skeletal muscle is:
A. ECF
B. cytosol
C. mitochondria
D. sarcoplasmic reticulum

41. Excitation and contraction of skeletal muscle are coupled by:
A. ATP
B. myosin
C. release of calcium into sarcoplasm
D. calmodulin

42. *Select all correct answers.* Which of the following slow skeletal muscle relaxation?
A. Slow myosin ATPase
B. Inhibition of Ca-Mg ATPase
C. ATP depletion

43. Rigor mortis is due to:
A. damage to actin and myosin
B. rapid sequestration of Ca in ER
C. increased myosin ATPase
D. ATP depletion

44. The gene coding which of the following proteins is the largest?
A. Titin
B. Dystrophin
C. Gigantin
D. Nebulin

45. Which of the following proteins is **absent** from smooth muscle?
A. Actin
B. Myosin

C. Troponin
D. Tropomyosin

46. The activity of which contractile protein is altered to regulate smooth muscle contraction?
A. Actin
B. Myosin
C. Calmodulin
D. Tropomyosin

47. The calcium-binding protein that plays a key role in the regulation of smooth muscle cell contraction is:
A. dystrophin
B. calmodulin
C. troponin C
D. calcineurin

48. Which of the following statements about visceral smooth muscle is **incorrect?**
A. Neighboring cells are electrically coupled by means of gap junctions.
B. Contraction can occur in the absence of extrinsic neural innervation.
C. Twitch duration is typically longer when compared to skeletal muscle.
D. Force is graded by varying intracellular calcium.
E. Stretch of smooth muscle consistently increases active tension.

49. An example for *multi-unit (nonsyncytial) smooth muscle* is:
A. stomach
B. uterine myometrium
C. iris
D. ureters

Questions 50-52. True/False

50. **Type I skeletal muscle fibers:**
A. They are called slow, oxidative fibers.
B. They are innervated by slow motor units.
C. They have slow myosin ATPase activity.
D. They contain myoglobin.
E. They have high oxidative capacity.

51. **Type IIA skeletal muscle fibers:**
A. They are called fast oxidative, glycolytic fibers.

B. They are innervated by fast motor units resistant to fatigue.
C. They have fast myosin ATPase activity.
D. They have some myoglobin.
E. They have moderate oxidative capacity.

52. **Type IIB skeletal muscle fibers:**
A. They are called fast glycolytic fibers.
B. They have little to no myoglobin.
C. They are innervated by fast motor units that are fatigable.
D. They have fast myosin ATPase activity.
E. They have low oxidative capacity.

53. Oxidative capacity is highest in:
A. type I muscle fibers
B. type IIA muscle fibers
C. type IIB muscle fibers

54. Which of the following statements is **incorrect?**
A. Contraction can occur without an appreciable decrease in the length of the muscle.
B. Contraction against a constant load with approximation of the ends of the muscle is called isotonic contraction.
C. Muscles can lengthen while doing work.
D. Isometric contractions do work whereas isotonic contractions do not.

55. When a heavy object in hand is lowered, the extension at the elbow is brought about by:
A. active shortening of the extensors
B. passive shortening of the extensors
C. active lengthening of the flexors
D. active shortening of the flexors

56. The total tension generated during skeletal muscle contraction is highest when the muscle:
A. is appreciably shorter than resting length
B. contracts isometrically at resting length
C. is stretched beyond its resting length

57. The smallest amount of muscle that can contract in response to excitation of a single motor neuron is:
A. 1 muscle fiber
B. a muscle fasciculus
C. the entire muscle
D. all muscle fibers supplied by that neuron

58. The number of muscle fibers innervated by a motor axon is smallest in:
A. gastrocnemius
B. orbicularis oculi
C. single-unit smooth muscle
D. soleus

59. Staircase phenomenon *(Treppe)* is due to:
A. increased availability of intracellular calcium
B. synthesis of stable troponic C molecules
C. summation
D. tetanus
E. increased excitability

60. The force of muscle contraction **cannot** be increased by:
A. increasing the frequency of activation of motor units
B. increasing the number of motor units activated
C. recruiting larger motor units
D. asynchronous firing of motor units
E. increasing the amplitude of action potentials in motor neurons
F. varying release of calcium from SR

61. The term 'size principle' refers to the fact that:
A. chronically denervated skeletal muscle decreases in size due to reduced release of growth factors from motor neurons
B. neurons in small motor units conduct slowly
C. small motor units are recruited for more forceful contractions
D. large, fast motor units are recruited after small, slow motor units

62. Recruitment and activation of motor units is investigated by:
A. electromyography
B. electroencepaholgraphy
C. nerve action potential recordings
D. clinical examination of tendon jerks

63. The minimum stimulus intensity that produces a compound action potential in nerve or muscle is called (or equal to):
A. rheobase
B. chronaxie
C. twice rheobase
D. twice chronaxie

64. Which of the following is **incorrect** about cardiac muscle?
A. T-system is located at the Z lines.
B. Adjacent muscle cells are coupled by gap junctions
C. Intercalated disks are at Z-lines.
D. Dependence on influx of calcium from ECF for release of calcium from the SR.
E. It contains myoglobin.
F. It contains mitochondria.
G. The twitch duration is shorter compared to type II skeletal muscle fibers.

65. When heart rate is 75 bpm, the duration of absolute refractory period of cardiac muscle is normally approximately:
A. 50 ms
B. 100 ms
C. 200 ms
D. 300 ms

66. When heart rate is about 75 beats/min, the duration of ventricular systole is about:
A. 100 ms
B. 200 ms
C. 300 ms
D. 400 ms

67. Regarding the ionic basis of action potential in working cardiomyocytes, which of the following is incorrect?
A. Phase 0: Na influx
B. Phase 1: K influx
C. Phase 2: Ca influx
D. Phase 3: K efflux

68. The shortest phase of the action potential in ventricular cardiomyocytes is:
A. Phase 0
B. Phase 1
C. Phase 2
D. Phase 3

69. Which of the following characteristics is unique to skeletal muscle and is **not** observed in normal cardiac muscle?
A. Gradation of force production
B. Refractoriness
C. Staircase phenomenon
D. Tetanizability
E. Conduction of impulse through gap junctions

70. Which of the following accelerates contraction as well as relaxation of heart muscle?
A. Norepinephrine
B. Calcium
C. Digoxin
D. Potassium

71. Under basal conditions, which is the predominant energy substrate utilized by cardiac muscle?
A. Carbohydrate
B. Amino acids
C. Ketones
D. Fatty acids

72. Which of the following is **not** a step in vascular smooth muscle contraction?
A. Ca binding to troponin C
B. Activation of calcium-calmodulin dependent myosin light chain kinase
C. Phosphorylation of myosin
D. Increased myosin ATPase activity

73. Resting membrane potential is most unstable in which of the following muscles?
A. Smooth muscle of the stomach
B. Gastrocnemius muscle
C. Orbicularis oculi
D. Muscle cells in the left ventricle

74. The addition of which of the following to a preparation of intestinal smooth muscle would **most likely** increase the frequency of spike potentials in vitro?
A. Acetylcholine
B. Epinephrine
C. Norepinephrine
D. Nitric oxide

75. The latch-bridge mechanism in smooth muscle is responsible for:
A. fast muscle twitch
B. sustained muscle contraction
C. excitation-contraction coupling
D. unstable membrane potential

76. The repolarizing phase of the action potential in nerve fibers is primarily due to:
A. Na-K ATPase

30

B. sodium influx via voltage gated sodium channels

C. potassium efflux via voltage gated potassium channels

D. calcium efflux mediated by Na-Ca exchanger

77. Denervation hypersensitivity:
A. is due to upregulation of neurotransmitter receptors in the denervated structure
B. does not occur in smooth muscle
C. partly explains the *release phenomenon* that occurs in neurological diseases

78. Neuromuscular transmission is impaired in conditions listed below (in *List A*), however, the pathogenesis of muscle weakness is different in each. Match items in *List A* with those in *List B*.

List A
1. Botulism
2. Cobra venom intoxication
3. Lambert-Eaton syndrome
4. Myasthenia gravis

List B
A. Antibodies to nicotinic Ach receptors in the motor end plate
B. Toxin inhibits Ach release from presynaptic nerve terminals in skeletal muscle neuromuscular junction
C. Competitive blockade of nicotinic Ach receptors in skeletal muscle motor end plate
D. Antibodies to voltage-gated calcium channels in presynaptic terminals

79. Kinemyography is a novel technique for monitoring neuromuscular function.

80. Which of the following is correct with regard to numbers of each of the following in the CNS?
A. neurons >> glia > synapses
B. glia >>> synapses >>> neurons
C. synapses >> glia > neurons
D. synapses >> neurons >> glia

81. Which of the following types of cells work as scavenger cells in the CNS?
A. Microglia
B. Oligodendroglia
C. Ependymal cells

D. Astrocytes

82. Which of the following cells in the CNS is primarily involved in the reuptake of excitatory neurotransmitters released by neurons?
A. Astroglial cell
B. Microglial cell
C. Oligodendroglial cell
D. Ependymal cell

83. Which is the commonest type of synapse in the CNS?
A. Axosomatic synapse
B. Axodendritic synapse
C. Axoaxonal synapse

84. Which of the following events in postsynaptic neuronal membrane underlie excitatory postsynaptic potentials?
A. Opening of Na channels
B. Closure of K channels
C. Opening of calcium channels
D. Opening of chloride channels

85. Which of the following events in postsynaptic neuronal membrane underlie inhibitory postsynaptic potentials? Opening of:
A. Na channels
B. Ca channels
C. Cl channels

86. Neuron C responds to stimulation of neuron A with a propagated action potential only when neuron B (which terminates only on neuron C) is also simultaneously stimulated. Which of the following inferences is justified?
A. Neuron C releases glycine.
B. Neuron B releases an excitatory neurotransmitter.
C. The synapse between A and C is axosomatic.
D. The neurotransmitter released by neuron A opens K channels in neuron C.

87. The minimum time for transmission across one synapse is:
A. 0.5 ms
B. 1 ms
C. 1.5 ms
D. 2 ms

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88. Inhibitory postsynaptic potentials (IPSP) are an example of:
A. postsynaptic inhibition
B. presynaptic inhibition
C. direct inhibition
D. indirect inhibition

89. Presynaptic inhibition occurs at:
A. axoaxonal synapses
B. axosomatic synapses
C. axodendritic synapses

90. Renshaw cell inhibition of *alpha*-motoneurone is an example of:
A. feedforward inhibition
B. negative feedback inhibition
C. presynaptic inhibition
D. postsynaptic inhibition
E. indirect inhibition
F. direct inhibition

91. Most excitatory neurotransmission in the brain is believed to be mediated by:
A. glutamate
B. glycine
C. GABA
D. GnRH

92. The inhibitory amino acid neurotransmitters in the CNS are:
A. glutamate and glycine
B. glutamate and aspartate
C. GABA and glycine
D. aspartate and glycine

93. Which of the following is/are examples of ligand-gated ion channels?
A. Nicotinic Ach receptor
B. IP$_3$ receptor
C. GABA-$_A$ receptor
D. Glycine receptor

94. IPSPs due to chloride influx are produced by:
A. acetylcholine
B. GABA
C. glycine
D. glutamate
E. substance P

95. Which of the following neurotransmitters has both excitatory and inhibitory effects?
A. Aspartate
B. GABA
C. Glutamate
D. Glycine

96. Which of the following toxins inhibits the release of acetylcholine from *alpha*-motor neurons?
A. Botulinum toxin
B. Cholera toxin
C. Saxitoxin
D. Tetanus toxin

97. Which of the following effects is **not** produced by stimulation of µ opioid receptor?
A. Analgesia
B. Constipation
C. Diuresis
D. Euphoria
E. Miosis
F. Sedation

98. Synaptic conduction is mostly orthodromic **because***:*
A. dendrites cannot be depolarized.
B. once repolarized, an area cannot be depolarized.
C. the strength of antidromic impulses is less.
D. the neurotransmitter is in the presynaptic terminal.

99. Which of the following statements about synaptic potentials is **incorrect?**
A. They are propagated down the postsynaptic neuron.
B. They undergo spatiotemporal summation.
C. They are analogous to generator potentials and end-plate potentials.
D. IPSP hyperpolarize the postsynaptic neuron.
E. They are proportional to the amount of transmitter released by the presynaptic neuron.

100. Following peripheral nerve injuries, which of the following investigations is **most useful** to assess likelihood of recovery of muscle and nerve function?
A. Electromyography
B. Muscle biopsy
C. Strength-duration curve

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D. CPK levels

Answers: Nerve, Muscle, Synaptic Physiology and Neurotransmission

1C	2B	3C	4B	5E
6C	7C	8C	9C	10B
11A	12B	13B	14C	15C
16B	17A	18B	19D	20ABC
21D	22B	23A	24B	25A
26	27B	28A	29C	30C
31A	32DE	33A	34D	35BC
36B	37A	38C	39B	40D
41C	42ABC	43D	44B	45C
46B	47B	48E	49C	50allT
51allT	52allT	53A	54D	55C
56B	57D	58B	59A	60EF
61D	62A	63A	64G	65C
66C	67B	68A	69D	70A
71D	72A	73A	74A	75B
76C	77AC	78	79 -	80C
81A	82A	83B	84ABC	85C
86B	87A	88AC	89A	90BDF
91A	92C	93all	94BC	95D
96A	97C	98D	99A	100A

78: 1B, 2C, 3D, 4A

Explanations:
11. Using the Nernst equation:
$E_K = - 61 \log [(K)i / (K)o]$
Case A: $E_K \approx RMP = - 70$ mV
Case B: $E_K \approx RMP = - 20$ mV
Case C: $E_K \approx RMP = - 122$ mV

When RMP is – 70 mV, the muscle cell is closest to the firing level, which is about – 55 mV. In contrast, when RMP is – 20 mV, it has crossed the firing level so it would be absolutely refractory or inexcitable. Hypokalemia makes the RMP more negative, and because at RMP the heart would be mechanically in diastole, it may stop the heart in diastole. Similarly, intense stimulation of the vagus nerve to the heart may stop the heart in diastole because acetylcholine activates an outwardly directed potassium current in SA node; i.e. it hyperpolarizes the SA and the AV nodes.

14. The resting nerve cell membrane is 50 times more permeable to K than Na. Therefore, K flux through potassium channels determines the RMP. When Na and Cl are removed from the Goldman-Hodgkin-Katz equation, it becomes the much simpler Nernst equation.

20. Conduction speed varies directly with diameter of the nerve fiber. See Ganong 2012, p. 92, Table 4-1. Myelination of axons increases conduction speed by about 50-100 times.

26. In the intact human, the action potential is initiated at the axon hillock and propagates through the axon membrane to the nerve terminal. However, if we stimulated axons at the median nerve with a threshold stimulus applied through electrodes at the elbow, action potential in excited axons would travel orthograde to the nerve terminal as well as retrograde into the cell body located in the spinal cord. In a motor axon, it is orthodromic conduction to the axon terminal that can release neurotransmitter. Antidromic conduction of the impulse to the cell body depolarizes it *sweeping it clean*, and rendering it refractory to stimulatory input for a definite period of time.

29. Type B fibers are most susceptible to hypoxia. Preganglionic autonomic neurons are type B fibers diameter (Ganong, 2012, p. 93, Table 4-3).

31. Type B fibers are more susceptible to blockade by anesthetics compared to type A fibers, which have a larger diameter (Ganong, 2012, p. 93, Table 4-3). Sympathetic preganglionic neurons, which originate in the intermediolateral column of the thoracolumbar segments of the spinal cord, are type B fibers.

32. 'Fast pain' is transmitted through myelinated A-delta fibers, and 'slow pain' is the result of transmission through unmyelinated C fibers.

40. Skeletal muscle depends on the sarcoplasmic reticulum (SR) as the major source of calcium. Cardiac muscle and smooth muscle depend on influx of calcium from ECF and Ca-induced calcium release (from SR) for contraction.

42. ATP is required for muscle contraction as well as relaxation.

46. Calmodulin is not a contractile protein; it is a calcium binding protein that activates myosin light chain kinase upon binding calcium. Actin and myosin are contractile proteins.

49. Few or no gap junctions are present in nonsyncytial smooth muscle (example, smooth muscle of iris). (Ganong, 2012, p. 114). This makes possible fine graded contractions of the iris and regulation of pupil diameter.

50-53. The terms slow and fast are applied to muscles based on twitch duration. Twitch duration is the duration of a single contraction followed by relaxation. The twitch duration in slow muscle is longer (example 100 ms) than in fast muscle (10-20 ms). However, each muscle is a composite of different types of fibers. The three types of muscle fibers recognized are type I, type IIA and type IIB. (See Ganong, 2012, Table 5-2, p. 106-7.)

54. Isotonic vs. Isometric contraction.

Isotonic contraction	Isometric contraction
Tension developed is constant; muscle shortens	Tension developed; muscle does not shorten
*External work is done	External work is not done
Example: Walking, bending, running	Trying to lift a heavy weight, sustained handgrip

*'External work' W = force × displacement; since the muscle ends are fixed in an isometric contraction, no external work is done in an isometric contraction.

55. Take a rather heavy object in your hand and try lowering it toward the ground. When you do so, you will feel the tension in your biceps, yet the elbow extends; that is, although biceps develops tension, it lengthens. Sarcomeres contract and develop force but the muscle can shorten or lengthen depending upon the load. If a muscle lengthens while developing force, external work done is negative.

57. Motor unit is an alpha motor neuron and all muscle fibers innervated by it. A motor unit is the smallest amount of muscle that can contract in response to excitation of a single motor neuron.

58. Where fine control of force is required, each motor unit innervates few muscle fibers (upto 10 muscle fibers). In contrast in large muscles, each motor axon may innervate over 100 muscle fibers.

59. At or above threshold intensity, an increase in the frequency of stimulation (successive stimulation rather) but below tetanizing frequency produces a gradual increase in the amplitude of successive contractions. This is called staircase phenomenon or *Treppe* or Bowditch effect. It occurs in skeletal as well as cardiac muscle. It is attributed to increased availability of intracellular calcium (beneficial effect of previous contractions). It should not be confused with summation of contractions or tetanus. In the Staircase phenomenon, there is complete relaxation following each contraction, whereas in the case of summation, relaxation of muscle is incomplete.

60. Gradation of force in skeletal muscle is achieved by:
- recruitment of motor units
- ↑ the frequency of stimulation of motor units
- asynchronous firing of motor units
- variations in preload.

Action potentials are all or none and occur with a constant magnitude. Gradation of force is also not achieved by varying calcium release from the sarcoplasmic reticulum because each action potential that enters the T tubule releases a constant amount of calcium from the terminal cisterns of the SR.

61. Slow motor units consist of small diameter and thus slow conducting motor axons. Fast motor units consist of large diameter axons that conduct rapidly. According to the size principle, slow motor units are recruited first in most movements; fast motor units, which are easily fatigable, are recruited for more forceful contractions.

62. In this technique, compound muscle action potentials (CMAP) are recorded by placing

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electrodes either on the surface of muscles or within the muscle (when needle electrodes are used); it is much like ECG which represents the compounded potentials generated by heart recorded by placing electrodes on the body surface. CMAP is examined at rest, during mild contraction, and forceful contractions. The pattern of EMG during these maneuvers is useful to distinguish between muscle weakness due to myopathy and neuropathy.

63. The strength-duration curve is a plot of the strength of the electrical stimulus required to elicit compound action potentials in nerve or muscle against the duration of the stimulus. Rheobase is the minimum stimulus strength that will produce a response. Chronaxie has been defined as the minimum stimulus duration at which twice the rheobasic current will produce a response. In a fatigued muscle, the chronaxie is longer. In denervated muscle, chronaxie is prolonged and the rheobasic current is likely to be higher.

65. Cardiac cycle time measured from the ECG as the RR interval, and the duration of action potential are both variable. If average HR is 75 bpm, then average cardiac cycle time = 0.8 s = 800 ms. At this rate, average action potential duration ~ 250 ms, the duration of absolute refractory period is ~ 200 ms, and the relative refractory period is ~ 50 ms. At higher heart rates, the duration of the action potential decreases.

69. Option D: Summation of the type seen in skeletal muscle cannot occur in cardiac muscle. That is, a second contraction cannot begin before the previous contraction (systole) is completed and diastole (filling) has commenced. However, a premature depolarization and premature contraction can occur when the ventricle is just filling with blood; this is an instance of *incomplete summation.*

Cardiac muscle fibers are refractory during the upstroke of the action potential and until at least repolarization is half complete. This is called *absolute refractory period*, and the heart cannot be excited during this time no matter how strong the stimulus is. In the *relative refractory period*, a supranormal stimulus can evoke an action

potential. Because of the long duration of absolute refractory period (about 200 ms at a heart rate of 75 bpm), diastole commences before the heart is reexcitable. Thus, summation of the type seen in skeletal muscle cannot occur in cardiac muscle and why cardiac muscle cannot be tetanized. This is a *safety* feature since the heart has to fill with blood between successive contractions.

Option E: Conduction of impulse through gap junctions occurs in the heart and single-unit smooth muscle but not in skeletal muscle.

70. Norepinephrine has a positive chronotropic (increases rate of contraction), inotropic (increases force of contraction), and lusitropic effect (i.e., it accelerates relaxation) on the heart.

75. The twitch duration in sphincters and smooth muscle is particularly longer. Latch bridges are actomyosin complexes that detach slowly; this is made possible by a slow myosin ATPase. This mechanism enables maintenance of tension for longer periods without consumption of more ATP.

80. The ratio of synapses to neurons in the brain is about 1000; glia outnumber neurons by about 50 times.

82. Indeed, reduced reuptake of excitatory neurotransmitters such as glutamate by astrocytes in ischemic zones is said to contribute to excitotoxicity in stroke.

83. 98% synapses in the CNS are axodendritic.

84. Opening of chloride ion channels in postsynaptic membrane would produce hyperpolarization of postsynaptic neurons.

86. It is easy if you draw a schematic diagram. You will see that both neurons A and B have to release excitatory neurotransmitters in order to fire C (i.e., by spatial summation of EPSP). However, repeated stimulation of either A or B may also elicit an action potential in C by temporal summation. With the data provided, there is no justification for inferences A, C or D.

88-90. Synaptic inhibition
Negative feedback inhibition: Renshaw cell inhibition is a classic example of negative feedback inhibition. Renshaw cells are inhibitory interneurons in the spinal cord. *Feedforward inhibition* occurs in cerebellar circuits.

Another classification of synaptic inhibition is as direct or indirect inhibition.

Direct inhibition involves direct inhibition of the postsynaptic neuron by producing IPSPs on it. It is also called **post-synaptic inhibition.** It is independent of previous discharges of the postsynaptic neuron. Renshaw cell inhibition of *alpha*-motoneurons in the spinal cord is an example of direct inhibition.

With reference to a synapse, if the presynaptic neuron is inhibited, then it is called **indirect** or **presynaptic** inhibition. It occurs in axo-axonal synapses.

91. Uncontrolled glutamatergic transmission due to defective reuptake of glutamate by glial cells can occur in the context of brain ischemia and strokes and may lead to neuronal damage and death due to 'excitotoxicity'.

93 and 94. GABA-A receptor and the glycine receptor are both chloride ion channels. (Ganong, 2012, p. 142-3). So activation of these receptors produces IPSPs. Nicotinic Ach receptor is a cation specific channel, and IP3 receptor is a calcium channel in the SR.

95. Glycine, an inhibitory neurotransmitter in the spinal cord, also has excitatory actions on NMDA receptors. In the absence of glycine, glutamate cannot exert its excitatory effects on the NMDA receptor. (Ganong, 2012, p. 143)

96. This is why botulinum toxin causes flaccid paralysis. In contrast, tetanus toxin inhibits the release of glycine from Renshaw cells (inhibitory interneurons) in the spinal cord; the consequence is increased frequency of discharge of *alpha*-motor neurons and extreme spasticity. Saxitoxin blocks voltage gated Na channels and K channels and inhibits nerve impulse generation.

97. Diuresis is mediated by an action on *kappa* receptors. (Ganong, 2012, p. 151, Table 7-3)

100. While the strength-duration (SD) curve can tell us if a nerve is functioning or not or what the degree of impairment is at a point in time, of late, it has been superseded by electromyography (EMG) which has this capability and a wider range of uses. The only advantage of the SD curve is that it is noninvasive. EMG can be recorded with surface as well as needle electrodes. The occurrence of reinnervation potentials or denervation potentials (obtainable only with an EMG) may be used for prognostication.

CENTRAL NERVOUS SYSTEM

Summaries:
1. Control of Posture and Movement
Animal preparations used to study the regulation of posture include:

- *Spinal preparation*: spinal cord transection at midthoracic level
- *Decerebrate preparation*: transection of the neuraxis at the superior border of pons
- *Midbrain preparation*: transection of the neuraxis on top of the midbrain
- *Decortication*: removal of cerebral cortex alone leaving subcortical structures intact

With regard to control of posture and movement, upper motor neurons may be classified as:

- Posture regulating upper motor neurons
- Movement regulating upper motor neurons

Posture regulating upper motor neurons:

Origin:	Brain stem
Termination:	On alpha and gamma motor neurons in spinal cord
Controlled by:	Inhibitory inputs from cerebral cortex (suppressor strip – 4s) in the anterior edge of the precentral gyrus and basal ganglia.

Movement mediating / regulating upper motor neurons:

Origin:	Corticospinal tract (layer V, pyramidal cell axons) from primary motor cortex, sensory cortex, and premotor area.
Termination:	On *alpha*-motor neurons / interneurons innervating alpha motor neurons in spinal cord
Lesions:	limited to the corticospinal and corticobulbar tracts produce "weakness" rather than paralysis and the affected musculature is generally "hypotonic". Isolated involvement of corticospinal tract is not clinically common.

Level of integration of principal postural reflexes:

Level	Postural reflexes
Spinal cord	Stretch reflexes, withdrawal reflexes
Medulla	Labyrinthine righting reflexes, tonic neck reflexes
Midbrain	Righting reflexes
Cerebral cortex	Hopping and placing reactions, optokinetic reflexes

Descending motor pathways are classified as lateral system and medial system pathways, and other pathways.

Lateral system pathways
- Lateral corticospinal tract
- Rubrospinal tract

Medial system pathways
- Ventral corticospinal tract
- Reticulospinal tract
- Vestibulospinal tract
- Tectospinal tract

Lateral system pathways are movement regulating pathways. If we could manage to cut only lateral corticospinal tract axons (for example, by sectioning pyramids in monkeys), posture would not be affected but the animal would lose its ability to perform fine skilled movements. The affected muscles would become hypotonic.

Medial system pathways are posture-regulating pathways.

Other descending monoaminergic pathways
- Raphespinal pathways
- Ceruleospinal pathway

One way of classifying descending motor pathways is to classify them as *lateral system pathways* and *medial system pathways*.

The lateral system pathways include the lateral

corticospinal tract and the rubrospinal tract (which originates in the red nucleus). The neurons of the lateral corticospinal tract typically (though not necessarily) end straight on alpha-motor neurons innervating skeletal muscles of the distal musculature used for fine, skilled voluntary movements; otherwise, they end on interneurons that regulate the alpha-motor neurons innervating these muscles. The lateral system pathways also course laterally (i.e., in the lateral funiculus) in the spinal cord.

The medial system pathways course medially in the spinal cord and end (at various levels) typically on interneurons in the medial aspect of the ventral horn of the spinal cord. Furthermore, these interneurons, on which the medial system pathways end, connect with their counterparts on the contralateral aspect of the spinal cord contributing to balance and posture. They mainly control axial muscles. The ventral corticospinal tract, the tectospinal tract, the reticulospinal tract and the vestibulospinal tracts are all medial system pathways.

Functional divisions of the cerebellum

Division	Function
Spinocerebellum (midline & paravermal zone)	Maintenance of posture
Vestibulocerebellum (flocculonodular lobe)	Maintenance of posture and equilibrium
Neocerebellum (lateral cerebellar hemispheres)	Coordination of voluntary movement

- Output from the Purkinje cells to the deep cerebellar nuclei is always inhibitory.
- Output from the deep cerebellar nuclei to the thalamus is excitatory.
- Cerebellum facilitates stretch reflexes and usually hypotonia occurs in cerebellar lesions.
- Selective ablation of the flocculonodular lobe of the cerebellum has been shown to abolish the symptoms of motion sickness. The symptoms of motion sickness occur due to excessive stimulation of the vestibular system via its connections to the brain stem and the flocculonodular lobe of the spinal cord

2. Thalamocortical Projections, EEG, Sleep
Types of thalamocortical projections:
Specific: function to transmit information to specific areas in the cortex; results in sensory perception; they end in layer IV of the cortex
Nonspecific: function to arouse the individual; end in layers I-IV of the cortex.

Notes on EEG: In an adult human at rest with mind wandering and eyes closed, the most prominent component of the EEG is a fairly regular pattern of waves at a frequency of 8-12 Hz, and amplitude of about 50 microvolts when recorded from the scalp. This pattern is the **alpha rhythm**. It is most prominent in the parieto-occipital area.

The alpha rhythm is replaced by a fast irregular low voltage beta rhythm (18–30 Hz). This phenomenon is called **alpha block.** A breakup of the alpha rhythm is produced by any kind of sensory stimulation such as mental arithmetic.

Large amplitude, regular 4–7 Hz waves called the **theta rhythm** occurs in children and is generated in the hippocampus in experimental animals.

Stages of sleep: Stages I – IV of NREM (slow wave sleep) followed by rapid eye movement (REM) sleep

Sleep spindles (occur in stage II sleep)
Frequency: 10–14 Hz; amplitude: 50 microvolts.

EEG waves	Frequency
Delta	0.5–4 Hz
Theta	4–7 Hz
Alpha	8–13 Hz
Beta	14–30 Hz
Gamma	30–80 Hz

Delta waves occur in deep sleep (stages III and IV).

REM sleep is called **paradoxical sleep** because it is marked by rapid, low voltage, irregular EEG activity. The threshold for sensory arousal from REM sleep is sometimes greater than NREM sleep presumably because the brain is actively

processing information during REM sleep (dreams).

EEG during sleep:

Stage	Characteristics
Stage 1	Alpha rhythm
Stage 2	Sleep spindles and K complexes (beginning of slowing; reduction in alpha content)
Stages 3 & 4	Characterized by slow waves (theta and delta)
REM sleep	High frequency, low amplitude rhythm similar to the wakeful state

Hypothalamus and food intake:
Satiety center works by inhibiting feeding center

Feeding center located in	Lateral hypothalamus
Satiety center located in	Ventromedial hypothalamus
Lesions in ventromedial nucleus lead to	Obesity
Lesions in lateral hypothalamus lead to	Anorexia

3. Learning and Memory

Types of learning:

Associative learning	Nonassociative learning
Associating a conditioned stimulus with a neutral stimulus	Learning about a single stimulus
Examples include classical (Pavlovian) conditioning, and operant / instrumental conditioning	Examples include habituation and sensitization

Classical conditioning
(Pavlovian conditioning)
- *Conditioned stimulus* (food)
- *Conditioned response* (salivation)
- *Conditioned reflex*
- *Neutral stimulus* (bell ringing)

- Pairing the neutral stimulus with the conditioned stimulus several times…
- The neutral stimulus (bell ringing) eventually elicits the same response as the conditioned stimulus (food).
- **Conditioned reflexes** (or behavior) are classic examples of associative learning.

Instrumental conditioning
(*Synonymous with* operant conditioning)
- This phenomenon was described by B.F.Skinner.
- Here the animal learns by operating on the environment.
- The main learning point here is that animal behavior is determined by the likely consequences of that behavior. From experiments conducted with the Skinner box arose concepts such as the presence in the limbic system of "**reward centers**" and "**punishment centers**"
- "We may apply this concept to reform society" – Skinner

Habituation: The response to a benign stimulus repeated over and over gradually decreases. This is due to decreased release of excitatory neurotransmitter from the presynaptic neuron. The opposite response where the response to a noxious stimulus repeated over and over gradually increases is termed **sensitization.** Both habituation and sensitization are examples of nonassociative learning because the organism learns about a single stimulus.

Memory is retention and storage of learnt information.
- **Implicit** memory is reflexive (nondeclarative). It is nondeclarative in that one is not aware of its execution. Examples include skills one has perfected.
- **Explicit** memory, which is declarative, requires conscious recall of events or facts. It requires processing in the hippocampus.
- **Working memory** is a form of short term memory used to plan actions; example, dialing a phone number one has just seen on the phone book. It is stored in prefrontal cortex.

- Short-term memory is prone to erasure; long-term memory ('true memory') is resistant to erasure.
- **Consolidation** refers to the formation of new long term memories from short-term memories, and it occurs in the hippocampus. The hippocampus is rich in NMDA receptors. NMDA receptors are a type of glutamate receptors.

Mechanisms implicated in memory:
❖ Post-tetanic potentiation
❖ Long-term potentiation
❖ Changes in synaptic strength
❖ Increases in synaptic contacts
❖ Formation of new neurons from stem cells in the olfactory bulb and hippocampus may play a role.

Post-tetanic potentiation: Enhanced postsynaptic potentials after a brief tetanizing train of stimuli in the presynaptic neuron.

Long-term potentiation: Long-lasting facilitation of transmission in neural pathways following a brief period of high-frequency stimulation. This process is important for **consolidation**, i.e. the formation of long term memories.

Conditions which influence consolidation (formation of new memories from short-term memory)
- Repetition of stimulus (facilitates)
- Sleep (facilitates)
- Convulsions, electroconvulsive therapy (inhibit)
- Anesthetics, tranquilizers (inhibit)
- Hypoxia (inhibits)
- Inhibitors of protein synthesis (inhibit)

QUESTIONS:
Most of the questions in this section have only one correct answer, as should be apparent from the question; however, some questions may have more than one correct answer – *please read all options!*

1. "No matter where a particular sensory pathway is stimulated along its course to the cortex, the conscious sensation produced is referred to the location of the receptor". This is:
A. the law of projection
B. Weber-Fechner law
C. Muller's law of specific nerve energies
D. Bell-Magendie Law

2. Muller's doctrine of specific nerve energies is otherwise known as:
A. Bell-Magendie law
B. labeled-line principle
C. Weber-Fechner law
D. law of projection

3. The relation between the magnitude of sensation and stimulus intensity is given by the:
A. law of specific nerve energies
B. labeled line principle
C. Weber-Fechner law
D. law of projection

4. The phantom limb phenomenon exemplifies:
A. Bell-Magendie law
B. the law of projection
C. Muller's doctrine of specific nerve energies
D. Weber-Fechner law

5. A single sensory axon and all of its peripheral branches constitute a:
A. receptive field
B. sensory unit
C. dermatome
D. sensory nerve

6. Intensity of a sensory stimulus (whether threshold or subthreshold) is **not** encoded by:
A. size of generator (receptor) potentials
B. frequency of action potentials in sensory neurons
C. recruitment of sensory units
D. size of action potentials

7. Which of the following is a rapidly adapting sensory receptor?
A. Muscle spindle
B. Carotid sinus
C. Pain receptor
D. Pacinian corpuscle

8. Which of the following fibers has the greatest threshold?
A. Touch
B. Pain
C. Pressure
D. Cold

9. The gate theory of pain was proposed by:
A. Cannon and Bard
B. Charles Sherrington
C. Wall and Melzack
D. Weber and Fechner

10. How does transcutaneous electrical nerve stimulation alleviate pain?

11. Anterolateral cordotomy does **not** interfere with perception of:
A. fine touch
B. pain
C. pressure
D. temperature

12. Which of the following has been suggested as a possible mediator of analgesia produced by stimulation of the raphespinal pathway?
A. GABA
B. Glutamate
C. Serotonin
D. Substance P

13. Joint position sense is transmitted by:
A. anterior spinothalamic tract
B. lateral spinothalamic tract
C. dorsal column-medial lemniscal system

14. Which of the following is/are termed 'synthetic senses'?
A. Fine touch
B. Joint position sense
C. Stereognosis
D. Two-point discrimination
E. Vibratory sensibility

15. Impaired stereognosis in the absence of a detectable defect in touch and pressure sensation points to a lesion in (the):
A. dorsal column
B. medial lemniscus
C. parietal lobe posterior to the postcentral gyrus
D. any of the above locations

16. An anterolateral cordotomy relieving pain in the right leg is effective because it interrupts the:
A. left dorsal column
B. left ventral spinothalamic tract
C. left lateral spinothalamic tract
D. right lateral spinothalamic tract

17. Ablation of somatosensory area (SI) does **not** significantly impair:
A. joint position sense
B. touch localization
C. two-point discrimination
D. pain perception

18. Which sensory modality is transduced by free nerve endings?
A. Vision
B. Taste
C. Smell
D. Sound

19. A modified neuroepithelial cell is **not** the sensory receptor in the:
A. visual pathway
B. olfactory pathway
C. auditory pathway
D. gustatory pathway

20. Which of the following neural pathways is predominantly an uncrossed pathway?
A. Gustatory pathway
B. Somatosensory pathway
C. Visual pathway
D. Auditory pathway

21. Which of the following sensory modalities does **not** have a separate neocortical projection?
A. Smell
B. Vision
C. Hearing
D. Taste

22. In which sensory system does excitation of the sensory receptor by an adequate stimulus results in hyperpolarization of receptor cells?
A. Visual pathway
B. Auditory pathway
C. Taste pathway
D. Olfactory signaling

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23. Axons of ganglion cells in the retina terminate in:
A. lateral geniculate nucleus
B. pretectal nucleus
C. suprachiasmatic nucleus
D. superior colliculus

24. The light reflex is integrated in the:
A. midbrain
B. frontal eye field
C. medulla
D. primary visual area

25. Which of the following is **not** a component of the near response?
A. Pupillary constriction
B. Convergence of the visual axes
C. Increase in convexity of the lens
D. Ciliary muscle relaxation

26. Central visual fields are mapped with:
A. tangent screen (campimeter)
B. perimetry

27. Which of the following statements about Argyll-Robertson pupil is **incorrect?**
A. Light reflex is absent
B. Accommodation reflex is present
C. The lesion is in the Edinger-Westphal nucleus
D. It occurs in neurosyphilis

28. Which of the following is most sensitive to light?
A. Rods
B. Cones maximally sensitive to light at 440 nm
C. Cones maximally sensitive to light at 535 nm
D. Cones maximally sensitive to light at 565 nm

29. Rod cell excitation by photons results in the conversion of:
A. 11-cis-retinal to 11-trans-retinal
B. 11-cis-retinal to all trans-retinal
C. all trans retinal to all cis-retinal
D. 11-trans-retinal to 11-cis-retinal

30. During the dark phase of the visual cycle, which form of vitamin A combines with opsin to make rhodopsin?
A. All trans retinaldehyde
B. All trans retinol
C. 11-cis retinaldehyde
D. 11-cis retinol

31. Rhodopsin has peak sensitivity to light at a wavelength of:
A. 405 nm
B. 505 nm
C. 605 nm
D. 705 nm

32. Which of the following changes occur in rod cells when rhodopsin is activated by light?
A. Increase in cGMP
B. Deactivation of phosphodiesterase
C. Depolarization of rod cells
D. Decreased release of neurotransmitter

33. Dark adaptation is nearly maximal in about:
A. 1 minute
B. 5 minutes
C. 20 minutes
D. 40 minutes

34. Which area is uniquely concerned with color vision?
A. V1
B. V3
C. LO
D. V8

35. Which eye movements bring new objects of interest onto the fovea?
A. Saccades
B. Convergence movements
C. Smooth pursuit movements
D. Vestibular movements

36. Saccades are
A. voluntary, slow eye movements
B. involuntary, slow eye movement
C. abrupt, involuntary, slow eye movements
D. abrupt, voluntary, rapid eye movements

37. Saccades are programmed in the:
A. frontal cortex
B. medial longitudinal fasciculus
C. hypothalamus
D. superior colliculus

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38. Which of the following reflexes is always absent in individuals who are totally blind?
A. Vestibulo-ocular reflex
B. Nystagmus
C. Visual accommodation
D. Light reflex

39. If light reflex is present and the accommodation reflex absent, then the lesion is most likely in the:
A. pretectal nucleus
B. ganglion cells
C. Edinger-Westphal nucleus
D. visual cortex

40. In the visual system, the term blobs refers to:
A. parvocellular pathway from the lateral geniculate nucleus
B. clusters of axons of ganglion cells in the retina
C. clusters of amacrine cells in the retina
D. clusters of cells in layers 2 and 3 of the visual cortex that have high levels of cytochrome oxidase

41. Impedance matching is a function of:
A. scala media
B. endolymph
C. ear ossicles and tympanic membrane
D. cochlear nucleus

42. What is the amplification provided by the lever action of the auditory ossicles and the large size of the tympanic membrane compared to the oval window?
A. 5 times
B. 10 times
C. 22 times
D. 45 times

43. Endolymph is produced by:
A. stria vascularis
B. inner hair cells
C. sustentacular cells
D. outer hair cells

44. Inner hair cells in the organ of Corti are depolarized by:
A. K influx
B. Na influx
C. Ca influx

D. closure of K channels

45. Which of the following functions as a frequency analyzer in hearing?
A. Reissner's membrane
B. Tectorial membrane
C. Basilar membrane
D. Middle ear ossicles

46. Which of the following structures is most involved in localization of sound stimuli?
A. Superior olivary complex
B. Inferior colliculus
C. Medial geniculate nucleus
D. Auditory cortex

47. In a 45 year old woman reporting diminished hearing in the right ear for the last 2 years, the Rinne's test (without masking) is negative on the right ear and positive on the left side. With the Weber's test, the tone is perceived as louder in the left ear. Which of the following is **most likely**?
A. Conduction loss in the right ear
B. Sensorineural hearing loss in the right ear
C. Sensorineural hearing loss in the left ear
D. Conduction loss in the left ear

48. Linear acceleration in the vertical plane is signaled by hair cells in:
A. anterior semicircular canal
B. saccule
C. posterior semicircular canal
D. utricle

49. The fifth taste modality is:
A. umami
B. imami
C. himami
D. emami
E. mami

50. A typical example of a monosynaptic reflex is:
A. stretch reflex
B. superficial abdominal reflex
C. withdrawal reflex
D. light reflex

51. The receptor for the stretch reflex is the:
A. muscle spindle
B. Golgi tendon organ

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C. Pacinian corpuscle

52. In the stretch reflex, the afferents are:
A. I a fibers
B. I b fibers
C. II fibers
D. A delta fibers

53. In the stretch reflex, relaxation of antagonist muscles is due to:
A. reciprocal innervation
B. presynaptic inhibition
C. Ia fiber stimulation
D. antidromic conduction

54. The muscle spindle is made to contract by stimulation of:
A. α-motor neurons
B. γ-motor neurons

55. The term 'small motor nerve system' refers to:
A. Ia afferents from muscle spindle
B. α-motor neurons
C. γ-motor neurons

56. Physiologically, an intact innervated muscle can normally be made to contract by stimulation of which of the following neurons innervating that muscle?
A. α-motor neurons
B. γ-motor neurons
C. Either one of the above

57. The muscle spindle is **not** innervated by:
A. Aα fibers
B. Aγ fibers
C. Ia fibers
D. II fibers

58. The muscle spindle remains capable of responding to stretch even the muscle is contracting. This is because of:
A. presence of stretch receptors in the tendon
B. co-activation of α- and γ-motor neurons
C. reciprocal innervation
D. autogenic inhibition

59. Muscle contraction in response to maintained stretch is initiated by sensory inputs from:
A. nuclear bag fibers

B. nuclear chain fibers
C. Golgi tendon organ
D. γ-motor neurons

60. The Jendrassik's maneuver facilitates stretch reflexes by:
A. exciting alpha motor neurons
B. increasing gamma efferent discharge
C. releasing glycine

61. The principal receptor mediating proprioception is:
A. muscle spindle
B. Golgi tendon organ
C. C mechanoreceptor
D. joint capsule receptor

62. The receptor for the inverse stretch reflex is:
A. muscle spindle
B. Golgi tendon organ
C. C fiber
D. delta fibers

63. Impulses from Golgi tendon organ pass to inhibitory interneurons in the spinal cord via:
A. I a
B. I b
C. II a
D. C fibers

64. The force of skeletal muscle contraction is sensed by:
A. nuclear bag fiber
B. nuclear chain fiber
C. Golgi tendon organ

65. Proprioceptive information reaches consciousness through the *(choose all correct answers)*:
A. spinothalamic system
B. dorsal column – medial lemniscal pathway
C. spinocerebellar pathway
D. olivocerebellar pathway

66. Inhibitory interneurons in the spinal cord release:
A. glycine
B. substance P
C. neuropeptide Y

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67. Neurons mediating direct inhibition in the spinal cord usually secrete:
A. glycine
B. substance P
C. glutamate

68. Tetanospasmin inhibits the release of:
A. GABA
B. glutamate
C. glycine
D. acetylcholine

69. All neural influences affecting muscle contraction ultimately funnel through:
A. α-motor neurons
B. γ-motor neurons
C. corticospinal tract
D. basal ganglia

70. In humans, spinal shock is characterized by:
A. hypertonia
B. hyperreflexia
C. spastic paralysis
D. loss of autonomic function

71. The *crossed extensor response* is seen in:
A. healthy humans
B. the phase of spinal shock
C. chronic paraplegia

72. The *mass reflex*:
A. is a sign of a central inhibitory state
B. occurs in the decerebrate animal
C. is due to irradiation of afferent impulses
D. is a manifestation of 'release of spinal reflexes' from inhibitory control by higher centers

73. Locomotion generators in spinal cord are turned on by pattern generators in the:
A. suppressor strip
B. midbrain
C. medulla
D. pons

74. Which of the following is **not** a feature of *lower motor neuron* lesions?
A. Muscle atrophy
B. Fasciculations
C. Fibrillations

D. Denervation hypersensitivity
E. Spasticity

75. Which of the following is the best example of a polysynaptic reflex?
A. Stretch reflex
B. Axon reflex
C. Inverse stretch reflex
D. Withdrawal reflex

76. Guarding is an example of:
A. stretch reflex
B. flexor withdrawal reflex
C. clasp knife effect
D. α-γ linkage

77. The procedure in which the hindbrain and the spinal cord are separated from the rest of the brain by transection at the superior border of pons is called:
A. decortication
B. decerebration
C. deafferentation
D. rhizotomy

78. Which of the following is pathognomonic of decerebration?
A. Exaggerated standing
B. Babinski sign
C. Absence of saccades
D. Relief of spasticity by cerebellectomy

79. Which type of rigidity is clinically more common?
A. Decorticate rigidity
B. Decerebrate rigidity
C. Extensor rigidity
D. Cog-wheel rigidity

80. Which of the following is **absent** in decorticate animals?
A. Gross movements
B. Temperature regulation
C. Hopping and placing reaction
D. Vestibulo-ocular reflex

81. Lesions of the ventral corticospinal tract result in:
A. difficulty with balance
B. deficits in skilled voluntary movements

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82. Which of the following is **not** a feature of corticospinal tract disease?
A. Cogwheel rigidity
B. Spasticity
C. Plantar extensor response
D. Exaggerated deep tendon reflexes

83. Righting reflexes are integrated for the most part in the:
A. medulla
B. midbrain
C. spinal cord
D. cerebral cortex

84. The *doll's eye reflex* is integrated in the
A. cerebral cortex
B. medial longitudinal fasciculus
C. thalamus
D. medulla

85. The hyperkinetic features of the Huntington's disease are due to the loss of neurons in the:
A. nigrostriatal dopaminergic system
B. intrastriatal cholinergic system
C. GABAergic and dopaminergic system
D. intrastriatal GABAergic and cholinergic system

86. The cerebellum receives sensory input from the:
A. labyrinth
B. proprioceptors
C. eyes
D. all of the above

87. Climbing fiber input to the cerebellum comes from:
A. superior olivary complex
B. red nucleus
C. inferior olivary complex
D. locus ceruleus

88. Feedforward inhibition has been well described in neural circuits in the:
A. spinal cord
B. cerebellum
C. stretch reflexes
D. nociceptive pathway

89. In which layer of the cortex do specific thalamic afferents end?
A. Layer VI
B. Layer IV
C. Layer I
D. Layer II

90. In which layer of the cerebral cortex do non-specific thalamocortical projections end?
A. Layer I-IV
B. Layer II
C. Layer IV
D. Layer VI

91. *Alpha block* is produced by:
A. mental arithmetic
B. stimulation of ascending reticular activating system
C. opening one eye only

92. Gamma oscillations in EEG, which occur when an individual is aroused and focuses attention on something, occur at a frequency of:
A. 0–0.4 Hz
B. 4–7 Hz
C. 0–12 Hz
D. 30–80 Hz

93. A 4–7 Hz rhythm normally occurs in:
A. hypothalamus
B. hippocampus
C. parieto-occipital area
D. frontal area

94. A low-frequency, high amplitude, synchronized cortical rhythm occurs during:
A. stage 1 & 2 slow-wave sleep
B. stage 3 & 4 slow-wave sleep
C. REM sleep
D. narcolepsy

95. Delta waves (0.5-4 Hz) are seen in:
A. stage 1 sleep
B. stage 4 sleep
C. an awake adult with eyes open
D. an awake adult with eyes closed

96. Which of the following states does a predominance of *beta* waveforms in an electroencephalogram suggest?

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A. Deep anesthesia
B. Surgical anesthesia
C. Light anesthesia, eyes closed, relaxed
D. Awake, alert state

97. Which of the following is **not** a characteristic of REM sleep?
A. Slow waves in the EEG
B. Hypotonia
C. Dreaming
D. PGO spikes

98. Which of the following phenomena is closely associated with slow wave sleep?
A. Dreaming
B. Atonia
C. Sleep walking
D. Irregular heart rate

99. REM behavior disorder is primarily characterized by:
A. lack of REM sleep
B. day-time somnolence
C. absence of hypotonia during REM sleep
D. absence of PGO spikes during REM sleep

100. Hypothalamus does **not** play a prominent role in the regulation of:
A. food and water intake
B. temperature
C. respiration
D. osmolality
E. circadian rhythms

101. In which region of the hypothalamus is sexual behavior integrated?
A. Anterior ventral hypothalamus
B. Supraoptic and paraventricular nuclei
C. Suprachiasmatic nucleus
D. Arcuate nucleus

102. Lesions of ventromedial hypothalamus typically result in:
A. anorexia
B. obesity
C. hypersexuality
D. amnesia

103. Cell bodies of orexigenic neurons are present in:

A. locus ceruleus
B. dorsal raphe nucleus
C. lateral hypothalamic area
D. hippocampus

104. The circadian rhythm generator in the hypothalamus receives inputs chiefly from:
A. retina
B. superior colliculus
C. thalamus
D. medial geniculate nucleus
E. suprachiasmatic nucleus

105. Stimulation of sympathetic nerves to the pineal gland:
A. increases synthesis of melanin
B. increases activity of serotonin N-acetyl transferase
C. reduces melatonin synthesis
D. increases release of serotonin

106. Exposure to darkness leads to increased melatonin secretion. It is brought about by:
A. decreasing the activity of suprachiasmatic nucleus
B. increasing activity of serotonin N-acyl transferase
C. decreasing the hydroxy-indole-O-methyl transferase activity.
D. blocking the release of norepinephrine from sympathetic nerve terminals.

107. In normal healthy adults on a daytime work shift, at what time does pineal hormone peak in blood?
A. 2 am
B. 8 am
C. 2 pm
D. 8 pm

108. Which of the following statements about the pineal gland in human beings is **correct?**
A. It directly responds to light.
B. It is part of the nervous system.
C. It is controlled by the hypothalamus.

109. Intercortical transfer of memory occurs via:
A. corpus callosum
B. anterior commissure
C. posterior commissure

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D. each of the above

110. The process of consolidation, i.e., the conversion of short-term memories to long-term memories occurs in the:
A. hippocampus
B. amygdala
C. cerebral cortex
D. hypothalamus

111. A long lasting facilitation of transmission in neural pathways following a brief period of high frequency stimulation is termed:
A. long-term potentiation (LTP)
B. post-tetanic potentiation (PTP)
C. sensitization
D. habituation

112. Which statement regarding the NMDA receptor is **incorrect?**
A. Its endogenous ligand is glutamate.
B. Glycine is essential for this receptor's response to its endogenous agonist.
C. It is a chloride ion channel.
D. It is present in hippocampal neurons.

113. Which receptor is directly involved in long-term potentiation?
A. Cholinergic receptors
B. P2 receptor
C. NMDA receptor
D. GABA-B receptor

114. Which of the following mechanisms is currently implicated in learning and memory?
A. Modulation of release of neurotransmitters in postsynaptic neurons in response to repeated firing of presynaptic neurons
B. Modulation of neurotransmitter receptor synthesis in postsynaptic neurons
C. Formation of new neurons
D. Spatial organization of association areas

115. The categorical hemisphere is chiefly concerned with:
A. language
B. recognition of faces
C. stereognosis
D. spatiotemporal relations

116. The representational hemisphere is concerned with:
A. spatiotemporal relations
B. stereognosis
C. recognition of faces
D. recognition of musical themes

117. When ambient temperature is about 20ºC, body heat is lost chiefly by:
A. radiation and conduction
B. vaporization of sweat
C. respiration
D. urination and defecation

118. Which of the following is a heat conserving mechanism?
A. Panting
B. Sweating
C. Curling up in a ball
D. Insensible water loss

119. Which is the **least important** heat generating mechanism in a neonate?
A. Crying
B. Curling up
C. Cutaneous vasoconstriction
D. Shivering
E. Sympathetic activation of brown adipose tissue

120. The first physiologic response to high environmental temperature is:
A. cutaneous vasodilation
B. decreased heat production
C. nonshivering thermogenesis
D. sweating

121. A 'reward center' is located in:
A. prefrontal cortex
B. nucleus accumbens
C. medial forebrain bundle
D. ventral tegmental area
E. dorsal brain stem

122. The Papez circuit consists of:
A. hypothalamus
B. anterior thalamus
C. cingulate cortex
D. hippocampus

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123. Emotional responses often outlast the duration of the stimulus **because:**
A. limbic cortex is made up of three layers
B. neocortex cannot modify emotional behavior
C. limbic circuits have prolonged afterdischarge

124. Kluver-Bucy animals exhibit:
A. hypersexuality
B. visual agnosia
C. bizarre exploratory behaviour
D. amnesia
E. fearlessness

125. Symptoms of the Kluver-Bucy syndrome have been shown to be reproduced by:
A. amygdalectomy
B. thalamectomy
C. decerebration
D. lesions in the internal capsule

Answers: Central Nervous System

1A	2B	3C	4B	5B
6D	7D	8B	9C	10
11A	12C	13C	14CDE	15C
16C	17D	18C	19B	20A
21D	22A	23all	24A	25D
26A	27C	28A	29B	30C
31B	32D	33C	34D	35A
36D	37AB	38C	39D	40D
41C	42C	43A	44A	45C
46D	47B	48B	49A	50A
51A	52AC	53A	54B	55C
56C	57A	58B	59B	60B
61A	62B	63B	64C	65AB
66A	67A	68C	69A	70D
71C	72CD	73B	74E	75D
76B	77B	78A	79A	80C
81A	82A	83B	84B	85D
86D	87C	88B	89B	90A
91ABC	92D	93B	94B	95B
96D	97A	98C	99C	100C
101A	102B	103C	104E	105B
106B	107A	108C	109D	110A
111A	112C	113C	114all	115A
116all	117A	118C	119D	120A
121all	122all	123C	124all	125A

Explanations:

2. The same sensation is perceived no matter how a sensory pathway is excited. Each pathway is labeled to transmit a specific sensory modality. This is the *labeled line* principle or Muller's doctrine of specific nerve energies.

3. Weber-Fechner Law (Power law):
Magnitude of the sensation felt $(R) = KS^A$ where S is stimulus intensity.

4. Bell Magendie law: In spinal nerves, dorsal roots are sensory and ventral roots are motor.

Muller's law of specific nerve energies (the labeled line principle): Each sensory pathway starting from the receptor up to the cortex is *labeled* for transducing a particular sensory modality.

7. Touch receptors:

Rapidly-adapting touch receptor	Pacinian corpuscle; Meissner's corpuscle
Slowly-adapting touch receptor	Merkel's disks; Ruffini endings
C mechanoreceptor	Stroking, erotic touch

Vibration, repetitive touch stimuli, is encoded by Pacinian corpuscle, a rapidly adapting touch receptor. Pressure is sustained touch and it is coded by Merkel disks, slowly adapting touch receptors.

9. The gate theory of pain, proposed by Wall and Melzack, posits that there is a mechanism to facilitate or inhibit transmission of nociceptive impulses at the level of the spinal cord. The putative gate is thought to be located at the substantia gelatinosa of the spinal cord. Higher centers exert influences on this gate. For example, serotonin released from raphe spinal neurons inhibits onward transmission of nociceptive inputs (endogenous analgesia system).

12. Serotonin acts presynaptically on the 'gate' in the dorsal horn of the spinal cord and reduce the efficacy of transmission in the pain pathway. Enkephalins are also implicated in this mechanism.

13. Ascending pathways and the sensory modalities they code:

Dorsal column – lemniscal system	Fine touch, touch localization, two-point discrimination, vibration, joint position sense
Anterior spinothalamic tract	Pressure, crude touch
Lateral spinothalamic tract	Pain, temperature

14. Synthetic senses are synthesized in the sensory association area in the brain (posterior parietal cortex) from component senses.

15. Since touch and pressure are both intact, one could presume that all sensory pathways right up to the somatosensory cortex are intact. Impaired stereognosis must therefore be due to a defect posterior to the somatosensory area (i.e. in the posterior parietal cortex).

17. Ablation of somatosensory area does not result in impairment of pain perception since the mere perception of pain does not require the cortex. Cortical processing is concerned primarily with finer aspects of information processing including discrimination of subtle differences in stimulus intensity, localization of stimulus.

20. There is no separate taste area in the brain as there is for other special senses. Impulses from taste buds finally reach the foot of the postcentral gyrus.

21. Steady state neurotransmitter release from rod cells occurs in the dark. Light causes activation of cGMP - phosphodiesterase, reducing intracellular cGMP, this resulting in closure of Na channels, hyperpolarization of rod cells and reduced release of neurotransmitter from rod cells.

27. Argyll-Robertson pupil: Light reflex absent; accommodation reflex present; lesion in the pretectal nucleus of the midbrain where light reflex is integrated.

Sometimes the light reflex is present; and the accommodation reflex absent. In this situation, the lesion could be present anywhere beyond the exit of the fibers from the optic nerve to the pretectal nucleus.

28. Rods are much more sensitive than cones to light; rods are essential for scotopic vision; cones mediate color vision.

30. In the dark, the prosthetic group retinene in retinaldehyde is in the 11-cis configuration. The action of light is to change the shape of this to the all-trans isomer.

33. Dark adaptation requires synthesis of more rhodopsin.

35-37. Saccades are sudden jerky movements and occur as gaze shifts from one object to the other. They are programmed in the frontal eye field (in the cerebral cortex) and the superior colliculus.

38. Think about how the accommodation reflex is elicited. We ask a person to look at an object placed nearby after he looks at an object placed farther away. Accommodation reflex is integrated in the multiple areas in the cerebral cortex (visual cortex followed by the frontal eye field in the frontal cortex) and then projects to the Edinger-Westphal nucleus in the midbrain. Thus, a person who is blind (on both eyes) because of a defect in the visual pathway anywhere beyond the optic chiasm will not have this reflex.

42. Amplification by lever action of ear ossicles = 1.3. Ratio of surface area of tympanic membrane and oval window = 17; thus, the total amplification = $17 \times 1.3 = 22$

43. Like ICF, endolymph is rich in K. Like ECF, perilymph is rich in Na. Endolymph and perilymph do not mix.

44. Hair cells are depolarized by K influx because the endolymph is rich in K.

46. Sound localization is disrupted by lesions of the auditory cortex. (Ganong, 2005, p.182)

47. If we were doing the Rinne's test on the right side, how sure are we that the person hears through the right ear and not on the left? To ensure this does not happen, the untested ear is masked using a Barany's noise box. Alternately, we could ask the patient to insert his finger in the left ear and make quick noisy movements during the Rinne's test.

Second, the results of Rinne's and Weber's test must be interpreted together and not in isolation.

In this case, the Rinne's test was negative (called 'false negative') because there is apparently no defect in ossicular conduction on the right side. Furthermore, Weber's test was localized to the left side. Taken together, this is indicative of sensorineural deafness on the right side.

Absolute bone conduction of a test subject may be compared with a reference subject whose hearing is known to be normal. The results of this test (Schwabach's test) are useful in detecting early sensorineural deafness.

48.

Stimulus	Sensory receptor
Linear acceleration in the vertical plane	Saccule
Linear acceleration in the horizontal plane	Utricle
Rotational acceleration	Semicircular canals in the plane of the rotation

49. Umami is the name given to the taste evoked by monosodium glutamate.

50-61. Notes on function of muscle spindle:
Muscle spindle is a stretch receptor. Contraction of the intrafusal fibers stretches the central portion of the intrafusal fiber (muscle spindle). The afferents from the muscle spindle pass via Ia and II fibers.

The **nuclear bag fiber** is activated whenever the spindle is stretched; i.e. it detects a change in length of the muscle *(dynamic response)*. The **nuclear chain fiber,** a slowly adapting receptor, fires even during maintained stretch; i.e. it detects the absolute length of the muscle *(static response)*.

Since α- and γ-motor neurons are coactivated, intrafusal fibers also contract whenever extrafusal fibers contract. Thus, the central portion i.e. the spindle is stretched and fires even while the muscle is contracting; thus the spindle is capable of responding to rate of change of stretch, as well as maintained stretch.

Aγ motor neurons innervate the intrafusal fibers whereas the extrafusal fibers (the regular contractile units of skeletal muscle) are made to contract by stimulation of alpha motor neurons. Aα motor neurons constitute the final common path for all neural influences causing muscle contraction.

Though stretch reflexes are called monosynaptic reflexes, relaxation of the antagonist muscle involves an inhibitory neuron (for reciprocal innervation).

In summary, the muscle spindle detects muscle fiber length and changes in muscle fiber length, and the stretch reflex operates to regulate muscle length. The stretch reflex is integrated in the spinal cord.

Stretch reflexes are lost in lower motor neuron type disease involving the corresponding spinal segments, phase of spinal shock, deafferentation. They are exaggerated with Jendrassik's maneuver and other conditions increasing gamma motor neuron discharge, upper motor neuron type disease, chronic spinal animals and humans.

62-64. Golgi tendon organ is a stretch receptor located in series with collagen fibers in the muscle tendon; it is innervated by Ib fibers
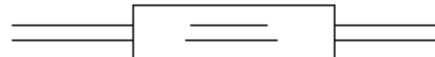
Inverse stretch reflex (autogenic inhibition)
Excessive muscle stretch
↓
Activation of Ia afferents
↓

Forceful contraction of muscle

↓

Stretch of Golgi tendon organ in tendon

↓

Activation of Ib afferents

↓

Muscle relaxation

65. Impulses in the spinothalamic tracts and the dorsal column-medial lemniscus pathways reach consciousness. Impulses in the spinocerebellar pathways terminate in the cerebellar cortex.

66. Golgi bottle neurons and Renshaw cells are two classic interneurons in spinal cord. Both release glycine. Both cause direct inhibition of postsynaptic neurons.

68. Tetanospasmin produces spastic paralysis by preventing the release of glycine from Renshaw cells, inhibitory interneurons in the spinal cord. Botulinum toxin causes flaccid paralysis by inhibiting the release of Ach from the neuromuscular junction. Strychnine blocks glycine receptors.

70. Spinal shock is presumably due to sudden loss of tonic bombardment of α-motor neurons by supraspinal neurons.

71. The **crossed extensor response,** which occurs due to irradiation of afferent stimuli, occurs only in spinal animals that have recovered from spinal shock. It is a sign of release of spinal lower motor neurons from the inhibitory control of higher centers.

72. The mass reflex is a sign of a central excitatory state; it is presumably a manifestation of release of spinal lower motor neurons from inhibitory control by higher centers. Denervation supersensitivity may contribute to the occurrence of the mass reflex.

74. Spasticity is a release phenomenon. It occurs as a result of release of brain stem motor neurons from inhibitory control by higher centers (i.e. the cerebral cortex and the basal ganglia)

75. Withdrawal reflexes consist of withdrawal of affected body part in response to a noxious stimulus and are integrated in the spinal cord. They are normally held in check by higher centers. They are exaggerated in chronic spinal animals as a result of "release" from inhibitory control from higher centers. Thus the crossed extensor component of the response is seen only in chronic paraplegics (i.e. following recovery from spinal shock)

84. The doll's eye reflex is the vestibulo-ocular reflex, used as a test of brain stem integrity, in patients who are comatose. The absence of the doll's eye reflex in comatose patients is a grave prognostic sign.

87. The only source of climbing fiber input to the cerebellum is the inferior olivary complex. There is evidence that this pathway is activated when a new motor task is learnt.

98. Sleep walking, bed wetting and night terrors occur during slow wave sleep or, more specifically during arousal from slow wave sleep. They are not associated with REM sleep.

99. In this condition, hypotonia does not occur during REM sleep and the person may act out his dreams. It is treated with benzodiazepines.

101. Ganong, 2012, p. 309, Table 17-1

103. Neurotransmitters that increase food intake are said to be orexigenic. Neurotransmitters with orexigenic effects include neuropeptide Y, orexin A and orexin B. Orexins are synthesized in neurons located in the lateral hypothalamus. The feeding center is located in the lateral hypothalamus. Ghrelin, a circulating hormone from the stomach acting on the hypothalamus stimulates food intake. In contrast, leptin from adipose tissue acts on the hypothalamus signaling satiety and inhibits food intake.

104. Circadian rhythms are 24-h biological rhythms entrained by the light-dark cycle. They are paced in the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN receives neural input from retina. In totally blind individuals, circadian

rhythms are "free running" (i.e., are not synchronized to environmental time cues) and have a periodicity ranging from 24.1-25 hr (averaging 24.5 hr).

105. Postganglionic sympathetic (noradrenergic) neurons innervating the pineal commence in the superior cervical ganglion and reach it via *nervi conarii*.

114. It is now established that the longheld belief that we do not add brain cells after birth is incorrect. New neurons arise from stem cells in the olfactory bulb and hippocampus and since formation of long-term memories occurs in the hippocampus, it is possible that the two are related; this hypothesis is currently intensely researched. (Ganong, 2012, p 287)

120. While cutaneous vasodilation and sweating go together, however, cutaneous vasodilation per se contributes to heat loss even if not accompanied by sweating.

124. Kluver and Bucy observed these to be effects of bilateral temporal lobectomy in monkeys. However, it was later shown that these features could be reproduced by bilateral resection of the amygdalae.

ENDOCRINOLOGY & REPRODUCTION

Summaries:
1. Congenital adrenal hyperplasia
2. Summary of consequences of deficiencies of some enzymes in the steroidogenic pathway
3. Physiologic principles in the diagnosis of disorders of sexual differentiation

1. Congenital adrenal hyperplasia (CAH)
The two most important causes include:
- *21 hydroxylase* deficiency (commonest)
- *11-beta hydroxylase 1* deficiency

Pathogenetic sequence:
1. Block in synthesis of glucocorticoids and or aldosterone
2. Increase in ACTH (as a result of loss of negative feedback effects of cortisol)
3. Compensatory bilateral adrenal hyperplasia
4. The *block* remains
5. Increased synthesis of adrenal androgens

Salt loss and Addisonian crises with severe deficiency of 21 hydroxylase (***salt losing form of CAH***) accompanied by adrenogenital syndrome in newborns (males as well as females). Screening a newborn for possible congenital adrenal hyperplasia is done by estimating serum 17-hydroxyprogesterone. If it is elevated then it should be confirmed by estimating aldosterone and cortisol.

Manifestations in females:
- With mild deficiency of 21 hydroxylase, the main consequence of clinical significance may be virilization at the time of birth (***simple virilizing form of CAH***)
- Precocious pseudopuberty
- *Nonclassic CAH (late onset)*: virilization in postpubertal females

Clinical presentation depends on severity of deficiency:
1. Salt losing form – with possible Addisonian crises

2. Ambiguous genitalia at birth in genetic females (*female pseudohermaphroditism*); adrenogenital syndrome
3. Precocious pseudopuberty or accentuation of male secondary sex characteristics in males
4. Virilization in postpubertal females

2. Summary of Consequences of deficiencies of some enzymes involved in steroidogenesis in the adrenal cortex:

Enzyme	Consequences of deficiency
Cholesterol desmolase (side-chain cleavage enzyme)	Fatal in utero as no steroid hormones can be synthesized
Steroidogenic acute regulatory protein (STAR)	This enzyme is not expressed in the placenta, and its deficiency has been described to be in some cases compatible with life. STAR is expressed in the adrenal cortex, testes and ovaries and is needed to transport cholesterol to the inner mitochondrial membrane in these tissues. STAR deficiency results in congenital lipoid adrenal hyperplasia.
3-beta hydroxysteroid dehydrogenase (type 2)	Rare; this isoform is expressed in the fetal zone of the adrenal cortex and the gonads but not in the placenta. It is characterized by deficiency of cortisol, aldosterone and neither estrogens nor testosterone can be synthesized. In genetic males, the result is development of female external genitalia. Affected infants typically present with *salt losing crises*.
17α-hydroxylase (CYP17)	Rare, no sex hormones, female genitalia develop regardless of genetic sex, characterized by an increase in plasma corticosterone, hypertension & hypokalemia
21 hydroxylase (CYP21)	95% congenital adrenal hyperplasia is due to deficiency of this enzyme; however, manifestations vary depending on severity of enzyme deficiency.

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Enzyme	Consequences of deficiency
	Three types of presentations are described: classic (salt-losing form) of CAH; simple virilizing form of CAH; and non-classic (late onset) form of CAH.
11β-hydroxylase (CYP11B1)	Cortisol deficiency; virilization due to excessive synthesis of adrenal androgens; hypertension due to mineralocorticoid activity of high levels of 11-deoxycorticosterone

3. Basic principles of diagnosis of disorders of sexual differentiation: These are the most important facts one needs to know in order to understand and diagnose disorders of sexual differentiation.

1. For our purposes, it is reasonable to think of development of female internal and external genitalia as a *default* genetic program in intrauterine development regardless of genotype.

2. However, the development of normal ovaries from the bipotential gonad requires the presence of 2 normal X chromosomes and the absence of the sex-determining region of the Y-chromosome (SRY). Several genes are required for the development of ovaries – therefore, development of ovaries should not be thought of as a default pathway.

3. A functional SRY gene, whether on the Y chromosome (normal), or 'hiding' in a X chromosome, dictates the formation of embryonic testes.

4. The differentiation of the gonadal ridge may be limited by deficiency of factors such as steroidogenic factor (SF-1), a nuclear receptor involved in transcriptional regulation of many genes including those need for steroidogenesis in the ovary and the testes.

5. Embryonic testes may or may not be functional. *Functional embryonic testes* secrete testosterone (Leydig cells) and Mullerian Inhibiting Substance (or Polypeptide, MIS or

MIP, from Sertoli cells).

6. Like in the adrenal cortex, **steroidogenic acute regulatory protein (STAR)** is expressed in the gonads and is required for normal synthesis of steroid hormones. As for intrauterine development, this is particularly important in males because embryonic testes produce testosterone.

7. Placenta does **not** express STAR and still synthesizes progesterone. Since STAR deficiency, at least, in some cases is compatible with life, it is likely because some of the progesterone from the placenta is channeled into other sites of steroidogenesis (fetal zone of the adrenal cortex, definitive adrenal cortex, testes and ovaries) and serves as the starting point for steroidogenesis. This mechanism potentially provides partial compensation for STAR deficiency.

8. With normal androgen receptors, testosterone (T) induces the development of 'male internal genitalia' (epididymis, vas deferens, seminal vesicles) from the Wolffian duct (mesonephric duct).

9. MIS (MIP) acts in a paracrine fashion and induces regression of the *ipsilateral* Mullerian duct. In the absence of MIS (MIP), Mullerian ducts develop into Fallopian tubes, uterus, uterine cervix and the upper third of the vagina. The lower one third of the vagina forms in the absence of the actions of dihydrotestosterone (DHT) on the pelvic part of the definitive urogenital sinus.

10. DHT, formed from T by the action of testosterone *5-alpha* reductase (type 2), is required for the development of male external genitalia from the urogenital sinus into (growth of the male phallus, urethra, complete fusion of labioscrotal swellings to form the scrotum). Of course, the concentration of androgen receptors (AR) and their sensitivity to androgens should be normal for this to happen. The formation of DHT occurs inside *target cells*.

Type 2 5-alpha reductase predominates in the genital tract, and the isoform of the enzyme in the pilosebaceous unit is *type 1*. Finasteride is a more

potent inhibitor of the type 2 *5-alpha* reductase; however, finasteride has also been used in the management of hirsutism in females.

11. T and DHT mediate their effects via the same AR. DHT-AR complexes are more stable. This explains why DHT is biologically the most potent androgen.

12. The embryonic ovary **does not** produce any hormones, and estrogens are not required for intrauterine development of female internal or external genitalia.

13. The *critical period* of differentiation of genitalia in intrauterine life is **8-12 weeks**. T synthesis by the Leydig cell during this time is under the control of hCG (LH receptor). After mid-gestation, fetal pituitary LH modulates fetal T synthesis and affects the growth of the differentiated penis.

14. **Genetic sex** - male (46 XY), female (46 XX); **gonadal sex** (male - if testes are present; female - if ovaries are present); **phenotypic sex** - based on external genitalia - male, female, ambiguous.

15. Gender assignment at birth is based on external genitalia (male; female; ambiguous)

16. **Gender identity**: Identification of self as male or female. This is affected by one's perception of his/her genitalia in comparison to others, how the child is raised (as female or male). The size of the phallus is a particularly important determinant.

When all of this is considered along with mechanisms involved in puberty and the actions of sex hormones, then we have most of the factual premises needed for understanding the phenotype in most disorders of sexual differentiation and therefore diagnosing them.

QUESTIONS

Instructions: Unless otherwise specified, choose the single best answer.

1. The term 'neurohormone' is applied to:
A. oxytocin and vasopressin
B. NO and CO
C. glycine and glutamate
D. FSH and LH

2. Which of the following hormones does **not** act through G-protein coupled receptors?
A. Dopamine
B. Epinephrine
C. Angiotensin II
D. ACTH
E. Retinoic acid
F. Thyroxine

3. The group of chemical messengers whose actions are known to be mediated by receptor tyrosine kinases includes:
A. angiotensin II, ANP and ET 1
B. EDRF, ANP and AVP
C. FSH, LH and GHRH
D. insulin, EGF, IGF 1, PDGF

4. JAK-STAT pathways mediate the effects of:
A. transducin
B. aquaporins
C. gusducins
D. growth hormone

5. Which of the following hormones is **not** a glycoprotein?
A. TRH
B. FSH
C. LH
D. hCG

6. The three glycoprotein hormones each containing 2 subunits (an alpha and a beta subunit) produced by the pituitary are:
A. FSH, LH and TRH
B. TRH, ACTH and LH
C. TSH, LH and FSH
D. GH, TSH and LH

7. Histamine released from mast cells in the stomach stimulates the secretion of HCl by parietal cells. What type of signaling is this?
A. Endocrine
B. Paracrine
C. Autocrine
D. Juxtacrine

8. Which of the following has the longest biologic half-life?
A. Insulin
B. Angiotensin II
C. Glucagon
D. Thyroxine
E. ADH
F. Nitric oxide

9. In the anterior lobe of the human pituitary, prepro-opiomelanocortin is processed mainly to:
A. *Alpha*-MSH
B. ACTH
C. *Beta*-endorphin
D. *Beta*-MSH

10. Selective section of the pituitary stalk in an experimental animal usually **increases** the secretion of which of the following hormones?
A. Growth hormone
B. FSH
C. LH
D. Prolactin

11. Growth hormone secretion is increased by all of the following **except:**
A. pharmacologic doses of hydrocortisone
B. hypoglycemia
C. exercise
D. protein meal

12. Which of the following hormones has intrinsic lactogenic activity?
A. TSH
B. MSH
C. GH
D. dopamine

13. A human growth hormone variant (hGH-V) is expressed primarily in:
A. liver
B. spleen
C. kidney
D. placenta

14. The commonest cell type in the anterior pituitary is:
A. somatotroph
B. lactotroph
C. corticotroph
D. thyrotroph

E. gonadotroph

15. Growth hormone stimulates the secretion of:
A. somatostatin
B. somatomedin (IGF-1)

16. Check all **correct** statements regarding oxytocin.
A. It is essential for milk ejection
B. It increases uterine contractility
C. It facilitates ejaculation of semen
D. It facilitates sperm transport in the uterus

17. ADH circulates in plasma primarily:
A. bound to neurophysin I
B. bound to neurophysin II
C. bound to plasma albumin
D. not bound to plasma proteins

18. Arrange the following steps in the order in which they occur in the thyroid gland.
1. Coupling reaction
2. Iodination
3. Endocytosis of thyroglobulin
4. Oxidation of iodine
5. Iodine uptake
6. Cleavage of thyroglobulin
7. Secretion of T4
8. Iodide trapping

19. Normally, the thyroid gland secretes:
A. CGRP
B. PTH related peptide
C. TSH
D. calcitonin

20. Which of the following hormones lowers plasma level of ionized calcium?
A. Calcineurin
B. Calcitonin
C. Parathyroid hormone
D. PTH related peptide

21. *Select all correct answers.* TSH secretion is inhibited by:
A. dopamine
B. somatostatin
C. T3 and T4
D. TRH

22. For a euthyroid woman who is neither pregnant nor nursing, and taking no medication, the recommended daily dietary allowance of iodine is:
A. 75 micrograms
B. 150 micrograms
C. 225 micrograms
D. 300 micrograms

23. In a healthy euthyroid adult, the thyroid gland predominantly secretes:
A. thyroxine
B. triiodothyronine
C. reverse T3

24. Iodine is concentrated in thyroid follicular epithelial cells by:
A. primary active transport
B. secondary active transport
C. simple diffusion
D. facilitated diffusion

25. Most of the T3 in the liver is formed from circulating T4 by the action of:
A. type 1 deiodinase (D1)
B. type 2 deiodinase (D2)
C. type 3 deiodinase (D3)

26. Which of the following enzymes protects the fetus from hyperthyroidism when the mother is hyperthyroid?
A. Type I deiodinase (5' deiodinase); outer ring deiodinase
B. Type 2 deiodinase (3' deiodinase)
C. Type 3 deiodinase (3,3,5 - deiodinase); inner ring deiodinase
D. Iodotyrosine deiodinase

27. Most of the circulating T4 is bound to:
A. prealbumin
B. albumin
C. thyroxine-binding globulin

28. In postnatal life, thyroid hormones do **not** increase oxygen consumption in the:
A. heart
B. skeletal muscle
C. adult brain
D. liver

29. The normal basal metabolic rate in a euthyroid adult male is (BSA is body surface area):
A. 10-15 kcal/m^2 BSA/hr
B. 20-25 kcal/m^2 BSA/hr
C. 35-40 kcal/m^2 BSA/hr
D. 45-60 kcal/m^2 BSA/hr

30. Which of the following statements is **incorrect?**
A. Thyroxine is biologically more active than triiodothyronine.
B. Cells of the anterior pituitary convert T4 to T3 using type 2 deiodinase

31. Clinically, in an unselected population of individuals, the most sensitive test to detect a disorder of thyroid gland function is measurement of:
A. TSH
B. free T3
C. free T4
D. total T4
E. free thyroxine index

32. Worldwide, the commonest preventable cause of mental retardation in the newborn is:
A. iodine deficiency
B. phenylalanine hydroxylase deficiency
C. cystic fibrosis
D. urea cycle defect
E. Down syndrome

33. Hyperthyroidism following administration of large amounts of iodine (iodine induced hyperthyroidism; Jod-Basedow mechanism) is least likely in an individual with:
A. panhypopituitarism
B. endemic (iodine deficiency) goiter
C. Hashimoto's thyroiditis
D. Graves' disease

34. The most abundant cell type in the islets of Langerhans is:
A. A cells
B. B cells
C. D cells
D. F cells

35. Insulin secretion from B-cells in pancreas is **inhibited** by:

A. acetylcholine
B. activation of *beta*-adrenergic receptors
C. activation of *alpha*-adrenergic receptors
D. glucagon
E. somatostatin

36. For the same plasma concentration of glucose achieved, the insulin secretory response to an oral glucose load is greater than the insulin secretory response to an intravenous infusion of glucose. This is because of the:
A. potentiation of insulin secretion by glucagon like polypeptide-1 and glucose dependent insulinotropic polypeptide (incretin effect) when glucose is ingested orally
B. secretion of preformed insulin occurs only when glucose is ingested orally.

37. Which of the following is a potent **stimulator** of insulin secretion?
A. Somatostatin
B. VIP
C. Glucagon like polypeptide-1 (GLP-1)
D. Leptin

38. Insulin dependent glucose uptake into skeletal muscle and adipose tissue is mainly mediated by:
A. GLUT 1
B. GLUT 2
C. GLUT 3
D. GLUT 4

39. Insulin secretion from *beta* cells of pancreas in response to a glucose load is mediated by:
A. GLUT 1
B. GLUT 2
C. GLUT 3
D. GLUT 4

40. In the management of a child with diabetic ketoacidosis and a plasma pH of 6.9, insulin infusion is typically continued even after plasma glucose is reduced to 250 mg/dL, and glucose is coadministered with insulin. This is done **in order to allow:**
A. muscle glycogen to be replenished
B. plasma potassium to be normalized
C. plasma osmolality to be reduced rapidly
D. complete oxidation of ketone bodies

41. Which of the following conditions **increases** the risk of fasting hypoglycemia?
A. Adrenocortical insufficiency
B. Hyperglucagonemia
C. Severe hypothyroidism
D. Acromegaly

42. Which tissues do **not** require insulin for glucose uptake? *(check all correct answers)*
A. Red blood cells
B. Most parts of the CNS
C. Adipose tissue
D. Skeletal muscle

43. The *hormone of energy storage* (hormone of plenty) is:
A. growth hormone
B. thyroxine
C. insulin
D. glucagon
E. epinephrine

44. Which of the following hormones is / are diabetogenic? *(Check all correct answers)*
A. Epinephrine
B. Cortisol
C. Growth hormone
D. Glucagon
E. Thyroid hormones

45. Glucagon, when present in high concentrations such as in a type I diabetic, facilitates all of the following **except:**
A. lipolysis
B. gluconeogenesis
C. hepatic glycogenolysis
D. muscle glycogenolysis

46. The two drugs that are commonly used to induce diabetes in rats are:
A. streptozotocin
B. alloxan
C. forskolin
D. capsaicin

47. Check all **correct** statements.
A. The *beta* cell releases equimolar amounts of insulin and C-peptide
B. Nonsuppressible insulin like activity (NSILA) is due to circulating C-peptide.

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C. C-peptide has a shorter half-life compared to insulin.

D. C-peptide level in plasma provides an index of B-cell function in patients receiving exogenous insulin.

48. Which of the following is the **most sensitive** test of pancreatic B-cell insulin secretory reserve?
A. Oral glucose tolerance test
B. Fasting plasma glucose
C. Urine glucose excretion
D. Random blood glucose

49. Which of the following increases insulin / glucagon molar ratio the most?
A. A large carbohydrate meal
B. Intravenous glucose
C. Overnight fast
D. A small protein meal
E. Low carbohydrate diet

50. Hypoglycemia does **not** stimulate the secretion of:
A. epinephrine
B. cortisol
C. growth hormone
D. insulin
E. glucagon

51. The satiety-producing hormone is:
A. orexin
B. resistin
C. adiponectin
D. leptin

52. *Select all correct answers.* Which of the following increase insulin resistance?
A. Leptin
B. TNF-α
C. Resistin
D. Adiponectin
E. Growth hormone secreting tumor
F. Epinephrine secreting tumor

53. Insulin sensitivity is **not** reduced in:
A. glucagon-secreting tumors
B. tumors of adrenal medulla
C. tumors of adrenal cortex
D. hypopituitarism

54. A diabetic woman who is pregnant and who has been taking recombinant insulin during the pregnancy delivered a baby weighing 5 kg. This is **most closely related to**:
A. passage of maternal insulin into the fetus
B. elevated levels of fetal insulin
C. uteroplacental insufficiency
D. hyperglycemia in the mother

55. Uptake of potassium into cells is enhanced by which of the following hormones / mechanisms?
A. Thyroid hormones
B. Insulin
C. *Beta*-adrenergic receptor activation

56. Somatostatin **inhibits** the secretion of:
A. insulin
B. glucagon
C. growth hormone
D. gastrin

57. Hans Selye defined "stressors" specifically as stimuli that increase the secretion of _____ in healthy humans or laboratory animals.
A. CRH
B. ACTH
C. TSH
D. cortisol

58. Which of the following organelles is a major site of steroidogenesis?
A. Peroxisomes
B. Ribosomes
C. Smooth endoplasmic reticulum
D. Rough endoplasmic reticulum

59. In which zones is corticosterone converted to aldosterone?
A. Zona glomerulosa
B. Zona fasciculata
C. Zona reticularis

60. Which of the following zones in the adrenal cortex does not normally express 17 *alpha* hydroxylase?
A. Zona glomerulosa
B. Zona fasciculata
C. Zona reticularis

61. The hormone that is synthesized only in the zona glomerulosa is:

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A. DHEA
B. aldosterone
C. corticosterone
D. deoxycorticosterone

62. New cortical cells are formed from reserve cells in the:
A. zona glomerulosa
B. zona fasciculata
C. zona reticularis

63. Injection of pharmacologic doses of ACTH in healthy experimental animals is **least likely** to produce a sustained increase in:
A. cortisol secretion
B. lymphocyte count
C. skin pigmentation
D. aldosterone secretion

64. Which of the following hormones has the **highest** mineralocorticoid activity?
A. Cortisol
B. Corticosterone
C. Deoxycorticosterone
D. Cortisone

65. Which of the following hormones has **maximum** glucocorticoid activity?
A. Cortisol
B. Corticosterone
C. Deoxycorticosterone
D. Cortisone

66. In humans, the **most abundant** adrenocortical hormone is:
A. cortisol
B. corticosterone
C. deoxycorticosterone
D. DHEA sulfate

67. The **most abundant** androgen in the plasma of both males and females is:
A. androstenedione
B. dehydroepiandrosterone sulfate
C. testosterone
D. dihydrotestosterone

68. Diurnal variation in eosinophil count is due to
A. cortisol
B. insulin

C. thyroid hormones
D. thrombopoietin

69. Glucocorticoids **decrease** the number of circulating:
A. eosinophils
B. lymphocytes
C. platelets
D. red blood cells

70. Hypophysectomy does **not** immediately affect the secretion of:
A. zona glomerulosa
B. zona fasciculata
C. zona reticularis

71. Which hormone also upregulates its receptors in the adrenal cortex?
A. Epinephrine
B. Angiotensin II
C. Cortisol
D. Aldosterone

72. In glucocorticoid-remediable aldosteronism:
A. angiotensin II has no effect on aldosterone synthesis
B. angiotensin II stimulates whereas angiotensin III inhibits aldosterone synthesis
C. aldosterone synthase is expressed in the zona fasciculata and exquisitely sensitive to stimulation by ACTH.
D. administration of glucocorticoids increases ACTH levels

73. Which of the following does **not** occur as a consequence of adrenalectomy?
A. Reduced alertness
B. Increased vulnerability to hypotension
C. Decreased ability to excrete a water load
D. Dextrose fever
E. Glucose intolerance

74. The release of androgens from the adrenal cortex is stimulated mainly by:
A. LH
B. FSH
C. ACTH
D. GnRH

75. In humans, the hormone that is mainly secreted by the adrenal medulla is:
A. epinephrine
B. norepinephrine
C. dopamine
D. adrenomedullin

76. The adrenal medulla does **not** normally secrete:
A. epinephrine
B. norepinephrine
C. chromogranin B
D. vasoactive intestinal polypeptide

77. Adrenaline, noradrenaline and dopamine act upon membrane receptors that span the membrane:
A. 2 times
B. 5 times
C. 7 times
D. 10 times

78. The lipolytic effect of catecholamines is mediated by:
A. ß1 adrenergic receptors
B. ß2 adrenergic receptors
C. ß3 adrenergic receptors
D. ß1 & ß3 adrenergic receptors

79. Which of the following hormones is critical for acute regulation of a falling serum ionized calcium?
A. Calbindin
B. Calcitonin
C. Calcitriol
D. Parathyroid hormone
E. T3

80. The major stimulator of parathyroid hormone release from the parathyroid gland is:
A. vitamin D
B. a fall in plasma ionized calcium
C. calcitonin
D. a fall in plasma phosphate concentration

81. Deficiency of which of the following hormones is **not** known to result in a clinically significant disorder of regulation of ionized calcium in plasma?
A. Parathyroid hormone

B. Calcitriol
C. Calcitonin
D. Calcium sensing receptor

82. A neonate scheduled for abdominal surgery has a serum calcium of 6 mg/dL (normal: 8.5-10.5 mg/dL). Before supplementing calcium, which of the following should be checked?
A. Blood glucose
B. Serum albumin
C. Serum bilirubin
D. Oxygen saturation

83. Calcitonin inhibits the activity of:
A. osteoblasts
B. osteoclasts
C. parafollicular cells
D. thyroid

84. Bone resorption is induced by abnormally elevated levels of:
A. IGF-1
B. insulin
C. estrogens
D. glucocorticoids

85. The testis-determining gene (or the SRY gene) is located normally on/in:
A. chromosome 6
B. chromosome 12
C. short arm of chromosome 22
D. Y chromosome

86. With regard to development of gonads, which of the following is **most likely** with a 46XX zyogote that contains a functional SRY gene?
A. Female internal and external genitalia develop
B. Both ovaries and testes develop
C. Only ovaries develop
D. Only testes develop

87. The hormone that is essential for intrauterine development of male external genitalia is:
A. testosterone
B. dihydrotestosterone
C. Mullerian regression factor
D. SOX factor

88. The *fetal zone of the adrenal cortex* in the predominantly secretes:

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A. progesterone
B. androstenedione
C. DHEA
D. DHEA sulfate

89. Complete fusion of labioscrotal swellings does not occur despite exposure to high concentrations of androgens beyond which point in intrauterine life?
A. 3 weeks
B. 6 weeks
C. 9 weeks
D. 12 weeks

90. The principal estrogen secreted by the fetoplacental unit is:
A. estriol (E3)
B. estradiol (E2)
C. estrone (E1)

91. A 4 year old girl presents with bilateral inguinal masses, thought to be hernias, but these were found to be testes in the inguinal canals. The karyotype would **most likely** be:
A. 46 XX
B. 46 XY
C. 47 XXY
D. 47 XYY

92. Testicular feminization syndrome is caused by mutations in genes coding for:
A. androgen-binding proteins
B. testosterone 5α reductase
C. androgen receptor
D. inhibin

93. In an adult female who underwent pelvic surgery, internal genitalia were found to be male, and the karyotype was 46 XY. The **most likely** explanation for this is:
A. loss of function mutation in SRY gene
B. deficiency of testosterone
C. deficiency of Mullerian inhibiting peptide
D. deficiency of testosterone 5α reductase
E. complete androgen insensitivity

94. The "penis-at-12" syndrome occurs due to a deficiency of:
A. 17α hydroxylase
B. testosterone 5α reductase

C. 11β hydroxysteroid dehydrogenase
D. CYP 450scc

95. The blood-testis barrier is formed by tight junctions between:
A. Leydig cells
B. Sertoli cells
C. spermatids
D. primary spermatogonia

96. Which of the following regarding the blood-testis barrier is **incorrect?**
A. It develops before spermatogenesis.
B. Leydig cells are part of the blood-testis barrier.
C. Disruption of the barrier makes spermatogonia prone to immunological attack.

97. The major trophic hormone for Sertoli cells and the major stimulator of aromatase activity of Sertoli cells is:
A. inhibin
B. LH
C. FSH
D. Melatonin

98. Sertoli cells produce:
A. androgen-binding protein
B. inhibin B
C. Mullerian inhibiting polypeptide

99. The biologically most active androgen is:
A. testosterone
B. dehydropepiandrosterone
C. androstenedione
D. dihydrotestosterone

100. Which of the following cells undergo meiotic division?
A. Primordial germ cells
B. Primary spermatocytes
C. Secondary spermatocytes
D. Spermatids

101. The average number of spermatids formed from a single spermatogonium is:
A. 16
B. 128
C. 512

102. The formation of mature sperm cells from a primitive germ cell takes an average of:
A. 2 days
B. 1 week
C. 74 days
D. 3 months

103. Sperm cells first acquire the ability to move forward (*progressive motility*) in the:
A. seminiferous tubules
B. epididymis
C. female genital tract

104. Which of the following hormones is **not** detectable in normal males?
A. Oxytocin
B. Estradiol (E2)
C. Estrone (E1)
D. Progesterone
E. Prolactin

105. Chronic androgen abuse by otherwise healthy male athletes is **least likely** to result in increased:
A. erythropoiesis
B. sperm count
C. respiratory endurance
D. muscle mass

106. Sildenafil citrate enhances penile erections by:
A. activating cAMP phosphodiesterase
B. activating cGMP phosphodiesterase
C. activating guanylyl cyclase
D. inhibiting cAMP phosphodiesterase
E. inhibiting cGMP phosphodiesterase
F. inhibiting guanylyl cyclase

107. The enhancement of penile erectile function produced by sildenafil citrate is primarily because of inhibition of:
A. cGMP-PDE3
B. cGMP-PDE4
C. cGMP-PDE5
D. cGMP-PDE6

108. The transient loss of the ability to discriminate between blue and green following the use of sildenafil is due to inhibition of:
A. cGMP-PDE3
B. cGMP-PDE4
C. cGMP-PDE5
D. cGMP-PDE6

109. Which of the following drugs produces therapeutic effects by downregulating hormone receptors in target cells?
A. FSH
B. Long acting GnRH analogs
C. Inhibin
D. Finasteride

110. Epiphysial closure in humans is mediated by:
A. androgens
B. estrogens
C. somatomedins
D. T3
E. insulin

111. Men castrated before puberty grow taller **because:**
A. release of growth hormone is increased
B. of androgen resistance
C. estradiol level in the epiphyseal growth plate takes longer to reach its threshold
D. of insensitivity to IGF-1

112. Patients with sexual precocity are apt to be dwarf **because of:**
A. increased levels of androgens
B. the estrogen surge during precocious puberty
C. deficiency of androgen receptors
D. increased levels of thyroxine

113. In terms of serum estradiol (E) and progesterone (P), and inhibin, the induction of the preovulatory LH surge is associated with which of the following?
A. High E and low P
B. High E, high P, and high inhibin B
C. Low E and low P
D. Low E and high P

114. Which enzyme catalyzes the conversion of androstenedione to estrone in the granulosa cells of the maturing ovarian follicle?
A. P450 side chain cleavage enzyme
B. 11 *beta*-hydroxylase
C. aromatase
D. 17-*beta* hydroxysteroid dehydrogenase

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115. In a 30 year old woman evaluated for infertility, the following data are obtained on a blood sample obtained on the 21st day of her menstrual cycle: Serum gonadotropins, estradiol, progesterone, TSH, prolactin and growth hormone. Which of the following would best indicate if this cycle was ovulatory or not?
A. Growth hormone
B. Prolactin
C. Estradiol
D. Progesterone
E. FSH
F. LH

116. Which of the following hormone peaks during the mid-luteal phase?
A. Inhibin B
B. FSH
C. LH
D. GnRH

117. Hormones produced by the ovary include:
A. estrogens
B. progesterone
C. relaxin
D. inhibin

118. In the absence of fertilization, the uterine endometrium is shed since:
A. involution of corpus luteum causes estradiol and progesterone levels to fall
B. there is an LH surge prior to ovulation.
C. theca lutein cells are the principal source of progesterone.
D. blood flow to the endometrium increases

119. Which of the following causes luteolysis?
A. PGF$_2$ *alpha*
B. Progesterone
C. Inhibin B
D. Relaxin

120. Which of the following hormones inhibits ovulation and downregulates GnRH release when present in high concentrations?
A. Prolactin
B. FSH
C. LH
D. Human menopausal gonadotropins

121. The *maternal growth hormone of pregnancy* is:
A. hGH-N
B. hCS
C. estriol
D. hCG

122. Which of the following is **not** detectable in the blood of a nonpregnant female?
A. Oxytocin
B. Relaxin
C. hCS
D. Inhibin B

123. Which of the following hormones is **not** detectable in normal females?
A. Androstenedione
B. Testosterone
C. Dehydroepiandrosterone sulfate
D. Dihydrotestosterone

124. With a sensitive radioimmunoassay, hCG can be detected in the blood of a pregnant woman as early as _____ days past fertilization.
A. 2 days
B. 6 days
C. 10 days
D. 14 days

125. Human chorionic gonadotropin is structurally and functionally similar to:
A. LH
B. FSH
C. growth hormone
D. inhibin

126. HCG acts upon the:
A. LH receptor
B. PRL receptor
C. GH receptor
D. FSH receptor

127. Which of the following hormones is lactogenic?
A. Chorionic growth hormone
B. HCG
C. Oxytocin
D. Relaxin

128. Which of the following inhibits lactation?
A. Prolactin
B. Chorionic somatomammotropin
C. Estrogen and progesterone
D. Growth hormone

129. Which of the following hormonal combinations in plasma is associated with normal lactation?
A. Cortisol + prolactin + oxytocin
B. Estrogen (E) + progesterone (P) + prolactin
C. E + P + insulin + cortisol + prolactin
D. Prolactin + oxytocin + E + P

130. During normal pregnancy, which hormone(s) peak during the first trimester? *(select all that apply)*
A. HCG
B. HCS
C. Prolactin
D. Estradiol
E. Estriol
F. Relaxin

131. The first polar body is extruded:
A. 24 hours prior to ovulation
B. at the time of ovulation
C. at the time of LH surge
D. 48 hours after ovulation
E. upon fertilization of the ovum

132. Which of the following is expected in a healthy pregnant woman in the third trimester of pregnancy relative to the nonpregnant state? Decrease in:
A. heart rate
B. cardiac output
C. breathing rate
D. viscosity of blood

133. Which of the following has an inhibitory influence on erythropoiesis?
A. Cortisol
B. Growth hormone
C. Estradiol
D. Thyroxine

134. Congenital lipoid adrenal hyperplasia occurs due to a lack of:
A. CYP450 scc (desmolase)

B. 3β-hydroxysteroid dehydrogenase
C. 17α hydroxylase
D. steroidogenic acute regulatory protein

135. The hypertensive form of congenital adrenal hyperplasia is due to a deficiency of:
A. 11β hydroxylase
B. 21 hydroxylase
C. 3β-hydroxysteroid dehydrogenase
D. DHEA sulfokinase

Answers: Endocrinology and Reproduction

1A	2EF	3D	4D	5A
6C	7B	8D	9D	10D
11A	12C	13D	14A	15AB
16all	17D	18	19D	20B
21ABC	22B	23A	24B	25A
26C	27C	28C	29C	30A
31A	32A	33A	34B	35CE
36A	37C	38D	39B	40D
41AC	42AB	43C	44all	45D
46AB	47AD	48A	49A	50D
51D	52BCEF	53D	54B	55ABC
56all	57B	58C	59A	60A
61B	62A	63D	64C	65A
66D	67B	68A	69AB	70A
71B	72C	73E	74C	75A
76D	77C	78D	79D	80B
81C	82B	83B	84D	85D
86D	87B	88D	89D	90A
91B	92B	93D	94B	95B
96B	97C	98ABC	99D	100B
101C	102C	103B	104none	105B
106E	107C	108D	109B	110B
111C	112B	113A	114C	115D
116A	117all	118A	119A	120A
121B	122C	123none	124B	125A
126A	127A	128C	129A	130A
131B	132D	133C	134D	135A

Explanations:
1. Neurohormones are hormones synthesized and secreted by neurons into the general circulation.

2. Retinoic acid, thyroxine, steroid hormones act mainly through receptors located in the cytosol or nucleus of target cells. However, recent evidence suggests that at least some of the physiologic effects of steroid hormones like estrogens,

aldosterone are mediated via receptors located in the cell membrane. These actions have come to be therefore called 'nongenomic actions' of steroid hormones.

4. Janus tyrosine kinases (JAK) are enzymes that phosphorylate signal transducers and activators of transcription (STAT). STAT proteins are transcription factors. Growth hormone, prolactin, and erythropoietin act via JAK-STAT pathways.

5. TRH is a tripeptide.

9. Pre-proopiomelanocortin (POMC) is processed differently in different tissues. See Ganong, 2012, p. 325, Fig 18-2 and the corresponding text. The major output of the human anterior pituitary is ACTH. The intermediate lobe is rudimentary in humans. While MSH is the trophic hormone for melanocytes, MSH detected in the circulation originates from keratinocytes, not anterior pituitary. The hyperpigmentation observed in states associated with ACTH excess is due to a stimulatory effect of ACTH on the melanocortin-1 (MC-1) receptor. The N-terminal of ACTH is identical to alpha-MSH. However, again, ACTH is not processed to alpha-MSH in the anterior pituitary.

10. Dopamine from the hypothalamus inhibits the release of prolactin.

14. 50% of cells in the anterior pituitary secrete growth hormone.

15. The somatomedins are insulin-like growth factors 1 (IGF-1) and IGF-2.

17. ADH is stored in the posterior pituitary bound to neurophysins. However, ADH circulates free in plasma.

18. Steps in thyroid hormone synthesis:
1. Iodine uptake (*aka.* Iodide trapping)
2. Oxidation of iodide to iodine
3. Iodination of tyrosine residues (organification)
4. Coupling of iodotyrosines
5. Endocytosis of thyroglobulin
6. Cleavage of thyroglobulin
7. Secretion of T4 and T3

25. One third of circulating T4 is normally converted to T3 in humans by the action of type 1 deiodinase in the liver and kidneys.

26. Type 1 deiodinase – Found in liver, kidney, and in the thyroid. It is a plasma membrane enzyme. It converts T4 to T3. Otherwise its preferred substrate is rT3. However, whatever extrathyroidal T3 is generated as a result of the action of D1 spills over into the circulation for entry into target cells.

Type 2 deiodinase (D2) – It is present in the anterior pituitary, brain, cardiac muscle, and skeletal muscle. This is an intracellular enzyme generates T3, biologically the most active form of thyroid hormone, inside target cells. This is dynamically regulated by its substrate thyroxine, such that elevated levels of the enzyme are found in hypothyroidism and suppressed levels are found in hyperthyroidism - this is a 'good' thing because it allows the euthyroid state to be maintained in the presence of low free T4.

Type 3 deiodinase (D3) is present in the placenta, brain. This enzyme **inactivates** T4 converting it to rT3, and also inactivates T3. Placental D3 thus protects the fetus from an excess of T4 and T3 should the mother be hyperthyroid. However, some T4 from the mother does cross the placenta (via specific transporters) and supports growth and development in the fetus before the fetal thyroid begins making T4.

28. T4 and T3 increase the oxygen consumption of all metabolically active tissues. The exceptions are the adult brain, testes, uterus, lymph nodes, spleen and anterior pituitary. (Ganong, 2012, p. 348, Table 19-5).

31. Serum TSH (and not free T4 or free T3) is the single most sensitive test of tissue thyroidism in an unselected population of individuals for the following reasons:

1) Primary hypothyroidism or hyperthyroidism are much more commoner than secondary hypo- or hyperthyroidism.

2) In primary hypo- and hyperthyroidism, there is a clear inverse relationship between free T4 and TSH, and between free T3 and TSH, as long as the hypothalamo-pituitary thyroid axis is normal. Even a normal free T3 does not rule out hypothyroidism. This is because negative feedback inhibition of TSH is mediated by intracellular T3 in the anterior pituitary cells, formed from circulating T3 or from conversion of T4 to T3 inside thyrotrophs by type 2 deiodinase. This is why consensus guidelines recommend **not** testing for free T3 in the evaluation of suspected primary hypothyroidism. TSH and free T4 should be obtained.

33. In individuals ingesting an "excess" of iodide, hyperthyroidism may develop if "autoregulatory mechanisms" in the thyroid fail to prevent an iodine induced increase in thyroid hormone synthesis. This is called iodide induced hyperthyroidism or the Jod-Basedow phenomenon. Most often, susceptible individuals include euthyroid individuals with a nodular goiter or an autonomous thyroid nodule. A patient with hypopituitarism (and consequently low TSH) is unlikely to demonstrate this effect. The Jod-Basedow phenomenon is likely when TSH levels are high or when there are antibodies that stimulate TSH receptor.

35. When acting via alpha 2 adrenergic receptors, epinephrine/norepinephrine inhibit insulin secretion; however, when acting via *beta*-adrenergic receptors, it stimulates insulin secretion. The significance of sympathetically mediated inhibition of insulin secretion is it reduces the likelihood of hypoglycemia during exercise. The physiologic significance of the inhibitory influence of somatostatin on insulin secretion is uncertain; however, individuals with somatostatin secreting tumors develop glucose intolerance because of impaired insulin secretion.

36. The insulin secretory response to an oral load of glucose is greater because of the release of glucose-dependent insulinotropic polypeptide (GIP) and glucagon like polypeptide-1 (GLP-1), GI hormones that have a direct action on B-cells promoting insulin secretion. This effect, called the *incretin effect*, is absent when glucose is administered intravenously. When glucose is administered intravenously, the insulin secretagogue is just glucose.

37. GLP-1 (7-36) is glucagon-like polypeptide, a GI hormone that is a potent stimulator of insulin secretion *(incretin)*.

39. Insulin increases K uptake by muscle probably by stimulating Na-K ATPase. Insulin increases the oxidation of ketone bodies; this is one reason why it is necessary in the treatment of diabetic ketoacidosis.

42. Red blood cells and most regions of the brain with the exception of cells in the satiety center do not require insulin for glucose uptake.

49. Non-suppressible insulin like activity (NSILA) is insulin activity that is not suppressed by anti-insulin antibodies. It is due to insulin-like growth factors IGF-I (somatomedin C) and IGF-II.

51. Leptin (polypeptide; coded by ob gene) is a hormone secreted by adipocytes. It has an action on the hypothalamus to inhibit food intake (anorexigenic hormone). It presumably signals the amount of fat to the CNS. Leptin levels increase after a meal. Leptin receptors are coded by *db* gene. Leptin deficiency as well as deficiency of functional leptin receptors have been implicated in the pathogenesis of obesity. Significant weight loss (fat loss) is accompanied by a reduction in serum leptin. Also, when serum levels of leptin are abnormally low, GnRH secretion is eventually downregulated. Low serum leptin may in part explain amenorrhea that occurs in athletes and individuals with thyrotoxicosis.

52. Leptin and adiponectin are adipokines (hormones from adipocytes) that increase insulin sensitivity. In contrast, TNF-α and resistin decrease insulin sensitivity. Growth hormone in excess causes insulin resistance because it has hyperglycemic effects and facilitates lipolysis.

53. Diabetogenic hormones are hormones which when present in excess reduce insulin sensitivity

and thus increase plasma glucose levels, particularly in individuals otherwise predisposed to impaired *beta*-cell function. They include:

- Epinephrine
- Norepinephrine
- Glucagon
- Growth hormone
- Cortisol
- Thyroxine

54. Hyperglycemia in the mother results in fetal hyperinsulinemia. High levels of insulin in the fetus cause it to have effects on insulin as well as IGF-1 receptors, and this causes the macrosomia. Unbound insulin is normally degraded by placental proteases and does not reach the fetus. However, insulin bound to anti-insulin antibodies is known to cross the placenta, and this mechanism is also believed to contribute to fetal macrosomia in women who took animal insulins during pregnancy.

55. Insulin and thyroid hormones increase the activity of the Na-K pump, and thereby facilitate uptake of potassium by cells. *Beta*-adrenergic receptor activation also stimulates potassium uptake by muscle. Insulin-dextrose infusions and nebulized *beta*-adrenergic receptor agonists are useful as temporizing measures in the management of acute hyperkalemia.

64. Aldosterone is the most potent endogenous mineralocorticoid hormone. However the question has listed other glucocorticoid hormones, and of these, deoxycorticosterone has the highest mineralocorticoid activity – it becomes clinically significant if the binding capacity of corticosteroid binding globulin is overwhelmed, or when 11-*beta* hydroxylase is deficient.

67. DHEA-sulfate levels peak in the third decade of life and decline thereafter. Thus, it has been looked upon as a marker of aging. There is no evidence that DHEA supplementation reverses changes associated with aging. However, the most abundant adrenocortical hormone in plasma is DHEA-sulfate. Thus, plasma DHEA sulfate is looked upon as an index of functioning adrenocortical mass.

69. Glucocorticoids decrease the number of eosinophils, basophils and lymphocytes in the circulation. Glucocorticoids, particularly in pharmacologic doses suppress cell-mediated immunity by multiple mechanisms including:

- inhibiting IL-2 gene transcription
- inhibiting T cell proliferation
- inducing apoptosis in lymphocytes

70. Although ACTH is trophic to all three zones in the adrenal cortex, the major trophic hormone for the zona glomerulosa (ZG) is angiotensin II and not ACTH. Angiotensin II, angiotensin III and a rise in serum K all stimulate the synthesis and secretion of aldosterone.

72. The basic defect in glucocorticoid-remediable aldosteronism (GRA; sometimes called *dexamethasone remediable aldosteronism*) is a *hybrid* aldosterone synthase gene that has a promoter sensitive to stimulation by ACTH, and this gene is expressed in the zona fasciculata. (Normally, aldosterone synthase is expressed only in the ZG). The ZF is 5 times larger than the zona fasciculata, and therefore, in GRA, serum aldosteroneis high even with normal levels of ACTH. The hypertension that occurs as a result of hyperaldosteronism suppresses plasma renin activity; thus this is an example of primary hyperaldosteronism. Hyperaldosteronism in GRA, as the name suggests, is remediable with glucocorticoid therapy ('low dose dexamethasone'); i.e., administered glucocortiocoids inhibit ACTH release and consequently reduce aldosterone synthesis.

73. Mechanism of 'dextrose fever' in adrenocortical insufficiency:
Suppose large amounts of 5% dextrose (an isoosmotic solution) is administered,
↓
Dextrose is metabolized
↓
The water added dilutes body fluids, but since the physiologic response to hypo-osmolality is defective
↓
ICF volume increases; water influx into temperature-sensitive neurons disrupts function of the hypothalamic thermostat causing fever.

82. Normally, total serum calcium ranges from 8-10 mg/dL. Normally, the ratio of protein bound calcium to ionized calcium is approximately 1:1. In this case, total calcium = 6 mg/dL. A decrease in total calcium could be due to:

- Decrease in serum protein
- Decrease in ionized calcium

Thus, it is appropriate to seek to determine if hypoalbuminemia is the cause of hypocalcemia.

86. The sex determining region of the Y chromosome dictates the formation of embryonic testes and inhibits the development of ovaries. Mullerian inhibiting polypeptide from the testes inhibits the growth of Mullerian duct structures. Testosterone induces the development of male internal genitalia.

91. The phenotypic sex is female (it is a baby girl); gonadal sex is male (because the surgeons are telling that the inguinal masses are testes). We are to *predict* genetic sex based on this information. Since testes are present, the sex-determining region (SRY) of the Y chromosome, which encodes a transcription factor that is required for the development of embryonic testes, must be present. This gene is normally located on the Y chromosome. Thus the most likely genotype is 46XY. In contrast the 47XXY genotype does not lead to feminization (the phenotype is that of Klinefelter's syndrome).

92. Testicular feminizing syndrome *(by definition testes are present but external genitalia are female)*

Genotype	46XY
Gonad	Testes
Testosterone	Levels normal or increased
Internal genitalia	Male or female
External genitalia	Female
Phenotype	Female
Defects	Loss of function mutations in genes coding for either the androgen receptor **or** testosterone 5α reductase (type 2)

This condition is an example of *male pseudohermaphroditism* (gonad is male, whereas

external genitalia are female).. Testosterone levels are increased in this condition. When the basic defect is a mutated androgen receptor, there is resistance to actions of testosterone and dihydrotestosterone and the resulting clinical syndrome is called ***androgen resistance syndrome.*** The resistance can vary from mild (*partial androgen insensitivity*) to severe (*complete androgen resistance*).

Causes of male pseudohermaphroditism:

- Androgen resistance syndrome
- Testosterone 5-*alpha* reductase (type 2) deficiency
- Deficiency of steroidogenic acute regulatory protein (STAR), rare
- 17α- hydroxylase deficiency, rare

94. Pathogenesis of the *"penis-at-12 syndrome":*

- It occurs due to a deficiency of the enzyme testosterone 5α- reductase (type 2).
- Testosterone (T) and DHT act on the same receptor.
- DHT is much more potent than T.
- In T 5α- reductase deficiency, during puberty, surges in LH are *greater* because of the lack of negative feedback effect of DHT on the pituitary and the hypothalamus; thus, induces synthesis of large amounts of T.
- Because of DHT deficiency, feedback inhibition of LH release is lower than normal.
- 'High levels' of T via their effects on the androgen receptor (normal in this case) may induce growth of the *clitoris.*
- However, despite high levels of T, labioscrotal fusion does not still occur because androgen receptors are downregulated at this site.
- These individuals have been raised as females and they may prefer to change their *gender identity* at the time of puberty; the management of this condition is complex.

99. DHEA sulfate and androstenedione are biologically very weak androgens if at all. They function mainly as precursors for the synthesis of testosterone in males and estrogens in females. However, when large amounts of adrenal androgens are present and depending on when the level of adrenal androgens is high, it can induce

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virilization in a female fetus or in postpubertal females.

105. Chronic use of pharmacologic doses of androgens suppress LH and FSH release from the pituitary thereby inhibiting spermatogenesis.

109. Long acting GnRH analogs suppress FSH and LH release by downregulating GnRH receptors in the pituitary, and thereby inhibit ovulation.

110. Estradiol (an estrogen) ultimately terminates linear growth by causing epiphyses to fuse to the long bones **(epiphysial closure) in males as well as females.** In males, this estradiol is **not** from that in the circulation; it is estradiol that is formed locally in the epiphysial growth plate by the action of bone aromatase enzyme on testosterone that reaches it from the testes. This is not to say that sex hormones inhibit linear growth. Rather the pubertal growth spurt is due to the synergism between sex hormones and other hormones (GH, IGF-1, thyroid hormones), and when the epiphyseal plate concentration of estradiol reaches a certain threshold, it mediates epiphyseal closure. Patients with sexual precocity are apt to be dwarfed because of premature epiphysial closure.

111. The testes is virtually the only source of circulating testosterone and very little testosterone is synthesized by the adrenal cortex. Thus, orchiectomy prior to puberty will result in a steep fall in testosterone levels in males; consequently the pubertal surge in androgens would be deficient. Thus, the formation of estradiol in the epiphyseal growth plates from circulating testosterone is also greatly reduced. In males as well as females, closure of epiphyseal plates occurs is mediated by estradiol (acting via estrogen receptors) when its level in the growth plate exceeds a certain *threshold* level. This happens following the pubertal growth spurt

116. Inhibin from the ovary inhibits the release of FSH from the pituitary.

120. Prolactin inhibits the release of GnRH from the hypothalamus, inhibits release of FSH and LH from the anterior pituitary and also inhibits the

actions of FSH and LH on the ovary. These effects of prolactin constitute the mechanism of *lactational amenorrhea.* However, oral contraceptive pills which inhibit ovulation usually contain a combination of estrogen and progesterone, and the dose is pharmacologic.

122. Human chorionic somatomammotropin is a placental hormone.

125. HCG is a glycoprotein with 2 subunits α & β The α subunit is identical with that in TSH, LH & FSH. The β subunit confers specificity. When [hCG] is high, stimulation of TSH receptors could result in mild hyperthyroidism. HCG maintains the corpus luteum of pregnancy; it is luteotropic in contrast to LH which is luteinizing; indeed both HCG and LH act upon the same receptor.

128. Estrogens stimulate breast growth but antagonize the milk producing effect of prolactin; lactation commences once the placenta is expelled and there is an abrupt decline in circulating levels of estrogens and progesterone.

131. The 46 XX primary oocyte undergoes meiosis which consists of two phases.
Phase 1: Meiosis (reduction division) results in the formation of secondary oocyte (with a large amount of cytoplasm) and the first polar body (with little cytoplasm). The first polar body is extruded at the end of the first phase of meiotic division. This is immediately followed by ovulation. Ovulation is the release of the secondary oocyte from the ovary.

Phase 2: The 23X secondary oocyte immediately begins a mitotic division but this is arrested in metaphase until fertilization occurs. After fertilization, the mitotic division is completed and the second polar body is extruded.

133. Androgens stimulate erythropoiesis. Estrogens have been noted to have an inhibitory influence on erythropoiesis. Cortisol stimulates erythropoiesis and polycythemia may be a striking feature of Cushing syndrome. Thyroxine also has a stimulatory influence on erythropoiesis.

GASTROINTESTINAL PHYSIOLOGY

Instructions: Unless otherwise specified, select the **single best** response.

1. Motor neurons in the myenteric plexus that stimulate the contraction of visceral smooth muscle in the gastrointestinal tract release:
A. acetylcholine
B. vasoactive intestinal polypeptide
C. nitric oxide
D. somatostatin
E. enkephalins

2. Postganglionic parasympathetic neurons innervating circular and longitudinal layers of gastrointestinal smooth muscle are located in:
A. myenteric plexus
B. submucosal plexus
C. paravertebral ganglia
D. prevertebral ganglia

3. The term "brain of the gut" is used to refer to the:
A. autonomic ganglia
B. enteric nervous system
C. migratory motor complex
D. interstitial cells of Cajal

4. Which of the following strategies would **most likely** be therapeutic in an individual with achalasia?
A. Injection of tetanus toxin into the lower esophageal sphincter
B. Surgical division of the lower esophageal sphincter
C. Administration of a muscarinic receptor agonist
D. Administration of a nitric oxide synthase inhibitor

5. Which of the following **inhibits** gastric acid secretion by an action on the parietal cell?
A. Acetylcholine
B. Epinephrine
C. Gastrin
D. Histamine
E. Prostaglandin E

6. Vagally mediated increase in gastric acid secretion is partly mediated by:
A. gastrin releasing peptide (GRP)
B. gastric inhibitory peptide (GIP)
C. vasoactive intestinal polypeptide (VIP)
D. somatostatin

7. The 'postprandial alkaline tide' is abolished by:
A. antrectomy
B. gastrin
C. parietal cell vagotomy
D. total inhibition of gastric H^+-K^+ ATPase
E. truncal vagotomy

8. The release of gastrin from G cells in the antrum of the stomach is **inhibited** by:
A. activation of vagal efferent fibers to the stomach
B. circulating epinephrine
C. blood-borne calcium
D. mechanical distention of the stomach
E. somatostatin

9. The basal acid output / maximum acid output ratio is normally closest to:
A. 0.1
B. 0.4
C. 0.7
D. 0.9

10. The optimum pH for the activity of pepsin is:
A. less than 1
B. between 1.6 and 3.2
C. between 3 and 5
D. between 6 and 7

11. From a physiologic standpoint, the advantage of a 'parietal cell vagotomy' over truncal vagotomy for treating duodenal ulcer is that in parietal cell vagotomy:
A. a gastrojejunostomy is not required
B. only basal acid output is reduced
C. G cells are also denervated
D. pyloric sphincter is also denervated
E. receptive relaxation is abolished

12. Which of the following hormone(s) is/are normally released by the stomach into the systemic circulation?
A. Ghrelin

B. Gastrin
C. Pepsinogen
D. Secretin
E. Vasoactive intestinal polypeptide

13. Gastric emptying is **slowest** after a meal containing:
A. fat
B. carbohydrate
C. protein
D. indigestible fiber

14. In which of the following segments in the splanchnic circulation is pressure **least** in a healthy individual at rest?
A. Hepatic arteriole
B. Hepatic sinusoid
C. Hepatic vein
D. Terminal branches of portal vein in the liver
E. Venule in the small intestinal mucosa

15. The **least oxygenated** and consequently the zone in the hepatic acinus **most vulnerable** to ischemia is:
A. zone I
B. zone II
C. zone III

16. Conjugation of bilirubin with glucuronic acid in the liver:
A. makes it hydrophobic
B. makes it hydrophilic
C. enables bilirubin to easily cross cell membranes
D. is always increased in neonatal jaundice

17. Normally, the rate-limiting step in the metabolism of bilirubin is:
A. uptake by ligandin
B. conjugation with glucuronic acid
C. secretion into bile

18. Which of the following is a bile acid synthesized by the hepatocyte?
A. Sodium taurocholate
B. Chenodeoxycholic acid
C. Deoxycholic acid
D. Lithocholic acid

19. Bile acids are synthesized starting from:

A. cholesterol
B. fatty acids
C. lecithin
D. bile salts

20. The most abundant bile acid is:
A. cholic acid
B. chenodeoxycholic acid
C. deoxycholic acid
D. lithocholic acid

21. Which of the following transporters is present only in the sinusoidal membrane of hepatocytes?
A. Bile Salt Export Pump
B. LDL-cholesterol receptors
C. MDR 3 (Flippase)
D. Multidrug Resistance associated Protein - 2 (MRP-2)

22. Bile salts are essential for absorption of fat because they:
A. solubilize dietary lipids in micelles
B. increase surface tension
C. are hydrophobic
D. contain pancreatic enzymes

23. Micelles in bile are formed by:
A. bile salts and phospholipids
B. bile acids and bile salts
C. cholesterol and bile salts
D. cholesterol and phospholipids

24. The total circulating bile salt pool is approximately:
A. 35 mg
B. 3.5 g
C. 150 mg
D. 30 g

25. The normal rate of bile salt synthesis is:
A. 0.05 – 0.1 g/day
B. 0.2 – 0.4 g/day
C. 0.8 – 1.2 g/day
D. 2 – 2.5 g/day

26. Physiologically, the most important choleretic(s) is/ are:
A. bile salts
B. CCK
C. secretin

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D. gastrin

27. Removal of the liver is fatal because:
A. blood urea rises
B. jaundice develops
C. clotting time is prolonged
D. progressive hypoglycemia occurs

28. *Slow waves* in the GIT are believed to be initiated by:
A. I cells
B. K cells
C. interstitial cells of Cajal
D. S cells

29. The most alkaline exocrine secretion is:
A. bile
B. pancreatic juice
C. intestinal juice
D. saliva

30. The term 'hormone' was coined by Ernest H. Starling to describe the actions of:
A. secretin
B. insulin
C. growth hormone
D. glucagon

31. Trypsinogen, a pancreatic proenzyme, is activated by:
A. enterokinase
B. hydrochloric acid
C. HCO_3
D. pancreatic trypsin inhibitor

32. Most pancreatic zymogens are activated in the duodenal lumen by:
A. enterokinase (enteropeptidase)
B. trypsin
C. trypsin activator protein

33. Trypsin inhibitor:
A. inhibits the action of pancreatic enzymes in the lumen of the duodenum
B. inhibits activation of trypsin in the pancreas
C. deficiency is implicated in acute pancreatitis
D. is produced by enterocytes

34. Which of the following enzymes is **not** synthesized by the pancreas?

A. DNAase
B. Proelastase
C. Aminopeptidases
D. Pepsin

35. Which of the following is an endopeptidase?
A. Carboxypeptidase A
B. Deoxyribonuclease
C. Trypsin
D. Dipeptidase

36. Which of the following enzymes is located in the brush border of enterocytes in the small intestine?
A. Lactase
B. Colipase
C. Cholesterol ester hydrolase
D. Lingual lipase

37. Disaccharidases are present in:
A. pancreatic acinar cells
B. brush border of enterocytes
C. D cells of pancreas
D. Brunner's glands

38. Quantitatively, the most important enzyme in the digestion of fat is:
A. lingual lipase
B. gastric lipase
C. pancreatic lipase
D. lipoprotein lipase

39. Normally, instillation of acid into the duodenum to reduce pH in its lumen to 4 would **most likely:**
A. stimulate gastrin release
B. increase output of trypsin
C. increase secretion of Brunner's glands
D. relax the pyloric sphincter

40. The major humoral mediator of meal-stimulated enzyme secretion is:
A. secretin
B. CCK
C. GIP
D. gastrin

41. The major humoral mediator of pancreatic duct cell secretion of bicarbonate rich juice is:
A. secretin

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B. CCK
C. somatostatin

42. The major humoral mediator of gall bladder contraction in response to a fat meal is:
A. CCK
B. gastrin
C. secretin
D. somatostatin

43. Which is the most important cholagogue?
A. Secretin
B. CCK
C. Gastrin
D. GIP

44. The most potent stimulus for release of secretin from the duodenum is:
A. a reduction in duodenal lumen pH to < 4.5
B. peptides
C. fatty acids with > 8 carbons
D. carbohydrates

45. Which of the following statements about CCK is **incorrect?**
A. It causes gall bladder contraction.
B. It relaxes the sphincter of Oddi.
C. It relaxes the pyloric sphincter.
D. It stimulates the secretion of an enzyme-rich pancreatic juice.

46. Which of the following statements regarding somatostatin is **incorrect?**
A. It inhibits release of growth hormone.
B. It inhibits release of insulin.
C. It decreases blood flow to the intestine.
D. It stimulates gastric acid secretion.

47. In which of the following conditions is a long acting analog of somatostatin of therapeutic value?
A. Acute mesenteric ischemia
B. Bleeding from esophageal varices
C. Cholelithiasis
D. Pancreatic exocrine insufficiency
E. Pernicious anemia

48. In healthy humans, the maximal rate of glucose absorption from the intestine is estimated to be about:

A. 10 g/hour
B. 40 g/hour
C. 120 g/hour
D. 180 g/hour

49. Intestinal absorption of which of the following does **not** directly utilize a Na^+ gradient?
A. Fructose
B. Galactose
C. Glucose
D. Phenylalanine
E. Tyrosine

50. Which of the following mechanisms allows complete absorption of glucose from the intestinal lumen into the cytosol of the enterocyte?
A. Simple diffusion through GLUT-5
B. Na-glucose cotransporter-1 (SGLT-1)
C. Na channels in enterocyte membrane
D. Paracellular uptake via gap junctions

51. Which of the following proteins is a regulator or iron absorption by enterocytes?
A. Ferritin
B. Hemosiderin
C. Hepcidin
D. Transferrin

52. The major protein that transports iron in the plasma from the site of absorption to cells engaged in erythropoiesis is:
A. hepcidin
B. transferrin
C. ferritin
D. hemosiderin

53. In healthy humans, iron in tissues other than red blood cells is stored principally in combination with:
A. ferritin
B. transferrin
C. hepcidin
D. hemosiderin

54. Which of the following statements regarding the thermic effect of feeding is **incorrect?**
A. It is most prominent at the time of eating.
B. It is *aka* specific dynamic action of food.
C. It is greater following a protein meal.
D. It is enhanced by sympathetic neural activity.

55. Normally, most of the water in the GI lumen is absorbed from:
A. stomach
B. duodenum
C. jejunum
D. colon

56. The Oral Rehydration Solution is helpful in rehydration in diarrheas **because:**
A. Na-glucose symporter is unaffected in toxigenic diarrheas
B. 1Na-1K-2Cl symporter is located only in the basolateral membrane
C. cAMP regulated Cl secretion is reduced
D. toxins inhibit facilitated glucose transport

57. The most frequent type of movement in the small intestine in the digestive state is:
A. peristalsis
B. antiperistalsis
C. slow wave
D. segmentation contraction

58. The pattern of intestinal motility that hastens transit of chyme in the small intestine in the digestive state is:
A. peristalsis
B. segmentation contraction
C. tonic contraction
D. migrating motor complex

59. *Select all correct answers.* The type(s) of contraction that normally occur(s) only in the colon is/are:
A. peristalsis
B. antiperistalsis
C. segmentation
D. mass action contraction (mass peristalsis)

60. The pattern of electrical and motor activity in the gastrointestinal tract during periods of fasting is called:
A. basic electrical rhythm
B. migrating motor complex
C. peristalsis
D. segmentation

61. Enterocytes are replenished by mitotically active undifferentiated cells located in:

A. Brunner's glands
B. crypts of Lieberkuhn
C. Peyer's patches
D. gut associated lymphoid tissue

62. Which of the following cells sample the antigenic milieu of the gastrointestinal lumen?
A. P cells
B. I cells
C. K cells
D. M cells (microfold cells)
E. Mo cells

63. In healthy humans, active absorption of bile acids and bile salts occurs mainly in the:
A. duodenum
B. jejunum
C. terminal ileum
D. colon

64. *Select all correct answers.* Calcium absorption from the intestine:
A. is facilitated by vitamin D
B. is decreased by phytates and oxalates
C. occurs mainly in the upper small intestine

65. Vitamin B_{12} is mainly absorbed in the:
A. terminal ileum
B. upper jejunum
C. duodenum
D. stomach

66. In healthy humans, the earliest the first part of a test meal reaches the cecum is in about:
A. 4 hours
B. 6 hours
C. 9 hours
D. 12 hours

67. Normally, the main function of the colon is absorption of:
A. Na, Cl and H_2O
B. triacylglycerols
C. secondary bile acids
D. iron

68. Normally, there is a net secretion of which ion in the colon?
A. Sodium
B. Potassium

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C. Chloride
D. Calcium

69. The defecation reflex is integrated in the:
A. brain stem
B. pons
C. medulla
D. spinal cord

70. The odor of feces is partly due to:
A. stercobilinogen
B. indole, skatole and sulfides
C. primary bile acids
D. secondary bile acids

Answers:

1A	2A	3B	4B	5E
6A	7D	8E	9A	10B
11A	12A	13A	14D	15C
16B	17C	18B	19A	20A
21B	22A	23A	24B	25B
26A	27C	28C	29B	30A
31A	32B	33BC	34D	35C
36A	37B	38C	39C	40B
41A	42A	43B	44A	45C
46D	47B	48C	49A	50B
51C	52B	53A	54A	55C
56A	57D	58A	59BD	60B
61B	62D	63C	64ABC	65A
66A	67A	68B	69D	70B

Explanations:
1. Nitric oxide relaxes visceral smooth muscle as well as sphincters. Norepinephrine constricts blood vessels in the gut like elsewhere, but it inhibits contraction of visceral smooth muscle.

2. The motor neurons innervating mucosal glands and influencing mucosal blood flow are located in the submucosal (Meissner's plexus).

3. The enteric nervous system is a self-contained complex network of sensory neurons, interneurons and motor neurons connected to the CNS via visceral afferents and influenced by the CNS through parasympathetic and sympathetic innervation.

4. Idiopathic achalasia is characterized by deficiency of nitric oxide and or vasoactive intestinal polypeptide in the LES. This is the basis for the failure of the LES to relax with swallowing. Thus, cholinergic motor neurons that stimulate LES contraction are 'unopposed'.

5. Circulating epinephrine stimulates the release of gastrin from G cells. Gastrin receptors (CCK-B or CCK-2 receptors) are present on parietal cells. Gastrin also stimulates histamine release from enterochromaffin like cells in the stomach.

6. Vagal neurons ending on G cells in the antrum release gastrin-releasing peptide instead of acetylcholine.

7. The H^+- K^+ ATPase in the parietal cell is the final common pathway for gastric acid secretion by the stomach. The *postprandial alkaline tide* refers to a slight increase in pH of plasma following a meal. It reflects gastric acid secretion by parietal cells since for every proton secreted by the parietal cell, one bicarbonate ion enters the blood stream. Though the liver, pancreas and the small intestine collectively secrete a large amount of alkaline fluid into the GI lumen, this does not produce a postprandial acid tide in plasma because the stomach secretes about 2-2.5 liters of gastric juice per day, and parietal cells concentrate protons a million fold in gastric juice relative to plasma.

8. Options A-D are factors that stimulate gastrin release.

9. Basal acid output (BAO) is gastric acid output in the fasting state. It is about 1-3 mmol/h. Maximum acid output is the maximal acid output following a standard meal or following a standard dose of pentagastrin. MAO is about 20-30 mmol/h. BAO and MAO are both increased and the BAO/MAO ratio is abnormally increased in Zollinger-Ellison syndrome. The effect of vagotomy is to virtually eliminate BAO; MAO is greatly reduced even if not abolished by vagotomy.

11. Option A is correct because the denervation in a parietal cell vagotomy (PCV) involves the branches that supply the fundic area but not the antrum. As a result G cell innervation, innervation

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of pyloric sphincters, and antral motility is preserved and a gastrojejunostomy is not required.

PCV reduces BAO as well as meal stimulated acid output.

Receptive relaxation of the fundus of the stomach is a vagovagal reflex response that occurs during deglutition. It is lost after PCV as well as truncal vagotomy. The loss of receptive relaxation after PCV is not the reason why it is advantageous over a truncal vagotomy.

12. Ghrelin is released from the stomach during the fasting state and it stimulates food intake by an action on the hypothalamus. Ghrelin is an orexigenic signal (induces appetite) unlike leptin which signals satiety. Ghrelin is also a stimulator of the growth hormone secretagogue receptor (GHS-R) in the anterior pituitary, a receptor that mediates growth hormone release.

14. Blood flows down a pressure gradient from: venule in small intestinal mucosa → portal vein → branches of portal vein in the liver → hepatic sinusoid → hepatic vein.

15. Zone is closest to the arteriole; zone III is closest to the central vein (perivenular zone). See Ganong, 2012, p. 510-511 incl. Fig 28-3.

18. Cholic and chenodeoxycholic acids are **primary bile** acids and are synthesized by the hepatocyte. Deoxycholic acid and lithocholic acids are formed in the intestine **(secondary bile acids)** by the action of bacteria on primary bile acids.

21. Presence on the sinusoidal membrane allows the hepatocyte to take up cholesterol from the bloodstream. Presence of a transporter on the canalicular (apical) membrane would allow for transport of a substance into bile.

23. A critical concentration of lecithin and bile salts (called critical micellar concentration) is required for micelles to form in bile and solubilize cholesterol. See Ganong, 2012, p. 515-516, Fig 28-2 and accompanying text.

24 and 25. The liver synthesizes about 0.5 g of bile salts per day. The total bile salt pool recycles repeatedly via the enterohepatic circulation six to eight times per day. When enterohepatic circulation is interrupted such as by terminal ileal resection, the liver responds by increasing bile salt synthesis, but this compensation typically cannot prevent fat malabsorption from eventually occurring.

26. Choleretics stimulate secretion of bile. Since bile secretion is osmotically driven (water follows active secretion of bile salts), bile salts are themselves amongst the most potent choleretics. Cholagogues (e.g. cholecystokinin) increase flow of bile from the liver or gallbladder into the duodenum.

27. Blood urea would be expected to fall, if at all, following hepatectomy. Hypoglycemia following hepatectomy can at least be managed partly by increasing glucose intake at regular intervals.

28. This is not firmly established but many texts allude to a role for interstitial cells of Cajal as being responsible for the basic electrical rhythm in the GIT. These cells may be thought of as pacemakers.

29. The pH of pancreatic juice can reach as high as 8 under maximal flow conditions.

31. Activation of trypsinogen requires enterokinase. Enteropeptidase (enterokinase) is an intestinal brush border enzyme that catalyzes the proteolytic activation of trypsinogen to trypsin.

32. Enterokinase activates trypsinogen to trypsin. Trypsin autocatalyzes activation of trypsinogen and activates other pancreatic zymogens.

33. Trypsin is the common activator of all pancreatic proenzymes. This ensures that pancreatic proenzymes are activated only when they reach the intestinal lumen.

38. This is evident from the fact that chronic pancreatic exocrine insufficiency results in steatorrhea. In contrast, fat digestion and

absorption is not significantly affected by deficiency of the other lipases as long as pancreatic lipase is available in adequate amounts.

39. The acidity of duodenum drives the release of secretin thereby evoking alkaline secretions from the liver, pancreas and intestine as well as submucosal glands in the duodenum.

45. CCK contracts the pyloric sphincter thereby inhibiting gastric emptying.

47. Somatostatin is a vasoconstrictor in the splanchnic circulation. Octreotide is a long acting somatostatin analog available for parenteral use.

49. Fructose is not absorbed by an active transport process. It enters enterocytes from the GI lumen down its concentration gradient through GLUT-5.

51. Hepcidin is synthesized by the liver and it inhibits iron absorption by enterocytes.

54. Specific dynamic action (SDA) of food (also called thermic effect of feeding or diet induced thermogenesis) is a physiological phenomenon that represents energy expended on all activities of the body incidental to the ingestion, digestion, absorption, and assimilation of a meal. Metabolic rate starts increasing 30 min after a meal, stays high for about 2 hours and declines to the resting level within 4 hours. The energy expended depends upon the volume, caloric content, consistency, and composition of meal.

55. Digestion and absorption of nutrients normally occur mainly in the jejunum. Active absorption of amino acids, glucose is coupled to a Na-gradient, and since we know that the intestine cannot maintain an osmotic gradient across its epithelium and water movement follows osmotically - it can be deduced that most of the water in the intestine is absorbed in the jejunum. In a healthy adult, about 5.5 liters of water is absorbed in the jejunum (out of 9 liters absorbed from the GI lumen). See Ganong, 2012, p. 466, Table 25-4.

57-59. One can summarize GI motility along these lines:
- Digestive vs. interdigestive motility
- Propulsive movements vs. mixing movements
- Anatomical: stomach, duodenum, proximal colon, sigmoid colon etc.

Digestive motility (occurs in the digestive state)	Interdigestive motility (occurs in the digestive state)
Peristalsis Segmentation Haustration	MMC

Propulsive movement	Nonpropulsive or mixing movement (fosters digestion & absorption)
Peristalsis MMC	Segmentation Haustral shuttling

In the small intestine, in the digestive state, segmentation contractions allow digestion and absorption to be completed before peristaltic waves propel chyme.

Antiperistalsis occurs as part of the vomiting response. But otherwise, normally, antiperistalsis is observed only in the ascending colon. It is actually a sequence of peristalsis-antiperistalsis sequences; the antiperistalsis is said to be 'weak' and eventually the peristaltic wave overrides and sweeps content aborally. Like segmentation contractions do, peristalsis-antiperistalsis sequences in the ascending colon allow more Na and Cl and water to be absorbed in the colon. Normal antiperistalsis in the ascending colon cannot propagate across a competent ileocecal valve.

60. The migrating motor complex (MMC) sweeps secretions from the mid-stomach through to the terminal ileum. By doing so it inhibits bacterial colonization of the small intestine, and prepares the gut for the next meal; i.e. it is the "housekeeper of the small intestine". It is augmented by motilin.

65. Receptors that can endocytose B12-intrinsic factor complexes are located in the apical membrane of enterocytes of terminal ileum.

68. The secretion of K in the distal colon is stimulated by aldosterone. Hypokalemia can

result from diarrheal losses of K in individuals with chronic diarrhea or those with severe acute diarrhea.

BLOOD AND CARDIOVASCULAR PHYSIOLOGY

Summaries
1. RBC Indices
2. Cardiac output and related definitions
3. Blood pressure indices
4. Arterial baroreflex mechanism

1. RBC Indices
Reference ranges for RBC indices (summarized below) are usually available at the point of care.

RBC Index	Derivation	Normal values
MCH	$\dfrac{\text{Hb in g/dL} \times 10}{\text{RBC in millions/mm}^3}$	29–32 pg
MCV	$\dfrac{\text{PCV} \times 10}{\text{RBC in millions/mm}^3}$	80–100 fL
MCHC	$\dfrac{\text{Hb in g/dL} \times 100}{\text{PCV}}$	32–35 g/dL

MCH, mean corpuscular hemoglobin;
MCV, mean corpuscular volume;
MCHC, mean corpuscular hemoglobin concentration;
fL, femtoliter; pg, picogram.

However, if a question requires you to calculate one or more RBC indices, then, one needs to remember the formula for each index.

One way to remember this easily is as follows. Remember a RBC count of 5 million/mm^3, blood Hb of 15 g/dL, and PCV of 45% as "perfect values". Second, remember 90 fL as the perfect MCV and 30 pg as the perfect MCH. The formula for MCV and MCH can then be readily derived as follows.

Index		Formula
MCV = 90	= 450 / 5 = 45 × 10 / 5	$= \dfrac{(\text{PCV} \times 10)}{\text{RBC}}$
MCH = 30	= 150 / 5 = 15 × 10 / 5	$= \dfrac{\text{Hb} \times 10}{\text{RBC count}}$

Having derived the formulae, you can plug values at hand to calculate the corresponding RBC index.

MCHC is the amount of Hb present in 100 ml of packed red blood cells; thus it has the same units as hemoglobin concentration.

Concentration = amount of a substance / volume of distribution in question. Thus:

The concentration of Hb in 1 ml of red blood cells is Hb/PCV g/dL. Thus, the concentration of Hb in 100 ml of packed red blood cells is [Hb × 100]/PCV.

RBC indices are useful in the differential diagnosis of anemias. Anemias may be classified as macrocytic, microcytic or normocytic based on MCV, and normochromic or hypochromic based on MCHC. Hyperchromia is uncommon but it may occur in hereditary spherocytosis.

2. Cardiac Output (and related terms):
Cardiac output: The volume of blood ejected by the left or the right ventricle per minute.

Cardiac output = stroke volume × heart rate

Cardiac index is the cardiac output per square meter of body surface area.

Regulation of stroke volume: Stroke volume is influenced by preload, afterload and myocardial contractility.

Preload: The load on a muscle before it contracts. In the ventricle, the preload (end-diastolic fiber length) varies directly with the end-diastolic volume.

Afterload: The load which contracting muscle has to overcome before it shortens. The velocity of shortening varies inversely with afterload. For the left ventricle, the afterload is the total systemic vascular resistance.

Within physiologic limits, the energy of cardiac contraction is directly proportional to preload. This is the **Frank-Starling law** of the heart. An increase in stroke volume for a given preload and afterload is due to an increase in **myocardial contractility.**

The best index of myocardial contractility is the rate of pressure rise (dP/dt) in the ventricle during isovolumetric contraction. However, clinically, the **ejection fraction** is used as a surrogate of myocardial contractility.

Myocardial contractility is markedly enhanced by sympathetic stimulation, digoxin and depressed by myocardial ischemia, acidosis.

Inotropic effects: the term refers to the effect of a stimulus on myocardial contractility.

3. Blood pressure indexes:

Systolic pressure (SBP): the highest pressure in the arteries during the cardiac cycle.

Diastolic pressure (DBP): the lowest pressure in the arteries during the cardiac cycle. Diastolic pressure reflects the total resistance offered to peripheral run off of blood (specifically, the resistance offered by the arterioles).

Pulse pressure: SBP – DBP
Ejection of blood produces an increment in arterial blood pressure; this is called pulse pressure. Pulse pressure depends upon volume of blood ejected (stroke volume) and arterial compliance. If arteries are thick and rigid (and thus less compliant), a given stroke volume produces a greater rise in pulse pressure. Conceptually, systolic pressure = diastolic pressure + pulse pressure

Mean arterial pressure = diastolic pressure + 1/3 (pulse pressure). However, this applies only when HR is in the 60-90 BPM range. MAP is actually determined by integrating the arterial pressure curve. MAP is also equal to (SP + 2DP)/3

Mean arterial pressure (MAP) = cardiac output × total peripheral resistance.

Rate-pressure product (RPP): It is calculated as the product of SBP and HR and generally divided by 100 to get a smaller number. If SBP is 120 mm Hg and HR is 80 BPM, then RPP is 96 mm Hg BPM 10^{-2}

RPP is a useful index because it reflects myocardial O_2 demand. Greater the HR, greater the myocardial oxygen demand; to generate a greater systolic pressure, greater wall tension needs to develop (according to Laplace's law) and this also increases oxygen consumption.

4. The arterial baroreflex mechanism for regulating blood pressure:

Inputs	Mean arterial pressure, pulse pressure
Receptor	Called "arterial baroreceptors"
Location of receptors	Adventitia of the carotid sinus and aortic arch
Receptor type	Free nerve endings
Adequate stimulus	Stretch (both tonic as well as phasic response)
Afferent	Via IX (from the carotid sinuses) and X nerves (from the aortic arch)
Termination of first order neurons	NTS in medulla
Receptor operating range	MAP between 70 and 110 mm Hg
Receptor characteristics	Increase in static (mean arterial pressure) as well as phasic stretch (pulse pressure) increase firing rate; decrease in stretch decreases firing rate. There are presumably two subtypes of receptors of which is adapting and the other nonadapting.
Response to an increase in BP	An increase in BP leads to a decrease in cardiac output and TPR through cardiac vagal excitation and inhibition of sympathetic outflow
Response to a decrease in BP	Sympathetic outflow from the medulla is "disinhibited"; and vagal outflow to the heart is disinhibited.
Response time:	It takes only about 1 second for a change in BP to result in a compensatory change in HR; it takes a little longer (about 10 seconds) for changes in TPR to occur following a primary change in BP

Instructions: Unless otherwise specified, choose the single best answer.

1. The most abundant protein in blood is:
A. albumin
B. hemoglobin
C. fibrinogen
D. beta-1 globulin

2. Macrocytes have a mean corpuscular volume greater than:
A. 70 fL
B. 80 fL
C. 90 fL
D. 100 fL

3. The amount of hemoglobin contained in normocytes is approximately:
A. 20 pg
B. 25 pg
C. 30 pg
D. 35 pg

4. The amount of hemoglobin present in 100 ml of red blood cells is defined as:
A. MCH
B. MCHC
C. hemoglobin index
D. RDW

5. In an individual with a blood hemoglobin concentration of 10 g/dL and a hematocrit of 40, MCHC is approximately:
A. 20 g/dL
B. 25 g/dL
C. 30 g/dL
D. 35 g/dL

6. A lab technician determines RBC count by manual hemocytometry, blood hemoglobin concentration by Sahli's acid hematin method, and hematocrit using a microcentrifuge. He follows all procedures correctly. Which of the following RBC indices calculated from these measurements would likely be the **most reliable**?
A. Mean corpuscular volume
B. Mean corpuscular hemoglobin
C. Mean corpuscular hemoglobin concentration
D. Mean cell diameter

7. Primary hemostasis refers to cessation of bleeding due to:
A. formation of a definitive clot
B. clot retraction
C. formation of a temporary platelet plug.

8. *Select all correct answers.* Platelet aggregation is stimulated by:
A. thromboxane A_2
B. fibrinogen
C. ADP
D. thrombin
E. epinephrine
F. serotonin
G. Prostaglandin I_2

9. The adhesion of platelets to subendothelial collagen is impaired in the absence of:
A. von Willebrand factor
B. plasmin
C. heparin
D. antithrombin III

10. Which of the following clotting factors is **not** vitamin K dependent?
A. Factor II
B. Factor V
C. Factor VII
D. Factor IX
E. Factor X

11. The extrinsic pathway is triggered by the release of:
A. factor VII
B. tissue factor
C. tissue factor pathway inhibitor
D. contact factor

12. The extrinsic pathway is inhibited by:
A. tissue factor
B. thromboplastin
C. tissue factor pathway inhibitor (TFPI)
D. contact factor

13. The test that screens the extrinsic pathway is:
A. prothrombin time (PT)
B. activated partial thromboplastin time (aPTT)
C. thrombin time
D. urea solubility test
E. clot lysis time

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14. The enzyme that ultimately lyses fibrin is:
A. plasminogen
B. TPA
C. urokinase
D. plasmin

15. Prolongation of prothrombin time does **not** occur when there is a deficiency of only:
A. factor VIII
B. factor IX
C. factor X
D. vitamin K

16. *Select all correct answers.* Mutations in which of the following have been implicated in the pathogenesis of hypercoagulable states?
A. Protein C
B. Protein S
C. Factor V
D. Antithrombin III

17. Factor V Leiden:
A. is a mutated form of factor IX
B. is inactivated by protein C
C. is present in a large subset of patients with venous thromboembolism

18. *Select all correct answers.* Which condition(s) is / are characterized by an increase in both bleeding time and clotting time?
A. Afibrinogenemia
B. Hypoprothrombinemia
C. Hemophilia A
D. von Willebrand's disease

19. Red cell antigens A and B are chemically:
A. phospholipids
B. glycosphingolipids
C. glycopeptides
D. polypeptides

20. *Select all correct answers.* Red blood cell antigens A and B are also present in:
A. saliva
B. semen
C. amniotic fluid
D. pancreas

21. The red blood cells of a person with the Bombay blood group do **not** have:
A. GLUT
B. H substance
C. spectrin
D. ankyrin

22. Most of the iron in the body is present in:
A. hemoglobin
B. myoglobin
C. ferritin
D. transferrin

23. In an Rh-negative mother not previously sensitized by the Rh antigen, Rh incompatibility does not usually have a serious consequence during the first pregnancy **because:**
A. antibodies are not able to cross placenta
B. the titer of IgG is low during the primary immune response
C. IgG is ineffective against fetal red cells
D. massive hemolysis in the fetus is compensated by increased erythropoiesis

24. In the context of blood transfusions, ABO compatibility is important because:
A. there are 3 antigens in this system
B. the A and B antigens are present in all cells
C. when an individual's RBC lacks the A or B antigen, the corresponding antibody is invariably present in serum.
D. O is a strong antigen

25. A 55-year-old male accident victim in the ED urgently requires a transfusion. His blood group could not be determined as his red cell group and plasma group did not match. Emergency transfusion should be done with:
A. RBC corresponding to his red cell group and colloids and crystalloids
B. Whole blood corresponding to his plasma group.
C. O positive RBC, colloids and crystalloids
D. AB negative blood

26. In the adult, most of the circulating erythropoietin originates from:
A. interstitial cells (fibroblasts) surrounding peritubular capillaries in the renal cortex
B. perivenous hepatocytes

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C. Kupffer cells of liver

27. Osmotic fragility of red blood cells is **decreased** in:
A. sickle cell anemia
B. hereditary spherocytosis
C. microcytic hypochromic anemia
D. macrocytic anemia

28. Hereditary spherocytosis occurs due to mutations in genes coding for:
A. spectrin and ankyrin
B. Na-K ATPase
C. glucose 6 phosphate dehydrogenase
D. pyruvate kinase

29. CO is formed as an end product of:
A. heme metabolism
B. arginine metabolism
C. oxidation of acetoacetate

30. Heme is converted to bilirubin mainly in the:
A. kidneys
B. liver
C. spleen
D. bone marrow

31. The protein that binds extracorpuscular hemoglobin is:
A. hemin
B. haptoglobin
C. hemopexin
D. haptopexin

32. When a serum sample is electrophoresed, which of the following bands is normally **absent?**
A. Albumin
B. α_1 globulin
C. α_2 globulin
D. Fibrinogen
E. γ-globulin

33. Which of the following is **not** synthesized in the liver?
A. IgG
B. α_2 macroglobulin
C. Albumin
D. Angiotensinogen

34. Which of the following plasma proteins are protease inhibitors?
A. α_1 antitrypsin
B. Transferrin
C. C-reactive protein
D. Antithrombin III

35. Which of the following is a 'negative' acute phase reactant?
A. Albumin
B. C-reactive protein
C. α_2 macroglobulin
D. Transferrin

36. ESR is increased in:
A. anemia
B. hypofibrinogenemia
C. spherocytosis
D. polycythemia

37. The average half-life of neutrophils in the circulation is:
A. 6 hours
B. 5 days
C. 2 weeks
D. 1 month

38. The protein content of lymph draining from the _____ is highest.
A. choroid plexus
B. skeletal muscle
C. liver
D. gastrointestinal tract

39. Which of the following is **incorrect** about fetal hemoglobin (Hb F)?
A. In comparison to HbA, Hb F has greater affinity for 2,3–BPG
B. The oxygen dissociation curve of HbF is shifted to the left relative to HbA.
C. At low PO_2, Hb F gives up more oxygen to tissues than Hb A.

40. The viscosity of blood is constant at all flow velocities. True/False.

41. The heart continues to beat even after all nerves to it are sectioned. This property is called:
A. excitability
B. conductivity

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C. automaticity
D. contractility

42. What is the primary ionic basis of the prepotential in the SA node?
A. Ca influx through transient T Ca channels
B. Inwardly directed long-lasting Ca current
C. Outward Na current
D. Potassium efflux through leak channels

43. Normally, the impulse that excites the left ventricular myocardium originates in the:
A. SA node
B. Purkinje system
C. left bundle branch
D. ventricle

44. Conduction speed is **slowest** in the:
A. SA node
B. atrial pathways
C. bundle of His
D. Purkinje system
E. Ventricular myocardium

45. What is the effect of vagal stimulation on the membrane potential of the SA node?
A. It increases an inward calcium current.
B. It increases the slope of the prepotential.
C. It activates a hyperpolarizing potassium current.
D. It increases intracellular cAMP.

46. Activation of *beta*-adrenergic receptors in the heart is normally associated with which of the following?
A. Decrease in the slope of phase 4 depolarization in SA nodal cells.
B. Decrease in conduction speed through AV node.
C. Inhibition of Ca induced Ca release following depolarization in ventricular myocytes.
D. Accelerated sequestration of Ca in the sarcoplasmic reticulum by the Ca-ATPase
E. Reduction in the rate of rise in ventricular pressure during isovolumic contraction

47. *Select all correct answers.* Prepotentials are normally **absent** from:
A. P cells in the SA node
B. AV nodal cells

C. Purkinje fibers
D. working myocardial cells

48. Cardiac muscle **cannot** be tetanized **because** of:
A. accommodation
B. its slow rate of repolarization
C. calcium influx during phase II
D. voltage inactivation of Na channels at membrane potentials < 80 mV

49. Intrinsic heart rate is determined by:
A. vagotomy
B. administration of atropine
C. *beta*-adrenergic receptor blockade
D. IV administration of atropine and atenolol

50. The ability of the AV node to generate its own impulses when the sinus node is "sick" is due to:
A. a constant phase 4 membrane potential
B. slow calcium entry during phase zero
C. spontaneous diastolic depolarization
D. the absence of prepotentials

51. The propagation of repolarization from the ventricular epicardium to endocardium is represented by the
A. QRS complex
B. QT interval
C. T wave
D. TP period

52. T wave inversion occurs when ventricular repolarization occurs from:
A. endocardium to epicardium
B. epicardium to endocardium
C. apex to base of the heart
D. base to apex of the heart

53. Which of the following is the shortest event in a cardiac cycle?
A. QRS interval
B. ST segment
C. ST interval
D. RR interval

54. Electrical activity in which region of the heart does **not** result in deflections on the surface electrocardiogram?
A. Atria

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B. Bundle of His
C. Free wall of the left ventricle
D. Free wall of the right ventricle
E. Muscular portion of the ventricular septum

55. In sinus rhythm, the last portion of the ventricle to depolarize is:
A. interventricular septum from left to right
B. anteroseptal region of the myocardium
C. most of the myocardium from endocardium to epicardium
D. posterobasal portion of left ventricle and the pulmonary conus

56. The most reliable index of AV nodal delay is:
A. AH interval
B. PA interval
C. PR interval
D. PR segment

57. AH interval is normally:
A. 30–50 ms
B. 60–125 ms
C. 100–200 ms
D. 80–120 ms

58. Hypocalcemia is associated with QT prolongation **because:**
A. it is invariably associated with bundle branch block
B. it increases ventricular activation time
C. it lengthens the duration of ventricular repolarization
D. it accelerates opening of potassium channels

59. Stimulation of sympathetic nerves to the heart decreases:
A. heart rate
B. force of cardiac contraction
C. speed of conduction
D. refractory period

60. If QRS deflection is highest and upright in lead I and equiphasic (or null) in lead aVF, then mean electrical axis of the QRS vector in the frontal plane is about:
A. 30 degrees
B. 0 degrees
C. +45 degrees
D. +90 degrees

61. Right axis deviation may occur in:
A. deep inspiration
B. emphysema
C. dextrocardia
D. pulmonary hypertension

62. In which of the following leads are you most likely to observe ST segment elevation when there is an acute and extensive infarction of the anterior and lateral wall of the heart?
A. Leads I, II and III
B. Leads aVR, aVL and aVF
C. Leads I, aVL, and V1-V6
D. Leads II, III and aVF

63. The AV node does not conduct more than:
A. 180 impulses per minute
B. 230 impulses per minute
C. 280 impulses per minute
D. 330 impulses per minute

64. *Select all correct answers.* The ST segment is elevated in acute myocardial infarction because of:
A. flow of current into the infarct during diastole
B. TP segment depression
C. late depolarization of infarct
D. early repolarization of infarct

65. During the cardiac cycle, aortic valve closes at the end of:
A. isovolumetric systole
B. rapid ejection
C. diastasis
D. protodiastole

66. The maximum pressure rise in the ventricle occurs during:
A. ejection
B. isovolumetric contraction
C. protodiastole
D. diastasis

67. Clinical examination of a 45 year old man reveals splitting of the second heart sound as A2 followed by P2 during deep inspiration, and the split was not apparent during expiration. S1 is normal in intensity, and there is no cardiac murmur. BP is 130/80 mm Hg and pulse is 80

bpm and regular. Which of the following is the most likely cause of this pattern of splitting of the second heart sound?
A. Aortic regurgitation
B. Left bundle branch block
C. Physiologic splitting of S2
D. Pulmonic stenosis

68. Normally, which of the following events in the cardiac cycle occurs at some point between S1 and the following S2?
A. Onset of ventricular diastole
B. Atrial systole
C. Rapid ventricular filling
D. The '*a*' wave of the JVP
E. The '*y*' descent in the JVP

69. Comparing left and right atria, the left atrium normally has a taller *v* wave than the right atrium because
A. left atrial filling pressure is high
B. pulmonary vessels empty into the left atrium
C. left atrium is more complaint
D. right ventricle is more compliant

70. Which of the following is a low pitched sound heard best in the apex just prior to S1 and is associated with effective atrial contractions in the setting of diminished ventricular compliance?
A. Pericardial knock
B. Opening snap
C. S3
D. S4

71. In which of the following states is isovolumetric ventricular relaxation abbreviated, assuming that the prevailing heart rate is identical in each?
A. Aortic regurgitation
B. Mitral regurgitation
C. Mitral stenosis
D. Tricuspid regurgitation
E. Patent ductus arteriosus

72. Results of cardiac catheterization in a 50-year-old man who presented with a history of acute breathlessness since the past 24 hours are as below. Coronary angiography showed no evidence of significant narrowing of the right or left coronary arteries or its branches.

Region	Pressure (mm Hg)	% Saturation of Hb with oxygen
Right atrium	5	70
Right ventricle	28/6	70
Pulmonary artery	30/15	70
Pulmonary capillary wedge	25	90
Left ventricle	102/25	88
Aorta	98/56	88

This data is **most consistent** with the possibility of which of the following as the underlying cause of breathlessness?
A. Tricuspid stenosis
B. Pulmonary stenosis
C. Mitral regurgitation
D. Aortic stenosis

73. In postnatal life, steady state outputs of the right and left ventricle are matched in vivo by:
A. the Frank-Starling mechanism
B. sympathetic influences on the SA node
C. vagal influences on the SA node
D. varying the afterload for each ventricle
E. matching the tension generated by each ventricle

74. While introducing the Swan Ganz catheter, its placement in the pulmonary artery (PA) **is best inferred** from which of the following?
A. Diastolic pressure is lower in PA than in right ventricle
B. Diastolic pressure is higher in PA than right ventricle
C. PA pressure tracing has dicrotic notch
D. Right ventricular pressure tracing for plateau and sharp drop in early diastole.

75. Which of the following statements represent the **most appropriate** interpretation of the ECG shown below?
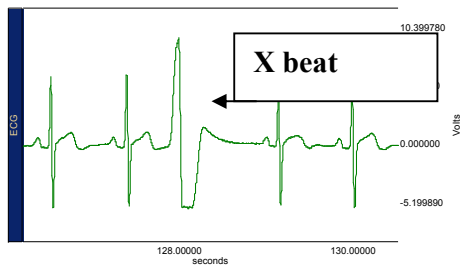
A. X beat originated from an atrial focus.
B. X beat reset the cardiac rhythm.
C. S1 & S2 would have been present at X beat.
D. The path of spread of excitation was normal.

76. Which of the following need to be recorded in order to determine systolic time intervals?
A. ECG, ECHO, and phonocardiogram (PCG)
B. ECG, PCG and carotid artery pulse (CAP)
C. ECHO, CAP and PCG
D. ECG, CAP and apexcardiogram

77. Which of the following is not essential to determine QS_2, left ventricular ejection time (LVET) and pre-ejection period (PEP)?
A. Pulse transducer
B. Electrocardiograph
C. Phonocardiogram
D. Swan-Ganz catheter

78. The dicrotic notch is **absent from**:
A. radial arterial pulse tracing
B. pulmonary arterial pulse tracing
C. aortic pulse tracing
D. none of the above

79. A cardiologist asked his lab technician to determine the systolic time intervals of a 60 yr old patient with a recent anterior wall infarction. The technician said that the pulse transducer was not working. Which of the following could he then have not determined?
A. QS2
B. Left ventricular ejection time (LVET)
C. Pre-ejection period (PEP)
D. Both LVET and PEP

80. The cardiac output of a 50 year old man at rest is 6 L / min; mean HR is 75 BPM. Left ventricular end-diastolic volume (LVEDV) is 120 ml. What is the mean ejection fraction?
A. 35 %

B. 50 %
C. 66 %
D. 75 %

81. During exercise, a man consumes 2 liters of oxygen per minute. His arterial O_2 content is 200 ml/L and the oxygen concentration of mixed venous blood is 120 ml/L. His cardiac output is:
A. 16 L/min
B. 25 L/min
C. 32 L/min
D. 40 L/min

82. If blood [Hb A] = 15 g/dL and Hb is fully saturated with oxygen, average stroke volume = 70 ml, average HR = 72 bpm, calculate whole-body oxygen delivery; i.e., the amount of oxygen delivered to the tissues per minute, assuming Hb is fully saturated with oxygen.
A. 1 L/min
B. 0.5 L/min
C. 2 L/min
D. 2.5 L/min

83. Which method is dependable for measuring cardiac output when cardiac output is **low?**
A. Fick's method (using oxygen uptake)
B. Thermodilution method

84. A dye ABC has been in use for the measurement of blood volume and cardiac output. This was rivaled by the introduction of XYZ, which crossed the capillaries. What difference would the use of XYZ make in this context?
A. No change in measured cardiac output & blood volume
B. Increase in measured blood volume alone
C. Increase in measured cardiac output alone
D. Cause an error in the measurement of both

85. The most recent technique for noninvasive measurement of cardiac output is:
A. pulmonary artery catheterization
B. thermodilution
C. echocardiography
D. impedance cardiography

86. The **best measure** of left ventricular preload is:
A. left ventricular end-diastolic volume

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B. left atrial pressure
C. pulmonary capillary wedge pressure
D. right atrial pressure
E. central venous pressure
F. jugular venous pressure

87. The **most appropriate index** of left ventricular afterload is
A. systolic arterial pressure
B. mean arterial pressure
C. systemic vascular resistance
D. aortic valve resistance
E. left ventricular systolic pressure

88. Right ventricular preload typically exceeds left ventricular preload during:
A. deep inspiration
B. deep expiration
C. Valsalva maneuver (done for 15 seconds)
D. quiet standing

89. LV preload is increased by a/an:
A. increase in intrapericardial pressure
B. decrease in left ventricular compliance
C. sympathetic stimulation of veins and the heart
D. inhibition of Na-K ATPase in cardiomyocytes

90. During severe exercise, a well-trained athlete may be able to achieve a cardiac output of:
A. 15 liters
B. 25 liters
C. 35 liters
D. 45 liters

91. An increase in whole body oxygen demand is met **chiefly** by:
A. increasing cardiac output
B. increasing oxygen content of arterial blood
C. increasing oxygen extraction from arterial blood
D. increasing blood pressure

92. Maximal oxygen consumption (VO_2 max) in healthy active men is about:
A. 10 ml/kg/min
B. 20 ml/kg/min
C. 40 ml/kg/min
D. 80 ml/kg/min

93. Windkessel vessels are represented by the:

A. aorta
B. internal jugular v.
C. arterioles
D. muscular arteries

94. The stopcocks of the circulation are:
A. arterioles
B. capillaries
C. valves
D. venules

95. Across which site in the circulation is the pressure drop maximum?
A. Arterioles
B. Venules
C. Capillaries
D. Aortic valve

96. At any time, the greatest fraction of blood volume is present in the:
A. heart
B. arteries
C. veins
D. capillaries

97. What fraction of total blood volume is present in the capillaries at any given time?
A. 5%
B. 20%
C. 15%
D. 1%

98. The term "capacitance vessels" is applied to:
A. pulmonary capillaries
B. thoroughfare channels
C. shunts
D. veins and venules

99. Hydraulic conductivity of capillaries is highest in:
A. glomeruli
B. intestinal villi
C. skin
D. brain

100. The mean systemic arterial pressure and the mean pulmonary artery pressure are respectively 90 and 15 mm Hg. What is the ratio of systemic and pulmonary vascular resistances?
A. Data inadequate

B. 1
C. 6
D. 10

101. In a circuit model of the systemic circulation of dog, the inflow pressure at Point A is 100 mm Hg and the downstream pressure at Point B is 10 mm Hg. Each of the vascular beds R1 through R5 offers a resistance of 5 Units. The total flow through the entire circuit is approximately:
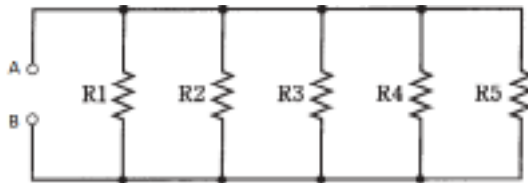
A. 5 liters per minute
B. 3.5 mm Hg / Unit
C. 10 mm Hg / Unit
D. 90 mm Hg / Unit

102. What would be the change in blood flow to a tissue if radius of the arterioles in that tissue is doubled and perfusion pressure is halved?
A. Increase 8 times
B. Increase 16 times
C. Increase 4 times
D. Decreases 4 times

103. The pressure in a blood vessel at which flow ceases is called:
A. mean arterial pressure
B. pulse pressure
C. critical closing pressure
D. perfusion pressure

104. Thin walled capillaries do not burst when intracapillary pressure is increased within physiologic limits because:
A. they lack smooth muscle cells
B. the blood flow rate is less
C. they have a small radius
D. capillary hematocrit is less than whole-body hematocrit.

105. That capillaries can withstand high internal pressures without bursting is explained using:
A. Bernoulli's principle

B. Laplace's law
C. Poiseuille Hagen law
D. Fahraeus-Lindquist effect

106. *Select all correct answers.* When determining BP with a sphygmomanometer, a spuriously high value (of either SBP or DBP) may be recorded when:
A. there is an auscultatory gap
B. the cuff is smaller than preferable
C. the person is obese
D. the arm is not placed at the level of the heart

107. If we compared wall tension at the following sites in a normotensive dog, it would be highest in:
A. aorta
B. capillaries in the lower limb
C. hepatic sinusoid
D. inferior vena cava
E. pulmonary arteriole
F. radial artery

108. Which of the following is usually associated with turbulence in blood flow?
A. Reynolds number less than 2000
B. Decrease in blood flow velocity
C. Decrease in density of blood
D. Increase in diameter of blood vessel

109. Turbulence is almost always present when Reynolds number is more than:
A. 2000
B. 2500
C. 3000

110. The average arm-to-tongue circulation time is:
A. 5 seconds
B. 10 seconds
C. 15 seconds
D. 20 seconds

111. Bernoulli's principle could be applied to explain why:
A. intravesical pressure does not change with increase in intravesical volume
B. mean pressure in the femoral artery is greater than that in the brachial artery

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C. coronary blood flow is compromised in aortic stenosis
D. tissue blood flow ceases below critical closing pressure

112. *Select all correct answers*. Which of the following statements is/are **correct**?
A. Pulse pressure is directly proportional to stroke volume.
B. Pulse pressure is inversely proportional to compliance of large arteries.
C. Reflected arterial pulse waves normally serve to increase coronary perfusion during diastole.

113. Filtration at the arterial end of capillary occurs mainly due to:
A. hydrostatic pressure in capillaries
B. hydrostatic pressure in interstitium
C. oncotic pressure in capillaries
D. oncotic pressure in interstitium

114. Patients with acute cardiac failure may not have edema if:
A. oncotic pressure of plasma proteins is high
B. renal compensation occurs
C. cardiac output is decreased
D. there is a fall in systemic capillary hydrostatic pressure

115. Venous return is transiently increased during:
A. strain phase of Valsalva maneuver
B. positive end-expiratory pressure
C. intravenous bolus of frusemide
D. deep inspiration

116. Which of the following does **not** occur when the body is immersed in water up to the neck?
A. Increase in central venous pressure
B. Increase in plasma level of renin

117. Quantitatively, the most important means of increasing flow to an actively metabolizing tissue is:
A. increasing cardiac output
B. increasing peripheral resistance
C. increasing blood pressure
D. decreasing local vascular resistance

118. Which of the following is **not** a vasodilator metabolite?

A. Adenosine
B. Potassium ions
C. Endothelin-1
D. Hydrogen ions
E. ADP

119. What is the chemical identity of endothelium-derived relaxing factor (EDRF)?
A. Nitrous oxide
B. Nitric oxide
C. Potassium
D. Carbon monoxide

120. Which of the following has a direct vasodilator effect on smooth muscle in arterioles in the presence of endothelial dysfunction?
A. Acetylcholine
B. Angiotensin II
C. Nitric oxide
D. Norepinephrine
E. Thromboxane A_2

121. Which of the following does **not** have vasodilator actions?
A. NO
B. CO
C. Potassium
D. Angiotensin III

122. Blood flow to exercising skeletal muscle is **decreased by:**
A. accumulation of K+
B. norepinephrine
C. ↑ in P_{CO2} in muscle
D. Adenosine
E. products of muscle metabolism
F. activation of *beta*-adrenergic receptors in skeletal muscle
G. activation of sympathetic cholinergic vasodilator system
H. nitric oxide

123. The most potent vasoconstrictor is:
A. endothelin 1
B. angiotensin II
C. norepinephrine
D. vasopressin

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124. Check whether the following statements about the arterial baroreflex mechanism are true or false.
1. Baroreceptors are free nerve endings responsive to stretch.
2. *Herring's nerve terminates in the nucleus tractus solitarius.*
3. An increase in discharge rate in afferents from the arterial baroreceptors reflexly excites vagal outflow to the heart and inhibits sympathetic outflow to resistance vessels.
4. The effect of a decrease in BP is a decrease in discharge frequency of arterial baroreceptor afferents.

125. *Select all correct answers.* On rising from the supine position:
A. central blood volume increases
B. heart rate decreases
C. central venous pressure decreases
D. discharge from arterial baroreceptors decreases
E. stroke volume decreases

126. Which of the following is a visceral afferent nucleus?
A. Rostral ventrolateral medulla
B. Pre-Bottzinger complex
C. Nucleus tractus solitarius
D. Caudal ventrolateral medulla

127. Intravenous injection of norepinephrine to a normotensive healthy adult human leads to:
A. an increase in BP & HR
B. a decrease in BP & HR
C. an increase in HR & decrease in BP
D. an increase in BP & decrease in HR

128. *Select all correct answers.* During the strain phase of the Valsalva maneuver (forced expiration with the glottis open and maintaining an expiratory pressure of 40 mm Hg for 15 seconds):
A. venous return decreases
B. cardiac output decreases
C. blood pressure decreases
D. heart rate increases
E. sympathetic outflow to blood vessels ↑
F. TPR gradually increases

129. The first reflex response to an increase in arterial pressure produced by intravenous injection of phenylephrine is:
A. increase in RR interval
B. increase in heart rate
C. decrease in cardiac output
D. decrease in total peripheral resistance

130. Which of the following is **most likely** to happen in a normal healthy adult seated in a centrifuge and spun at a force equal to 2 times that of gravity?
A. Increase in intracranial tension
B. Increase in BP
C. Increase in cardiopulmonary blood volume
D. A doubling of pressure in the veins of the foot

131. Loss of 500 ml of blood over 30 minutes will lead to:
A. an increase in HR, fall in BP
B. a fall in BP and HR
C. a prominent increase in HR and BP
D. a slight increase in HR

132. *Select all correct answers.* Which of the following maneuvers evokes an increase in vagal discharge to the heart?
A. IV infusion of phenylephrine
B. Carotid massage
C. Pressure on the eyeball
D. Irrigation of the ear canals

133. Marey's law states that:
A. when BP increases, HR decreases
B. when BP decreases, HR increases
C. when BP decreases, HR decreases
D. when BP increases, HR increases

134. A healthy 24-year-old male athlete is performing symptom limited bicycle ergometry. During exercise at 60% of maximal oxygen uptake, which of the following would be *least likely*? An increase in:
A. heart rate
B. stroke volume
C. systemic vascular resistance
D. mean arterial pressure

135. During exercise, an increase in O_2 uptake by exercising muscles does **not** occur due to:

A. shift of the oxyhemoglobin dissociation curve to the left
B. decrease in vascular resistance in exercising skeletal muscle
C. ↑ blood flow

136. Vasomotor ischemia triggers an increase in sympathetic outflow increasing BP and thereby facilitating restoration of cerebral blood flow. This is called:
A. Bainbridge reflex
B. the CNS ischemic pressor response
C. Head's paradoxical reflex
D. Marey's reflex

137. The mechanism that regulates cerebral blood flow during cerebral compression is the:
A. CNS ischemic response
B. Cushing's reflex
C. Bezold-Jarisch reflex
D. Bainbridge reflex

138. The 'last ditch stand' in defense of a falling blood pressure is the:
A. arterial baroreflex mechanism
B. arterial chemoreflex mechanism
C. CNS ischemic pressor response
D. Bainbridge reflex

139. *Select only one response.* Heart rate is slowed by:
A. deep inspiration
B. Bainbridge reflex
C. increased intracranial tension
D. carotid massage

140. In a healthy normotensive individual at rest, heart rate is typically increased by:
A. deep expiration
B. fear
C. anger
D. IV infusion of phenylephrine

141. Atrial natriuretic peptide is metabolized by:
A. dicarboxypeptidase
B. kininase II
C. neutral endopeptidase
D. kininase I

142. Cardiac output increases during:

A. Valsalva maneuver
B. positive pressure ventilation
C. negative 'g'
D. head-up tilt

143. As part of a space-research program, a physiologist was asked to investigate the effect of flight-induced stress on blood pressure. Accordingly, the blood pressures of the cosmonauts were to be measured twice: once before take-off and once after the spacecraft entered the designated orbit around the earth. For a proper comparison, the pre-flight blood pressure should be recorded in (the):
A. lying down position
B. sitting position
C. standing position
D. any position as long as the post-flight recording is made in the same position.

144. Which of the following is **least likely** following prolonged space missions?
A. Cardiac hypertrophy
B. Postural hypotension
C. Weight loss
D. Motion sickness

145. The acute effect of bilateral clamping of the carotid arteries proximal to the carotid sinuses is a/an:
A. increase in heart rate and mean arterial pressure
B. decrease in heart rate and mean arterial pressure
C. decrease in heart rate and an increase in mean arterial pressure
D. increase in heart rate and a decrease in mean arterial pressure

146. The acute effect of clamping internal carotid arteries proximal to the carotid sinuses in a dog is most likely:
A. an increase in discharge rate in afferent fibers from the carotid sinus
B. a decrease in discharge rate of neurons in the rostral ventrolateral medulla
C. an increase in sympathetic outflow to the heart and resistance vessels
D. an increase in cardiac vagal outflow

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147. In a dog, what would be expected to happen to BP upon clamping both internal carotids above the carotid sinus as to completely stop flow?
A. No change
B. Increase
C. Decrease

148. Two students, AB and CD were asked to demonstrate in dogs the role of sinus nerve in hypovolemic shock. AB severed the sinus nerve when the mean blood pressure was 85 mm Hg and CD cut the sinus nerve when the mean arterial pressure (MAP) was 60 mm Hg. On cutting the sinus nerve:
A. AB recorded an ↑ in MAP, CD recorded a ↓
B. AB recorded a ↓ in MAP, CD recorded an ↑
C. both recorded an ↑ in MAP
D. both recorded a ↓ in MAP

149. In hemorrhaged dogs with marked hypotension (mean arterial pressure < 50 mm Hg), denervation of arterial chemoreceptors would:
A. increase BP since chemoreceptors reduce sympathetic outflow
B. produce no change in BP since chemoreceptors do not influence sympathetic outflow
C. result in a further fall in BP since the arterial chemoreflex is sympathoexcitatory
D. depend on whether arterial baroreceptors are reset or not

150. Normally, in an adult at rest, total blood flow to the brain is about:
A. 250 ml/min
B. 500 ml/min
C. 750 ml/min
D. 1200 ml/min

151. Normally, the brain is perfused with what fraction of resting cardiac output?
A. 5%
B. 10%
C. 15%
D. 20%

152. Normally, cerebral metabolic rate for oxygen (CMRO$_2$) is about:
A. 2 ml/100 g/min
B. 3.5 ml/100 g/min

C. 5 ml/100 g/min
D. 7 ml/100 g/min

153. A 10ºC decrease in body temperature decreases cerebral metabolic rate (i.e., cerebral consumption of oxygen) by:
A. 10%
B. 30%
C. 50%
D. 70%

154. Which of the following is **least likely** to aggravate insult in an injured brain?
A. Hypercapnia
B. Hypoxia
C. Hypotension
D. Hypothermia

155. Which of the following is **not true** about cerebrospinal fluid?
A. Its pH is less than that of arterial plasma
B. It is formed in arachnoid villi.
C. Leakage of CSF during dural tap causes headache.

156. *Select all correct answers.* Areas where the blood-brain barrier is leaky include:
A. Posterior pituitary
B. Median eminence
C. Subfornical organ
D. Organum vasculosum of lamina terminalis
E. Area postrema
F. Subcommissural organ
G. Pineal

157. The blood-brain barrier is formed by:
A. tight junctions between vascular endothelial cells in the cerebral capillaries
B. choroidal epithelial cells
C. ependymal cells
D. foot processes of oligodendroglia

158. The plasma/CSF ratio of proteins is:
A. 3
B. 10
C. 20
D. 300

159. The arteriovenous O$_2$ concentration difference is **highest** across the:

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A. brain
B. heart
C. kidneys
D. liver

160. Stimulation of sympathetic nerves to which of the following tissues invariably **reduces** blood flow to that vascular bed?
A. Skin
B. Heart
C. Brain

161. An increase in discharge of noradrenergic nerves to the heart causes / has:
A. coronary vasoconstriction
B. coronary vasodilation
C. no effect on blood flow

162. If the noradrenergic nerves to the heart are stimulated after giving a β-blocker, then what would be the effect on coronary blood flow?
A. Coronary vasodilation
B. Coronary vasoconstriction
C. No change
D. Unpredictable

163. Normally, in postnatal life, the left ventricle is more vulnerable to ischemia and infarction compared to the right ventricle **because:**
A. diastolic pressure is comparable in both ventricles
B. pulmonary vascular resistance is greater than systemic vascular resistance
C. the left ventricle pumps much more blood than the right ventricle
D. left ventricular subendocardial perfusion is limited to ventricular diastole
E. flow through the right ventricle is largely passive

164. Capillaries empty when mechanically stimulated. This is called the:
A. axon reflex
B. white reaction
C. flare response
D. red reaction

165. The wheal in the triple response is due to:
A. contraction of precapillary sphincters
B. increased capillary permeability

C. axon reflex
D. decreased absorption of fluid

166. Which of the following physiologic responses has a neural basis?
A. Red reaction
B. White reaction
C. Flare
D. Reactive hyperemia

167. In which of the following organs is the flow **least** under sympathetic control?
A. Brain
B. Heart
C. Viscera
D. Skin

168. Orthopnea in heart failure occurs when the reservoir function of which of the following is overwhelmed?
A. Pulmonary veins
B. Pulmonary arteries
C. Right atrium
D. Systemic veins

169. Palpable enlargement of the liver in an individual with heart failure is **most closely** related to:
A. a decrease in pulmonary venous pressure
B. an increase in left ventricular compliance
C. an increase in mean arterial pressure
D. an increase in mean right atrial pressure
E. an increase in systemic vascular resistance

170. Plasma level of brain natriuretic peptide is **least likely** to be elevated in:
A. acute mitral regurgitation
B. cardiac tamponade due to chest trauma
C. heart failure due to dilated cardiomyopathy
D. heart failure due to acute aortic regurgitation
E. heart failure post myocardial infarction

Answers:

1B	2D	3C	4B	5B
6C	7C	8A-F	9A	10B
11B	12C	13A	14D	15A
16all	17C	18ABD	19B	20all
21B	22A	23B	24C	25C
26A	27AC	28A	29A	30C
31B	32D	33A	34AD	35A

36A	37A	38C	39A	40F
41C	42A	43A	44A	45C
46D	47CD	48B	49D	50C
51C	52A	53A	54B	55D
56A	57B	58C	59D	60B
61A	62C	63B	64all	65D
66B	67C	68A	69A	70D
71A	72C	73A	74C	75C
76B	77D	78D	79D	80C
81B	82A	83A	84D	85D
86A	87E	88A	89C	90C
91A	92C	93A	94A	95A
96C	97A	98D	99A	100C
101D	102A	103C	104C	105B
106all	107A	108D	109C	110C
111C	112all	113A	114D	115D
116B	117D	118C	119B	120C
121D	122B	123A	124allT	125CDE
126C	127D	128allT	129A	130D
131D	132all	133AB	134C	135A
136B	137AB	138C	139D	140C
141C	142C	143A	144A	145A
146C	147?	148A	149C	150C
151C	152B	153D	154D	155B
156all	157A	158D	159B	160C
161B	162B	163D	164B	165B
166C	167A	168A	169D	170B

Explanations:

6. MCHC is the most reliable index because it does not depend on the RBC count. This is because the estimation of RBC count is more error prone than the estimation of Hb or PCV.

8. Fibrinogen is essential for platelet aggregation. Also fibrinogen is a clotting factor. Von Willebrand's factor mediates the attachment of platelets to subendothelial collagen. Also vWD binds factor VIII and prolongs its half-life in the circulation. When there is a deficiency of vWF, more factor VIII spills over into the urine. Thus, bleeding time and clotting time are both increased in hypofibrinogenemia and VWD. Thrombin is a potent stimulator of platelet aggregation. At least, theoretically, prothrombin deficiency would be expected to delay platelet aggregation. Prostacyclin inhibits platelet aggregation. Aspirin therapy lowers TXA_2/PGI_2.

10. Vitamin K dependent clotting factors are factors II, VII, IX and X and Protein C and Protein S. Protein C and protein S inhibit clotting.

11. The extrinsic pathway is called so because it is triggered by a factor extrinsic to plasma (tissue thromboplastin). Simply, it is triggered by "tissue injury". The extrinsic pathway is also the fastest limb of the clotting cascade. Normally, PT = 12 – 14 seconds.

13.

Test	*Screening*	*Clotting factors screened*
Prothrombin time	Extrinsic pathway & common pathway	VII, X, Prothrombin, Fibrinogen
Activated partial thromboplastin time	Intrinsic pathway & common pathway	VIII, IX, X, XI, XII

14. The conversion of plasminogen to plasmin requires tissue plasminogen activator (TPA). The conversion of Fibrin to fibrin degradation products is catalyzed by *plasmin* (fibrinolysin).

16. Loss-of-function mutations in protein C, protein S, antithrombin III and mutations in factor V resulting in resistance to inactivation to protein C have all been implicated in hypercoagulable states.

17. Factor V Leiden, a mutated form of Factor V, resists inactivation by protein C.

20. If red cell antigens are also present in exocrine secretions, such individuals are called secretors. In some, they are not secreted. The significance of this is unknown.

21. H substance is absent in persons with the Bombay phenotype. Normally, if an individual has H substance (but lacks the A and B genes), her blood group would be O. An individual lacking H substance will have anti H antibodies in plasma and can receive transfusions only from a person with the Bombay blood group.

22. 70% of iron in the body is present in Hb. Under abnormal circumstances, a large amount of iron may be present in hemosiderin.

23. Sensitization of the mother's immune system with fetal Rh antigens results in the production of anti-Rh immunoglobulin. First, IgM is formed but this is too large to cross the placental barrier.

The major antibody in the primary immune response is IgM. However, over a time period that varies from individual to individual, IgG is also produced as part of this response, although the titer of IgG is usually not sufficient to evoke significant hemolysis in the first pregnancy. On the other hand, in a woman who has been previously sensitized with Rh antigen and anti D IgG titers were significant, significant hemolysis could occur even during the first pregnancy.

27. Osmotic fragility increases when the RBC cytoskeleton is abnormal, as in hereditary spherocytosis. *Normal range:* 0.5 - 0.3% NaCl Osmotic fragility is increased in hereditary spherocytosis. Sickle cells and microcytes show greater resistance to osmotic lysis by virtue of their smaller size and normal cytoskeleton.

28. Hereditary spherocytosis occurs due to mutations in cytoskeletal proteins spectrin, ankyrin, Band 3. Defects in ankyrin are reported to be commoner.

30. Heme oxygenase activity is highest in the spleen. Second, the spleen is much more sensitive to red cell injury. (Wintrobe's Clinical Hematology, Lee GR et al, 10th ed, Lippincott Williams and Wilkins, volume 1, p 280.)

31. Haptoglobin binds extracorpuscular hemoglobin. Hemopexin binds heme. Haptoglobin binds extracorpuscular hemoglobin and prevents it from being filtered and excreted by the kidney. Serum haptoglobin levels are reduced in hemolytic anemias.

32. Fibrinogen is consumed when blood clots leaving very little of it in serum if at all.

35. Albumin is a 'negative' acute phase reactant; i.e., its synthesis is reduced during the acute phase response.

36. ESR in anemia is high because PCV is low; secondly, viscosity is low as well and it reduces resistance to sedimentation of cells. By the same reasoning, ESR is reduced in polycythemia since PCV as well as viscosity are elevated. However, for a given PCV, if blood is more viscous because of an increase in plasma levels of globulins and fibrinogen, its effect is to enhance sedimentation since these proteins facilitate rouleaux formation.

39. Hb F binds 2,3 BPG less avidly compared to Hb A and therefore has a greater affinity for oxygen relative to Hb A. This is one reason why it is able to draw O2 from Hb A.

40. The viscosity of blood varies with flow rate, and it increases at very low flow rates such as in postcapillary venules due to aggregation of RBCs. This is why blood is considered a non-Newtonian fluid.

41. Automaticity is attributed to the presence of pacemaker cells that demonstrate spontaneous depolarization in the absence of extrinsic innervation.

43. Normally, it is the impulse that originates in the SA node that excites the ventricular myocardium. Such a rhythm is called sinus rhythm.

44. There are two regions in the heart where the inhibitory effect of vagal stimulation on conduction speed is profound. These are the SA and AV nodes. The conduction speed in the SA and AV nodes is about 0.05 m/s. (Ganong, 2012; p. 524, Table 29-1). Conduction speed is about 4 m/s in the Purkinje system, about 80 times faster than in the SA and AV nodes.

45. Stimulation of the right vagus nerve, which predominantly innervates the SA node, decreases the firing rate of the SA node. The effect of acetylcholine on pacemaker cells in the SA node is to activate a hyperpolarizing potassium current.

46. *Beta*-adrenergic receptor activation in the SA node increases the slope of phase 4 depolarization in SA nodal cells, thereby increasing SA nodal firing rate. Conduction speed through AV node increases. Calcium influx (I_{Ca}) and calcium induced calcium release are facilitated. Sequestration of Ca in the SR is enhanced; this is how it accelerates myocardial relaxation. Remember, an increase in HR entails an acceleration of the rate of contraction as well as relaxation. The rate of pressure increase during isovolumetric ventricular contraction is increased because of enhanced calcium influx and an increase in sensitivity of contractile proteins to calcium (*positive inotropic effect*).

47. Note that the terms prepotential, pacemaker potential and spontaneous diastolic depolarization are often used interchangeably. They all mean the same. Normally prepotentials are present only in the SA node and AV node which contain pacemaker cells (P cells). However, in abnormal situations (e.g. hypoxemia) other regions of the heart (e.g. a ventricular focus) exhibit prepotentials. This state is one of "increased automaticity", and premature ventricular or atrial depolarizations are manifestations of increased automaticity.

48. The long duration of action potential (or the absolute refractory period) in the heart is due to slow repolarization. This is a safety features that ensures that the ventricles relax to fill with blood before contracting again.

49. Intrinsic heart rate (IHR) is the rate at which the heart will beat when completely denervated. This is determined, in humans, by intravenous administration of a standard dose of atropine and atenolol. In healthy humans, IHR is about 100-110/min. The magnitude of IHR reflects the automaticity of the SA node. The fact that resting heart rate in healthy humans is around 70 beats per minute indicates that the effects of cardiac vagal tone at rest are greater than the effect of sympathetic outflow to the heart. Patients with transplanted hearts have higher resting heart rates closer to IHR because of cardiac denervation. Also, because of denervation, they are less able to increase their heart rate in response to exercise.

50. The AV node, like the SA node, exhibits prepotentials but its rate of discharge is much less compared to the SA node.

52. Depolarization and repolarization are electrically opposite processes. Normally, ventricular depolarization occurs from endocardium to epicardium, and repolarization occurs from epicardium to endocardium. This is why the T wave is upright, i.e. in the same direction as QRS. An inverted T wave indicates that the direction of ventricular repolarization is reversed, i.e. occuring from endocardium to epicardium.

56-57. His Bundle Electrogram:
PA interval (approximately 30 ms) reflects the time taken for conduction across the atrial pathways to the AV node. PR segment is a combined index of AV nodal delay and conduction in infranodal pathways. PR interval is a rather poor index of AV nodal delay. AH interval, which is obtained by a His bundle electrogram specifically reflects AV nodal conduction time. The AH interval, from the A wave to the start of the H spike is normally 60-125 ms.

Interval	Physiologic correlate	Time (ms)
PA interval	Atrial activation time	30
AH interval	AV nodal delay	60-125
HV interval	His Bundle - ventricle	35-50

Ganong, 2012, p. 528-9.

61. Right axis deviation may occur in a healthy young adult male during deep inspiration.

64. The mechanisms are incompletely understood but this is what has been postulated. First, the infarct is deprived of blood supply. With ATP depletion, its RMP becomes less negative. Remember, the Na-K ATPase is an electrogenic mechanism that contributes a bit to making the RMP negative inside (with respect to the exterior). The other reason RMP becomes less negative in the infarct zone is potassium (the most abundant intracellular cation) is lost from injured cells.

99
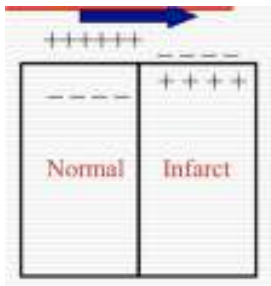
Thus, as depicted in the schematic above, extracellularly, the infarct zone, at rest, becomes negative with respect to surrounding normally polarized tissue. Therefore, during diastole, extracellularly, current flows into the infarct. This is what is called the ***diastolic current of injury.*** TP segment, the EKG segment corresponding to ventricular diastole, is normally isoelectric because normally there is no current flow during diastole. The current flow into the infarct during diastole depresses the baseline, i.e., the TP segment is depressed. However, the arrangement in ECG recorders is such that TP segment depression is recorded as ST segment elevation.

Secondly, the infarct depolarizes late with respect to surrounding normal tissue probably due to a decrease in velocity of conduction of impulses in the infarcted tissue; the effect of this late depolarization is to simply delay the QRS complex, causing ST segment elevation.

Thirdly, ischemic myocardium repolarizes faster due to accelerated opening of potassium channels. *(One can't predict this from first principles; it simply, is a property of potassium channels in the myocardium)* Normally, ventricular repolarization is evident as the T wave. But the effect of early repolarization is also ST segment elevation.

Thus, myocardial infarction is characterized by ST segment elevation in leads facing an acute myocardial infarction (Ganong, 2005, pp. 563-4). It should be added that the definition of an acute myocardial infarction has evolved over the years, and now non-ST segment elevation myocardial infarction (NSTEMI) is an entity distinguished from ST-segment elevation MI (STEMI). Thus, based on recent definitions of MI, not all MIs cause ST segment elevation. But when ST segment elevation does occur in multiple contiguous leads, the mechanisms are believed to be those described above.

68. Ventricular relaxation commences and ventricular pressure begins to fall before the aortic valve snaps shut (S2). *Options B* and *D*, atrial systole (*a* wave) occurs just prior to S1. Rapid ventricular filling commences after S2. *Option E* - the *'y'* descent of the JVP represents the fall in atrial pressure during ventricular filling and occurs between S2 and S1.

72. There is no abnormal pressure gradient across the tricuspid valve, pulmonic valve or aortic valve. Pulmonary capillary wedge pressure is abnormally high, suggestive of acute left ventricular failure. The resulting pulmonary venous congestion and pulmonary edema may account for the reduction in percentage saturation of Hb with oxygen. The data are most consistent with acute mitral regurgitation.

73. The right and left ventricles are in series and so they pump the same volume of blood. They, of course, normally beat at the same rate. Thus, their stroke volumes are matched over time. This can be explained by the Frank-Starling mechanism which states that stroke volume varies directly with preload (ventricular end-diastolic volume) within physiologic limits.

75. The depolarization at X beat is from a focus in the ventricle. The beat could not have originated in an atrial focus since it has not reset the sinus rhythm. An atrial premature beat is not usually followed by a compensatory pause; it is conducted to the SA node and it "resets" sinus rhythm. In contrast, a ventricular premature beat is usually not conducted retrograde through the AV node to the SA node, so it does not reset normal sinus rhythm.

The duration of premature ventricular depolarization is longer than a normal QRS complex since it is conducted much slowly through the myocardium rather than through the normal conducting pathway. Thus the resulting ventricular contraction is unlikely to have been really "premature". So enough ventricular filling

would likely have occurred and the beat must have been strong enough for the aortic valve to open (and then close). Thus both heart sounds would most likely have been present at beat X. The learning point here is that a *premature ventricular depolarization* does not always result in a *premature beat*.

76-79. Systolic time intervals (STI)

QS2 is the time duration from the beginning of the Q wave to the first high frequency component of the aortic component A2 of the second heart sound. Note that this is an electromechanical interval; QS2 is called *electromechanical systole*. It is remarkably constant.

Left ventricular ejection time (LVET) is the period from the upstroke of the carotid artery pulse to the dicrotic notch (an oscillation on the falling wave of the carotid artery pulse). The dicrotic notch in the carotid artery pulse tracing represents the closure of the aortic valve. Note that ejection is a part of systole.

Pre-ejection period (PEP) is calculated as QS2 – LVET. It denotes the time taken for electrical excitation of left ventricle, excitation-contraction coupling and isovolumetric ventricular contraction.

If the duration of ventricular excitation and excitation-contraction coupling can be assumed to be constant, then, PEP can be taken to reflect the duration of isovolumetric ventricular contraction.

PEP, which reflects the duration of isovolumetric contraction, is prolonged in heart failure. This is also associated with a decline in left ventricular ejection time. Thus, PEP/LVET ratio is a sensitive index of left ventricular systolic performance. STI cannot be used for diagnosis of specific heart conditions. Of late, STI have been superseded by echocardiography.

Without the carotid pulse transducer, LVET cannot be determined. Since PEP = QS2-LVET, PEP cannot also be determined.

80. Cardiac output = SV × HR
HR = 75/min; cardiac output = 6 L/min.

Therefore, average SV = 80 ml.
Average LVEDV = 120 ml.
Therefore, ejection fraction = SV/LVEDV = 0.66 = 66%.

81. The Fick's principle states that the amount of a substance (X) consumed by an organ per unit time (A) = A-V conc. difference of X across that organ (circuit) × blood flow through that organ (or circuit)

Thus, blood flow (Q) = A / A-V conc. diff
In this example, O_2 consumption = 2000 ml/min.
AV O_2 difference = 80 ml/L. Cardiac output = 2000/80 = 25 L/min.

82. Whole body oxygen delivery = cardiac output × oxygen content of arterial blood.

Cardiac output = 5 L/min; Blood Hb = 15 g/dL. Oxygen carrying capacity of blood is approximately 20 ml/dL i.e. 200 ml/L.

Therefore about 1L of oxygen will be delivered to the tissues per minute.

83. When cardiac output is low, blood flow velocity is reduced and temperature of injected saline is quickly dissipated into tissues thereby rendering an accurate measurement of cardiac output (pulmonary blood flow) by the thermodilution difficult.

84. For correct estimation of blood volume as well as cardiac output, the dye must remain in the blood stream.

90. Ganong, 2012, p. 546, Table 30-3.

91. At rest, blood flow through the systemic circulation (i.e., cardiac output) = 5 L/min
Assuming that functional Hb A concentration is 15 g/dL and PaO2 is 100 mm Hg and that Hb is fully saturated with oxygen,
Oxygen content of arterial blood = 200 ml/L
Whole body oxygen delivery = 1 L/min
Whole body oxygen consumption = 250 ml/min
Whole body oxygen extraction = 0.25
This is sometimes called 'oxygen utilization coefficient (OUC)'.

Theoretically, oxygen extraction can increase up to 1. Thus, an increase in oxygen extraction is one mechanism of fulfilling an increase in oxygen demand. However, in trained athletes, cardiac output can be increased 7 times from its resting value.

92. VO$_2$ max is the maximum amount of oxygen that can be utilized during dynamic exercise; it can be increased by training.

97. At any time, 54% of blood volume is contained in the veins and venules & vena cava.

99. Ganong, 2012, p. 572, Table 31-10

100. Since pulmonary and systemic circulations are in series, the flows are identical
Cardiac output = P / R;
(P is mean arterial pressure and R is vascular resistance)
Ps / Pp = Rs/Rp (s and p refer to systemic and pulmonary vascular beds respectively)
Ps / Pp = 90 / 15 = 6
Ratio of systemic and pulmonary vascular resistance = 6
Thus, the pulmonary circulation is a low resistance, low pressure system.

101. For resistors in series, net resistance is the sum of all resistances. For resistors in parallel, 1/R = 1/R1 + 1/R2 + 1/R3 + .. + 1/Rn, and the net resistance is R **not 1/R.**

Flow = Pressure gradient / Net resistance to flow

102. Tissue blood flow = BP / local vascular resistance. Blood flow is directly proportional to the fourth power of radius.

104. For a cylindrical structure, transmural pressure (P) = T/r (Laplace's law) where T is wall tension and r is radius

Though capillaries are thin walled, they have a smaller radius and consequently need to develop less tension in order to withstand a given distending (transmural) pressure.

106. When there is an auscultatory gap and the palpatory method is not used, systolic pressure will be underestimated. When there is an auscultatory gap and you use the palpatory method, you will get a correct estimate of systolic pressure (say 210 mm Hg). Sounds will cease at some point (say 160 mm Hg). However, if the cuff is not deflated any further (because sounds disappeared at 160), one may not realize that there is an auscultatory gap with the result that diastolic pressure is overestimated. Something like 210/160 mm Hg will be recorded when the actual pressure is 210/90 mm Hg.

108. Reynolds number Re = $\rho DV/\eta$
ρ is the density of the fluid;
D is the diameter of the vessel;
V is the blood flow velocity; and
η is the viscosity of fluid.
Flow is turbulent when Re exceeds 3000.

111. Bernoulli's principle: The greater the velocity of flow in a vessel, the lower the lateral pressure distending its walls. Coronary arteries originate virtually at a right angle from the aorta, above the aortic valve. Thus, in aortic stenosis, the lateral pressure at the level of the origin of coronary arteries is reduced, and this in turn reduces coronary blood flow. However, this is only one of many mechanisms that contribute to the reduction in coronary blood flow in aortic stenosis.

112. The stiffer the arteries, i.e., the less distensible they are, higher the pulse pressure for a given stroke volume. This is the basis of higher systolic pressure in isolated systolic hypertension, the commonest type of hypertension in the elderly.

113. The major force driving filtration is the capillary hydrostatic pressure, which is normally about 40 mm Hg at the arterial end of the capillary in a capillary that is at the level of the heart. More precisely, transcapillary hydrostatic pressure gradient is the major factor.

114. In *forward heart failure*, cardiac output is low, and as a result, mean arterial pressure may be low, since MAP = cardiac output times TPR. This

may cause capilary hydrostatic pressure to be low. If edema is not observed in an individual who truly has heart failure, then this is the most likely explanation. However, in advanced heart failure, salt and water retention by the kidneys causes an increase in total body sodium and water and edema ensues.

117. Tissue blood flow = mean arterial pressure / local vascular resistance. A doubling of radius of all arterioles can increase flow to a tissue 16 times assuming all other factors affecting flow remain the same. Thus, quantitatively, changes in local vascular resistance achieved mainly through local autoregulatory mechanisms contribute the most to regulating tissue blood flow.

125. Central venous pressure decreases upon rising due to a decrease in venous return. A decrease in arterial pressure, which occurs on rising from the supine position, also decreases the stretch of arterial baroreceptors (i.e., arterial baroreceptors are said to be 'unloaded') and the firing rate in the carotid sinus nerves decreases. This reflexly inhibits vagal outflow to the heart and increases sympathetic outflow from the brain resulting in an increase in heart rate and a rise in total peripheral resistance.

127. Norepinephrine has a greater affinity for alpha adrenergic receptors than beta adrenergic receptors. So when it is administered intravenously to a healthy individual with normal BP, it elicits a rise in total peripheral resistance because of alpha adrenergic receptor mediated vasoconstriction. The rise in BP elicits a baroreflex mediated lowering of HR that overwhelms the direct cardioacceleratory effect of norepinephrine.

128. Valsalva maneuver:

Maneuver	Forced expiration against a closed glottis sustained for 15 seconds.
Stimulus	Decrease in BP due to a decrease in venous return and consequently stroke volume (SV)
Response	Immediate increase in HR and a more gradual increase in TPR
'Goal'	To maintain BP
Immediately after the	Venous return suddenly increases, SV increases, TPR is already high.
maneuver	Thus BP = SV × HR × TPR 'overshoots'
Response	The BP overshoot triggers a baroreflex mediated lowering of HR
Significance	BP maintained

131. Blood loss occurs over a 30-minute period (a common example is venesection of a healthy adult blood donor). There occurs only a slight increase in HR because of a reduction in central blood volume. BP is maintained in the steady state, and one cannot detect the fall in BP by intermittent sphygmomanometry.

132. Phenylephrine is an alpha adrenergic agonist, so it raises TPR and BP and elicits a baroreflex mediated lowering of HR. Carotid massage mechanically activates the vagus nerve contained within the carotid sheath increasing cardiac vagal outflow.

133. Marey's law states that HR (the dependent variable) is inversely related to BP (the independent variable) and that the converse is not true. When Marey's law holds, it is because the arterial baroreflex works as a negative feedback mechanism to maintain BP. However, when the arterial baroreflex is reset – for example, during exercise, HR as well as BP increase.

134. Systemic vascular resistance (or total peripheral resistance) would most likely reduce at such exercise intensity because of accumulation of products of metabolism.

136. Vasomotor ischemia stimulates sympathetic outflow. This leads to an increase in BP that in turn serves to restore cerebral blood flow. This is the CNS ischemic pressor response.

137. The Cushing's reflex is a subtype of the CNS ischemic pressor response in which the cause of vasomotor ischemia is raised intracranial tension.

138. Arterial BP is affected by numerous neural and humoral mechanisms. The arterial baroreflex mechanism buffers BP fluctuations when mean arterial pressure (MAP) is in the 70-150 mm Hg range. But when MAP is lower than 70 mm Hg, baroreceptors are maximally deactivated and the

arterial chemoreflex mechanism assumes greater importance in defending against a further fall in BP.

In severe hypotension such as when MAP is < 50 mm Hg), ischemia of the vasomotor center in the medulla triggers a powerful increase in sympathetic outflow. This mechanism, the CNS ischemic pressor response (called the "last ditch stand" in defense of a falling BP), contributes to restoring cerebral blood flow.

Reflex mechanism	MAP (mm Hg) range in which it operates
Arterial baroreflex	70–110
Arterial chemoreflex	40–70
CNS ischemic pressor response	< 50

139. Regarding *option C:* Raised intracranial tension (ICT) is not necessarily associated with bradycardia. An individual with raised ICT may be hypotensive due to blood loss. In this instance, hypotension is usually associated with tachycardia. Rather, if raised ICT leads to hypertension, this usually elicits a baroreflex mediated lowering of heart rate.

142. When intrathoracic pressure is raised as occurs during the Valsalva maneuver, venous return reduces and cardiac output decreases. Similarly, during positive pressure ventilation, the increase in ITP reduces venous return and decreases cardiac output. During negative 'g', i.e. acceleration in the long axis of the body from foot to head, there is a headward shift of body fluids and central blood volume, cardiac output and blood pressure increase. Passive head-up tilt is associated with a decreased cardiac output since venous return is reduced.

143. Tolerance for g forces across the body (chest to back) is much better than that acting along the long axis of the body (head to foot). Thus, astronauts are positioned to take g forces of space flight chest to back. (Ganong, 2005, p. 632).

144. Cardiac atrophy rather than hypertrophy occurs following prolonged space missions since the load on the heart is reduced. This is because skeletal muscles are not regularly used in microgravity conditions. Postural hypotension occurs upon return to earth (where the effects of earth's gravity are again fully manifest) because of autonomic as well as physical deconditioning. Motion sickness in space occurs due to conflicting neural inputs from visual cues and vestibular system and diminished input from muscle proprioceptors.

145-146. This procedure reduces the pressure at the level of the carotid sinuses. The result is inhibition of arterial baroreceptor discharge and a reflex increase in sympathetic discharge to the heart and blood vessels. This is an instance of neurogenic hypertension. Ganong, 2012, p. 592.

148. When MAP is in the normal range, i.e., between 70 and 110 mm Hg, an increase in BP results in an increase in discharge rate from the carotid sinus. Activity in the buffer nerves inhibits tonic vasoconstrictor discharge from the medulla. Therefore, sectioning of the buffer nerves when MAP is normal would result in acute elevation of BP. This is called **neurogenic hypertension.**

A MAP less than 70 mm Hg is a **hypotensive state**. When MAP is as low as 60 mm Hg, discharge rate in carotid baroreceptors is already at its minimum, and the resulting reflex sympathoexcitation is fully manifest. Thus, sectioning of afferents from arterial baroreceptors at a low MAP would not be expected to have further sympathoexcitatory effects.

On the other hand, when MAP is as low as 60 mm Hg, blood flow through the arterial chemoreceptors near the carotid sinus would be reduced. A reduction in either PaO_2 and or a decrease in flow through the chemoreceptors lead to a reflex increase (via afferents from carotid bodies) in sympathetic outflow that serves to bring BP back into the normal range. Thus, when the buffer nerves are sectioned at a time when MAP is lower than normal, BP falls further. (Ganong, 2005, p. 628).

Summary: When MAP is reduced below 70 mm Hg, arterial baroreceptor discharge is maximally inhibited and sympathetic outflow is disinhibited as a result of this; apart from this, activation of the arterial chemoreflex contributes significantly to "increasing" MAP at such low pressures.

149. This is a simpler version of *Question 148*.

151. In a young healthy adult at rest, cardiac output = 5 L/min. Cerebral blood flow = 750 ml/min (this is 15% of cardiac output)

152. Mass of the brain = 1400 g
Cerebral oxygen consumption per minute = 50 ml
CMRO$_2$ (i.e. oxygen consumption per minute per 100 g of brain tissue) = 3.5 ml/100 g/min

153. A 1ºC decrease in temperature reduces cerebral metabolic rate for oxygen by 7%.

154. This is because induced hypothermia reduces cerebral demand for oxygen.

157. While foot processes of astrocytes end on cerebral capillaries and induce the formation of tight junctions, the actual anatomic basis of the blood brain barrier is the tight junctions between endothelial cells in cerebral capillaries. In the circumventricular organs such as area postrema, subfornical organ, this barrier is absent.

158. Plasma protein concentration = 6000 mg/dL
CSF protein concentration = 20 mg/dL. Since CSF protein concentration is extremely low, protons in brain interstitial fluid readily stimulate breathing.

159. If the arteriovenous concentration difference of a substance (example, oxygen) across a vascular bed is high, it means that the vascular bed extracts a large fraction of this substance.

Oxygen extraction ratio across the heart is 0.5-0.7 at baseline, much higher compared to other tissues. Cardiac venous oxygen tension is low and little additional oxygen can be extracted from the blood in the coronaries, so increases in myocardial oxygen consumption require increases in coronary blood flow. If that cannot happen, myocardial

ischemia would result with predictable consequences.

At rest, oxygen extraction ratio in the heart
= (A–V O$_2$ difference / arterial O$_2$ content) × 100
= (114 / 200) × 100 = 0.55
This is based on data in Ganong, 2012, Table 33-1, p. 602.

162. Activity in the noradrenergic nerves to the heart increases myocardial oxygen demand since it would increase the force as well as rate of cardiac contraction. However, this normally results in coronary vasodilation caused by products of metabolism. The pressor effect of norepinephrine on alpha-adrenergic receptors in the coronary arteries is not manifest therefore. However, the direct effect of norepinephrine on segments of isolated coronary arteries is vasoconstriction. On the other hand, the increase in myocardial oxygen demand (and consumption) during exercise is attenuated in individuals taking beta-blockers because the norepinephrine mediated rise in heart rate and contractility are also diminished, and consequently their ability to exercise is diminished. The learning point here is that the coronary circulation is capable of excellent autoregulation.

163. The right ventricle is perfused throughout the cardiac cycle and the work done by the right ventricle is 6-7 times lower than that done by the left ventricle since pulmonary vascular resistance is that much lower compared to systemic vascular resistance.

164-166. The triple response:

Response	Mechanism
Wheal production	Increased capillary and venular permeability
Red reaction	Venodilation
Flare	Axon reflex

The white reaction is the response to a benign stimulus. It occurs due to contraction of precapillary sphincters. The triple response is evoked by a noxious stimulus. With the exception of the flare which is mediated by an axon reflex, the triple response, indeed, is an example of autoregulation.

167. All organs are capable of autoregulating their blood flows. Although cerebral vessels have noradrenergic innervation, cerebral blood flow itself is not chronically under neural control. Cerebral blood flow is excellently autoregulated in the steady state when mean arterial pressure is between 65 and 140 mm Hg.

Although the heart is also capable of excellent autoregulation, under certain circumstances, neural regulatory mechanisms override local regulatory mechanisms. For example, sudden excessive discharge in the sympathetic fibers to the heart can cause severe coronary vasospasm and a severe reduction in coronary blood flow.

Cutaneous blood flow is most often varied in response to neural signals from the hypothalamus. It is the vascular bed that is most consistently under neural control.

170. BNP is released in response to abnormal stretch (increased passive tension) of ventricular myocytes such as in heart failure. In tamponade, the increase in ventricular diastolic pressure is because of compression by high intrapericardial pressure rather than increased stretch of ventricular myocytes.

PULMONARY PHYSIOLOGY

1. Lung Volumes and Capacities, and the distinction between Obstructive and Restrictive Lung Disease.

Respiratory minute volume = V_T × respiratory rate, where V_T is tidal volume.

Alveolar ventilation =
(V_T – anatomical dead space) × respiratory rate

Anatomical dead space is roughly equal to body weight in pounds.

If V_T = 500 ml and respiratory rate = 12 per minute, then respiratory minute volume = 6 liters

If the anatomical dead space = 150 ml, then alveolar ventilation = (500 – 150) × 12 = 4.2 liters/minute. Note that only alveolar ventilation contributes to gas exchange.

Each lung volume is an independent fraction of total lung capacity (TLC). **Lung capacities** are combinations of **lung volumes.** Values given below are for a healthy young adult male weighing 80 kg with a body surface area of about 1.8 m^2. Values in females are about 10% lower. Note that lung volumes and capacities are greatly influenced by height, weight, body surface area.

Tidal volume V_T	500 ml
Inspiratory reserve volume (IRV)	3200 ml
Expiratory reserve volume (ERV)	1100 ml
Residual volume (RV)	1200 ml

Tidal volume is about 5–7 ml/kg body weight;

By definition, the reserve volumes are recruited with effort.

FRC is the resting lung volume or the volume of air present in the lungs at the end of a tidal expiration. It is the lung volume at which the inward elastic recoil of lung parenchyma is balanced by the natural tendency of chest wall to recoil outward.

Lung capacities in a healthy adult male weighing 70 kg:

Capacity	Definition	Typical Value (ml)
Functional residual capacity (FRC)	RV + ERV	2300
Inspiratory capacity	V_T + IRV	3700
Vital capacity (VC)	V_T + IRV + ERV	4800
Total lung capacity (TLC)	RV + ERV + V_T + IRV	6000

The term expiratory capacity is not used. Unless otherwise stated, vital capacity (often called forced vital capacity) is the maximum amount of air that can be expelled after a forced inspiration. If measured during inspiration, it is specifically called **inspiratory vital capacity.**

The following 4 factors affect vital capacity:
1. Strength of muscles of inspiration
2. Lung compliance
3. Strength of muscles of expiration
4. Airways resistance

Evaluating airways resistance:
Air flow = transairway pressure / airway resistance

Transairway pressure = intrathoracic pressure – pressure at the mouth. The latter is zero mm Hg with reference to atmospheric pressure.

FEV1, the volume of air expelled during the first second of a forced vital capacity maneuver, varies directly with expiratory pressure and inversely with airways resistance. It is normally at least 80% of FVC; FEV1/FVC is > 0.8.

If vital capacity is reduced, FEV1 will be reduced, yet FEV1/FVC may be normal as in restrictive lung disease.

FEV1/FVC is a specific index of airways resistance and helps discriminate restrictive from obstructive lung disease. See Table OLD vs. RLD *next page.*

Peak expiratory flow rate (PEFR) is the highest flow rate during forced expiration (vital capacity maneuver). When vital capacity is reduced, flow rates are reduced as well. Thus, for example, the peak flow rate during tidal expiration is much

lower than that during forced expiration. Normally, PEFR is about 12 liters/second or 720 liters/minute (values are 10-15% lower in age matched females).

PEFR is dependent upon vital capacity. Thus, it does not make sense to use PEFR as an index of airways resistance in a patient with restrictive lung disease. (Note that FEV1/FVC is normalized for flow whereas PEFR is not.) Thus, monitoring PEFR as an index of airways resistance is appropriate only in individuals known to have obstructive airways disease or asthma (low FEV1/FVC).

Forced expiratory time: this is a useful bedside index of airways resistance. Auscultate the trachea during forced expiration, if expiratory sounds are heard for longer than 4 seconds, airways resistance is increased.

Maximum mid-expiratory flow rate (MMEFR): The first 25% of expired air comes mainly from the major airways; MMEFR is the highest rate at which the middle 50% of VC is expelled; it is also called forced expiratory flow rate (FEF $_{25–75}$), and it is more sensitive than PEFR in reflecting the resistance of the small airways that are narrowed in bronchial asthma.

"Air trapping" occurs whenever there is expiratory flow limitation. Since flow is driven by pressure and opposed by resistance, air trapping is usually a consequence of an increase in airways resistance. Air trapping occurs in chronic obstructive pulmonary disease. As a result of this, total lung capacity increases, however the vital capacity is subnormal; in other words, patients with obstructive lung disease breathe at a higher FRC compared to normal subjects. The fraction of FRC that increases is the residual volume.

Lung compliance is the change in lung volume for a given change in pressure.
Compliance = $\Delta V / \Delta P$
The normal compliance of human lungs and chest wall is about 0.2 L/cm H_2O. Compliance is reduced in restrictive lung disease.

Mechanism of reduction	Disease
of vital capacity	
Weakness of muscles of respiration	Myasthenia gravis, poliomyelitis
Lung compliance reduced	"Restrictive" lung disease
Increased airways resistance	Major airway obstruction; bronchial asthma

To summarize, vital capacity is always reduced in lung disease; however, total lung capacity may be increased or decreased depending on the cause.

Obstructive (OLD) vs. Restrictive Lung disease (RLD)

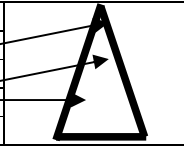|	FEV1	FVC	FEV1/FVC	PEFR
OLD*	↓	↓	< 80%	↓
RLD*	↓	↓	Normal or > 80%	↓

2. Lung Zones:
P_A = Alveolar pressure;
Pa = Pressure at the arterial end of the pulmonary capillary;
Pv = Pulmonary venous pressure;
Pi = Pulmonary interstitial pressure.

Zone	Definition	
Zone 1	P_A > Pa > Pv	
Zone 2	Pa > P_A > Pv	
Zone 3	Pa > Pv > P_A	
Zone 4	Pa > Pi > P_A	

Zone 1: above the heart; arterial pressure is lower and may be lower than alveolar pressure if the alveoli are well expanded. Flow may be minimal. V/Q approaches infinity.

Zone 2: pulmonary arterial pressure is greater than alveolar pressure and flow is determined by arterial – alveolar pressure difference; however, during inspiration when alveolar pressure becomes more negative, blood flows from the arteries into the pulmonary veins. This is called the **'waterfall effect'.**

Zone 3: flow is continuous and is driven by pulmonary arterial – venous pressure gradient.

Zone 4: it occurs in pulmonary edema (always abnormal). When pulmonary interstitial pressure is > than alveolar pressure, alveolar collapse (atelectasis) would result.

When a Swan Ganz catheter is wedged in the pulmonary capillary to estimate left ventricular end diastolic pressure (LVEDP) in a patient who is on a ventilator with positive end expiratory pressure (PEEP) added, the measured pressure would reflect alveolar pressure rather than LVEDP; thus, the catheter must be placed in Zone 3 conditions (perhaps by momentarily discontinuing PEEP) to reliably estimate LVEDP

3. Gas Exchange:

Ventilation–perfusion ratio is the ratio of alveolar ventilation to pulmonary blood flow. For example, at rest, alveolar ventilation = $12 \times (500-150) = 4.2$ L/min;
Assuming $V_T = 500$ ml, $V_D = 150$ ml;
If pulmonary blood flow = 5 L/min;
Thus, whole lung V/Q ratio = 0.84;
In the lung apices, V/Q approaches infinity;
In the lung bases, V/Q is lower than 1.

As a result of regional differences in intrapleural pressure, upper lung zones are already in a more expanded position at the start of inspiration. In contrast, the lower lung zones are less distended at the start of inspiration and therefore more compliant. Thus, alveolar ventilation is much higher at the lung bases than the apices

Shunt: Perfusion of unventilated alveoli results in shunting of deoxygenated blood across the lungs to the heart, i.e. a right-to-left shunt.

Dead space: Ventilation of unperfused alveoli is effectively an extension of anatomic dead space since it cannot contribute to gas exchange.

At rest, a healthy adult weighing 70 kg uses about 250 ml of oxygen per minute and 200 ml of CO_2 is produced.

Respiratory exchange ratio (RER, sometimes abbreviated R) is the ratio of the volume of CO_2 to O_2 exchanged across the lungs per minute. At rest, it is normally $200 / 250 = 0.8$. Respiratory exchange ratio reflects the average respiratory quotient (RQ) when gas exchange across lungs is normal.

RQ is different for different energy substrates.

Carbohydrate	1
Protein	0.8
Fat	0.7
Average RQ on a mixed diet	0.8

Average RQ depends upon the metabolic state as well.

What factors determine the tension of oxygen in alveolar gas? This is summarized by the alveolar gas equation:

Alveolar oxygen tension PA_{O2}
$$= [(P_B - P_{H20}) \times Fi_{O2}] - [(PA_{C02})/R]$$

P_B is barometric pressure (760 mm Hg at mean sea level);
P_{H20} is the pressure of water vapor at body temperature (it is 47 mm Hg);
FiO_2 is the percentage of oxygen in inspired air; and P_ACO_2 is the CO_2 tension in alveolar gas (normally about 40 mm Hg). When ventilation-perfusion balance is optimal, it is equal to $PaCO_2$ because CO_2 is highly soluble and readily equilibrates across the alveolocapillary membrane, and $PaCO_2$ can be substituted for for $PACO_2$. RER (or R) may be assumed to be 0.8.

Substituting values for someone breathing room air at mean sea level, we get,
$P_{AO2} = [(760-47) \times 0.21] - [40/0.8]$
$\quad = 150-50 = 100$ mm Hg

The alveolar gas equation is used to calculate the expected alveolar PO_2. **The alveolar-arterial oxygen gradient normally is less than 10 mm Hg.**

One can this calculate the expected PaO_2 in various conditions and compare it to the actual PaO_2 and assess gas exchange in various conditions.

Diffusion capacity of the lungs: *The "single breath technique":* The subject inhales a mixture containing 0.01% CO.
Diffusion rate $J = (P_ACO - PcCO) \times DA/x$
In a nonsmoker, $PcCO = 0$ mm Hg and P_ACO is constant.

Diffusion capacity is defined as DA/x
Normally, diffusion capacity of lungs for CO = 25 ml/min/mm Hg. The value for oxygen is similar. Since CO exchange is diffusion limited, it is used for assessing diffusion capacity of lungs.

The oxygen cascade: Factors that affect oxygen delivery to the tissues include the following (the *oxygen cascade*):
• Alveolar ventilation
• Pulmonary blood flow
• Ventilation / perfusion balance
• Diffusion capacity of lungs for oxygen
• Cardiac output
• Hb concentration of arterial blood
• Affinity of Hb for oxygen
• Blood flow to each tissue

Questions:
Instructions: **Below, there are questions every now and then that have multiple correct answers. This may be apparent from the phrasing of the question. Read all options and choose all correct answers.**

1. In a healthy individual breathing spontaneously, which of the following pressures is positive with reference to atmospheric pressure?
A. Alveolar pressure during inspiration
B. Alveolar pressure during expiration
C. Intrapleural pressure during inspiration
D. Intrapleural pressure during expiration

2. The maximum amount of gas that can be exhaled after a full inspiration is called:
A. expiratory reserve volume
B. vital capacity
C. total lung capacity
D. functional residual capacity

3. The largest volume of gas that can be moved into and out of the lungs in 1 minute by voluntary effort is called:
A. respiratory minute volume
B. minute ventilation
C. maximal voluntary ventilation
D. vital capacity

4. Which muscle does **not** contract during forced expiration?

A. Internal intercostals
B. External intercostals
C. Transversus abdominus
D. Rectus abdominis

5. In a healthy individual with a total lung volume of 6 liters, the amount of oxygen present in the lungs at the end of a tidal expiration is about:
A. 100 ml
B. 210 ml
C. 400 ml
D. 1000 ml
E. 2300 ml

6. During mouth-to-mouth resuscitation, what is the oxygen concentration of the resuscitating gas mixture?
A. 16%
B. 21%
C. 28%
D. 35%

7. Which of the following **cannot** be determined by spirometry?
A. Functional residual capacity
B. Residual volume
C. Total lung capacity
D. Vital capacity
E. Inspiratory capacity
F. Expiratory reserve volume

8. Functional residual capacity can be determined using:
A. routine spirometry
B. computerized spirometry
C. helium dilution method
D. whole body plethysmography

9. A person breathes into and from a spirometer (volume 12 liters) containing 10% helium gas mixture. After equilibration, helium concentration of expired gas was found to be 6.7%. His vital capacity is 4.2 liters. What is his residual volume?
A. 1000 ml
B. 1200 ml
C. 1500 ml
D. 1800 ml

10. In volume constant, whole body plethysmography, which of the following happens during a deep inspiration?
A. Box pressure remains constant
B. Box pressure increases
C. Box pressure decreases

11. For a respiratory minute volume of 6 liters, which of the following combinations of breathing rate and tidal volumes allows for maximum alveolar ventilation in a healthy individual?
A. 10 breaths per minute; and 600 ml
B. 15 breaths per minute; and 400 ml
C. 20 breaths per minute; and 300 ml
D. 30 breaths per minute; and 200 ml

12. Anatomic dead space is determined using:
A. whole body plethysmography
B. spirometry
C. single-breath nitrogen curve
D. single-breath carbon monoxide method

13. Physiologic dead space ventilation is decreased in / by:
A. the upright position compared to supine position
B. positive pressure ventilation
C. neck flexion
D. emphysema

14. Which of the following is **not** required to calculate total dead space using Bohr's equation?
A. End-tidal CO_2
B. PaO_2
C. $PaCO_2$
D. Tidal volume

15. During a tidal inspiration, air flow velocity is **least** in:
A. nasopharynx
B. trachea
C. major bronchi
D. bronchioles

16. The major area of airway resistance during breathing is located in:
A. oropharynx
B. trachea and large bronchi
C. intermediate-sized bronchi
D. bronchioles < 2 mm in diameter

17. If the PO_2 of blood in the pulmonary capillaries is 100 mm Hg and it is 98 mm Hg in the left ventricle, which of the following is most likely to account for this?
A. Some bronchial venous blood drains into pulmonary veins.
B. Some return from the coronary veins occurs into the chambers of the left side of the heart.
C. Pulmonary arteriovenous anastomoses
D. Patent foramen ovale

18. In the adult, which of the following is **most different** between the systemic and pulmonary circulations?
A. Volume of blood flowing through it
B. Stroke volume
C. Capillary hydrostatic pressure
D. Oncotic pressure

19. The pattern of ventilation in lungs is assessed by:
A. injection of radioactive xenon
B. inhalation of radioactive xenon
C. angiography
D. inhalation of carbon monoxide

20. Intrapleural pressure is normally negative **because:**
A. intrapulmonary pressure is always negative
B. chest wall and lungs recoil in opposite directions at functional residual capacity
C. surfactant prevents lung collapse
D. transpulmonary pressure determines the negativity

21. Which of the following is true at functional residual capacity (relaxation volume)?
A. Intrapulmonary pressure = atmospheric pressure
B. Intrapleural pressure > atmospheric pressure
C. Intrapulmonary pressure = intrapleural pressure
D. Transrespiratory pressure is positive.

22. Intrapleural pressure is positive during:
A. deep inspiration
B. tidal expiration
C. forced expiration
D. tidal inspiration

23. Lung compliance is increased in:
A. pulmonary emphysema
B. pulmonary fibrosis
C. surfactant deficiency
D. acute pulmonary edema

24. The major constituent of surfactant is:
A. neutral lipid
B. dipalmitoyl phosphatidyl choline
C. phosphatidylglycerol
D. surfactant proteins A & D

25. Alveolar surfactant:
A. reduces surface tension of alveoli
B. helps prevent alveolar collapse
C. reduces movement of fluid from pulmonaru capillaries into interstitium

26. Which of the following produce bronchodilation?
A. Vasoactive intestinal polypeptide
B. Epinephrine
C. Leukotriene C4
D. Platelet activating factor

27. Dilation of bronchial smooth muscle is mediated by activation of:
A. α_1 receptors
B. α_2 receptors
C. M_2 receptors
D. β_2 adrenoceptors

28. Which of the following produces bronchoconstriction?
A. VIP
B. Platelet activating factor
C. Leukotriene B_4
D. Epinephrine

29. Activation of muscarinic cholinergic receptors in bronchial smooth muscle leads to:
A. activation of adenylate cyclase
B. activation of phosphatidylinositol biphosphate hydrolysis to IP_3 and DAG
C. decrease in intracellular calcium
D. activation of protein kinase A

30. Which of the following is a specific index of airways resistance?
A. PEFR
B. Vital capacity
C. FEV_1/FVC
D. Minute ventilation

31. The **most sensitive** index of small airways resistance in a patient with bronchial asthma is:
A. vital capacity
B. FEV_1
C. FEV_1/FVC
D. Peak expiratory flow rate
E. Maximum mid-expiratory flow rate

32. In advanced emphysema:
A. VC is decreased
B. RV is increased
C. FRC is increased
D. TLC is increased

33. Breathing in individuals with restrictive lung disease is typically:
A. slow and deep
B. slow and shallow
C. rapid and deep
D. rapid and shallow

34. Which of the following statements is **incorrect?**
A. In the upright position, ventilation is greater at lung bases than the apex.
B. In the upright position, lower lung zones are more compliant compared to upper lung zones.
C. In the upright position, blood flow is greater at the lung bases than at the apices.
D. In the upright position, V/Q is normally highest in the lung apices.
E. Positive intrapleural pressures during forced expiration prevent airways from closing.

35. Despite a three to four fold increase in cardiac output, mean pulmonary artery pressure was observed to increase only by 20% during dynamic exercise. This is **most likely** due to:
A. recruitment of collapsed pulmonary capillaries
B. increase in left atrial pressure
C. increase in sympathetic outflow
D. increase in heart rate

E. increase in pulmonary vascular resistance

36. When the concentration of plasma proteins is normal, cardiogenic pulmonary edema occurs when pulmonary capillary pressure exceeds:
A. 10 mm Hg
B. 15 mm Hg
C. 20 mm Hg
D. 25 mm Hg

37. What is the effect of alveolar hypoxia on pulmonary vascular resistance?

38. Pulmonary vascular resistance is **lowest** when lung volume is:
A. total lung capacity
B. residual volume
C. functional residual capacity

39. Alveolar oxygen tension (P_AO_2) is influenced by:
A. barometric pressure
B. fraction of oxygen in inspired air (FiO_2)
C. P_ACO_2
D. respiratory exchange ratio (R)

40. Arterial blood gas analysis of a 5-year-old child at sea level gives the following results: pH 7.41, PaO_2 100 mmHg, and $PaCO_2$ 40mm Hg. The child is being mechanically ventilated with 80% oxygen. What is the (A-a) PO_2?
A. 420 mm Hg
B. 470 mm Hg
C. 520 mm Hg
D. 570 mm Hg

41. An 8-year-old girl is being treated with mechanical ventilation and other disease-specific therapy for acute respiratory distress syndrome. She is being administered 60% oxygen. Her $PaCO_2$ and PaO_2 were found to be 20 and 100 mm Hg respectively. Which of the following statements is correct?
A. Gas exchange in the lungs is normal.
B. There is a defect in pulmonary gas exchange.
C. She has alkalosis.
D. Her oxygen carrying capacity is at least 20 ml per dL of blood.

42. Inhaled particles of which size generally reach the alveoli?
A. 50-100 microns
B. 10-20 microns
C. 5-10 microns
D. < 2 microns

43. Which of the following substances is **activated** to a potent vasoconstrictor primarily during its passage through the lungs?
A. Angiotensin I
B. Prostaglandin I
C. Histamine
D. Serotonin
E. Norepinephrine

44. What is the maximum amount of oxygen a gram of Hb A can bind?
A. 1 ml
B. 1.34 ml
C. 15 ml
D. 20 ml

45. The concentration of O_2 in blood was calculated to be 0.0025 ml/ml of blood in a person breathing room air at mean sea level. The approximate oxygen tension of arterial blood is:
A. 50 mm Hg
B. 60 mm Hg
C. 70 mm Hg
D. 80 mm Hg

46. Each molecule of hemoglobin can bind a maximum of 4 molecules of oxygen.

47. Each molecule of hemoglobin can binds a maximum of 1 molecule of 2,3-BPG.

48. The P_{50} of hemoglobin is the partial pressure of oxygen at which hemoglobin is 50% saturated with oxygen.

49. The P_{50} of hemoglobin A is 26 mm Hg.

50. Arterial blood contains more oxygen than carbon dioxide.

51. Venous blood is normally 40% saturated with oxygen.

52. If blood Hb is 10 g/dL, PaO_2 is 100 mm Hg, and hemoglobin is 50% saturated with oxygen, the volume of oxygen contained in 100 ml of blood is approximately:
A. 5.6 ml
B. 6.7 ml
C. 9.5 ml
D. 19.5 ml

53. The sigmoid shape of the oxygen-hemoglobin dissociation curve is due to:
A. allosteric effects
B. steric effects of oxygen binding on the configuration of Hb
C. the effects of 2,3–BPG on oxygen affinity of Hb

54. What is the effect of 2, 3 BPG on the affinity of Hb for oxygen?
A. Binding of 2, 3 BPG to Hb increases the affinity of Hb for oxygen
B. Binding of 2, 3 BPG to Hb decreases the affinity of Hb for oxygen

55. Which of the following has the highest P_{50}?
A. Myoglobin
B. Hb F
C. Hb A

56. The normal value of P_{50} on the oxyhemoglobin dissociation curve in an adult is:
A. 1.8 kPa
B. 2.7 kPa
C. 3.6 kPa
D. 4.5 kPa

57. Which of the following shifts the oxyhemoglobin dissociation curve to the right?
A. CO_2
B. 2, 3-BPG
C. Increase in tissue temperature
D. Decrease in tissue pH

58. The decrease in oxygen affinity of Hb when the pH of blood in tissues falls is:
A. Bohr effect
B. Haldane effect
C. Hawthorne effect
D. Hamburger effect

59. Which of the following reduces synthesis of 2,3-BPG in red blood cells?
A. Acidosis in red blood cells
B. Anemia
C. Exercise
D. Ascent to high altitude
E. Thyroid hormones
F. Androgens
G. Growth hormone

60. Which of the following shifts the oxyhemoglobin dissociation curve to the left?
A. CO
B. Increase in 2,3 BPG in RBC
C. Increase in tissue temperature
D. Decrease in tissue pH

61. The amount of oxygen dissolved in plasma relates most closely with:
A. FiO_2
B. PAO_2
C. PaO_2
D. Blood [Hb]

62. HCO_3 cannot buffer protons formed from:
A. lactic acid
B. sulfuric acid
C. carbonic acid

63. The major buffer of carbondioxide in blood is:
A. bicarbonate
B. albumin
C. hemoglobin

64. CO_2 is chiefly transported in blood:
A. as bicarbonate
B. bound to hemoglobin
C. as carbaminohemoglobin
D. as carboxyhemoglobin
E. in combination with plasma proteins

65. The hematocrit of venous blood is slightly greater than that of arterial blood **because:**
A. the pH of venous blood is lower
B. the addition of CO_2 increases osmoles in RBCs in venous blood
C. the exit of bicarbonate from RBCs increases water content of RBCs
D. the chloride-bicarbonate exchanger is electroneutral

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66. Binding of oxygen to hemoglobin reduces its affinity for carbondioxide. This is the:
A. Bohr effect
B. Haldane effect
C. Hawthorne effect
D. Hamburger effect

67. The neurons pacing spontaneous breathing are located in:
A. pneumotaxic center
B. apneustic center
C. pre-Bottzinger complex
D. dorsal motor nucleus of vagus

68. What is/are the consequence(s) of a selective lesion of the pneumotaxic center?
A. Respiratory frequency increases
B. Tidal volume decreases
C. Respiration becomes slower
D. Tidal volume becomes greater
E. Prolonged inspiratory spasms

69. Apneusis occurs typically after:
A. damage to phrenic motor neurons
B. damage to pneumotaxic center
C. lesions of pneumotaxic center and vagotomy
D. denervation of peripheral chemoreceptors

70. Normally, the major stimulus for spontaneous respiration is:
A. CO_2
B. O_2
C. lactate
D. HCO_3

71. Medullary (central) chemoreceptors are chiefly stimulated by:
A. an increase in $[H^+]$ of brain interstitial fluid
B. a fall in PaO_2
C. a decrease in $PaCO_2$
D. all of the above

72. When someone inhales a gas mixture consisting of 10% CO_2 for 2 minutes, which of the following is **least likely?**
A. $PaCO_2$ remains at 40 mm Hg
B. Respiratory minute volume increases
C. Alveolar PO_2 decreases
D. pH of brain interstitial fluid drops

73. Following removal of both carotid bodies:
A. ventilatory response to hypoxia is increased
B. ventilatory response to CO_2 is increased
C. breath holding time is increased

74. An increase in the duration of expiration produced by lung inflation is called (due to):
A. Hering-Breuer inflation reflex
B. Hering-Breuer deflation reflex
C. pulmonary chemoreflex
D. Bezold-Jarisch reflex

75. If inflation of the lungs induces further inflation, it is called:
A. Hering-Breuer inflation reflex
B. Hering-Breuer deflation reflex
C. Head's paradoxical reflex
D. J-reflex

76. J receptors are located in:
A. pulmonary interstitium
B. alveoli
C. bronchial mucosa
D. roof of the fourth ventricle

77. Stimulation of J receptors results in:
A. apnea
B. tachypnea
C. hyperpnea
D. apnea followed by tachypnea
E. bradycardia and hypotension

78. Which of the following structures or mechanisms is / are **least important** in the regulation of breathing at rest in humans?
A. Medullary chemoreceptors
B. Carotid and aortic bodies
C. Hering-Breuer reflexes

79. Which of the following statements regarding Cheyne-Stokes respiration are **correct?**
A. It is characterized by periods of hyperpnea punctuated by apnea.
B. It is attributed to increased sensitivity of the respiratory center to CO_2.
C. It may occur if lung-to-brain circulation time is prolonged.
D. It may occur in severe congestive heart failure.

80. Regarding physiologic changes during moderate isotonic exercise in a healthy young adult, which of the following are true and which are false?

1. PaO_2 declines
2. $PaCO_2$ increases
3. pH of arterial blood decreases eventually during intense exercise
4. Whole body arteriovenous oxygen concentration difference increases.
5. Saturation of mixed venous blood with O_2 increases.
6. Plasma $[K^+]$ increases
7. The impulse rate from carotid bodies increases.
8. During maximal exercise, O_2 consumption may reach up to 4 L /min, about 16 times basal oxygen consumption.
9. VO_2 max (maximum oxygen consumption during intense exercise) is increased by training.
10. Heart rate may remain elevated for as long as 1 hour after severe exercise.

81. The hematocrit in a healthy 36-year-old male residing at an altitude of 3000 m for the past 20 years is 60. The **most likely** cause of the high hematocrit is:
A. chronic obstructive pulmonary disease
B. contraction of plasma volume
C. high-altitude hypoxia
D. primary proliferative polycythemia

82. Life is impossible without pressurization at an altitude greater than:
A. 12000 m
B. 14000 m
C. 17000 m
D. 19000 m

83. PaO_2 is / may be normal in tissue hypoxia due to:
A. hypoventilation
B. decompression at high altitude
C. severe circulatory shock
D. a reduction in diffusion capacity of lungs
E. anemia
F. carbon monoxide poisoning
G. cyanide poisoning

84. *Choose all correct answers.* Severe hypoxia:
A. leads to accumulation of lactate ions in tissues
B. stimulates the sympathetic nervous system
C. decreases cerebral vascular resistance
D. induces erythropoietin secretion
E. increases synthesis of 2,3-BPG
F. increases P_{50} of Hb

85. Administration of O_2 rich gas mixtures improves tissue oxygenation most in:
A. hypoxic hypoxia
B. anemic hypoxia
C. hypokinetic hypoxia
D. histotoxic hypoxia

86. Which one of the following has been recently postulated to function as a sensor of oxygen levels and a facilitator of oxygen transport in the brain?
A. Myoglobin
B. Neuroglobin
C. Nitric oxide
D. Cytochrome oxidase c

87. Which of the following occurs as a consequence of increased barometric pressure?
A. 'Rapture of the deep'
B. Black out
C. Bends
D. Air embolism

88. Deep sea divers breathing compressed air have been known to offer their mouths to fish! This is because, at high ambient pressures:
A. nitrogen solubility in blood decreases
B. oxygen toxicity is likely
C. nitrogen impairs intellectual functions
D. work of breathing increases

89. Which of the following is used during deep sea diving?
A. Compressed room air
B. 100% oxygen
C. A helium–oxygen mixture
D. 50% N_2 and 50% oxygen

90. In which of the following situations does decompression sickness **not** occur?
A. During ascent in an unpressurized cabin of an airplane
B. At a depth of 100 ft in the ocean

C. During rapid ascent from a deep-sea dive

91. Forced hyperventilation to exhaustion may result in:
A. a decrease in serum ionized calcium
B. an increase in plasma protein level
C. an increase in blood pH

92. Hypocapnia is usually due to:
A. hypoxemia
B. alkalosis
C. decreased CO_2 production
D. alveolar hyperventilation

93. Which of the following data suggests type II respiratory failure? (pH, $PaCO_2$ and plasma [HCO_3] given below in that order).
A. 7.4, 60 mm Hg, 30 mmol/L
B. 7.2, 80 mm Hg, 30 mmol/L
C. 7.33, 46 mm Hg, 20 mmol/L

94. Caution needs to be exercised in administering O_2 to patients with:
A. acute respiratory distress syndrome
B. metabolic acidosis
C. type I respiratory failure
D. type II respiratory failure

95. Which of the following combinations of arterial blood gas results is **most likely** in a normal person after a month's residence at 4000-meter altitude? Arterial pH, $PaCO_2$ and HCO3 (mmol/L) respectively would be:
A. 7.36, 36 mm Hg, 30
B. 7.4. 40 mmHg, 24
C. 7.46, 26 mm Hg, 19
D. 7.6, 20 mm Hg, 40

96. The arterial blood gas values, pH 7.58, PCO_2 23 mm Hg, PO_2 300 mm Hg and oxygen saturation of hemoglobin 60% are **most consistent** with a diagnosis of:
A. carbon monoxide poisoning
B. ventilatory (type 2 respiratory) failure
C. voluntary hyperventilation
D. methyl alcohol poisoning

97. Which of the following conditions leads to tissue hypoxia without an alteration of oxygen content of blood?

A. Carbon monoxide poisoning
B. Methemoglobinemia
C. Cyanide poisoning
D. Respiratory acidosis

98. What is the treatment of choice for air embolism?
A. Continuous positive airway pressure
B. Gradual decompression
C. Hyperbaric oxygenation
D. Positive pressure ventilation

99. If 100% oxygen is administered at 4 atmospheres, how much oxygen would be expected to transported in 100 ml of plasma?
A. 0.3 ml
B. 3 ml
C. 6 ml
D. 9 ml

100. Hyperbaric oxygen therapy is useful in the management of:
A. cyanide poisoning
B. carbon monoxide poisoning
C. diabetic leg ulcers
D. gas gangrene
E. decompression sickness

Answers:Pulmonary Physiology

1B	2B	3C	4B	5C
6A	7ABC	8CD	9D	10B
11A	12C	13C	14B	15D
16C	17AB	18C	19B	20B
21A	22C	23A	24B	25ABC
26AB	27D	28BC	29B	30C
31E	32all	33D	34E	35A
36D	37	38C	39all	40A
41B	42D	43A	44B	45D
46T	47T	48T	49T	50F
51F	52B	53B	54B	55C
56C	57all	58A	59A	60A
61C	62C	63C	64A	65B
66B	67A	68CD	69C	70A
71A	72A	73C	74A	75C
76A	77DE	78C	79all	80
81C	82B	83EFG	84all	85A
86B	87A	88C	89C	90B
91AC	92D	93B	94D	95C
96A	97C	98C	99D	100all

80. Physiologic changes during exercise:

1F	2F	3T	4T	5F
6T	7T	8T	9T	10T

Answer Explanations:

1. During spontaneous inspiration, intrapleural pressure becomes negative as a result of contraction of the diaphragm, and this is transmitted to alveoli. However, spontaneous expiration is due to elastic recoil of alveoli – so the alveolar pressure becomes slightly positive during expiration, and pleural pressure lags changes in alveolar pressure but remains negative. Ganong, 2012, p. 628, Fig 34-7.

5. Since the question is about a healthy individual with a TLC of 6 liters, we can assume FRC to be about 2300 ml. Because alveolar oxygen is diluted with CO_2, the fraction of oxygen in alveolar gas is only about 16%. Thus, the amount of oxygen present in lungs at the end of a tidal expiration = $(16 / 100) \times 2300 = 370$ ml. So 400 ml is the best answer.

7. Residual volume and anything that depends on RV cannot be measured by spirometry.

9. The helium-dilution method is based on the indicator dilution principle. Helium is used as the indicator it has a very low molar mass (low density), that it does not dissolve in blood when it is inhaled at 1 atmosphere. Initially, the helium gas is present only in the spirometer. The person breathes from as well as into the spirometer. ***The circuit is closed.*** After a few breaths, the helium concentration in the spirometer will reduce because it would have also got diluted in lung volume.

Initially,
C1: Helium concentration in spirometer = 10%
V1: Spirometer volume = 12 liters
C2: Helium concentration in spirometer (= lungs) = 6.7%
V2: Volume of distribution is now total lung capacity + spirometer volume.
Very little helium actually dissolves in blood. So it can be neglected.
Applying law of conservation of mass,
C1V1 = C2 (V1+V2)

Substituting, we get,
$10 \times 12 = 6.7 (12 + TLC)$
TLC = $[10 \times 12 / 6.7]-12 = 18-12 = 6L$
VC = 4.2 L
So RV = 6-4.2 = 1.8 L = 1800 ml.

10. Whole body plethysmography is based on Boyle's law which states that for a fixed amount of gas in a closed compartment the relative changes in the compartment's volume are always equal in magnitude but opposite in sign to the relative changes in pressure. Changes in lung volume can be inferred from changes in box pressure. The method is helpful to measure FRC as well as airways resistance. This link has a 2 min video clip that shows how the test is performed:
http://www.artp.org.uk/en/patient/lung-function-tests/lung-volumes.cfm The subject sits in a sealed box with rigid walls, and therefore, any change in lung volume must be equivalent to an opposite change in the free volume of the box outside the body, independent of whether pressure equilibration has been achieved or not. Box pressure is measured by a pressure transducer connected to the box. Body plethysmography – its principles and clinical use. Criee et al. *Respiratory Medicine* (2011) 105, e959-971.

11. Remember the dead space is ventilated with each breath. If dead space volume is 150 ml, the minute ventilation with 10 breaths and a tidal volume of 600 ml is 4.5 liters whereas it is only 1.5 liters with a respiratory rate of 30 breaths per minute and a tidal volume of 200 ml.

13. Extension of the neck, positive pressure ventilation, and emphysema increase ventilation of dead space. In the case of positive pressure ventilation, total dead space increases depending on:
- the volume of the tubing used;
- regional differences in lung compliance in patients with lung disease

14. Bohr's equation for determining total dead space: $P_ECO_2 \times V_T = PaCO_2 (V_T – V_D)$
If $P_ECO_2 = 28$ mm Hg, $PaCO_2 = 40$ mm Hg, and $V_T = 500$ ml, then, dead space = 150 ml

End-tidal carbondioxide is measured by capnometry. Note that $PaCO_2$ represents gas equilibrated with perfused alveoli. If there is significant V/Q mismatch, $PaCO_2$ will be higher than P_ACO_2. V_D is an index of dead space ventilation; V_D/V_T is used as yet another index of dead space ventilation.

15. It is least in bronchioles because the total flow through bronchioles per breath is the same as that through the trachea. In a continuous system of tubes with a constant flow, the product of velocity of flow and total cross-sectional area is constant.

16. This is because of the high airflow velocity in these segments. Bronchioles less than 2 mm in diameter normally represent less than 10% of total airway resistance. (NMS Physiology, Bullock et al, 2001, p. 282)

18. Systemic capillary hydrostatic pressure is about 40 mm Hg at the level of the heart and pulmonary capillary hydrostatic pressure is about 10 mm Hg.

20. At functional residual capacity, lungs and the chest wall recoil in opposite directions causing intrapleural (intrathoracic) pressure to be negative.

21. When intrapulmonary pressure = atmospheric pressure, there is no air flow. Ganong, 2012, p. 630-1, Fig 34-10.

22. Voluntary contraction of accessory muscles of expiration generates positive intrapleural pressures during forced expiration.

24. Dipalmitoyl phosphatidyl choline constitutes about 60% of surfactant. Surfactant is produced by type II alveolar epithelial cells. Surfactant synthesis is accelerated by glucocorticoids. Ganong, 2005, p. 656, Table 34-2.

26. VIP is released by nonadrenergic noncholinergic neurons. VIP relaxes bronchial smooth muscle. VIP deficiency has been implicated in asthma.

30-31. See discussion on p. 108.

34. Option E is incorrect - positive intrapleural pressures during forced expiration tend to cause compression of small bronchi (dynamic airway compression).

36. At rest, systolic pulmonary artery pressure is about 25 mm Hg, diastolic pulmonary artery pressure averages 10 mm Hg, mean pulmonary artery pressure is about 15 mm Hg, and pulmonary capillary pressure averages about 10 mm Hg. Clinically, it is considered elevated when PCWP exceeds 18 mm Hg. The osmotic pressure of plasma proteins is normally about 25 mmHg, and so when capillary hydrostatic pressure exceeds 25 mmHg, pulmonary edema may result.

37. Block ventilation to a lung zone
↓
Perfusion of that lung zone decreases

Hypoxic pulmonary vasoconstriction serves to shunt blood to well ventilated lung zones and optimize oxygen uptake in the lungs. However, chronic hypoxia leads to a chronic increase in pulmonary vascular resistance and pulmonary hypertension.

38. At TLC, pulmonary capillaries surrounding the alveoli are compressed raising pulmonary vascular resistance (PVR). At residual volume, medium sized airways are compressed (and closed) by high intrathoracic (intrapleural) pressure. The extra-alveolar vessels that run along these airways are compressed by the high intrathoracic pressure as well. Relative to other lung volumes, PVR is lowest at FRC i.e., at the end of a tidal expiration.

40. Using the 'alveolar gas equation' we get, P_AO_2 = 520 mm Hg. Given, PaO_2 = 100 mm Hg Thus, D (A-a) O_2 = 420 mm Hg. This represents a considerable defect in gas exchange as normally the difference between alveolar and arterial oxygen tension is not greater than 10 mmHg. The teaching point here is that a PaO_2 of 100 mmHg is not necessarily reflective of gas exchange function of lungs as it is influenced by the oxygen concentration of inspired gas. Rather, (A-a) O_2 gradient is a measure of oxygen exchange

function of lungs in the absence of right to left shunts due to heart disease.

41. To assess pulmonary gas exchange, use the 'alveolar gas equation' and determine the oxygen tension of alveolar gas P_AO_2.
$P_AO_2 = [(P_B - P_{H20}) \times FiO_2] - [(P_ACO_2) / R]$.
Here $P_B = 760$ mm Hg, $P_{H20} = 47$ mm Hg,
$FiO_2 = 0.6$, $R = 0.8$].
Since $PaCO_2 = 20$ mm Hg, P_ACO_2 will be about the same, since CO_2 rapidly equilibrates across the alveolar capillaries.
Substituting and simplifying, we get:
Expected $P_AO_2 = 400$ mm Hg;
Expected $PaO_2 = 390$ mm Hg;
Actual $PaO_2 = 100$ mm Hg;
(A–a) O_2 difference = 290 mm Hg

This represents a considerable defect in gas exchange since alveolar–arterial O_2 gradient does not normally exceed 10 mm Hg. *Option C:* It is impossible to tell whether she has alkalosis because plasma pH is not known or can not be estimated unless we also know her serum bicarbonate. *Option D:* We cannot assess oxygen carrying capacity of blood not knowing what her blood Hb concentration is.

45. O_2 carrying capacity of blood:
0.003 ml O_2 per mm Hg O_2 tension per deciliter of blood
i.e., 3×10^{-3} ml O_2 per mm Hg O_2 tension per deciliter of blood
$= 3 \times 10^{-5}$ ml of O_2 per mm Hg O_2 tension per ml of blood
Here, O_2 carrying capacity = 0.0025 ml.
Oxygen tension should have been 2.5×10^{-3} divided by $3 \times 10^{-5} = 80$ mm Hg

50. 100 ml of blood contains about 45 ml of CO_2 when PCO_2 is 40 mm Hg however it contains only 20 ml of oxygen. CO_2 is much more soluble in plasma.

51. Venous blood is normally 75% saturated with oxygen. Its PO_2 is 40 mm Hg.

56. 1 atm = 760 mm Hg = 100 kPa; 7.6 mm Hg = 1 kPa

58. The presence of higher levels of CO_2 and H^+ in the capillaries of metabolically active tissue promotes the release of O_2 from hemoglobin. This is the Bohr effect.

59. Acidosis in red blood cells inhibits glycolysis and thereby reduces synthesis of 2,3 BPG.

60. CO is a competitive inhibitor of oxygen binding of hemoglobin. Exposure for 1 hour to a CO concentration of 0.1% in inspired air leads to the occupancy by CO of about 50% of heme sites in Hb, a proportion that is frequently fatal. Apart from being a competitive inhibitor of oxygen binding to Hb, CO also inhibits the dissociation of oxyhemoglobin (prevents unloading of oxygen at the tissues). That is, it shifts the ODC to the left.

62-64. When there is an increase in CO_2 production, the reaction equilibrium is as follows:
$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3$
The presence of carbonic anhydrase in RBCs accelerates this reaction. The protons formed from this reaction are buffered mainly by Hb and plasma proteins. The bicarbonate formed in RBC enters plasma and chloride enters RBCs in exchange for bicarbonate (chloride shift).

68. The pneumotaxic center in the pons may play a role in switching between inspiration and expiration. Prolonged inspiratory spasms that resemble breathholding (apneusis) occur when the vagi are also cut in addition to lesion of the pneumotaxic center. (Ganong, 2012, p. 658-9, incl. Fig 36-2).

69. The effect of afferent vagal input from stretch receptors in the lungs is to inhibit efferent discharge in phrenic nerve. Thus, after vagotomy alone, the depth of respiration is greater than normal.

71. CO_2 in plasma quickly equilibrates across the blood-brain barrier. In brain interstitial fluid, it is quickly hydrated to H_2CO_3. Carbonic acid is unstable and dissociates to H^+ and HCO_3. The protein content of brain interstitial fluid and CSF is extremely low that it cannot buffer H^+ formed from CO_2. Thus, H^+ in CSF stimulate medullary

chemoreceptor neurons which in turn drive respiratory neurons.

72. 10% CO_2 corresponds to a partial pressure of 76 mm Hg at mean sea level. Although the rise in P_ACO_2 and hence $PaCO_2$ stimulates breathing, the resulting hyperventilation cannot restore $PaCO_2$ to 40 mm Hg. Arterial PCO_2 will rise with symptoms that include headache, confusion and eventually coma. As alveolar PCO_2 increases, alveolar PO_2 decreases (*Option C* is true). (Ganong, 2012, p. 662.)

73. Ganong, 2012, p. 660-663

74-75. **Nonchemical influences on respiration**

Reflex	Stimulus	Response
Hering Breuer inflation reflex*	Lung inflation	Increase in the duration of expiration
Hering Breuer deflation reflex*	Lung deflation	Increase in the duration of inspiration
Head's paradoxical reflex$^\epsilon$	Lung inflation	Further inflation

*Hering Breuer reflexes are probably initiated by considerable changes in lung volume (deep inspiration or deep expiration).
$^\epsilon$ This reflex helps a newborn child inflate its liquid filled lungs.

78. Ganong, 2012, p. 664-5

79. Periodic breathing may also occur in uremia, brain stem disease, during sleep, and in normal individuals following a bout of voluntary hyperventilation.

80. $PaCO_2$ changes little because the increased production of CO_2 is also accompanied by an increase in alveolar ventilation. pH of arterial blood is initially maintained but eventually decreases and that is when one fatigues. Whole body arteriovenous O_2 difference increases because oxygen extraction by the systemic circulation increases and saturation of mized venous blood with oxygen SvO_2 decreases for the same reason. Plasma K increases because K is released from actively metabolizing skeletal muscle. The impulse rate from the carotid bodies

increases possibly because of an increase in body temperature, plasma [K], and [H] formed from lactic acid. Heart rate may remain elevated for as long as 1 hour after severe exercise because the increase in sympathetic nerve activity also persists. This is due to the oxygen debt incurred during exercise. Until this debt is cleared, minute ventilation and cardiac output are higher compared to preexercise levels.

82. At an altitude of 14000 meters, consciousness is lost despite administration of 100% oxygen. This is because the barometric pressure at this altitude is far too low to permit adequate oxygenation of arterial blood.

84. Cerebral blood flow is regulated by local metabolites and hypoxia causes cerebral vasodilation and thereby slightly increases cerebral blood flow. Similarly, hypercapnia produces cerebral vasodilation and an increase in cerebral blood flow.

85. The exception is hypoxic hypoxia due to right-to-left shunts due to heart disease.

87. If a diver breathes compressed air, the increased partial pressure of nitrogen can result in a constellation of neurological symptoms known as "rapture of the deep".

88. The euphoria is attributed to increased solubility of nitrogen in body fluids. This is why a helium-oxygen mixture is used and while increased solubility of helium is associated with impairment of manual dexterity, intellectual function is apparently not significantly impaired. (Ganong 2005, p. 694-5.)

90. At a depth of 100 ft in the ocean, barometric pressure is about 4 atmospheres, four times greater than at mean sea level. The problems that occur are therefore due to increased solubility of gases in blood and depend on the gas mixture used for breathing. You may want to remember this as 'compression sickness'. In contrast, decompression sickness (the exact opposite of compression sickness) occurs during rapid ascent following a deep-sea dive or when an airplane cabin loses pressure at high altitude. Gases

dissolved in body fluids come out of solution because of the reduction in ambient pressure, forming bubbles and blocking blood flow to tissues.

92. If minute ventilation reduces, then $PaCO_2$ increases (hypercapnia). Hypercapnia is a $PaCO_2$ > 45 mm Hg. Hypercapnia is almost always due to inadequate alveolar ventilation, although it can occur as a result of significant ventilation-perfusion mismatch. Conversely, hypocapnia ($PaCO_2$ < 35 mm Hg) is almost always due to hyperventilation, i.e. minute ventilation in excess of that required to maintain arterial plasma pH at 7.4.

94. In chronically hypercapnic patients, CO_2 depresses rather than stimulates respiration and respiration is driven by hypoxia. Administration of 100% oxygen may remove the hypoxic drive and breathing may stop. Such a patient will require mechanical ventilation to bring down CO_2 a level which would stimulate respiration.

95. Despite acclimatization, pH does not return to normal. In the steady state, there is mild respiratory alkalosis partially compensated by the kidneys.

96. The fact that oxygen saturation of Hb is as low as 60% although PaO_2 is as high as 300 mm Hg suggests a diagnosis of carbon monoxide poisoning.

97. *Option A:* Carbon monoxide poisoning reduces oxygen content of arterial blood by competing with oxygen to bind heme. *Option B:* Methemoglobin cannot transport oxygen. Less than 1% of Hb is in the Fe^{3+} state. Methemoglobin cannot also unload oxygen much like carboxyhemoglobin. Thus, there is also a leftward shift of the oxyhemoglobin dissociation curve. Taken together, the oxygen content of blood is reduced in methemoglobinemia and the oxygen unloading capacity of blood is reduced even more. *Option D:* Clinically, respiratory acidosis is invariably accompanied by arterial hypoxemia (type II respiratory failure). **Option C (correct):** However, in cyanide poisoning, oxygen content of blood is normal, yet

utilization of oxygen in the mitochondria is inhibited because cyanide inhibits cytochrome oxidase, the final donor of electrons to molecular oxygen.

98. By applying high pressure, solubility of gas (air emboli *in this question*) in plasma is increased. At a constant temperature, solubility of a gas in plasma is directly proportional to partial pressure of gas (Henry's law). Regarding *option B*, gradual ascent to surface following a deep sea dive is appropriate as a preventive measure.

99. O_2 solubility in plasma is limited, hence Hb required for oxygen transport.
O_2 solubility in plasma = 0.003 ml O_2/100 ml plasma/ mm Hg PO_2.
Greater the PaO_2, greater the dissolved oxygen (Henry's Law)
Expected PaO_2 using the alveolar gas equation:
$P_AO_2 = [(4 \times 760) - 47] \times 1 - (40/0.8)$
Expected PaO_2 is approximately 3000 mm Hg. Thus, about 9 ml of oxygen will be transported in 100 ml of plasma.

100. Hyperbaric oxygenation consists of administering 100% oxygen at pressures exceeding atmospheric (usually 2–4 atmospheres) for brief periods of time. This greatly increases arterial oxygen tension if pulmonary gas exchange is normal.

Option A: High concentrations of oxygen might serve to displace cyanide from cytochrome oxidase. *Option B:* In carbon monoxide poisoning, high concentrations of oxygen help overcome competitive inhibition by carbon monoxide. *Option C:* Diabetic leg ulcers due to obliterative peripheral vascular disease might benefit from an increase in the content of dissolved oxygen content of blood. *Option D:* In gas gangrene, the causative organisms are anerobic and may be killed by high oxygen concentration. *Option E:* In decompression sickness, the rationale is to "recompress" as well as "oxygenate" and this is achieved by hyperbaric oxygenation, and of course, this is followed by slow decompression.

RENAL AND ACID-BASE PHYSIOLOGY

This Chapter consists of 2 **Summaries.**
1. Anion gap
2. Disorders of micturition

Other points are noted as explanations under the appropriate questions.

These abbreviations are used in this chapter:
ADH – antidiuretic hormone
ANG II – angiotensin II
CCD – cortical collecting duct
MCD – medullary collecting duct
MD – macula densa
DCT – distal convoluted tubule
GFR – glomerular filtration rate
MI – medullary interstitium
PT – proximal tubule
PCT – proximal convoluted tubule
PST – proximal straight tubule
RBF – renal blood flow
RPF – renal plasma flow
TAL – thick ascending limb
TDL – thin descending limb
OMCD – outer medullary collecting duct
IMCD – inner medullary collecting duct
FENa – fractional excretion of sodium

1. Anion gap is calculated as:
$\{[Na^+] + [K^+]\} - \{[Cl^-] + [HCO_3^-]\}$

All of them are expressed in mmol/L. Calculated this way, the reference range is usually 8-16 mmol/L. Some authors omit $[K^+]$ from the above equation. That is OK, but if this is done, then the reference range changes to 8-12 mmol/L.

Here is an easy way to understand the anion gap:
- In plasma, the sum of charges of positive ions is equal to the sum of negative charges.
- Plasma is thus electroneutral
- Some ions in plasma are routinely measured *(measured ions)*
- Some are not *(unmeasured ions)*
- Na and K are measured cations.
- Chloride and HCO_3 are measured anions.
- Unmeasured cations incl. Ca and Mg

- Normally, the principal unmeasured anions in plasma are protein anions followed by phosphate, sulfate. But there may be an accumulation of other unmeasured anions such as lactate, oxalate, acetoacetate, beta-hydroxybutyrate in disease states.
- [Measured cations] – [measured anions] = [unmeasured anions] – [unmeasured cations]
- The concentration of unmeasured cations (Ca and Mg) is small (< 2 mmol/L) that it can be ignored.
- **In summary, for practical purposes, the anion gap reflects the concentration of unmeasured anions.**

When does anion gap increase and why?
In metabolic acidosis (for example, due to lactic acidosis), pH decreases. The excess H ions are buffered by HCO3. The concentration of lactate (an unmeasured anion) increases. Therefore, anion gap increases. An increase in anion gap reflects an increase in the concentration of one or more unmeasured anions in plasma. This happens in metabolic acidosis.

Anion gap may also be increased in metabolic alkalosis; one can plug some chloride, Na and bicarbonate values in and try. However, in clinical practice, the anion gap is used mainly in the differential diagnosis of metabolic acidosis.

Examples of high anion gap metabolic acidoses and the unmeasured anions:

Cause of metabolic acidosis	Unmeasured anion(s)
Lactic acidosis	Lactate
Ethylene glycol poisoning	Oxalate
Ketoacidosis	Acetoacetate, beta-hydroxybutyrate
Acute renal failure; end-stage renal disease	Multiple anions

2. Disorders of Micturition:
Urinary Frequency: > 8 voids per day (Cecil 24 e, p. 111)

Urinary incontinence: inability to voluntarily restrain bladder emptying;

Stress Incontinence (SI) – a significant increase in intra-abdominal pressure (called 'stress' here) triggers the emptying.

Urge Incontinence (UI) – the urge to micturate is perceived, but one is unable to voluntarily inhibit it at bladder volumes an age-matched normal individual can hold.

Some individuals have both SI and UI.

A weakness of the pelvic floor (in females) and the external urethral sphincter (in both males and females) due to any cause (example, denervation) is a basic abnormality underlying both SI and UI.

UI is a bit more problematic because **"detrusor instability"** (sometimes known as an **over-reactive bladder** is believed to additionally contribute (Cecil 24e, p. 110). The over-reactive bladder is often 'idiopathic' but may be due to an upper motor neuron type lesion (see under Chronic Spinal Cord Injury below). Note however that an over-reactive bladder is not necessarily one with good contractility; i.e. it may not empty completely. Detrusor hyperactivity may also be associated with a bladder calculus, urethral obstruction.

Overflow incontinence: A distended bladder contracts and empties in an individual with no voluntary control of micturition (see below).

Bladder function in the acute phase of spinal cord injury (spinal shock): There is abrupt loss of tonic facilitation of parasympathetic motor neurons from supraspinal influences. **Urinary retention** is due to lack of neural drive for detrusor contraction but is additionally likely to uninhibited contraction of the internal urethral sphincter**;** the bladder distends (overfills) and empties reflexly (at which the point the IUS relaxes), and no voluntary control is present **("overflow incontinence")**; nonetheless the contractions of the detrusor are not as forceful and emptying may be incomplete; with risk for UTI. Bladder catheterization is necessary.

Bladder function in chronic spinal cord injury:

Spinal reflexes below the level of the transection are **"released"** from the inhibitory influences of supraspinal centers.

The basic sacral reflex arc for micturition becomes hyperactive; i.e., the threshold for the micturition reflex is a lower bladder volume **(hyperactive voiding reflex)**. Marked by bladder wall hypertrophy; reduced bladder capacity; increased urinary frequency [called **Spastic Neurogenic Bladder].** Furthermore, neural influences on detrusor and the sphincter may not be coordinated in the absence of supraspinal influences (detrusor-sphincter dys-synergia).

Deafferentation: Sacral afferent roots sectioned experimentally; clinical equivalent – tabes dorsalis affecting sacral sensory roots. Here, the brain is slow to perceive bladder filling – therefore, the bladder in the long run becomes **thin walled, distended; it becomes hypotonic** because of loss of afferents in the sacral micturition reflex arc. Contractions of detrusor that occur are an intrinsic response of smooth muscle to stretch.

Denervation (deafferentation + injury to efferent nerves innervating the bladder) as with cauda equine tumors compressing on filum terminale. In this case, information about bladder distension does not promptly reach the CNS. Neither is the efferent nerve supply intact. Thus, the bladder is effectively "decentralized"

The bladder becomes flaccid **(flaccid, areflexic bladder).** The muscle becomes active gradually with contraction waves expelling dribbles of urine out of the urethra. Since the spinal reflex arc itself is interrupted, incontinence of the 'overflow type' occurs here.

Lesion of the parasagittal medial frontal micturition center, as can happen with parasagittal meningiomas, hydrocephalus, or with a stroke of the frontal cortex.

The **medial frontal micturition centers** in the cortex are presumably the origins of descending pathways that activates the voiding reflex.

With a lesion in this region, the voiding reflex per se is normal, but there is no voluntary control. The individual may or may not be aware of the incontinence; commonly called **"frontal-type incontinence"**

The term "neurogenic bladder" is a nonspecific term – it may refer to flaccid bladder, or a hyperreflexic bladder, and therefore it should be used only with further qualification.

References: Ganong's Review of Medical Physiology (2012); Cecil's Textbook of Medicine 24e (Ch 25 Incontinence)

Instructions: In this Section, occasionally there are questions with multiple correct answers. Read all options!

1. The 'gold standard' for estimation of glomerular filtration rate is the estimation of urinary clearance of:
A. inulin
B. creatinine
C. urea
D. mannitol
E. glucose
F. para-amino hippuric acid

2. In clinical practice, the urinary clearance of which substance is most frequently estimated as a surrogate of GFR?
A. Inulin
B. Creatinine
C. Urea
D. Mannitol

3. Which of the following substances should **not** be used to measure GFR?
A. Inulin
B. Creatinine
C. Iothalamate
D. Glucose
E. Phenol red

4. The term filtration fraction is used to refer to:
A. RPF / GFR
B. GFR / RPF
C. RPF × GFR

5. What fraction of renal plasma flow is normally filtered in the glomerular capillaries?
A. 0.1
B. 0.2
C. 0.3
D. 0.4

6. When mean arterial pressure is held constant, selective constriction of glomerular efferent arterioles:
A. increases GFR
B. decreases filtration fraction
C. decreases renal plasma flow

7. Mesangial cells are similar to:
A. pericytes
B. fibrocytes
C. mast cells
D. ependymal cells

8. In humans, what percentage of nephrons has long loops of Henle?
A. 5
B. 15
C. 25
D. 85

9. The macula densa is located in the:
A. juxtaglomerular cells
B. extraglomerular mesangium
C. beginning of distal tubule
D. peritubular capillaries

10. The kidneys do **not** synthesize or secrete:
A. calcitriol
B. rennin
C. erythropoietin
D. PGE_2

11. The brush border on the luminal membrane is most extensive in cells of the:
A. PCT
B. loop of Henle
C. DCT
D. collecting duct

12. Which of the following increases renal cortical blood flow?
A. Prostaglandin E_2
B. Norepinephrine

C. Angiotensin II
D. Vasopressin

13. In the kidneys, type I medullary interstitial cells secrete:
A. renin
B. PGE_2
C. aquaporins
D. aldosterone

14. The para-aminohippuric acid (PAH) clearance of a 56-year-old male with sustained elevations of blood urea nitrogen, creatinine and potassium was estimated to be 100 ml/min. His PCV is 20. Assuming renal extraction of PAH to be complete, his renal blood flow is approximately:
A. 25 ml/min
B. 125 ml/min
C. 250 ml/min
D. 600 ml/min

15. The renal plasma flow (RPF) of a patient was to be estimated through the measurement of para-amino hippuric acid (PAH) clearance. The technician observed the procedures correctly but due to an error in weighing inadvertently used thrice the recommended dose of PAH. The RPF estimated thus is likely to be:
A. falsely high
B. falsely low
C. high or low depending on GFR
D. correct and is unaffected by the overdose of PAH

16. If the glomerular capillary hydrostatic pressure, osmotic pressure of plasma proteins, hydrostatic pressure in the Bowman's space and oncotic pressure in the interstitium are respectively 40, 25, 5, and 0 mm Hg respectively, what is the net pressure driving filtration of fluid into the Bowman's space?
A. 10 mm Hg
B. 15 mm Hg
C. 20 mm Hg
D. 25 mm Hg

17. In an experimental animal with acutely induced bilateral obstruction of ureters, glomerular filtration rate declines within 30 min of ligation of ureters primarily due to a/an:
A. increase in filtration fraction

B. increase in renal plasma flow
C. increase in hydrostatic pressure in Bowman's space
D. decrease in glomerular capillary permeability

18. Which of the following substances is cleared the most by the kidneys?
A. Inulin
B. PAH
C. Creatinine
D. Urea

19. Which of the following substances normally has a "clearance ratio" of about 1.2?
A. Inulin
B. Creatinine
C. Urea
D. PAH

20. Which of the following substances has a clearance ratio close to 1?
A. Creatinine
B. Mannitol
C. Urea
D. Glucose

21. Arrange the following substances in the descending order of their clearance. [Cr: creatinine; PAH: para-aminohippuric acid]
A. PAH > Inulin > Urea > Cr > Glucose
B. Inulin > PAH > Cr > Urea > Glucose
C. PAH > Cr > Inulin > Urea > Glucose

22. The tubular transport maximum for glucose (Tmax for glucose) in a healthy young man is about:
A. 100 mg/min
B. 225 mg/min
C. 375 mg/min
D. 500 mg/min

23. If urine [Na] = 100 mM, plasma [Na] = 140 mM, urine [Cr] = 100 mg/dL, serum [Cr] = 1.4 mg/dL, and urine flow rate = 2 ml/min, then, fractional excretion of sodium (FE_{Na}) is approximately:
A. 0.1%
B. 0.5%
C. 1%
D. 2%

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24. In a healthy individual with a normal renal plasma flow, in which segment of the nephron would the concentration of PAH be the **least?**
A. Proximal convoluted tubule
B. Thin descending limb of loop of Henle
C. Thick ascending limb of loop of Henle
D. Cortical collecting duct

25. Autoregulation of GFR is achieved through changes in:
A. renal perfusion pressure
B. renal blood flow
C. glomerular afferent arteriolar resistance
D. glomerular efferent arteriolar resistance

26. In a healthy adult human with a resting BP averaging about 110/70 mm Hg who is not on any medication, the earliest MAP at which renal autoregulation of GFR is overwhelmed is when mean arterial pressure falls **below:**
A. 30 mm Hg
B. 50 mm Hg
C. 70 mm Hg
D. 90 mm Hg

27. In an individual with normal renal function but with fluctuations in glomerular filtration rate (GFR) of 10% around a mean GFR of 100 ml/min, fractional reabsorption of Na and Cl in which segment of the nephron is relatively constant?
A. Proximal tubule
B. Thick ascending limb of loop of Henle
C. Distal convoluted tubule
D. Cortical collecting duct

28. The rate-limiting step in the biosynthesis of angiotensin II is the secretion of:
A. renin
B. angiotensinogen
C. angiotensin I
D. angiotensin II

29. Renin in the circulation originates mainly from:
A. macula densa
B. juxtaglomerular cells
C. type I medullary interstitial cells
D. peritubular capillaries

30. The substrate for renin is:
A. angiotensinogen

B. angiotensin I
C. angiotensin II
D. bradykinin

31. Angiotensin converting enzyme is a / an:
A. dipeptidyl carboxypeptidase
B. aminopeptidase
C. aspartyl protease

32. Physiologically, important stimulators of aldosterone production by the zona glomerulosa cells include (*tick all that apply*):
A. a rise in plasma $[K^+]$
B. angiotensin II
C. angiotensin III

33. Several hormones regulate tubular reabsorption of water and electrolytes at different sites in the nephron. Which of the following combinations is/are **correct?**
A. Angiotensin II acts in the DCT
B. Aldosterone acts in the collecting ducts
C. ADH acts in the PT
D. ANP acts in the loop of Henle

34. The actions of aldosterone are antagonized by:
A. angiotensin III
B. arginine vasopressin (AVP)
C. ANP

35. Which hormone directly induces proton secretion by *alpha*-intercalated cells in the collecting ducts?
A. Aldosterone
B. Atrial natriuretic peptide
C. Vasopressin
D. Parathyroid hormone

36. *All about angiotensins:* Which of the following are true and which are false?
1. Angiotensin converting enzyme is a dipeptidyl carboxypeptidase.
2. ANG II is a much more potent vasopressor compared to norepinephrine.
3. ANG III is a more potent pressor than ANG II.
4. ANG II stimulates aldosterone release from adrenal cortex.
5. ANG II inhibits ADH release.
6. ANG II has a dipsogenic effect (i.e., induces hirst)
7. ANG II causes mesangial cells to contract.

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8. ANG II facilitates norepinephrine release from postganglionic sympathetic neurons.
9. ANG II has a greater constrictor effect upon glomerular afferent arterioles.
10. ANG II reduces renal plasma flow.
11. When GFR is reduced, ANG II's actions enable a decrease in filtration fraction.
12. ANG II increases Na and H_2O reabsorption by a direct action on PT.
13. ANG II increases Na and Cl reabsorption by the DCT.
14. ANG II increases Na reabsorption by P cells in the collecting duct.
15. ANG II directly stimulates potassium secretion by P cells in the collecting duct.
16. ANG II plays an important role in cardiac remodeling after a myocardial infarction.

37. Chronic licorice ingestion is characterized by:
A. low blood pressure
B. hyperkalemia
C. metabolic acidosis
D. a decrease in plasma renin activity

38. In the nephron, glucose reabsorption occurs mainly in the:
A. proximal tubule
B. loop of Henle
C. distal convoluted tubule
D. collecting duct

39. The following data were obtained on a patient: Creatinine clearance = 125 ml/min; plasma [glucose] = 400 mg/dL. If the tubular maximum for glucose were 350 mg/min, what would the glucose excretion rate be?
A. 50 mg/min
B. 100 mg/min
C. 150 mg/min
D. 200 mg/min

40. In the presence of vasopressin, most of the water filtered by the kidneys is reabsorbed in the:
A. proximal tubule
B. thin descending limb
C. thick ascending limb
D. collecting ducts

41. The tubular fluid at the end of the PT is _____ with respect to plasma

A. isotonic
B. hypotonic
C. hypertonic

42. Which is the 'concentrating segment' of the nephron?
A. Descending limb of loop of Henle
B. Thin ascending limb of loop of Henle
C. Thick ascending limb of loop of Henle
D. Collecting ducts

43. Which portion of the tubule is **least permeable** to water?
A. Proximal tubule
B. Thin descending limb of Henle's loop
C. Thick ascending limb of Henle's loop
D. Cortical collecting duct

44. Which is the fundamental mechanism generating hypertonicity in the medullary interstitium?
A. Active transport of NaCl in thick ascending limb
B. Action of ADH in the collecting ducts
C. Passive recirculation of NaCl in the medullary interstitium
D. Urea permeability of collecting ducts

45. Which of the following transport mechanisms in the macula densa allows it to sense Na and Cl concentrations in the tubular fluid that flows past this segment?
A. Apical chloride channels
B. 1Na-1K-2Cl transporter (NKCC2)
C. Na-Cl cotransporter
D. Na-H exchanger
E. ROMK exchanger

46. What does the macula densa sense?
A. Na concentration of fluid delivered to it
B. Cl concentration of the fluid delivered to it
C. Volume of fluid delivered to it

47. The 'diluting segment' of the nephron is:
A. proximal tubule
B. descending limb of loop of Henle
C. thick ascending limb of loop of Henle
D. cortical collecting duct

48. 'Free water' is formed mainly in the:

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A. descending limb of loop of Henle
B. thin ascending limb of loop of Henle
C. thick ascending limb of loop of Henle
D. collecting duct

49. What fraction of filtered water is reabsorbed in the loop of Henle?
A. 15%
B. 25%
C. 35%
D. 5%

50. What fraction of filtered Na is reabsorbed in the loop of Henle?
A. 15%
B. 25%
C. 35%
D. 5%

51. In the absence of medication or disease processes affecting transport in the nephron, fluid entering the early distal tubule is:
A. always isotonic
B. always hypotonic
C. always hypertonic
D. isotonic or hypotonic
E. hypertonic when urine is concentrated
F. hypotonic when urine is dilute

52. Principal cells (P cells) in the cortical collecting duct of the nephron are mainly involved in:
A. secretion of protons
B. potassium reabsorption
C. reabsorption of sodium and chloride
D. ADH-stimulated water reabsorption

53. The retention of 'free water' by ADH in the collecting ducts is mediated mainly by which aquaporin in the luminal membrane?
A. AQP-1
B. AQP-2
C. AQP-3
D. AQP-4

54. Vasa recta receive blood from:
A. afferent arterioles of cortical nephrons
B. afferent arterioles of juxtamedullary nephrons
C. efferent arterioles of cortical nephrons
D. efferent arterioles of juxtamedullary nephrons

55. Hypertonicity in the inner medulla is maintained because:
A. vasa recta receive 50% of renal blood flow
B. of the low blood flow rate through vasa recta
C. NaCl passively moves into the medullary interstitium from the thin ascending limb

56. The system for the formation of concentrated or dilute urine does **not** include the:
A. proximal convoluted tubule
B. loop of Henle
C. collecting ducts
D. vasa recta
E. medullary interstitium

57. Urea is reabsorbed from:
A. thick ascending limb of loop of Henle
B. distal convoluted tubule
C. cortical collecting ducts
D. inner medullary collecting ducts

58. The reabsorption of urea by the inner medullary collecting ducts is dependent on facilitation by:
A. angiotensin II
B. aldosterone
C. antidiuretic hormone
D. atrial natriuretic peptide

59. Which segment of the nephron is permeable to urea?
A. Descending limb of loop of Henle
B. Thin ascending limb of loop of Henle
C. Thick ascending limb of loop of Henle

60. In the inner medullary interstitium, which of the following contributes the most to osmolality?
A. NaCl
B. Urea

61. 'Free water' formation in the lumen of the nephron is essential for production of:
A. dilute urine
B. concentrated urine

62. The principal regulator of plasma osmolality is:
A. plasma [Na]
B. antidiuretic hormone
C. aldosterone

D. angiotensin II
E. renin

63. Plasma potassium concentration is **chiefly** regulated by:
A. aldosterone
B. vasopressin (ADH)
C. renin
D. ANP

64. Which ion is both secreted and absorbed by the nephron?
A. Na
B. K
C. Cl
D. Ca

65. Potassium secretion occurs mainly in:
A. PT
B. early distal tubule
C. late distal tubule
D. cortical collecting ducts
E. loop of Henle

66. In a euvolemic normotensive healthy adult with, ADH secretion is **most likely** to be stimulated by:
A. intake of 500 ml water
B. intake of 30 ml of 10% ethanol
C. 2.5 mg of enalapril
D. ingestion of a 400 g meal consisting exclusively of simple sugars

67. Which of the following inhibits ADH secretion?
A. Hyperosmolality
B. Exercise
C. Angiotensin II
D. Ethanol

68. Which of the following is consistent with hypotonic urine?
A. A high U_{osm} / P_{osm} ratio
B. A urinary pH of 7
C. Positive free water clearance
D. Urine specific gravity of 1015

69. In humans, when urine is maximally concentrated, the ratio of osmolality of urine to plasma is about:

A. 1.2
B. 2
C. 4.6
D. 7.5

70. The obligatory 24 hr urine volume to maintain solute homeostasis in a healthy adult male weighing 65 kg and consuming a balanced 2000 calorie diet is approximately
A. 100 ml
B. 500 ml
C. 1000 ml
D. 1500 ml

71. Water deprivation fails to produce an increase in urine osmolality in:
A. neurogenic diabetes insipidus
B. nephrogenic diabetes insipidus

72. When the osmolality of urine is 1400 mOsm/Kg H_2O, the greatest amount of water is reabsorbed in:
A. cortical collecting ducts
B. outer medullary collecting ducts
C. inner medullary collecting ducts
D. proximal tubule
E. descending thin limbs

73. In a healthy adult, the urge to void urine is first felt at a bladder volume of about:
A. 50 ml
B. 150 ml
C. 250 ml
D. 350 ml

74. In a healthy adult, the volume of urine in the bladder that initiates reflex contraction of the bladder is about:
A. 50–100 ml
B. 100–200 ml
C. 200–300 ml
D. 300–400 ml

75. What is the immediate effect of spinal cord transection on bladder function?
A. Urinary retention
B. Overflow incontinence
C. Anuria

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76. Which of the following is characterized by a hypercontractile, shrunken bladder, increased frequency of urination and incontinence?
A. Deafferented bladder
B. Denervated bladder
C. Spastic neurogenic bladder
D. Bladder in acute paraparesis

77. Which of the following is **not** a feature of tabes dorsalis?
A. Bladder wall hypertrophy
B. Distended bladder
C. Urinary retention
D. Incontinence

78. The most abundant buffer in proximal tubular fluid is:
A. bicarbonate
B. phosphate
C. ammonia

79. Normally, most of the filtered HCO_3 is reabsorbed from:
A. PT
B. distal tubule
C. cortical collecting duct
D. loop of Henle

80. In the nephron, the highest amount of H ions is secreted into tubular lumen in the:
A. PCT
B. DCT
C. collecting ducts
D. loop of Henle

81. The principal mechanism of H^+ secretion in the proximal convoluted tubule is via:
A. Na–H exchanger
B. H–ATPase
C. H–K ATPase
D. H–Ca exchanger

82. The principal site of ammoniagenesis in the nephron is:
A. PT
B. Loop of Henle
C. Early distal tubule
D. Late distal tubule
E. Outer medullary collecting duct

83. The principle site of acidification of tubular fluid is:
A. proximal convoluted tubule
B. loop of Henle
C. the *aldosterone sensitive distal nephron*
D. urinary bladder

84. The principal mechanism for acid secretion by type A intercalated cells in the nephron is:
A. H–ATPase
B. Na–H exchanger
C. H–Ca exchanger
D. H–K ATPase

85. Normally, in urine, most of the H^+ is tied up with:
A. bicarbonate
B. phosphate
C. ammonia

86. Urinary ratio of NH_4^+ to titratable acid ranges from:
A. 1-2.5
B. 2-5
C. 0.1-0.5
D. 5-7

87. Normally, most of the *titratable acidity* of urine is attributable to acid buffered by:
A. bicarbonate
B. phosphate
C. ammonia
D. uric acid
E. creatinine

88. Type B intercalated cells in the collecting duct are concerned with:
A. secretion of protons
B. controlled bicarbonate secretion
C. ADH-stimulated water reabsorption
D. Na reabsorption

89. In arterial blood gas analysis, which of the following is calculated?
A. Arterial pH
B. Plasma bicarbonate
C. $PaCO_2$
D. PaO_2

90. In a healthy human with an arterial plasma pH of 7.38, and normal levels of electrolytes, the *anion gap* reflects the plasma concentration of:
A. HCO_3
B. chloride
C. protein anions

91. In a normal adult human on an average diet, and with an arterial plasma pH of 7.37, which of the following is least likely to be present in urine obtained first thing in the morning?
A. Calcium
B. Urea
C. Uric acid
D. HCO_3

92. If $PaCO_2$ is 80 mm Hg and arterial plasma $[H^+]$ is 80 nmol/L, then plasma $[HCO_3]$ is:
A. 40 mmol/L
B. 28 mmol/L
C. 24 mmol/L
D. 10 mmol/L

93. In *Question 92,* what is the acid-base status?
A. Compensated metabolic alkalosis
B. Uncompensated respiratory acidosis
C. Compensated respiratory acidosis
D. Uncompensated metabolic acidosis
E. Normal acid-base status

94. Sodium bicarbonate should **not** be administered to a patient with a/an:
A. arterial blood pH of 7.1
B. serum $[HCO_3]$ of 12 mM
C. PaO_2 of 50 mm Hg
D. $PaCO_2$ of 68 mm Hg

95. The most common acid-base disturbance in patients who are on mechanical ventilators is:
A. metabolic acidosis
B. metabolic alkalosis
C. respiratory acidosis
D. respiratory alkalosis

96. In a patient with acidosis, arterial plasma bicarbonate is 12 mmol/L. If the acidosis were solely due to loss of bicarbonate, $PaCO_2$ is expected to be between
A. 16 and 20 mm Hg
B. 20 and 24 mm Hg

C. 24 and 28 mm Hg
D. 28 and 32 mm Hg

97. The following values were obtained from a patient diagnosed to have metabolic acidosis. $PaO_2 = 90$ mm Hg, $PaCO_2 = 30$ mm Hg, plasma $[HCO_3] = 10$ mM, the pH of CSF in this patient would be about:
A. 7.20
B. 7.25
C. 7.33
D. 7.40

98. Which of the following is **not** elevated in ethylene glycol poisoning?
A. Anion gap
B. Base excess
C. Osmolar gap
D. Serum osmolality

99. The severity of acidosis is related to:
A. anion gap
B. pH of arterial plasma
C. pH of ICF and plasma
D. plasma HCO_3

100. The following data are obtained on a patient on a 2000 kcal diet that includes 1 g of protein per kg body weight.
Creatinine clearance = 100 ml/min
Plasma pH = 7.4
Serum Na = 140; K = 5; HCO_3 = 24; Cl = 105 mmol/L
Urine NH_4 = 20 mmol/L
Urine titratable acidity = 20 mmol/L
Urine volume = 2 liters per day
Approximately how much new HCO_3 is generated per day?
A. 20 mmol
B. 40 mmol
C. 60 mmol
D. 80 mmol

Answers: Renal & Acid-Base Physiology

1A	2B	3DE	4B	5B
6ABC	7A	8B	9C	10B
11A	12A	13B	14B	15B
16A	17C	18B	19B	20B
21C	22C	23C	24A	25CD

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26C	27A	28A	29B	30A
31A	32ABC	33AB	34C	35A
36	37D	38A	39C	40A
41A	42A	43C	44A	45B
46BC	47C	48C	49A	50B
51B	52CD	53B	54D	55B
56A	57D	58C	59B	60B
61AB	62B	63A	64B	65D
66D	67D	68C	69C	70B
71AB	72D	73B	74D	75A
76C	77A	78A	79A	80A
81A	82A	83C	84A	85C
86A	87B	88B	89B	90C
91D	92C	93B	94D	95D
96C	97D	98B	99C	100D

Explanations:

1-3. Renal clearance is the volume of plasma that is cleared of a substance in urine per minute. Clearance of a substance X = $U_X V / P_X$, where
U_X: concentration of substance in urine
P_X: concentration of substance in plasma
V: urine flow rate in ml/min

Inulin clearance gives the best estimate of GFR since it is freely filtered and neither reabsorbed nor secreted by the nephron. Further, inulin does not affect hemodynamics. Despite being the gold standard for measurement of GFR, inulin clearance measurement is invasive and is not feasible in clinical practice. Endogenous **creatinine clearance** is slightly higher than inulin clearance since some creatinine is also secreted by the tubules. Despite this shortcoming, creatinine clearance remains the most common clinical method to estimate GFR when accurate measurements are needed. However, for routine practice, creatinine clearance is estimated inputting age, sex, ethnicity, and serum creatinine, deploying regression equations such as the MDRD equation or the Cockcroft Gault equation, An e-GFR calculator is available online at
http://www.nephron.com

Iothalamate is handled like inulin is, and its clearance has been used to measure GFR. Glucose is normally not excreted by the nephron. So it cannot be used to measure GFR. Phenol red has been used to estimate renal plasma flow. Tubular cells secrete it.

7. When mesangial cells contract, surface area available for filtration reduces.

13. In the kidneys, PGE_2 has vasodilator effects.

14. Given, PAH clearance = 100 ml/min
PAH clearance = effective renal plasma flow. True renal plasma flow actually equals ERPF/PAH extraction ratio. In this question, we are asked to assume that PAH extraction is complete (i.e., PAH extraction ratio = 1).

Renal blood flow (RBF) = RPF × (100 / 100 – Hct). PCV = 20; thus RBF = 125 ml/min.

15. PAH clearance gives effective RPF. Clearance of PAH depends upon its plasma concentration. Secretory and reabsorptive processes have a rate maximum i.e., they are saturable. When a high dose of PAH is used, PAH secretory capacity is overwhelmed and clearance of PAH reflects Tmax of this PAH secretory system rather than actual RPF. So $U_{PAH} V / P_{PAH}$ i.e. the measured PAH clearance will be low, and estimated RPF will be falsely low.

16. Recall Starling's equation describing fluid movement across capillaries. In this instance, the pressure gradient for filtration across the glomeruli is (40 + 0) – (25 + 5) = 10 mm Hg.

17. The hydrostatic pressure in Bowman's space increases in this case because of retrograde transmission of pressure from the obstructed ureters.

18-20. *Clearance ratio* is the ratio of the clearance of a substance by the kidneys to the clearance of inulin. The clearance of substances secreted by the nephron is greater than inulin clearance. In contrast, the clearance of substances (such as glucose) that are reabsorbed by the nephron is less than inulin clearance.

22. In women, it is about 300 mg/min.

23. Fractional excretion of a solute is the ratio of the clearance of the solute to the clearance of creatinine.

Thus, FENa = clearance of Na / creatinine clearance

Clearance of Na = $U_{Na} \times V / P_{Na}$
Clearance of creatinine = $U_{Cr} \times V / P_{Cr}$
Simplifying, FENa = $[U_{Na} \times P_{Cr}] / [P_{Na} \times U_{Cr}]$

One can get FENa from a spot urine sample; a 24 hr. urine collection is not required; i.e., FENa is independent of urine flow rate. Normally, it is less than 1%. An individual with untreated pre-renal acute kidney injury and an individual with intrinsic acute kidney injury may both be oliguric, yet their FENa will very likely be different – normal in pre-renal AKI and elevated in intrinsic AKI. FENa used for this purpose should of course be obtained prior to starting diuretics.

24. PAH is secreted mainly by the S3 segment of the proximal tubule (called Late Proximal Tubule); or Proximal Straight Tubule – PST or Pars Recta (Boron, 2012, p. 808 and Fig 36-9). The proximal tubule (PT) consists of proximal convoluted tubule (pars convoluta of the PT; PCT) followed by the proximal straight tubule (pars recta of the PT). The S1 segment and some of S2 for the PCT, and the rest of S2 and all of S3 form the PST.

Option C: The thick ascending limb is permeable to Na, K and Cl and is relatively impermeable to water, and it is not permeable to PAH or creatinine. Na and Cl move out of tubular fluid into the corticomedullary interstitium. Although the osmolality of the fluid in the TAL progressively decreases, the concentration of PAH would not decrease in this segment. **Option B:** In the thin descending limb, and in the collecting duct (with ADH present), the concentration of PAH increases because of movement of water out of the tubular lumen.

25. Renal autoregulation defends changes in GFR and renal blood flow in the face of changes in renal perfusion pressure.

26. As the name suggests, renal autoregulation is essentially independent of extrinsic innervation, although in vivo it is influenced by renal sympathetic nerve activity. The effect of intense stimulation of the renal sympathetic nerves is to reduce GFR.

Steady state renal blood flow and GFR are autoregulated when mean arterial pressure is between 70 and 140 mm Hg. The autoregulatory range depends on an individual's typical resting mean arterial pressure.

27. When GFR is normal, a relatively constant fraction of filtered Na, Cl and water is reabsorbed in the proximal tubule despite variations in GFR around this normal value. This phenomenon is called glomerulotubular balance. One mechanism underlying this phenomenon is the variation in oncotic pressure in peritubular capillaries. For example, when there is a 5% increase in GFR, there is a relative increase in oncotic pressure of plasma leaving efferent arterioles and it favors reabsorption of Na, Cl and water into the peritubular capillaries. Thus, variations in Na and water excretion are achieved primarily by regulating Na, Cl and water absorption in the distal convoluted tubule and collecting ducts.

28. Synthesis and secretion of renin by juxtaglomerular cells is regulated by renal blood flow as well as by sympathetic innervation of JG cells. The synthesis of ANG II is what is manipulated pharmacologically by ACE inhibitors but physiologically, this is not the rate-limiting step.

32. Angiotensin II (and not ACTH) is the most important trophic factor for the zona glomerulosa and one of the two most important stimulators of aldosterone release. Even a 0.5 mM increase in plasma [K] stimulates aldosterone release. In turn, aldosterone regulates plasma [K] by promoting K secretion in the collecting ducts. Angiotensin III has 100% aldosterone releasing activity but only 40% of the pressor activity of aldosterone. ACTH as well as a decrease in plasma [Na] stimulate aldosterone release but the stimulatory effects of acute administration of pharmacologic doses of ACTH on aldosterone release are transient if at all.

36. All about angiotensins: The renin-angiotensin-aldosterone axis is a salt and water conserving and blood pressure raising system set in motion by stimuli such as hypovolemia, hypotension, a decrease in renal blood flow, and a decrease in GFR.

Ang II stimulates thirst as well as release of ADH by an action on the subfornical organ (SFO) and the organum vasculosum of lamina terminalis (OVLT) – two circumventricular organs. It stimulates Na reabsorption, and proton secretion in the PCT. Glomerular efferent arterioles are more susceptible to the constrictor effects of angiotensin II compared to afferent arterioles. This action allows the renin-angiotensin system to stabilize GFR in the context of a falling GFR. However, at much higher concentrations ANG II constricts afferent arterioles as well. Ang II stimulates Na and Cl reabasorption in the DCT (via an action on the Na-Cl cotransporter) and P cells of the collecting duct (via an action on epithelial Na channels). Angiotensin II does not appear to directly cause K secretion (it is aldosterone that does this). As noted above, ANG II is a major trophic factor for sustenance of zona glomerulosa, and an important stimulator of aldosterone release by the adrenal cortex. Angiotensin III, formed from angiotensin II, has only 40% of the pressor activity of angiotensin II but it has 100% aldosterone stimulating activity.

37. Licorice contains glycyrrhyzinic acid which inhibits 11-*beta* hydroxysteroid dehydrogenase (HSD) type 2 in the collecting duct cells in the nephron. 11-*beta* HSD type 2 is an enzyme that inactivates cortisol and thereby prevents it from stimulating the mineralocorticoid receptor. (Otherwise, cortisol is capable of binding and activating the mineralocorticoid receptor.) This is why, physiologically, the mineralocorticoid receptor is activated only by aldosterone. With chronic licorice ingestion or with inherited deficiency of 11-*beta* HSD type 2, cortisol activates the mineralocorticoid receptor. The concentration of cortisol is much higher than that of aldosterone; the result is hypertension, hypokalemia and metabolic alkalosis and feedback suppression of plasma renin activity and thereby aldosterone secretion by high BP. This is

an instance of pseudohyperaldosteronism. Similarly, hypertension that occurs in 11 *beta*-hydroxylase deficiency is due to the actions of high levels of deoxycorticosterone on the mineralocorticoid receptor.

39. Filtered load = plasma [glucose] × GFR
Thus, the amount of glucose filtered per minute = 500 mg
Tmax for glucose is given to be 350 mg/min
Thus, glucose excretion rate
= filtered load – Tmax for glucose
= 500-350 = 150 mg/min.

40. 60-70% of the filtered water is reabsorbed in the proximal tubule. This does **not** depend upon vasopressin. Water reabsorption in the collecting ducts requires vasopressin facilitated aquaporin 2 molecules on the luminal membrane of collecting duct epithelial cells, and a hypertonic medullary interstitium. When vasopressin is absent, 24-hr urine volume may increase to as high as 12% of filtered water load, about 22 liters for a GFR of 125 ml/min (180 liters per day).

42. Luminal fluid becomes more and more concentrated in the thin descending limb because this portion of the nephron is relatively impermeable to solute and freely permeable to water. Water exits the descending limb into the hypertonic medullary interstitium. Thus osmolality of tubular fluid is greatest at the tip (apices) of the loops of Henle.

47. The ascending limb of the loop of Henle is impermeable to water but actively reabsorbs salt, and is thus called the diluting segment of the nephron. As long as active transport of salt occurs in the thick ascending limb, fluid emerging from the ascending limb of the loop of Henle is always hypotonic whether the urine eventually formed is dilute or concentrated.

53. Rapid diffusion of water across cells depends upon the presence of water channels called aquaporins. There are several types of aquaporins. Vasopressin mediates its antidiuretic effect by increasing the number of AQP-2 channels in the luminal membrane of collecting duct epithelial cells. Loss of function mutations in AQP-2 are

one cause of congenital nephrogenic diabetes insipidus.

61. Solute is separated from water by active transport of salt in the thick ascending limb. This 'free water' is excreted in the absence of ADH's effects on the collecting ducts. When the countercurrent mechanism operates normally, serum ADH is elevated, and ADH is effective on the collecting ducts, urine has a concentration higher than that of plasma, and 'free water clearance' is negative.

62. Option A: Plasma [Na] is the principal determinant **(not** regulator) of plasma osmolality. **Option B (correct):** Changes in water excretion are a commoner cause of changes in plasma Na concentration rather than changes in Na excretion. ADH, being the hormone that regulates water excretion, is an important determinant of plasma Na concentration and osmolality. For example, diabetes insipidus, which is caused by ADH deficiency, is characterized by excretion of large volumes of dilute urine, and plasma [Na] increases. Hyperaldosteronism does not cause hypernatremia because the increase in NaCl absorption in the collecting ducts is followed by iso-osmotic water absorption. Thus while aldosterone's actions increase total body sodium, they do not affect osmolality. Aldosterone, on the other hand, is the hormone regulating secretion of potassium in the collecting ducts, and hyperaldosteronism is typically associated with hypokalemia though most patients with primary hyperaldosteronism are normokalemic.

63. See explanation for *Question 62*.

68. 'Free water clearance' is the amount of solute-free water excreted. When urine is concentrated (i.e. hypertonic compared to plasma), free water clearance is negative. When water is lost in excess of osmoles cleared, free water clearance is positive - as in diabetes insipidus. The SG of normal plasma is 1008 (approximately '1010'), and when urine is dilute (or hypotonic), its SG is less than 1010. Also see explanation for *Question 61*.

69. Maximum urine osmolality = 1400 mOsm/kg H_2O. Plasma osmolality ~ 290 mOsm/kg H_2O. When urine is maximally concentrated, Uosm/Posm ~ 4.6.

70. A 2000 calorie diet consisting of at least 1g protein per kg body weight per day generates a solute load of about 600 mOsm per day the kidneys excrete. Even if urine osmolality were 4 times that of plasma, the obligatory urine volume needed to eliminate this load is about 500 ml per day.

71. Normally, water deprivation (for say 7 hr) produces a significant increase in ADH secretion, and urine osmolality exceeds 700 mOsm/kg H_2O. In neurogenic diabetes insipidus, urine does not become concentrated because of a deficiency of ADH. In nephrogenic diabetes insipidus, urine does not become concentrated because the kidneys do not respond to ADH. This is usually due to a defect in V2 receptors or ADH responsive aquaporins (AQP-2) in the collecting ducts. After administration of a vasopressin analog, the osmolality of urine increases significantly in neurogenic diabetes insipidus whereas urine remains dilute in nephrogenic diabetes insipidus.

74. Laplace's law states that pressure (P) in a hollow viscus is directly proportional to wall tension (T) and inversely with radius (r). P = T/r

As the bladder is distended with urine, its radius as well as passive wall tension increase proportionately so there is little change in intravesical pressure. However, at an intravesical volume of about 300-400 ml, any further stretch results in "active contraction" of the smooth muscle of the bladder and a sharp increase in intravesical pressure. This results in emptying of the bladder. (See Ganong, 2012, p. 693-695).

75. The immediate effect of spinal cord transection is urinary retention. This is, of course, followed by overflow incontinence; i.e., excessive stretch of the urinary bladder, and local reflex contractions of the detrusor that is not under voluntary control. (Ganong, 2012, p. 693-695).

76. In chronic paraplegics, the voiding reflex returns and it may be hyperactive. The hyperactive reflex may be because of release of the spinal mechanism for micturition from the inhibitory effects of higher control. The bladder wall becomes hypertrophied and bladder capacity is reduced. This condition is called spastic neurogenic bladder. See the *Summary on Disorders of Micturition,* earlier in this Chapter.

77. Tabes dorsalis predominantly affects the dorsal roots; thus, the effects observed are those due to deafferentation: the bladder becomes distended, thin walled and hypotonic. See the *Summary on Disorders of Micturition,* earlier in this Chapter.

80. In a healthy adult with a serum bicarbonate of 24 mmol/L and a GFR of 125 ml per min (180 L/day), the highest amount of acid is secreted in the proximal tubule (about 4370 mmol per day). 4320 mmol of H^+ contribute to reclaiming 4320 mmol of filtered HCO_3. The remaining 50 mmol of protons which are usually bound to ammonium and or phosphate contribute to 'net acid excretion' in the urine. In the collecting ducts, about 20 mmol of protons is secreted (generating about 20 mmol of new bicarbonate in plasma). Protons secreted in the collecting ducts acidify tubular fluid substantially. See explanation for *Question 83.*

83. pH of proximal tubular fluid drops from 7.4 to 6.8 whereas in the 'classic distal tubule' (i.e., connecting segment, initial collecting tubule, cortical collecting ducts), it can drop to as low as 4.4; thus, although the amount of protons secreted is much higher in the PT, acidification of tubular fluid occurs to a greater extent in the aldosterone sensitive distal nephron. The tubular lumen concentration of phosphate increases however in the cortical collecting duct where water is absorbed, and HPO_4 buffers some of the secreted H^+ and forms H_2PO_4.

86. Normally, the ratio of NH_4^+ to titratable acid in urine is 1-2.5.

87. The amount of alkali required to titrate acidic urine to the pH of arterial plasma is called *titratable acidity*; normally, most of this is due to protons buffered by phosphate as H_2PO_4. However, in patients with chronic renal failure, protons buffered by creatinine and uric acid constitute about 20% of titratable acid.

88. Type A intercalated cells secrete protons (and conserve bicarbonate); acid-secretion by intercalated cells is stimulated by aldosterone. Proton secretion is also affected by transepithelial voltage; a lumen negative transepithelial voltage favors secretion of protons and potassium ions in the collecting duct. Type B intercalated cells have been observed in the context of metabolic alkalosis. They express pendrin, a $Cl-HCO_3$ exchanger, on the luminal membrane, and secrete bicarbonate in exchange for luminal chloride.

89. Plasma pH and total CO_2 concentration are measured, and plasma $[HCO_3]$ is calculated using the Henderson equation.

90. See discussion on anion gap on *page 123.*

91. The typical diet generates a net acid load of about 70 mmol per day (1 mmol/kg body weight), and acid-base homeostasis requires reclamation of almost all filtered bicarbonate.

92-93. Using the modified Henderson equation, we get, plasma HCO_3 = 24 mmol/L. This is uncompensated respiratory acidosis because there is no compensatory increase in bicarbonate.

94. Injected $NaHCO_3$ dissociates to give Na and HCO_3. The HCO_3 buffers H ions in ECF to form H_2CO_3. H_2CO_3 will dissociate to give CO_2 and H_2O. Normally, lungs eliminate CO_2 readily. However, if the $PaCO_2$ is already as high as 68 mm Hg, this points to inadequate minute ventilation due to some cause and such a patient would require mechanical ventilation since he/she has respiratory acidosis. Administration of $NaHCO_3$ in this instance will aggravate acidosis. Appropriate management consists of getting CO_2 out down to a level that will make him/her breathe (intubation and mechanical ventilation). Sodium bicarbonate is appropriate only for the

management of metabolic acidosis; even in metabolic acidosis there are specific clinical guidelines for its use. It depends on what the cause of metabolic acidosis, the pH and certain other factors.

95. As long as alveolar ventilation and pulmonary blood flow are adequate and ventilation-perfusion matching is optimal, CO_2 elimination is not a concern even if there is a reduction in diffusion capacity of the lungs for oxygen. This is because CO_2 rapidly equilibrates across the alveoli. In contrast, oxygenation of blood is more readily compromised by a reduction in diffusion capacity of lungs even when ventilation-perfusion balance and pulmonary blood flow are optimal.

96. Winter's formula is used to assess whether respiratory compensation for metabolic acidosis is appropriate. Expected $PaCO_2 = [1.5 \times HCO_3] + 8 +/- 2$ mm Hg. When the actual $PaCO_2$ is higher than expected, coexisting respiratory acidosis is likely, and when the actual $PaCO_2$ is lower than expected, coexisting respiratory alkalosis is likely.

97. Using Henderson equation, $[H^+]$ of blood can be calculated to be 72 nanomoles/L. This calculation is however not necessary to answer the question. From the data provided it is clear that bicarbonate has dropped by more than 50% while $PaCO_2$ has dropped by 25%. So the primary abnormality is metabolic acidosis. CSF $[H^+]$ is directly proportional to $PaCO_2$. Since $PaCO_2$ is 30 mm Hg (10 mm Hg lower than it normally is), CSF pH must be higher than normal. Normally, CSF pH is 7.33. From the options given, 7.4 is the only answer one can choose.

98. Base excess = Observed buffer base – normal buffer base. Normal buffer base is approximately 48 mmol/L. If observed buffer base is 52 mmol/L, then base excess is 4 mmol/L. Base excess is present in metabolic alkalosis, and it is negative in metabolic acidosis.

Serum osmolality is elevated in ethylene glycol poisoning because of an increase in the serum level of oxalate; thus, *osmolar gap*, which is the difference between measured and calculated osmolality increases.

The elevation of anion gap in this condition is primarily because of an increase in serum oxalate.

99. If bicarbonate and $PaCO_2$ are abnormal and the pH of arterial plasma appears to be WNL, this suggests the possibility of a mixed acid-base disturbance, such as mixed metabolic acidosis and respiratory alkalosis; or mixed respiratory acidosis and metabolic alkalosis. In either case, the pH of ICF would be abnormal because of changes to PCO_2 of ICF.

100. 'Net acid excretion' in urine = urinary NH_4 + titratable acidity. For every proton lost in urine as ammonium or buffered by phosphate, one 'new' bicarbonate is generated in plasma. Thus, net acid excretion in urine is synonymous with 'new bicarbonate' generation.

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