HUMAN PHYSIOLOGY
SPRING 2004

FIRST HANDOUT

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SPRING 2004 COURSE SYLLABUS FOR HUMAN PHYSIOLOGY LECTURE (BIRU 3232) AND LAB (BIRU 3242) COURSES

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Textbooks: Sherwood, L., Human Physiology: from cells to systems. 5th edition. Brooks Cole, 2003. ISBN 0534395015

The book is available from the bookstore or from internet retailers such as www.ecampus.com or www.amazon.co.uk

Recommended Books: Guyton, A. C. and J. E. Hall, Textbook of Medical Physiology. 10th edition. W.B. Saunders Co., Philadelphia, PA, 2000.
Kandel, E. R., J. H. Schwartz, and T. M. Jessel, Essentials of Neural Science and Behavior, Appleton and Lange, Norwalk, CT, 1995.

Course on the web: Electronic Reserve Room at Fordham Library (http://reserves.library.fordham.edu)
Course Home Page at http://www.geocities.com/fordhamphysiology

Grading of the lecture course:	5 lecture exams @ 100 points each	= 500 points
	1 final exam (comprehensive)	= 200 points
	TOTAL:	= 700 points
Grading of the lab course:	2 lab exams @ 30 points each	= 60 points
	Journal Club	= 30 points
	1 final exam (comprehensive)	= 50 points
	lab reports, quizzes	= 40 points
	participation	= 40 points
	TOTAL:	= 220 points

The lecture exams cover the information discussed during lecture and the reading assignments. The laboratory exams include the information summarized in the laboratory introduction, methods, and analysis of the results. The standard Fordham University grading system will be used to determine the final grade for the entire course: A = 93-100%, A- = 90-92%, B+ = 87-89%, B = 83-86 %, B- = 80-82%, C+ = 77-79%, C = 73-76%, C- = 70-72%, D = 60-70%.

Attendance: You are required to attend all lectures and laboratory exercises. If a student is absent from an exam, he/she will receive a grade of 0 for that exam; he/she can take a substitute exam if a letter from a physician is presented stating that he/she was too ill to attend class on the day of the exam. The data sheets will be examined during each laboratory period; ten points will be deducted from the course total for each laboratory period not attended.

The Fordham College policy on Academic Integrity will be enforced.

Laboratory Rules:

1. No eating, drinking or smoking in the laboratory.
2. Any injury must be reported to the instructor.
3. Some laboratory exercises require that the students make measurements on themselves. If you have a medical condition that you feel may be aggravated by the exercise, please inform the instructor. No one will be compelled to perform an exercise if it will adversely affect his/her health.

Schedule

Date	Lecture	Pages	Lab
01/22	Introduction	2-16	.
01/26	Cell and Membrane	50-103	
01/29	Muscle	240-281	Blood
02/02	Blood and Immune System	369-432	
02/05	Heart I.	283-300	Histology I., **Lecture Exam 1.**
02/09	Heart II.	301-321	
02/12	Circulation I.	323-350	Histology II.
02/17	Circulation II.	351-367	
02/19	Respiration I	343-450	Heart, Circulation
02/23	Respiration II.	451-481	
02/26	Excretion	484-515	Respiration, Statistics, **Lecture Exam 2.**
03/01	Excretion and Acid-Base Balance	516-558	
03/04	Gastrointestinal System I.	560-590	Urine Analysis, **Lab Exam 1.**
03/08	Gastrointestinal System II. Energy	591-633	
03/10	Endocrinology I.	635-650	Rat dissection, **Lecture Exam 3.**

03/22	Endocrinology II.	651-670	
03/24	Endocrinology III.	671-714	EEG, Polygraphy, EMG, EOG, Stretch Reflex,
03/29	Endocrinology IV.	715-765	
04/01	Introduction to the Nervous System	89-121, 222-238	Digestive System, **Lecture Exam 4.**
04/05	Autonomic Nervous System		
04/15	Sensory Functions of the N.S.	123-140	Sensory Organs, **Lab Exam 2.**
04/19	Vision	174-200	
04/22	Hearing, Equilibrium, Chemical Senses	200-220	Journal Club
04/26	Motor Functions of the N.S.	162-172, 229-238	
04/29	Memory, Sleep	TBA	Lab Final Exam
05/03	**Lecture Exam 5.**		

INTRODUCTION

What Is Physiology?

1. Physiology
2. Human physiology
3. Supplementary disciplines

The Scope of Physiology

1. The main questions in physiology
    - Purpose of action
    - Mechanism of action
    - Regulation of action

2. Approaches to problems
    - Analytical approach
    - Integrative approach
    - Reductionist approach

Homeostasis

Cell physiology

THE PHYSIOLOGY OF THE CELL MEMBRANE

The Structure of the Cell Membrane

Passive Transport Mechanisms

1. General characteristics
2. Diffusion rate
3. Special forms of diffusion
    - Facilitated diffusion
    - Osmosis

Active Transport Mechanisms

1. Carrier-mediated active transport
    - Primary active transport
    - Secondary active transport

2. Endocytosis, pinocytosis, phagocytosis and exocytosis

The Role of the Cell Membrane in Cell-to-Cell Communication

1. Membrane surface receptors
    - Function
    - Principles
    - Structure

2. Second messengers
    - Function
    - Mechanisms
    - Most common types of second messengers

The Electrical Properties of the Cell Membrane

Cell Excitability: The Role of the Cell Membrane

1. Graded potentials
2. Action potential

THE PHYSIOLOGY OF THE MUSCLE

The Structure of the Muscle

1. Muscle types
2. Structure of the skeletal muscle fibers
3. The structure of the myofibrils

Contraction of the Muscle Fiber

1. Neuromuscular transmission
2. Excitation-contraction coupling
3. Molecular mechanisms of muscle contraction: sliding filament mechanism

The Contraction of the Whole Muscle

1. Factors tat determine the strength of contraction
2. Isotonic – isometric contraction, muscle tone
3. Adaptive changes in the muscle

Energy Requirements For the Muscle Contraction

1. Energy need
2. Energy sources
3. Fatigue
4. Muscle types with different metabolic characteristics
    - Slow-oxidative fibers
    - Fast-glycolytic fibers
    - Fast-oxidative fibers

The Pathology of the Skeletal Muscle

1. Myasthenia gravis
2. Muscular dystrophies

Smooth Muscle

1. Similarities and differences between skeletal and smooth muscle
2. The types of smooth muscle
    - Multiunit smooth muscle
    - Single-unit smooth muscle

THE PHYSIOLOGY OF THE BLOOD

Blood Constituents

1. Plasma
2. Blood cells
    - Erythrocytes
        i. Constituents
        ii. ABO blood groups
        iii. Rh blood groups
        iv. Pathology
    - Leukocytes
        i. Function
        ii. Types
        iii. Pathology
    - Thrombocytes

Hematopoesis

Hemostasis

1. The events of hemostasis
2. Intravascular anticoagulants
3. The pathology of hemostasis

THE IMMUNE SYSTEM

Nonspecific Defense System

1. Players
2. Inflammation

Specific Defense System

1. Players
2. The differentiation of lymphocytes
3. Humoral immune response
4. Cell-mediated immune response

The Pathology of the Immune System

1. Immune deficiencies
    - The types of immune deficiencies
    - AIDS

2. Inappropriate immune attacks
    - Autoimmune diseases
    - Immune-complex diseases
    - Allergies
        i. Immediate hypersensitivities
        ii. Delayed hypersensitivities

INTRODUCTION

WHAT IS PHYSIOLOGY?

I. PHYSIOLOGY

Physiologia: the study of all natural phenomena ("*physis"* = nature + "*logos"* = word), "natural philosophy"

↓

Physics
Chemistry
Medicine
Zoology
Botany
Anatomy
Pharmacology, etc.

Physiology: a branch of biology that deals with the ***functions*** and ***activities*** of life or of living matter (as systems, organs, tissues, or cells) and of the physical and chemical phenomena involved

Subdisciplines in physiology:

- viral physiology
- bacterial physiology
- plant physiology
- animal physiology
- comparative physiology
- mammalian physiology
- human physiology, etc.

II. HUMAN PHYSIOLOGY

- cell physiology
- the physiology of blood
- immunology
- cardiovascular physiology
- the physiology of respiration
- the physiology of excretion
- the physiology of the gastrointestinal tract
- energy balance and thermoregulation
- reproductive physiology
- endocrinology
- neurophysiology

- the physiology of pregnancy, parturition, and lactation
- sports physiology
- aviation, high altitude, and space physiology

- developmental physiology (intrauterine life, neonates, children, adolescents, puberty)

- the physiology of aging

III. SUPPLEMENTARY DISCIPLINES TO PHYSIOLOGY

- Pathophysiology
- Anatomy-histology
- Biochemistry, organic chemistry

THE SCOPE OF PHYSIOLOGY

I. THE MAIN QUESTIONS IN PHYSIOLOGY

1. What is the purpose of the action?: teleological approach.

    - homeostasis
    - growth and development
    - reproduction

2. How does it happen? The mechanism of action: mechanistic approach.

3. What the action triggered by? What stops the action? The regulation of the function.

II. TYPICAL APPROACHES TO PROBLEMS

a. Analytical approach: The analysis of the function at progressively lower levels in progressively more detail (tissue → cell → molecules). **Get the details.**

b. Integrative approach: How the action of an individual organ fits in the function of the entire organism and how the simultaneous, coordinated involvement of several organs maintains the organism and help propagate the species. **Get the big picture.**

c. Reductionist approach: Find the governing principles in the action, i.e., what is the most simple way a function can be described and understood, (e.g. to understand the function of blood vessels through the physical laws of pressure and fluid flow, to understand how the human brain works by analyzing the characteristics of simple neural networks of primitive species, etc.). **Make it simple.**

HOMEOSTASIS

The physical and chemical characteristics of the environment to which cells are directly exposed must be compatible with the survival of the cells. For example:

- Temperature
- Nutrients
- Oxygen
- Pressure
- Ion concentrations
- pH
- Toxic chemicals

1. Unicellular organisms: - directly exposed to external environment

   The physical and chemical characteristics of the external environment must be compatible with the survival of the cells.

   Unicellular organisms do not have effective mechanisms to change the external environment

2. Multicellular organisms:
   - external environment
   - individual cells exposed to the internal environment (milieu interieur; Claude Bernard) = extracellular fluid (i.e., blood plasma + interstitial fluid)

In multicellular organisms, the physical and chemical characteristics of the internal environment must be compatible with the survival of the cells.

Multicellular organisms are capable of regulating the physical and chemical characteristics of the internal environment.

Homeostasis: maintaining the stability of the internal environment
(*homeo* = "same" *stasis* = "to stand or stay")

Generation of the internal environment: each cell contributes to it.

Maintaining the stability of the internal environment: preventive and restorative function
a coordinated physiological process
most of the organs contribute to it by:

- exchanges between the internal and external environments
- exchanges between the internal and intracellular environments

Coordination: by feedback systems, mainly negative feedback mechanisms

sensory mechanisms → detect changes in internal environment
integrative mechanisms → evaluate
effector (motor) mechanisms → carry the command to the organs

- nervous system: rapid, precise changes, esp. muscular and secretory functions
- endocrine system: slower and longer lasting changes, esp. metabolic functions
- immune system

The three control systems are intertwined

Examples for controlled, homeostatic variables:

- blood pressure
- body temperature
- ion levels
  - calcium
  - sodium
  - potassium
  - hydrogen
- O_2 and CO_2 levels
- levels of nutrients (glucose, aa., etc.)
- concentration of waste products
- water balance

CELL PHYSIOLOGY

Chemical constituents of the cell:

1. water (70-85%)

2. electrolytes
   - potassium
   - sodium
   - calcium
   - magnesium
   - phosphate
   - sulfate
   - bicarbonate
   - chloride

3. proteins (10-20%)
   - fibrillar proteins (structural proteins)
   - globular proteins (enzymes)

4. lipids (~2 %)
   - phospholipids
   - cholesterol
   - triglycerides

5. carbohydrates (1-6 %)

Components of the cell:

1. cell membrane

2. cytosol

3. cell organelles:
   - endoplasmic reticulum (granular - agranular)
   - Golgi apparatus
   - lysosomes
   - peroxisomes
   - secretory vesicles
   - mitochondria
   - filaments and microtubules
   - vaults
   - nucleus

1. The physiology of the cell membrane
   - transport across the membrane
   - communication between cell membrane and the extracellular environment (cell surface receptors)
   - communication between cell membrane and the intracellular environment (second messenger systems)
   - electrical signals generated across the cell membrane

2. Secretory activity of neurons and endocrine cells

3. Cell motility and shortening: the physiology of muscle cells

CELL MEMBRANE

STRUCTURE OF THE CELL MEMBRANE: FLUID MOSAIC MODEL

Function: isolation and connection

Lipid bilayer:	phospholipids cholesterol glycolipids
Proteins:	integral proteins (channels, carriers, enzymes, receptors, cell adhesion molecules, antigens) peripheral proteins (enzymes)
Carbohydrates:	glycoproteins glycolipids glycocalyx

TRANSPORT ACROSS THE CELL MEMBRANE
I. TRANSPORT THAT DOES NOT REQUIRE ENERGY

General characteristics
- down to energy gradient
- does not require external energy (no ATP used)
- cell membrane: through lipid bilayer or specific channels

Diffusion rate determined by:

1. Membrane permeability
   - thickness
   - number of protein channels
   - area of the membrane

2. Characteristics of the substance
   - lipid solubility
   - molecular weight
   - temperature

3. Energy gradient for the substance
   - concentration difference
   - pressure difference
   - electrical potential

Special cases of diffusion:

1. Facilitated Diffusion

   carrier mediated
   does not require external energy
   V_{max}

2. Osmosis: diffusion of water through semipermeable membranes

   Water flow depends on the concentration difference of the nonpenetrating solutes across the membrane.

   Osmolarity: measure of the concentration of nonpenetrating ions in the solution (osmol/liter)
   Water flow: from the low to the high osmolarity compartment
   isosmotic concentrations across the membrane: no osmotic water flow

   Osmotic Pressure

TRANSPORT ACROSS THE CELL MEMBRANE
II. TRANSPORT MECHANISMS THAT REQUIRE ENERGY

I. CARRIER-MEDIATED ACTIVE TRANSPORT

Characteristics:
- external energy (ATP) is required
- carrier mediated
- specificity
- saturable

Types:
- Primary or secondary active transport
- Uniport or co-transport (symport or antiport)

1. PRIMARY ACTIVE TRANSPORT

examples:
a) Sodium-potassium pump (antiport)
b) Primary active transport of calcium (uniport)
c) Primary active transport of hydrogen ions (uniport)

2. SECONDARY ACTIVE TRANSPORT

examples:
a) Sodium-glucose co-transport (symport)
b) Sodium-calcium co-transport (antiport)
c) Sodium-hydrogen co-transport (antiport)

II. ENDOCYTOSIS, PINOCYTOSIS, PHAGOCYTOSIS, EXOCYTOSIS

CELL-TO-CELL COMMUNICATION: THE ROLE OF THE CELL MEMBRANE

I. MEMBRANE SURFACE RECEPTORS

Function: Receive signals from other cells

Principles:
1. Cells communicate
2. Cells send messages (i.e., release messenger molecules, e.g., hormones, neurotransmitters, etc.)
3. Cells receive messenger molecules: receptors
4. Messenger molecules that cannot cross the cell membrane: bind to membrane surface receptors (extracellular receptors)
5. Messenger molecules that can cross the cell membrane: bind to intracellular receptors
6. A certain type of receptor is specific to a certain type of messenger molecule (e.g., epinephrine receptors, acetylcholine receptors, etc.)
7. An individual cell has several receptor types – a certain receptor type may be present in thousands of copies on a single cell
8. If a cell does not have a receptor specific to a certain messenger then the cell is not responsive to that messenger

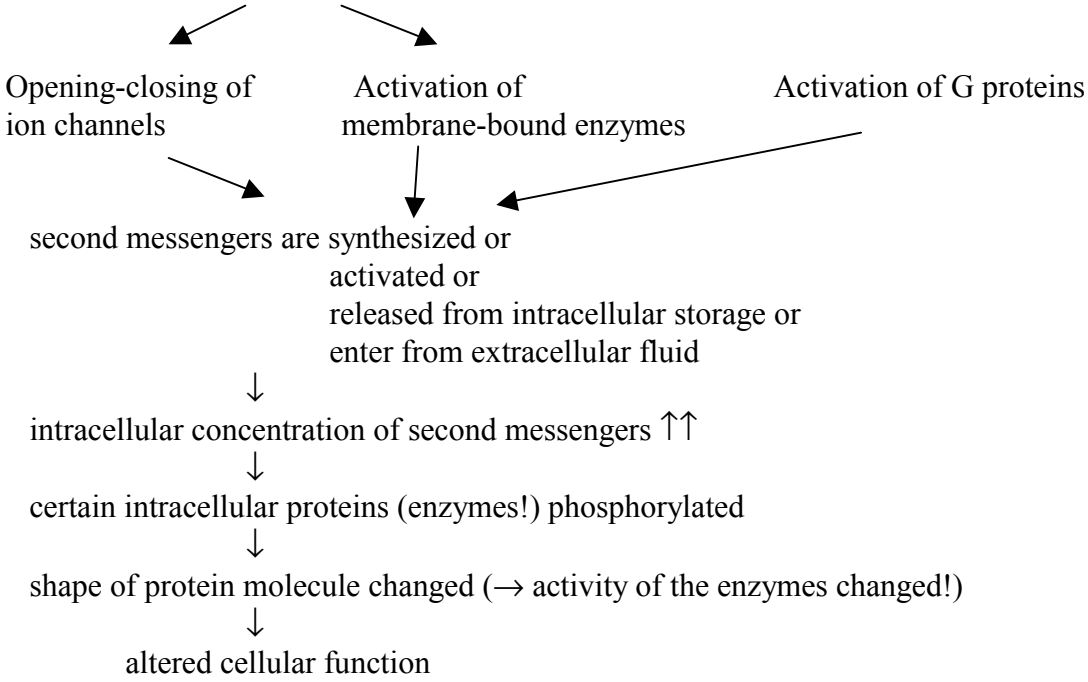
Structure of extracellular receptors: Transmembrane proteins (glycoproteins)

- Extracellular moiety: ligand binding site
- Membrane-spanning segment(s) (single pass transmembrane protein, multipass t.p.)
- Intracellular moiety: catalytic site

II. SECOND MESSENGERS

Function: Messenger molecules within the cell, forward and amplify signals from the cell membrane to intracellular enzymes
(= signal transduction)

Mechanism: Ligand binds to the receptor



Most common second messengers:

1. Ions (calcium)
2. cAMP
3. cGMP
4. Inositoltriphosphate (IP_3)
5. Diacylglycerol (DAG)

THE ELECTRICAL PROPERTIES OF THE CELL MEMBRANE

Principles:

- ions carry electrical charge
- uneven distribution of positive and negative ions generates electrical potential

Origin of membrane potential:

Membrane is not equally permeable to all ions (transport characteristics)
↓
Some ions accumulate intracellularly (e.g., protein anions, potassium) others extracellularly (sodium)
↓
Slight excess of negative ions intracellularly, slight excess of positive ions extracellularly: membrane is polarized
↓
Intracellular surface of the cell membrane is slightly negative as compared to the extracellular surface
Resting membrane potential: -50 – -90 mV.

Major players in the development of resting membrane potential:

1. Na^+ ions (IC concentration << EC concentration)
2. K^+ ions (IC concentration >> EC concentration)
3. intracellular proteins: anions (IC concentration high, EC concentration ≈ 0)
4. Na^+-K^+ pump (pumps Na^+ out in exchange to K^+)

CELL EXCITABILITY: THE ROLE OF THE CELL MEMBRANE (CHANGES FROM THE RESTING MEMBRANE POTENTIAL)

Cause: in response to the chemical (activation of membrane surface receptors) or physical stimuli or, in special cases, spontaneously

Mechanism:

Membrane transport characteristics change: ion channels open
↓
Ion distribution changes
↓
Membrane potential changes from resting value

- more negative (hyperpolarization) → inhibition of cell function
- less negative (hypopolarization, depolarization) or positive → stimulation of cell function (excitation)

I. GRADED POTENTIALS: caused by relatively low-intensity stimuli
the magnitude of changes is proportional to the stimulus intensity
non-propagated: local potentials on the cell membrane at the site of the stimulus
→ electrical signal fades away quickly over a short distance

Types:
1. postsynaptic potential
2. receptor potential
3. spontaneous (pacemaker) potential
4. end-plate potential

Mechanism: opening chemically or physically gated ion channels

Characteristics:
1. graded
2. can be hyper- or hypopolarization (= depolarization)
3. the strength of the potentials decreases as they spread from the point of origin
4. can be summed (additive)
5. no refractory phase
6. duration proportional to stimulus duration

If the amplitude of the graded depolarization reaches a threshold in EXCITABLE tissues

↓

II. ACTION POTENTIAL:
- rapid spreading of the electrical signal along the cell membrane
- electrical signal transmitted over a long distance with its original strength.
- intracellular membrane surface becomes transiently positive (depolarization-repolarization).

Mechanism:
depolarization: caused by the opening of voltage-gated Na^+ channels
repolarization: closing the voltage-gated Na^+ channels and opening the K^+ channels

Characteristics:
1. all-or-none response
2. only depolarization
3. the strength of the potentials does not decrease as they spread from the point of origin
4. cannot be summed
5. refractory phase
6. duration is constant; frequency code

MUSCLE

THE STRUCTURE OF THE MUSCLE

1. Muscle types

    1. Striated muscle: - skeletal muscle
       - cardiac muscle

    2. Smooth muscle

2. The structure of the skeletal muscle fibers (muscle cells)

    1. Nuclei
    2. Mitochondria
    3. Myofibrils: 1500 myosin and 3000 actin filaments
    4. Sarcoplasmic reticulum
    5. Transverse tubules
    6. Sarcoplasm
    7. Sarcolemma: plasma membrane and polysaccharide coat

3. The structure of myofibrils

    Myosin filament:

    Myosin molecule: 6 polypeptide chains
    tail and head (cross-bridges; ATPase site, actin-binding site)

    Myosin filament: 200< myosin molecules

    Actin filament:

    Actin: doublestranded helix, binding site

    Tropomyosin: wrapped spirally around the actin helix

    Troponin: three subunits, troponin I, troponin T, troponin C

    Myofibrils are assembled into **sarcomere**s (the functional unit)

    - I bands
    - A bands
    - Z line
    - M line
    - H zone

CONTRACTION OF THE MUSCLE FIBER

I. THE EXCITATION OF THE SKELETAL MUSCLE: NEUROMUSCULAR TRANSMISSION

Motor unit: motor neuron + innervated muscle fibers

Neuromuscular junction (i.e., the synapse between the motor neuron and the muscle fiber)

1. Axon terminal of the motor neuron (mitochondria, synaptic vesicles contain the neurotransmitter acetylcholine)
2. Synaptic cleft (acetylcholinesterase)
3. Postsynaptic membrane (= motor end plate; ACh receptors associated with ion channels)

Drugs that affect the function of the neuromuscular junction

1. Stimulation of transmission: by drugs that mimic the effects of ACh, e.g.,
   carbachol, nicotine
   neostigmine, physostigmine

2. Inhibition of transmission: by drugs that inhibit the effects of ACh, e.g.,
   curare (binds to and inhibits ACh receptors)
   botullinum toxin (inhibits ACh release from motor neuron)

II. EXCITATION-CONTRACTION COUPLING

End-plate potential (postsynaptic membrane)
↓
Action potential (transverse tubules)
↓
Calcium release from the sarcoplasmic reticulum (longitudinal tubules and terminal cisternae)
↓
Calcium binds to troponin C
↓
CONTRACTION
↓
Calcium pumped back into SR

III. MUSCLE CONTRACTION: MOLECULAR MECHANISMS (SLIDING FILAMENT MECHANISM)

Walk-along theory of contraction (crossbridge cycling)

THE CONTRACTION OF THE WHOLE MUSCLE

Single muscle fibers: all-or-nothing twitches
Whole muscle: contraction (muscle strength) is graded

1. Factors that influence the strength of whole muscle contraction:

    a. Number of contracting fibers (motor units)
    b. Strength of the contraction by each fiber
        - frequency of the stimulus (temporal summation, tetanization)
        - length of the fiber at the onset of contraction

2. Isotonic contraction vs. isometric contraction

    Muscle tone

3. Adaptive changes in the muscle:

    Muscle hypertrophy (fiber hypertrophy) ↔ hyperplasia
    Muscle atrophy

ENERGY REQUIREMENTS FOR MUSCLE CONTRACTION

1. Energy is needed for:
    - walk-along mechanism
    - calcium pump
    - sodium-potassium pump

2. Energy sources for ATP rephosphorylation:

    1. Creatine phosphate
    2. Oxidative phosphorylation (aerobic)
        glucose → pyruvate → Krebs cycle → H_2O and CO_2; net: 36 ATP
    3. Glycolysis (anaerobic)
        glycogen → glucose → pyruvate → lactate; net: 2 ATP

    Dynamics of the use of energy sources: ATP → Creatine phosphate → aerobic → anaerobic

3. Fatigue:
    - Muscle fatigue
    - Neuromuscular fatigue
    - Central fatigue

4. Types of muscle fibers based on their metabolism:

   1. Slow-oxidative (red) fibers:
      aerobic
      resistant to fatigue
      mitochondria↑
      blood supply ↑
      Mgb ↑

   2. Fast-glycolytic (white) fibers:
      anaerobic
      fatigue ↑
      blood supply ↓
      sarcoplasmic reticulum ↑

   3. Fast-oxidative (red) fibers:
      aerobic (→ glycolysis)
      Mgb ↑
      blood supply ↑
      fatigue →

THE PATHOLOGY OF THE SKELETAL MUSCLE

1. Myasthenia gravis:
   - an autoimmune disease of the neuromuscular junction.
     (autoimmune diseases = antibodies are produced "mistakenly" against the body's own antigens)
   - pathomechanism: antibodies destroy ACh receptors on the motor end plate;
   - symptom: very weak skeletal muscles

2. Muscular dystrophies: a group of inherited, progressive muscle disorders.
   Duchenne dystrophy:
   - it is the most common and important form of muscle dystrophies
   - an X-linked recessive disorder, it affects 1 in 3000 live male births.
   - characterized by progressive proximal muscle weakness with destruction and regeneration of muscle fibers and replacement by connective tissue.
   - caused by the absence of *dystrophin*, a protein found inside the muscle cell membrane.
   - progression is steady, most patients are confined to a wheelchair by age 10 or 12 and die of respiratory complications by age 20 yr.

SMOOTH MUSCLE

Similarities between smooth and skeletal muscle:

1. Actin and myosin filaments
2. Contraction triggered by calcium ions
3. Energy supplied by ATP

Differences from skeletal muscle:

1. Structure
   - filaments do not form myofibrils and sarcomeres
   - no striated arrangement
   - dense bodies
   - few myosin filaments interspersed among many actin filaments

2. Excitation-contraction coupling
   - no troponin complex
   - presence of calmodulin ($\rightarrow$ myosin kinase $\rightarrow$ myosin head phosphorylated)
   - calcium enters from the EC fluid

3. Contraction
   - prolonged, tonic contractions
   - slow cycling of cross bridges
   - able to contract when considerably stretched
   - stress relaxation
   - 1/10 - 1/300 of the energy needs of skeletal muscle
   - shortens to 1/3 of its original length
   - "latch" mechanism

Types: 1. Multiunit smooth muscle

- separate units, separately stimulated
- large blood vessels, bronchi, eye, hair follicles

2. Single-unit (visceral) smooth muscle

- fibers contract as a single unit (functional syncytium)
- self-excitable
  - pacemaker potential
  - slow-wave potential
- gradation of contraction: cytosolic Ca^{++}
- resting muscle tone
  - (autonomic) neural and hormonal stimuli: only modify the strength/frequency of contractions

THE PHYSIOLOGY OF BLOOD

BLOOD CONSTITUENTS

Blood volume: 5-5.5 liters (~80 ml/kg)

Cellular elements and plasma → **Hematocrit**

1. PLASMA

1. Water
2. Electrolytes
3. Nutrients, wastes, gases, hormones
4. Proteins: 6-8 g/100 ml
   - albumin
   - globulins (α, β, γ globulins)
   - fibrinogen

2. CELLULAR ELEMENTS

1. ERYTHROCYTES: 4.5-5.5 x 10^6/µl, 7-8 µm

FUNCTION: gas transport (predominantly O_2)

CONSTITUENTS

Hemoglobin (16 g/100 ml)

- 4 heme
  - iron (recycled)
  - porphyrin (→ bilirubin)

- 4 globin (recycled)

oxyHgb, deoxyHgb, carbaminoHgb

Glycolytic enzymes
Carbonic anhydrase
Surface antigens

A agglutinogen
B agglutinogen
Rh agglutinogen

ABO BLOOD GROUPS

	Antigen (RBC)	Antibody (plasma)
A	A agglutinogen	anti-B agglutinin
B	B agglutinogen	anti-A agglutinin
AB	A and B agglutinogen	neither anti -A nor anti-B agglutinin
O	neither A nor B agglutinogen	anti-A and anti-B agglutinin

RH BLOOD GROUPS

	Antigen (RBC)	Antibody (plasma)
Rh positive	Rh agglutinogen	Rh agglutinin is never present
Rh negative	no Rh agglutinogen	normally Rh agglutinin is not present, but it appears upon Rh agglutinogen challenge (transfusion, pregnancy)

PATHOLOGICAL CHANGES IN ERYTHROCYTE COUNT

I. Anemias (O_2-carrying capacity ↓)

1. Blood loss (hemorrhage)

2. Defective erythropoiesis
   bone marrow function ↓
   iron deficiency
   vitamin B_{12} deficiency (pernicious anemia)
   folate deficiency
   renal anemia

3. Hemolytic anemias
   erythroblastosis fetalis
   sickle cell anemia
   malaria

II. Polycythemias

1. Primary polycythemia
2. Secondary polycythemia
3. Relative polycythemia

2. LEUKOCYTES: 4,500-8,000/µl

Only transported by blood, they carry out their function in the tissues.

FUNCTION

1. Defend against pathogens
2. Eliminate virus-infected, mutant or foreign cells
3. Clean up tissue debris
4. Modulate the function of the nervous and endocrine systems by secreting special hormones, called *cytokines*.

TYPES

1. Neutrophil granulocytes: 50-70%, 12-15µm
   chemotaxis, phagocytosis

2. Eosinophil granulocytes: 2-4%, 12-17 µm
   allergic reactions

3. Basophil granulocytes: 0.5-1%, 10-12 µm
   → mast cells
   inflammatory responses (histamine, heparin)

4. Monocytes: 2-8%, 12-20 µm
   → macrophages, e.g., Kupffer cells, alveolar macrophages, and microglia;
   phagocytosis, antigen presentation

5. Lymphocytes: 30-40%, 6-15µm
   T and B lymphocytes: humoral and cellular immune responses
   Natural killer (NK) cells: non-specific immunity

PATHOLOGICAL CHANGES IN LEUKOCYTE COUNT

1. Leukopenia (granulopenia, lymphopenia)
2. Leukocytosis
3. Leukemia

3. THROMBOCYTES: 150,000-350,000/µl

Cell fragments (of megakaryocytes)

CONSTITUENTS: contractile elements (actin, myosin)
"thrombocyte factors"

FUNCTION: hemostasis

PATHOLOGICAL CHANGES

1. Thrombocytopenia
2. Thrombocytosis

HEMATOPOESIS

Pluripotent stem cell in red bone marrow

Regulated by various hematopoietic hormones

- proerythroblast →→→→→ reticulocyte → **erythrocyte**
  stimulated by *erythropoietin* (from kidney in response to hypoxia)

- myeloblast →→→→→ **granulocytes**
- monoblast →→ **monocyte**
- lymphoblast →→→ **lymphocyte** (become "committed" T or B lymphocytes in thymus or bone marrow)

  leukocyte formation is stimulated by "*colony-stimulating factors*", e.g., granulocyte colony-stimulating factor (G-CSF), granulocyte-monocyte colony-stimulating factor (GM-CSF), etc.

- megakaryoblast →→ megakaryocyte → **thrombocyte**
  stimulated by *thrombopoietin*

HEMOSTASIS

I. THE EVENTS OF HEMOSTASIS

First step: Vasoconstriction (local myogenic factors and activation of the sympathetic nervous system)

Second step: Formation of platelet plug (sufficient for microruptures)
collagen fibers exposed → thrombocyte adhesion → ADP, thromboxane A_2 → thrombocyte adhesion↑↑

Third step: Blood coagulation
cascade activation of clotting factors
intrinsic pathway and extrinsic pathway

result: fibrin meshwork

Fourth step: Clot retraction (thrombocytes)

Tissue repair

Lysis of blood clots: Factor XII together with the delayed release of "tissue plasminogen activator"
↓
plasminogen activated to plasmin (a proteolytic enzyme).

II. REGULATORY MECHANISMS: INTRAVASCULAR ANTICOAGULANTS

Prevention of blood clotting in the normal vascular system.

1. Endothelial surface factors:
   - smoothness of the endothelium
   - prostacyclin
   - glycocalyx
   - thrombomodulin

2. Heparin-antithrombin III. complex (removes thrombin from the blood)

3. α_2-macroglobulin

III. THE PATHOLOGY OF HEMOSTASIS

1. Excessive bleeding

   - Thrombocytopenia (bleeding starts <50,000 platelet/µl; frequently lethal <10,000)
   - Hemophilia (Hemophilia A: deficiency of factor VIII)
   - Vitamin K deficiency (Factors II, V, VII, IX)
   - Liver diseases

2. Thromboembolic conditions

   - Thrombus: abnormal clot in the blood vessel
   - Embolus: runaway thrombus

THE IMMUNE SYSTEM

Immune responses: elimination of foreign materials, abnormal cells, and tissue debris

Innate immune responses:	first line of defense any foreign material upon initial exposure immediate response
Acquired immune responses:	selective adaptive responses that improve on repeated exposure after prior exposure response after a latency

Antigens: molecules recognized by receptors on lymphocytes

Immunogens: Those antigens that elicit immune responses. Small antigens (haptens) often elicit immune response only if they are coupled to larger molecules (carriers)

INNATE IMMUNE RESPONSES

Physical barriers, lysozyme, gastric acid

I. CELLULAR COMPONENTS

1. Phagocytes: neutrophil granulocytes and macrophages

   Recognize non-vertebrate carbohydrates, antibody or complement-coated microorganisms and dying cells
   ↓
   engulfed microorganisms exposed to toxic intracellular molecules (superoxides, nitric oxide, lysozyme, etc.)

2. Dendritic cells (e.g., Langerhans' cells in skin)
   - endocytose extracellular antigens
   - when activated migrate to local lymph node → present antigens to T cells

3. Eosinophil granulocytes: kill parasites by releasing reactive oxygen metabolites and cationic proteins

4. Basophil granulocytes and mast cells: posses high-affinity receptors for IgE → IgE binds → inflammatory mediators are released (e.g., histamine). Allergies!!

5. NK cells: destroy infected or malignant cells

   - possess high-affinity receptors for IgG → NK cells bind to IgG-coated target cells → kill target cells

- posses killer-activating receptors and killer-inhibitory receptors

  when NK cells bind to <u>healthy</u> cells both receptors are activated → no killing occurs

  when NK cells bind to malignant or infected cells → inhibitory receptor not activates → killing occurs

II. <u>MOLECULAR COMPONENTS</u>

1. <u>Complement system</u>: an enzymatic amplifying cascade system

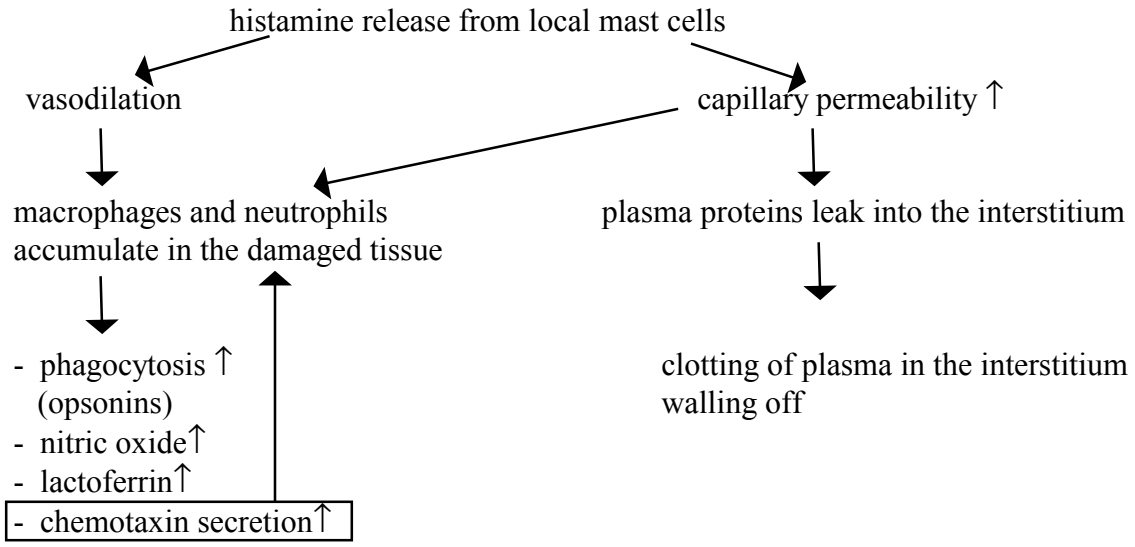
   The presence of antibody-antigen complexes or bacterial cell wall components
   ↓
   A cascade is triggered
   ↓
   A number of immunologically active substances are generated which cause:
   - opsonization
   - activate macrophages to release inflammatory mediators
   - chemotaxis of phagocytes
   - formation of membrane-attack complexes

2. <u>Acute-phase proteins</u>: plasma proteins that enhance resistance and help repair tissue damage

3. <u>Cytokines</u>: messenger molecules released by immune cells, virus-infected non-immune cells, neurons, etc.
   - interferons
   - interleukins
   - tumor necrosis factors

ACUTE INFLAMMATORY RESPONSE

A complex local tissue reaction to infection, trauma, chemicals or heat; cells and molecules of the immune system move to the affected site.



Inflammatory mediators:
- histamine
- kallikrein (→ bradykinin)
- prostaglandins
- clotting factors
- complement system
- cytokines (interleukins, tumor necrosis factors)

Symptoms: rubor, tumor cum calore et dolore et functio laesa

ACQUIRED IMMUNE RESPONSES

PLAYERS:

1. Antigens

2. Antibodies: γ globulins (immunoglobulins), secreted by B-lymphocytes
   - IgM
   - IgG
   - IgE
   - IgA
   - IgD

3. B-lymphocytes: humoral immunity

4. T- lymphocytes: cell-mediated immunity
   capable of recognizing and binding to antigens (foreign) and major histocompatibility markers (self)

DIFFERENTIATION OF LYMPHOCYTES

- antigen-independent differentiation: gains antigen specificity
  stem cells → thymus or bone marrow → lymphoid tissue

- antigen-dependent differentiation (clonal selection theory): lymphocytes multiply into a clone of identical lymphocytes (effector cells and memory cells)

HUMORAL IMMUNE RESPONSE: augments the effects of nonspecific defense mechanisms

Example: defense against bacteria

1. Macrophage phagocytosis, antigen display on the surface together with major histocompatibility complex (MHC) class II molecules

2. Helper T-ly recognizes the antigen and the MHC markers on the macrophage surface; T_H-ly binding

3. Monokine release (IL-1, TNF) from macrophage

4. Lymphokine release (B cell growth factor) from T_H-ly → B-ly proliferation (effector/plasma cells and memory cells)

5. Antibody secretion ↑↑

6. Antibody-antigen complexes:
   - activate B lymphocytes
   - act as opsonins
   - direct neutralizing effect
   - agglutination- precipitation
   - stimulate killer T cells and mast cells
   - activate complement system

CELL-MEDIATED IMMUNE RESPONSE

Immune cells kill the body's own cells that display specific foreign antigens

For example, defense against viruses, tumor cells, and implanted tissues

Killer T cells: destroy the body's own cells that display foreign antigens + MHC class I molecules
perforin, apoptosis

Helper T cells: T cell growth factor (IL-2)
Chemotaxins
Macrophage migration inhibition factor

Suppressor T cells

Memory T cells

THE PATHOLOGY OF THE IMMUNE SYSTEM

I. IMMUNE DEFICIENCIES

1. Types of immune deficiencies

According to the affected cell type:

1. T cell (e.g., AIDS)
2. B cell
3. T and B cell deficiency

According to the onset of the disease:

1. Congenital or
2. Acquired immune deficiency (e.g., AIDS)

2. Acquired Immune Deficiency Syndrome (AIDS): deficiency of a subpopulation of T lymphocytes

Definition: The term AIDS applies to the most advanced stages of HIV infection.

AIDS is the fifth leading cause of death among all adults aged 25 to 44 in the United States. Among African-Americans in the 25 to 44 age group, AIDS is the leading cause of death for men and the second leading cause of death for women

HIV virus: belongs to a subgroup of retroviruses known as lentiviruses, or "slow" viruses; their genes composed of RNA.

Retroviruses use an enzyme called reverse transcriptase to convert their RNA into DNA, which then is incorporated into the host cell's genes.

HIV is present in the blood, sexual fluids and breast milk of people who are infected with the virus. It is passed on when these infected fluids get into another person's system. Newborns born to HIV positive women can be infected during pregnancy and birth, or through breast feeding.

Pathogenesis: HIV progressively destroys the body's ability to fight infections and certain cancers by destroying the ***T helper cells*** (CD4+ cells).
Normal CD4+ cell count: 600-1,500/mm^3
AIDS: CD4+ cell count below 200/ mm^3

Symptoms: indicative of severe immunosuppression

- **Infections**, such as tuberculosis, malaria and herpes.

- **Opportunistic infections** (infections caused by common bacteria, funguses and parasites which healthy bodies can fight, but which can cause illness and in some cases death in people with damaged immune systems), such as *Pneumocystis carinii* pneumonia (PCP), a condition extraordinarily rare in people without HIV infection. Infections of the brain and meninges

- **Cancers**, especially those caused by viruses such as *Kaposi's sarcoma* (round brown, reddish, or purple spots that develop in the skin or in the mouth) and *cervical cancer*, or cancers of the immune system (*lymphomas*).

Treatment: By a combination of "antiretroviral drugs". They block the virus's ability to replicate and they can delay the onset of AIDS by slowing the loss of CD4+ cells, but they are not a cure.

- Entry inhibitors: bind to the proteins on the outside of the HIV virus and stop it from entering the target cell

- Reverse transcriptase inhibitors (e.g., AZT)

- Protease inhibitors: disable protease, an enzyme which plays a key role in the formation of the new virus.

II. INAPPROPRIATE IMMUNE ATTACKS

1. Autoimmune diseases

2. Immune-complex diseases

3. Allergies (hypersensitivities)

   a. Immediate hypersensitivities

   Mechanism: IgE↑↑ from B-ly → IgE attached to mast cell, basophil gr. → antigen (allergen) binds to IgE → → histamine↑, slow-reacting substance A (SRS-A)↑, eosinophil chemotactic factor↑ from mast cells/basophil gr.

   Symptoms: immediately following the exposure to allergen; caused by histamine and SRS-A and depend on the site of their production:
   - local allergic responses: asthma, hives, diarrhea, hay fever, etc.
   - generalized allergic response: anaphylactic shock

   b. Delayed hypersensitivities

   Mechanism: caused by T-ly
   Symptoms: skin eruptions, 1-3 days after the exposure to allergens, e.g., cosmetics, chemicals, poison ivy

ESSAY QUESTIONS: FIRST EXAM

1. Analytical, integrative and reductionist approaches in physiology.
2. What is homeostasis?
3. Give examples for variables in the body that are under homeostatic control.
4. The major chemical constituents of the cell and their importance.
5. The structure of the cell membrane.
6. The function of membrane proteins.
7. The general characteristics of diffusion and the major factors that determine diffusion rate.
8. Facilitated diffusion.
9. Osmosis.
10. The general characteristics of active transport mechanisms.
11. The characteristics of primary active transport mechanisms; examples for primary active transport mechanisms.
12. The characteristics of sodium-potassium pump.
13. The characteristics of secondary active transport mechanisms; examples for secondary active transport mechanisms.
14. The basic factors that determine resting membrane potential.
15. Graded potentials: types, causes, and characteristics.
16. Action potential: cause and characteristics.
17. List the major differences between graded potentials and action potential.
18. The structure of the sarcomere.
19. The structure of the myofibrils.
20. The contraction of the skeletal muscle fiber: neuromuscular transmission, excitation-contraction coupling, molecular mechanism of contraction.
21. The contraction of the whole muscle.
22. The energy needs and energy sources of muscle contraction.
23. Fatigue.
24. Types of muscle fibers according to their metabolism and the speed of the contraction; the characteristics of various fiber types.
25. The pathology of the skeletal muscle.
26. The differences in the structure of smooth and skeletal muscles.
27. The differences in the function of the smooth and skeletal muscles.
28. The basic types of smooth muscle and their main characteristics.
29. The functions of plasma proteins.
30. The formation of red blood cells.
31. The formation and structure of thrombocytes.
32. The structure and function of hemoglobin.
33. ABO blood groups.
34. The physiology of Rh blood groups and the significance of Rh in pregnancy.
35. Erythroblastosis fetalis.
36. Anemias.
37. Polycythemias.
38. The percent distribution of the various leukocyte types.
39. Pathological changes in leukocyte count.
40. The major events of hemostasis.
41. Blood coagulation.
42. The lysis of blood clots.
43. Intravascular anticoagulant systems.

44. The pathology of hemostasis.
45. Similarities and differences between the innate and acquired immune responses
46. The cellular and molecular elements of the innate immune response
47. The mechanism and symptoms of the acute inflammatory response.
48. The function and structure of antibodies. The function of various antibody subclasses.
49. The differentiation of lymphocytes.
50. The major events during a primary humoral immune response.
51. The major effects of antibodies in the immune response.
52. The major players and their roles in the cell-mediated immune response.
53. Immune deficiencies.
54. AIDS
55. Inappropriate immune attacks.

Practice Test for the First Lecture Exam

1. Which one of the following is under homeostatic regulation?
a. Growth
b. Aging
c. Intrauterine development
d. Reproduction
e. Body temperature

2. Homeostasis is the maintenance of the optimal conditions in the
a. Internal environment
b. Milieu interieur
c. Interstitial fluid
d. All of the above
e. None of the above

3. Which cells are involved in generating the internal environment?
a. Specialized secretory cells
b. Specialized excretory cells
c. Bone marrow by producing blood cells
d. Nervous and endocrine systems
e. Practically almost all living cell in the organism

4. Which regulatory system causes relatively long-lasting changes in metabolic functions?
a. Immune system
b. Endocrine system
c. Nervous system
d. All of the above
e. None of the above

5. What is **NOT** a function of the cell membrane?
a. Provides a barrier between the intracellular environment and the extracellular fluid.
b. Provides transport mechanisms for certain substances between the intra- and extracellular environment.
c. Generates electrical signals
d. Stores genetic material
e. All of the above is a function of the cell membrane

6. The concentration of which molecule(s) is significantly higher in the extracellular fluid as compared to the cytoplasm?
a. Protein anions
b. Potassium
c. Glucose
d. Calcium
e. RNA

7. What is the most abundant in the cytoplasm?
a. Water
b. Electrolytes
c. Proteins
d. Lipids
e. Carbohydrates

8. What is the function of peripheral proteins on the inner surface of the cell membrane?
a. They form ion channels across the membrane.
b. They function as receptors on the surface of the membrane.
c. They play a role in connecting cells to each other.
d. They function as enzymes.
e. They determine the antigenity of the cell.

9. Which one of the following favors the diffusion of a substance across the cell membrane?
a. Increased thickness of the membrane
b. Decrease in the number of protein channels in the membrane
c. Increased molecular weight of the substance that diffuses across the membrane
d. Increased lipid solubility of the substance that diffuses across the membrane
e. Decrease in temperature

10. What is true for osmosis?
a. It takes place through semipermeable membranes.
b. It is the movement of ions, such as sodium and potassium across a membrane.
c. It requires carrier molecules.
d. It requires external energy.
e. It has a transport maximum (Vmax) point.

11. Find the **FALSE** statement.
a. If a cell does not have acetylcholine receptors, then the cell will not be responsive to acetylcholine.
b. Messenger molecules that cannot cross the cell membrane bind to extracellular receptors.
c. Lipid soluble messenger molecules can bind to intracellular receptors.
d. A certain cell has receptors for only one type of messenger molecule.
e. Extracellular receptors have membrane-spanning segments.

12. What is true for G proteins?
a. They directly bind to hormones (extracellular messengers).
b. Their activation requires the binding of ATP to one of the subunits.
c. The activation of G proteins induces changes in the intracellular concentration of second messenger(s).
d. They are bound to the extracellular surface of the cell membrane.
e. They are bound to the endoplasmic reticulum.

13. Which one is **NOT** a second messenger molecule?
a. Calcium
b. cGMP
c. cAMP
d. Diacylglycerol
e. Acetylcholine

14. What is the function of the sodium-potassium pump?
a. Pumps out potassium from the cell in exchange to sodium.
b. Pumps out both sodium and potassium from the cell.
c. Pumps potassium into the cell in exchange to sodium.
d. Pumps both sodium and potassium into the cell.
e. Pumps sodium into the cell in exchange to potassium.

15. What do graded potentials and action potentials have in common?
a. Both are due to ion flows across the cell membrane.
b. Both can be hyperpolarization of the cell membrane.
c. Both can be summed.
d. Refractory phase follows both.
e. Both are all-or-none responses.

16. The part of the sarcomere that contains myosin filaments forms the
a. A bands
b. I bands
c. H zones
d. M lines
e. Z lines

17. Which one of the following proteins is built up from three subunits?
a. Myosin
b. Actin
c. Tropomyosin
d. Troponin
e. None of the above

18. What is true for tropomyosin?
a. It binds calcium ions.
b. It may cover the actin-binding sites of the myosin molecules.
c. It forms cross bridges with the myosin heads
d. When it covers the myosin-binding sites of the actin molecules, prevents cross bridge formation.
e. It is made up from 6 polypeptide chains.

19. Which one of the following chemicals binds to and inhibits acetylcholine receptors?
a. Carbachol
b. Neostigmine
c. Curare
d. Botullinum toxin
e. None of the above

20. Find the **FALSE** statement.
a. A drug that inhibits the calcium pump on the membrane of the sarcoplasmic reticulum, would stimulate the contraction of skeletal muscle fibers.
b. The tetanization of skeletal muscle is possible.
c. Hyperplasia is an adaptive mechanism in skeletal muscle to exercise.
d. Aerobic metabolism of glucose results in the formation of more ATP molecules than glucose metabolism through anaerobic pathway.
e. Smooth muscle fibers contain actin and myosin filaments.

21. Normal leukocyte count is
a. 4,500 – 8,000/ml
b. 4,5 – 8 million/µl
c. 4.5 – 8 x 10^3/µl
d. 45,000 – 80,000/µl
e. 4.5 – 8/mm^3

22. Natural killer (NK) cells are a special form of
a. Neutrophil granulocytes
b. Killer erythrocytes
c. Monocytes
d. Lymphocytes
e. None of the above

23. Hypoxia stimulates the formation of
a. Erythrocytes
b. Lymphocytes
c. Thrombocytes
d. Leukocytes
e. All of the above

24. What is true for carbamino-hemoglobin?
a. It is not present in blood under normal conditions
b. It is a toxic compound
c. It is formed when the Fe-ion of hemoglobin binds CO
d. It is formed when the globin part of hemoglobin binds CO_2
e. None of the above

25. Anti-Rh agglutinin is present
a. In the red blood cells of every RH negative person
b. In the plasma of every Rh negative person
c. In the red blood cells of every Rh positive person
d. In the plasma of every Rh positive person
e. None of the above

26. What is a common cause of hemolysis?
a. Blood loss
b. Vitamin B12 deficiency
c. Iron deficiency
d. Malfunction of the kidneys
e. Malaria

27. What is the significance of endothelial prostacyclins?
a. They activate thrombocytes
b. They prevent thrombocyte adhesion to the endothelium
c. They trigger the intrinsic pathway of blood coagulation
d. They trigger the extrinsic pathway of blood coagulation
e. All of the above

28. Which cell plays a key role in cell-mediated specific immune responses?
a. Killer T cells
b. B cells
c. Plasma cells
d. Macrophages
e. Monocytes

29. Which one of the following plays a key role in fighting against viral infections?
a. Interferons
b. γ globulins
c. IgG
d. IgM
e. B lymphocytes

30. Find the **FALSE** statement.
a. Histamine is an important inflammatory mediator
b. Antibodies belong to the γ-globulin class of proteins
c. Complement system is part of the non-specific defense system
d. B lymphocytes play a key role in cell-mediated immune responses
e. IgE immune globulins play a role in allergic responses

31. Which cell organelle plays a role in intracellular digestive processes?
a. Mitochondria
b. Lysosomes
c. Golgi apparatus
d. Rough endoplasmic reticulum
e. Smooth endoplasmic reticulum

32. Typically, enzymes are
a. triglycerides
b. phospholipids
c. fibrillar proteins
d. globular proteins
e. carbohydrates

33. Membrane surface receptors are composed of
    a. peripheral proteins
    b. integral proteins
    c. cholesterol
    d. carbohydrates
    e. glycolipids

34. What is **NOT** true for diffusion across the cell membrane?
    a. It does not require ATP from the cell
    b. Its rate depends on the thickness of the membrane
    c. Lipid soluble substances diffuse more easily than water soluble chemicals
    d. The molecular weight of the substance affects its diffusion rate
    e. Positive ions always diffuse from the positive side to the negative side of the membrane.

35. Guanylyl cyclase plays a role in the formation of
    a. calcium ions
    b. cAMP
    c. cGMP
    d. Inositoltriphosphate (IP_3)
    e. Diacylglycerol (DAG)

36. Find the **FALSE** statement.
    a. In response to an excitatory stimulus, protein anions leave the cell thereby making the intracellular environment less negative
    b. In response to an excitatory stimulus, positive ions enter the cell thereby making the intracellular environment less negative
    c. In response to an inhibitory stimulus, the intracellular surface of the cell membrane will become more negative
    d. In response to an inhibitory stimulus, the cell membrane becomes hyperpolarized
    e. The duration of the graded potentials is proportional to stimulus duration

37. Which one of the following structures binds ATP?
    a. Myosin molecule
    b. Actin molecule
    c. Troponin molecule
    d. Tropomyosin molecule
    e. All of the above

38. What would you expect from a drug that inhibits acetylcholinesterase?
    a. It would inhibit the release of acetylcholine from the motor neuron
    b. It would stimulate the release of acetylcholine from the motor neuron
    c. It would inhibit muscle contractions
    d. It would stimulate muscle contractions
    e. It would not have effect on the function of the neuromuscular junction

39. What is **NOT** true for the single unit (visceral) smooth muscle?
    a. The muscle fibers contain actin and myosin
    b. It contracts only if stimulated by a motor neuron
    c. They make up the muscle layers of the intestinal walls
    d. The muscle cells behave as a functional syncytium
    e. Increase in intracellular calcium concentration induces the contraction of the muscle fibers

40. Which one is the most numerous blood cell type?
    a. Erythrocyte
    b. Thrombocyte
    c. Neutrophil granulocyte
    d. Leukocyte
    e. Monocyte

41. What is true for a person who belongs to the "A" blood group?
    a. His/her plasma contains anti-A antibodies
    b. His/her plasma contains A antigens
    c. His/her red blood cells may or may not display Rh antigens
    d. His/her plasma always has anti-Rh antibodies
    e. His/her plasma does not contain anti-B antibodies

42. What is the normal range for hematocrit?
    a. 4-5 million per μl
    b. 42-46%
    c. 0.1-1%
    d. 150-300,000
    e. 7-8 μm

43. What may cause erythroblastosis fetalis?
    a. Iron deficiency
    b. Vitamin B12 deficiency
    c. Hemorrhage
    d. Blood group incompatibility between mother and fetus
    e. Kidney disease

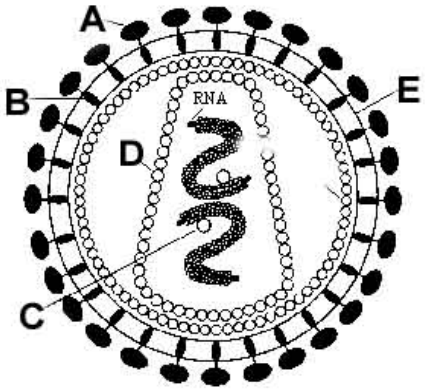
44. Which step is common between the intrinsic and extrinsic pathways of blood coagulation?
    a. The activation of factor XII
    b. The activation of factor IX
    c. Prothrombin $\rightarrow$ thrombin conversion
    d. The activation of factor VII
    e. The appearance of tissue factor III in the circulation

45. Which cells belong to the specific defense system?
    a. Neutrophil granulocytes
    b. Macrophages
    c. Lysozyme
    d. NK cells
    e. Memory T cells

46. Where do T lymphocytes gain their antigen specificity?
    a. Bone marrow
    b. Lymph nodes
    c. Thymus
    d. Peyer's patches
    e. Liver

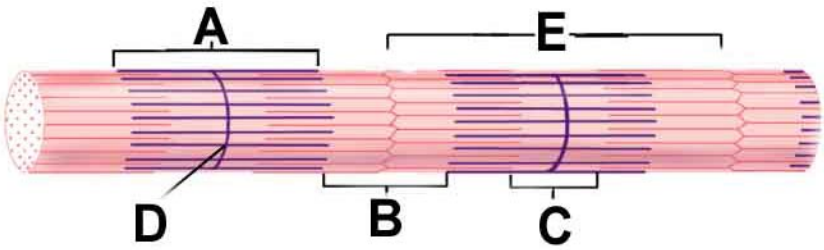
47. What is **NOT** an effect/function of antibodies?
    a. Osponization
    b. Neutralization of certain toxins
    c. Stimulation of certain T cells
    d. Activation of the complement system
    e. Destruction of virus-infected host cells

48. What is **NOT** true for AIDS.
    a. Opportunistic infections are common
    b. Certain forms of cancer are common
    c. CD4 cell count is below 200/µl
    d. It is caused by a retrovirus
    e. The presence of the human immunodeficiency virus in the someone's body means that he/she suffers from AIDS.

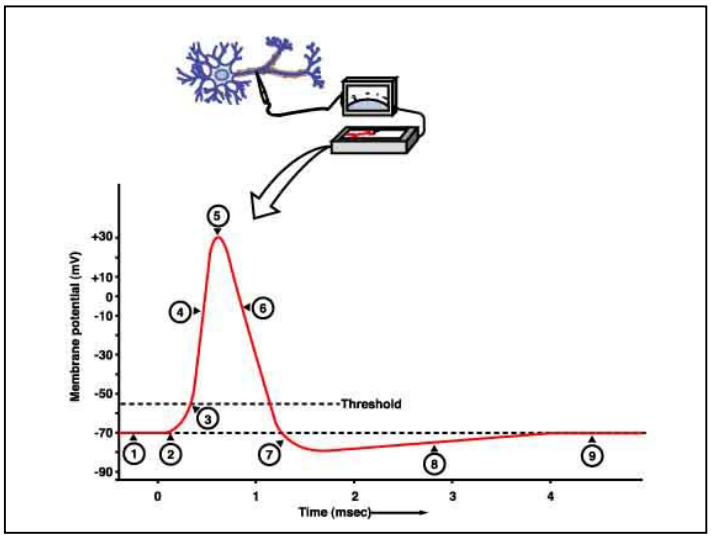


49. Which one is an enzyme important for the replication of HIV virus in the host cell?

    a. A
    b. B
    c. C
    d. D
    e. E



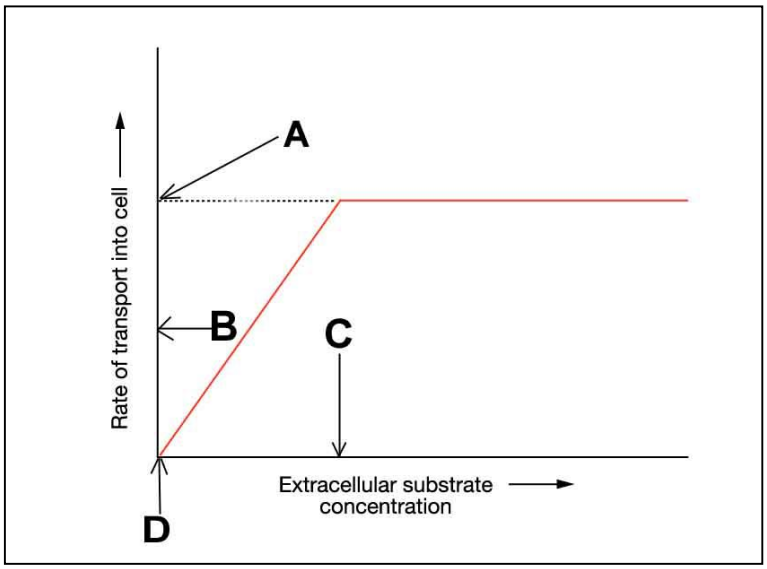
50. Which zone/band/segment shortens during muscle contraction?
    a. Only A
    b. Only B
    c. C and B
    d. Only E
    e. B and C and E



51. What is true for "phase 4" on the action potential curve?
    a. The membrane is hyperpolarized
    b. Voltage-gated potassium channels are open
    c. Large amounts of potassium enter the cell
    d. Large amounts of potassium leave the cell
    e. None of the above

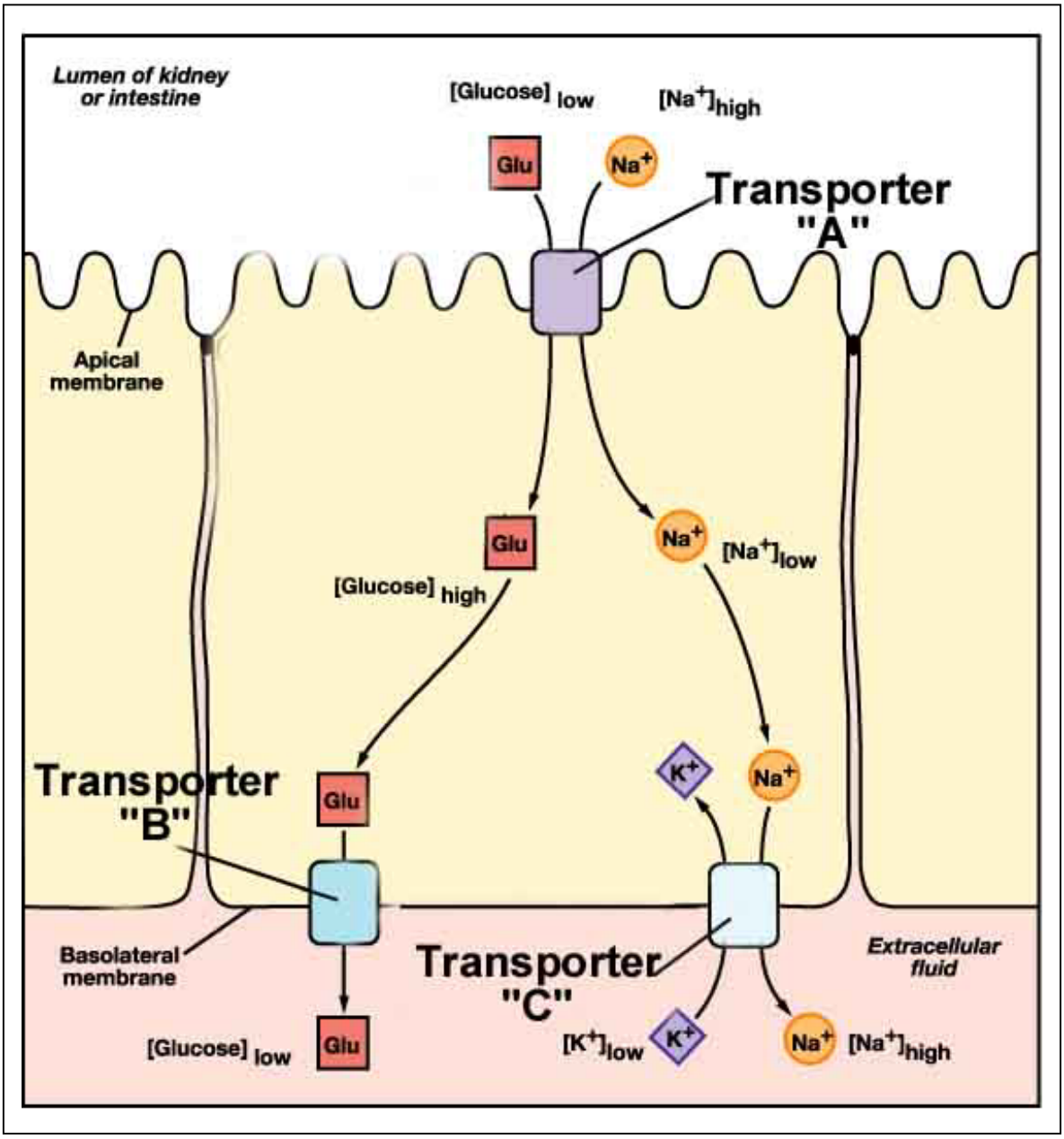
52. During which phase are the voltage-gated sodium channels open?
    a. 1
    b. 4
    c. 6
    d. 7
    e. 9

53. During which phase is the membrane hyperpolarized?
    a. 1
    b. 4
    c. 6
    d. 8
    e. 9



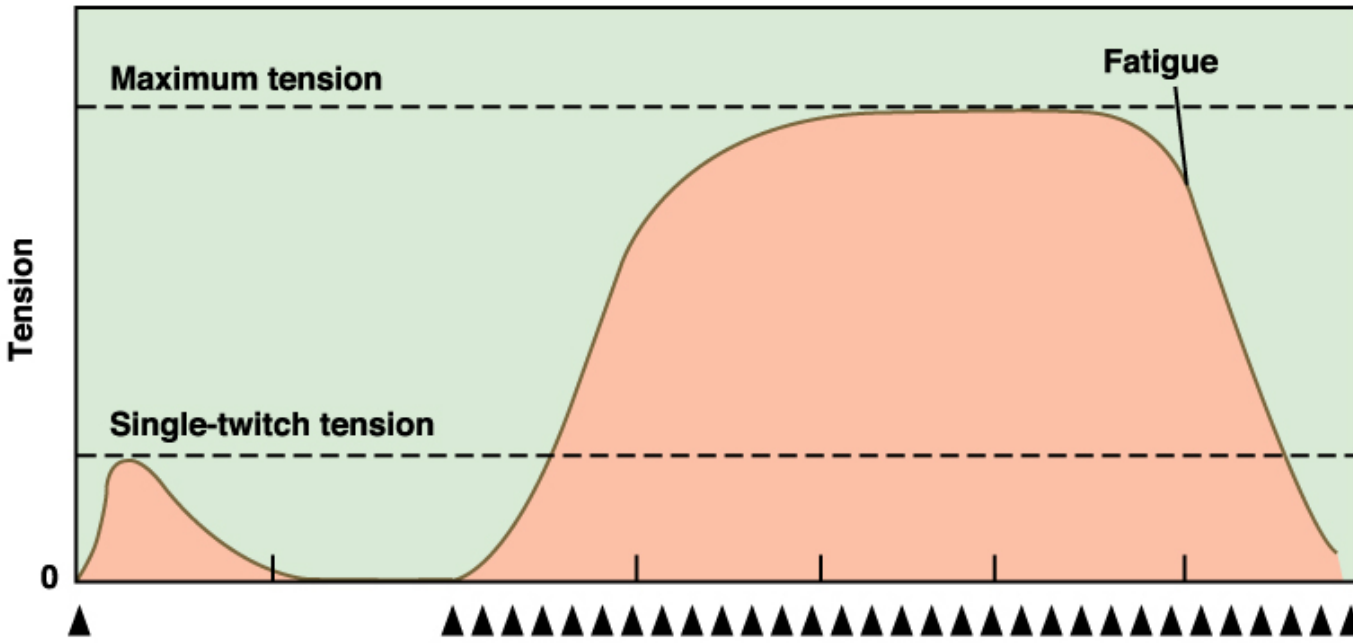
54. What is the Tm point?
    a. Value A on the y axis
    b. Value B on the y axis
    c. Value C on the x axis
    d. Value D on the x axis
    e. None of the above

55. This pathological form of red blood cell shown by the arrow is characteristic of
    a. pernicious anemia
    b. iron deficiency
    c. polycythemia
    d. a hereditary cell membrane defect
    e. leukemia

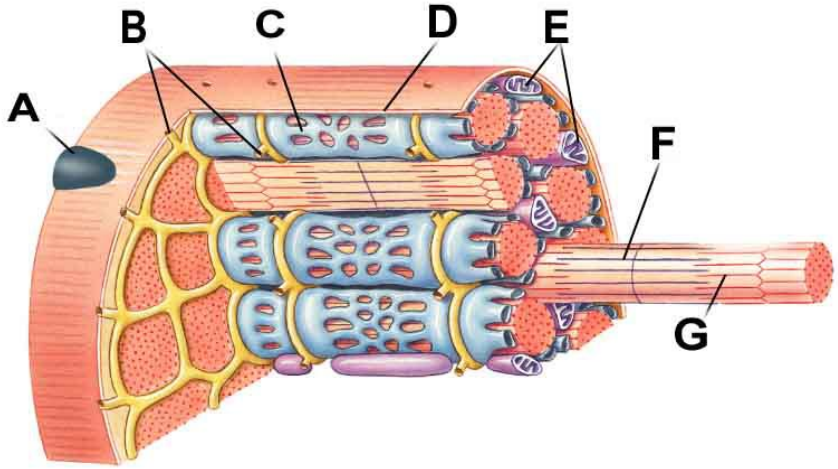


56. Which transporter has to be phosphorylated by ATP?
    a. A
    b. B
    c. C
    d. A and C
    e. B and C

57. The function of transporter B is to perform/aid
    a. active transport
    b. osmosis
    c. simple diffusion
    d. facilitated diffusion
    e. an antiport transport mechanism



58. What is true for the figure above?
   a. It shows the phenomenon of temporal summation
   b. It shows the phenomenon of complete tetanus
   c. It shows the effects of repeated stimuli on muscle contraction
   d. None of the above
   e. All of the above



59. Which one is the sarcoplasmic reticulum?
   a. A
   b. B
   c. C
   d. F
   e. G

60. Which structures form the contractile elements?
   a. B and D
   b. C and E
   c. G and F
   d. E
   e. None of the above