CONTENTS

49. All of the following statements pertaining to the rate constant for drug elimination are correct, EXCEPT:
1. For first-order kinetics it is equal to fraction of drug, which is eliminated per unit of time.
2. It is independent on dose.
3. For zero-order kinetics it is equal to fraction of drug, which is eliminated per unit of time.
4. For zero-order kinetics it is equal to amount of drug, which is eliminated per unit of time.

50. The volume of plasma, from which drug can be completely removed by the kidney per unit of time, is termed:
1. Volume of distribution.
2. Renal clearance.
3. Constant for drug elimination.
4. Half-life.

51. If the renal clearance increases when urinary pH increases, the drug is:
1. A weak acid.
2. A weak base.
3. A non-ionizable substance.

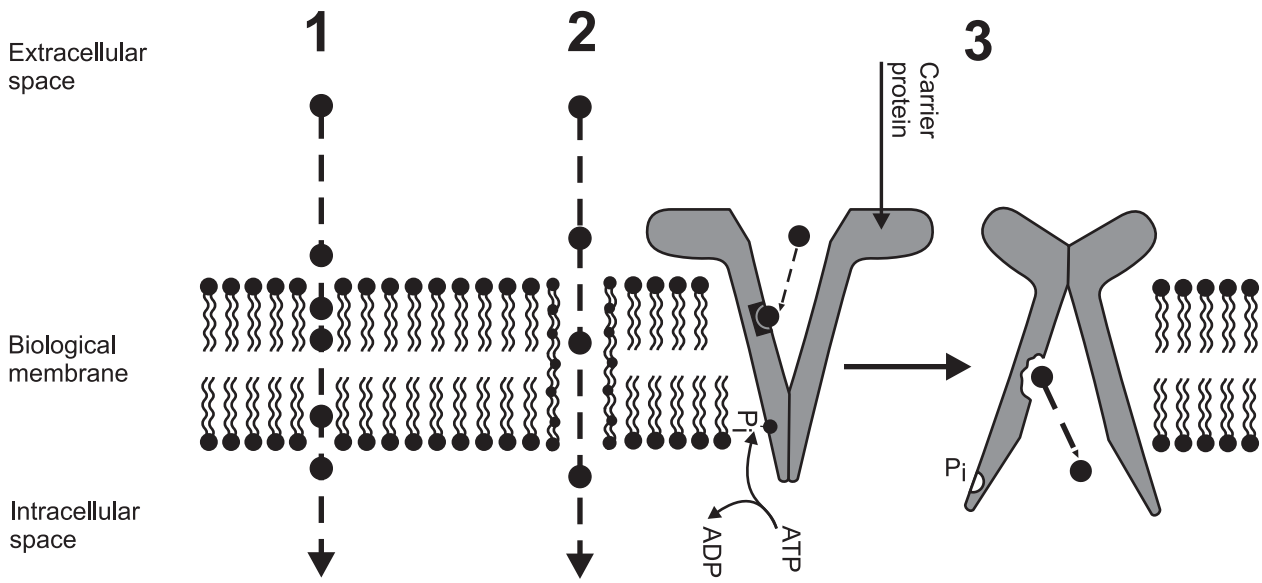
52. If the renal clearance increases when urinary pH decreases, the drug is:
1. A weak base.
2. A weak acid.
3. A non-electrolyte.

53. All of the following statements about drug clearance are correct, EXCEPT:
1. Renal clearance characterizes excretion of unchanged drugs by the kidney.
2. Systemic clearance characterizes elimination of drugs by all routes (liver, kidney, lung and others).
3. Drugs with high hepatic clearance should be avoided in patients with renal diseases.
4. Hepatic clearance characterizes metabolism of parent drug in the liver and/or biliary drug excretion.

3. TASKS

TASK 1

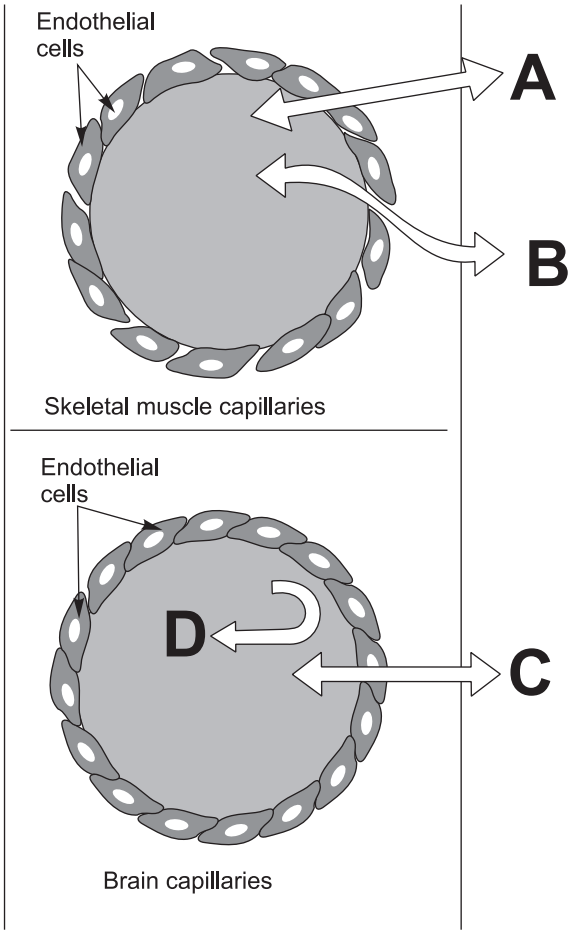
Identify and put down in the spaces provided the mechanisms of penetration of drug molecules across the cell membrane (1–3).



1.	2.	3.

TASK 2

The figure given below shows how drugs A, B, C, D penetrate the wall of blood capillaries in skeletal muscle and brain. Identify these drugs as lipophilic (__) or hydrophilic (__) putting appropriate letters in the brackets. Give explanations in the spaces provided below.

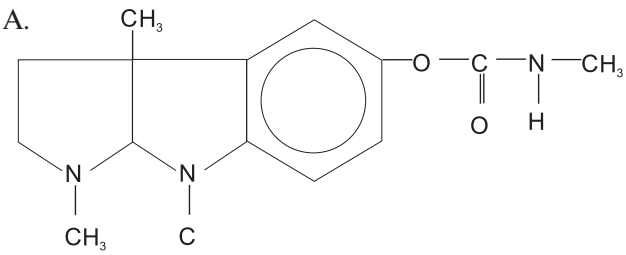


TASK 3

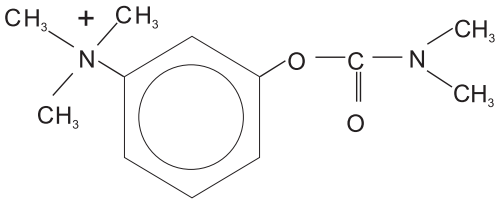
Analyze the penetration of drugs A and B through the cell membranes. Which of these drugs is more likely:

1) to penetrate blood-brain barrier;
2) to be excreted by the kidney in unchanged form;
3) to be metabolized before being excreted by the kidney?

A.



B.



Give rational explanations in the spaces provided.

1) _____

_____

2) _____

3) _____

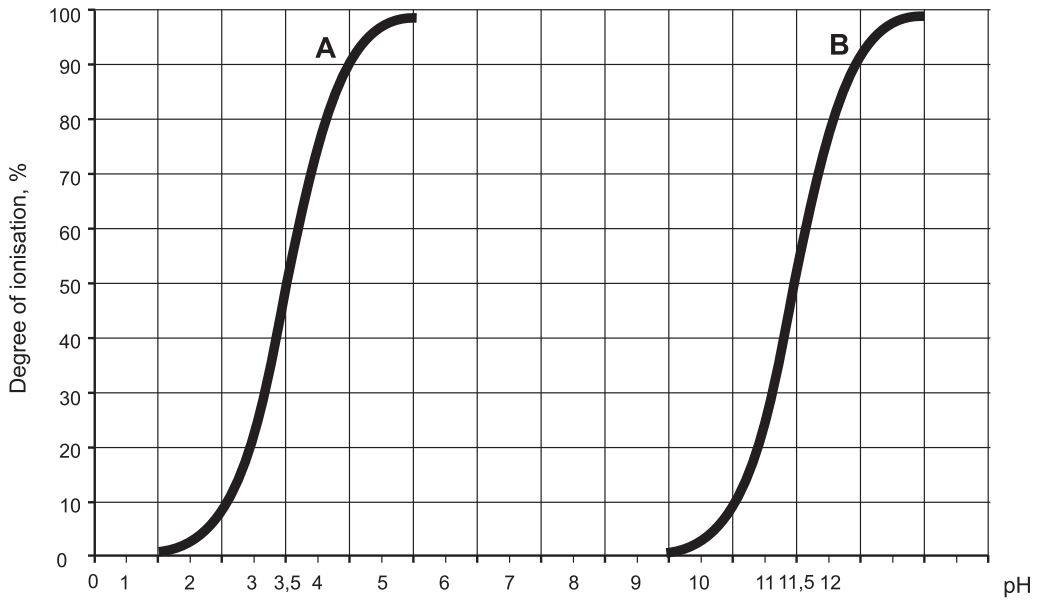
_____

TASK 4

The figure given below shows the curves (A and B), which reflect the degree of ionization as a function of pH for two weak acids: A — acetylsalicylic acid (pKa = 3.5) and B — ascorbic acid (pKa = 11.5).

Analyze these curves and answer the questions:

1) which weak acid would more easily and to a greater extent penetrate the blood-brain barrier (plasma pH = 7.4);
2) which weak acid would be better excreted by the kidney if urine filtrate pH is equal to 4.5;
3) how the reabsorption of both weak acids will change if pH of urine filtrate increases from 4.5 to 8.0.



Give explanations in the spaces provided.

1) _____

_____

2) _____

3) _____

_____

Background information

Penetration of weak acids and weak bases through membranes

Many drugs are weak acids or bases and therefore in solution, they exist in both ionized and nonionized forms.

The degree of ionization of weak acids and weak bases depends on the pH of the medium and the pKa of drugs. The pKa is the measure of the strength of the interaction of a drug with proton. pKa is equal to the pH of the medium at which 50% of a drug is ionized. pKa values for some acidic and basic drugs are given in reference-books and can be used for simple calculations of degree of drug's ionization at a certain pH. There is Henderson–Hasselbalch equation, which may be used for such calculations. It is given in two forms.

For weak acids: $\log [AH]/[A^-] = pKa - pH$

For weak bases: $\log [BH^+]/[B] = pKa - pH$

The nonionized molecules of weak acids and weak bases are usually more lipid-soluble and can easily diffuse across cell membranes. In contrast, ionized forms being more hydrophilic are unable to penetrate the lipid membrane. Therefore, they can be trapped on one side of the membrane if there is a difference in the pH of the medium on two sides of the membrane. As a rule weak acids are trapped in the alkaline medium (at higher pH) and weak bases — in the acidic medium (at lower pH). Body fluids with potential for drug "trapping" (which pH differences from plasma pH may cause trapping) include contents of the stomach and the small intestine, breast milk, aqueous humor, vaginal and prostatic secretions, urine filtrate.

TASK 5

Answer the following questions using Henderson–Hasselbalch equation.

1. Aspirin (acetylsalicylic acid) is a weak organic acid with a pK_a of 3.5. What percentage of a given dose will be in the nonionized form at a stomach pH of 2.5? Choose the correct answer and prove it using Henderson–Hasselbalch equation.

1. About 1%
2. About 11%
3. About 52%
4. About 91%
5. About 99%

_____

_____

_____

_____

How many milligrams will be absorbed in the stomach if 500 mg of aspirin is given to relieve headache?

_____

2. Compare the absorption of acetylsalicylic acid (a weak acid, pKa=3,5) and diazepam (a weak base, pKa=3,5). Which drug is better absorbed from the stomach (pH=1,5) and from the lower intestine (pH=7,5)? Give rational explanations based on calculations of degree of drug's ionization.

3. Calculate the degree of ionization of phenobarbital (a weak acid, pKa=7,4) in plasma (pH=7,4) and tubular filtrate (pH=5,4). Specify: 1) the extent of penetration of phenobarbital into the CNS; 2) the extent of its reabsorption from renal tubules. What should be done to increase renal excretion of phenobarbital? Explain this.

TASK 6

UNDERSTANDING TERMINOLOGY

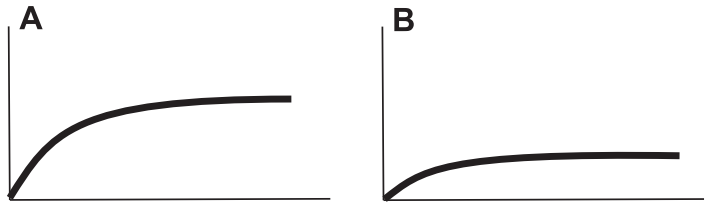
Match the definition in the left column with the appropriate term in the right column.

1. The study of processes of drug absorption, distribution, metabolism, and excretion	a. rate constant for drug elimination
2. The volume of fluid that would be required to contain homogeneously the total amount of drug in the body at the same concentration as that present in the plasma	b. bioavailability
3. The volume of plasma, from which drug can be completely removed by the kidney per unit of time	c. half-life
4. The time, which is required for the drug concentration in plasma to decline by one half	d. pharmacokinetics
5. Fraction of a drug, which is eliminated per unit of time	e. renal clearance
6. The fraction of administered drug that reaches the systemic circulation in chemically unchanged form	f. apparent volume of distribution

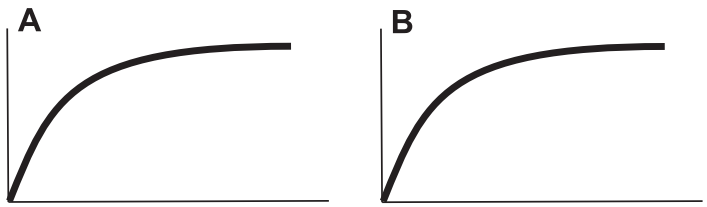
TASK 7

Study the graphs representing plasma concentrations of drugs A and B after oral and sublingual use. Explain in the spaces provided below why drug B has lower bioavailability after oral administration than drug A.

I Concentration of drugs in the systemic circulation after oral administration of drugs in equal doses



II Concentration of drugs in the systemic circulation after sublingual administration of drugs in equal doses



III Concentration of drugs in the portal circulation after oral administration of drugs in equal doses