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Харківський національний медичний університет

PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS

Self-study methodical instructions for international students (majoring in «Medicine» and «Dentistry»)

ПАТОФІЗІОЛОГІЯ ОРГАНІВ ТА СИСТЕМ

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Subject plan

CHANGES IN THE TOTAL VOLUME OF BLOOD. QUALITATIVE CHANGES OF ERYTHROCYTES. ERYTHROCYTOSIS

Relevance of the topic. The internal environment of an organism uniting all bodies and systems at the humoral level is presented by three components – blood, a lymph and interstitial liquid, whose structure and properties are closely connected, and coherence in work provides constancy of the internal environment of an organism – a homeostasis. The system of blood, as well as other systems of a human body, can change under the influence of environment factors, or, it can be caused by the violation of the organs and systems' activity which provides constancy of morphological, protein, ionic, electrolytic, gas and other components of blood. Ability to interpret changes of the total amount (mass) of blood and its form elements (erythrocytes and leukocytes) are important for the doctors. Erythrocytosis has very frequent hematologic symptoms in different diseases, and can be of primary character, acting as an independent hematologic disease. Pathophysiological mechanisms of erythrocytosis development are very difficult and various. The knowledge of the main hematologic manifestations of an erythrocytosis, the reasons and mechanisms of development in each case gives the chance to the doctor to make the diagnosis.

General aim – to be able to define changes in the total amount of blood, qualitative changes of erythrocytes and leukocytes.

The student should be able to (specific objectives):

1) toreveal changes of total amount of blood and to give their characteristic on the basis of data of a hematocrit;

2) to characterize possible qualitative changes of erythrocytes at anemias to find them at blood dab microscopy of an animal with an experimental anemia;

3) to describe possible qualitative changes of leukocytes.

The student should be able to (the required knowledge and skills):

1) know the normal values of hematocrit of an adult (dep. of normal physiology);

2) characterize the main stages of erythrocyte formation (dep. of normal physiology);

3) know the normal values of reticulocytes of an adult (dep. of normal physiology);

4) define the quantity of reticulocytes on blood (dep. of normal physiology);

5) make the Giemsa-Romanovsky stain and to define the erythrocyte raw cells.

QUESTIONS FOR THE LESSON

1. Violations of total amount of blood. Normovolemia. Types of a normovolemia, causes of their development.
2. Hypervolemia. Types of a hypervolemia, causes and mechanisms of development. Pathogenetic value of a hypervolemia.
3. Hypovolemia. Types of a hypovolemia, causes and mechanisms of development. Pathogenetic value of a hypovolemia.
4. Definition of the terms "blood loss", "bleeding", "hemorrhage", "hematoma". Etiology and classification of blood loss.
5. Acute blood loss. Pathogenesis. The pathological changes in case of blood loss. Protective and compensatory reactions in blood loss.
6. Qualitative changes of erythrocytes, their causes.
7. Qualitative changes of leukocytes, their causes.
8. Erythrocytosis. Definition of the term, types, etiology, pathogenesis.
9. Clinical manifestations, changes in peripheral blood and marrow at an erythrocytosis.

EXPERIMENTAL PART OF THE LESSON

Experiment 1: studying qualitative changes of erythrocytes in experimental hemolytic anemia.

The object of the experiment: rabbits.

Apparatus and reactives: microscopes, immersion oil, subject slides, polish slides, hydrochloric acid solution, distillates for painting of smears, fixation, Romanovsky's paint, pins.

Procedure: get the blood from marginal vein of a rabbit's ear. Prepare smears. Put the blood on the fatless subject slide. Place the polished slide slopingly to the subject slide (at 45 degree) to the contact with the drop. When the drop of blood spills on the rim of the polished slide, move it along the subject slide. The smear must be rather thin and proportional. Dry the smear, then fix it in the mixture of spirit with the ether for 5 min, after that stain with Romanovsky's stain for 15 min. Wash the smear by thin stream of the water and dry it. Microscope the smear. Put the drop of immersion oil on the smear and look at it under the microscope. Pay attention to hypochromic erythrocytes, anisocytosis, poikilocytosis, polychromatophils (erythrocytes stained by acid and basic stains, which have violet or violet-blue colour in destinction from mature erythrocytes stained in pink colour) and normoblasts erythrocytes with nuclears. Compare the content of qualitatively changed erythrocytes in the blood of experimental and control rabbits.

RESULTS: _____
_____
_____

Experiment 2: studing of reticylocytes in experimental hemolytic anemia.

The object of the experiment: rabbits.

Apparatus and reactives: microscopes, immersion oil, injector, pins, subject and hydrochloric acid solution, disti polish slides, Petri-dish, solution of brilliantkresilblue.

Procedure: take the thin part of brilliantkresilblue subject slide and mark this site by colour pencil. Make the smear of the blood and without drying quickly place it into a humid chamber. In 15 min take the smear off, dry it in the air and microscope it. Rythrocytes are stained into green colour. In some of them there is a thin dark blue net which is placed either in all cells or in its center, where a more dense ball is formed. This net is called substantia reticulo-granulofilamentosa. Erythrocytes with such granules are called reticulocytes. Compare the amount of reticulocytes in the blood of experimental and control rabbits. Describe and draw the slides in details.

RESULTS:_____
_____
_____
_____

THEORETICAL MATERIAL FOR PREPARATION TO LESSON.

CHANGES IN THE TOTAL VOLUME OF THE BLOOD

HYPOVOLEMIA

In physiology and medicine, hypovolemia (also hypovolaemia) is a state of decreased blood volume; more specifically, decrease in volume of blood plasma.

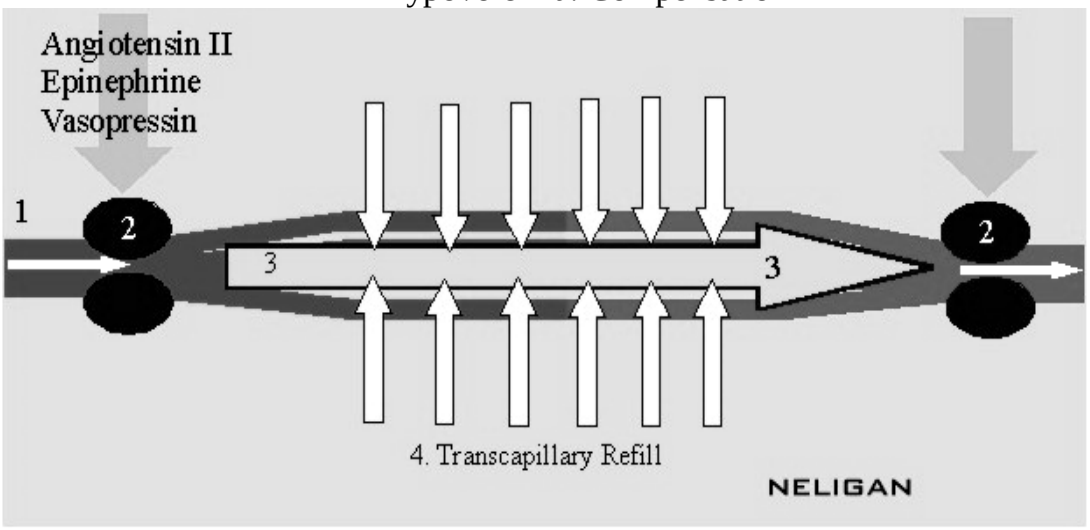
It is the intravascular component of volume contraction (or loss of blood volume due to things such as hemorrhaging or dehydration), but, as it also is the most essential one, hypovolemia and volume contraction are sometimes used synonymously.

Hypovolemia is characterized by salt (sodium) depletion and thus differs from dehydration, which is defined as excessive loss of body water.

Causesof hypovolemia are:

1. Loss of blood (external or internal bleeding or blood donation).
2. Loss of plasma (severe burns and exudative lesions).
3. Loss of body sodium and consequent intravascular water; e.g. excessive sweating, diarrhoea or vomiting.
4. Vasodilatory such as trauma leading to neurogenic dysfunction and inhibition of the vasomotor centre or drugs such as vasodilators typically used to treat hypertensive individuals.
5. Other examples include during surgery due to the use of anesthetics and in-operation bleeding or a ruptured ovarian cyst associated with PCOS (polycystic ovarian syndrome) which may cause severe internal bleeding, leading to hypovolemic shock.

Hypovolemia: Compensation



1. The blood pressure falls, reflex vasoconstriction follows.
2. The pre-capillary and post-capillary sphincters contract.
3. This reduced the volume and increases the velocity of blood passing thru
4. Fluid is sucked back into the circulation by the flow of blood, this process is called "transcapillary refill, and allows remobilization of fluid

Diagnosis

The symptoms of blood loss include:

1. Abdominal pain or swelling (a symptom of internal bleeding)
2. Bleeding during surgery
3. Bleeding from the mouth
4. Blood coming from a break in the skin
5. Blood coming from the vagina (unexpectedly, or much more than expected)
6. Blood in the stool (the stool may be black and tarry or red)
7. Blood in the urine (the urine may be pink, red, or brownish in colour)
8. Bruising (a bruise forms when there is blood under the skin)
9. Cool, clammy skin

10. Dizziness, weakness, or confusion
11. Fast, weak pulse
12. Paleness
13. Trouble breathing
14. Vomiting blood or material that looks like coffee grounds

The complications of blood loss are related to the role blood plays in the body. If too much blood volume is lost, a condition known as hypovolemic shock can occur. Hypovolemic shock is a medical emergency in which severe blood and fluid loss impedes the heart to pump sufficient blood to the body. As a result, tissues cannot get enough oxygen, leading to tissue and organ damage. If left untreated, this condition can be fatal. Complications can be more serious in people taking blood thinners or those with bleeding disorders.

Note that in children, compensation can result in an artificially high blood pressure despite hypovolemia. Children will typically compensate (maintain blood pressure despite loss of blood volume) for a longer period than adults, but will deteriorate rapidly and severely once they do begin to decompensate. This is another reason (aside from initial lower blood volume) that even the possibility of internal bleeding in children should almost always be treated aggressively.

Also look for obvious signs of external bleeding while remembering that people can bleed to death internally without any external blood loss.

Also consider possible mechanisms of injury that may have caused internal bleeding such as ruptured or bruised internal organs. If trained to do so and the situation permits, conduct a secondary survey and check the chest and abdomen for pain, deformity, guarding, discoloration or swelling. Bleeding into the abdominal cavity can cause the classical bruising patterns of Grey Turner's signor Cullen's sign.

Stages of hypovolemic shock

There are 4 stages of hypovolemic shock, known as the "Tennis" staging of hypovolemic shock, as the 4 stages of % volume of blood loss mimic the scores in a game of tennis: 15, 15–30, 30–40, 40. It is basically the same as used in classifying bleeding by blood loss.

Stage 1. Up to 15 % blood volume loss (750 mL)

1. Compensated by constriction of vascular bed
2. Blood pressure maintained
3. Normal respiratory rate
4. Pallor of the skin
5. Normal mental status to slight anxiety
6. Normal capillary refill
7. Normal urine output

Stage 2. 15–30 % blood volume loss (750–1500 mL)

http://en.wikipedia.org/wiki/Hypovolemia - cite_note-ambulancetechnicianstudy.co.uk-9

1. Cardiac output cannot be maintained by arterial constriction
2. Tachycardia >100 bpm
3. Increased respiratory rate
4. Blood pressure maintained
5. Increased diastolic pressure
6. Narrow pulse pressure
7. Sweating from sympathetic stimulation
8. Mildly anxious/Restless
9. Delayed capillary refill
10. Urine output of 20-30 milliliters/hour

Stage 3. 30–40 % blood volume loss (1500–2000 mL)

1. Systolic BP falls to 100 mmHg or less
2. Classic signs of hypovolemic shock
3. Marked tachycardia >120 bpm

4. Marked tachypnea >30 bpm
5. Alteration in mental status (confusion, anxiety, agitation)
6. Sweating with cool, pale skin
7. Delayed capillary refill
8. Urine output of approximately 20 milliliters/hour

Stage 4. Loss greater than 40 % (> 2000 mL)

1. Extreme tachycardia (> 140) with weak pulse
2. Pronounced tachypnea
3. Significantly decreased systolic blood pressure of 70 mmHg or less
4. Decreased level of consciousness, lethargy, coma
5. Skin is sweaty, cool, and extremely pale (moribund)
6. Absent capillary refill
7. Negligible urine output

Treatment. Minor hypovolemia from a known cause that has been completely controlled (such as a blood donation from a healthy patient who is not anemic) may be countered with initial rest for up to half an hour. Oral fluids that include moderate sugars and electrolytes are needed to replenish depleted sodium ions. Furthermore the advice for the donor is to eat good solid meals with proteins for the next few days. Typically, this would involve a fluid volume of less than one liter, although this is highly dependent on body weight. Larger people can tolerate slightly more blood loss than smaller people.

First aid. External bleeding should be controlled by direct pressure. If direct pressure fails, a tourniquet should be used in the case of severe hemorrhage that cannot be controlled by direct pressure. Tourniquet use in civilian first-aid, especially by less-trained individuals, remains controversial as it can cause potentially serious adverse effects. Other techniques such as elevation and pressure points are not always effective. To be verified. If a first-aid provider recognizes internal bleeding the life-saving measure to take is to immediately call for emergency assistance.

Hospital treatment. If the hypovolemia was caused by medication, the administration of antidotes may be appropriate but should be carefully monitored to avoid shock or the emergence of other pre-existing conditions.

Fluid replacement is beneficial in hypovolemia of stage 2, and is necessary in stage 3 and 4. Blood transfusions coupled with surgical repair are the definitive treatment for hypovolemia caused by trauma.

Treatment of blood loss focuses on two areas: stopping the bleeding and treating the effects of blood loss. The techniques used to stop bleeding depend on the cause and location of the bleeding. For external bleeding such as cuts and tears, direct pressure followed by bandaging or stitching can be used. For internal bleeding, surgery may be needed.

Treatment for the effects of blood loss depends on how much blood was lost; how quickly it was lost; and the person's medical conditions, medications, and religious beliefs. For mild blood loss, treatment with fluids and medications is often enough. For more severe blood loss, a blood transfusion or transfusion alternative is often needed. Some groups, such as Jehovah's Witnesses, will not accept transfusions for religious reasons.

Blood transfusion risks include:

1. Transfusion reactions: If donor blood does not properly match to the blood type of the recipient, or if blood is given to the wrong person by mistake, severe illness may result, including hemolysis (breakdown of red blood cells), kidney damage, and even death.

2. Infectious disease: Even though the blood supply is thoroughly screened, there is still a small risk of getting a viral (including HIV, hepatitis, and West Nile virus), bacterial, or parasitic infection from a blood transfusion.

3. Allergic reactions: Allergic reactions to the transfused blood may be mild and easily treated, or severe and potentially leading to death.

Medications can be used to stimulate the body to produce more blood cells. Erythropoietin is used to increase the body's production of red blood cells. G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte macrophage colony stimulating factor) are used to increase white blood cells. Other medications can be used to reduce bleeding during or after surgery or sudden blood loss. Special fluids such as pentastarch, saline, or Ringer's lactate can be used to temporarily replace the lost blood volume.

Devices such as blood salvage ("cell saver") machines can help reduce blood loss during surgery by collecting blood lost during surgery, processing it, and returning it to the patient. Specialized scalpels can cut through tissue and stop bleeding at the same time (by using heat, electric current, or ultrasonic vibration).

Surgical techniques and pre-surgery planning can also reduce blood loss. Large surgeries may be divided into several small ones, and new techniques such as laparoscopy reduce the need for large incisions. In pre-surgery planning, medications that increase the risk of bleeding are stopped or reduced before surgery, and other medications are taken to build up the body's reserve of blood cells. Some people choose to donate and store their own blood before an operation. In other cases, a technique called hypotensive anesthesia can be used to reduce surgical bleeding.

HYPERVOLEMIA

Hypervolemia, otherwise known as fluid overload, is a condition where there is excess fluid in the blood.

Here, excess fluid plasma leads to the increased volume. Hypervolemia is associated with diseases of lung, liver, kidney, heart and few other conditions. The opposite of this condition is known as hypovolemia, where there is insufficient fluid volume in the blood, having decreased plasma amount.

Hypervolemia Facts

1. Average water intake is 2000 ml/day
2. Average output = 2000 ml
3. In hypervolemia, fluid intake is more. Hence, edema occurs.
4. ADH and Aldosterone maintain water/fluid balance.

Hypervolemia pathophysiology

The recommended sodium and water intake for normal adults is:

1. Sodium – 70 mmol per 24 hours
2. Water 1.5 to 2.5 L (25 to 35 mL/kg/24 hours)

In normal individuals, both the sodium concentration in the extracellular fluid and osmolality are regulated by the kidneys.

3. Osmoreceptors and any change in the secretion of vasopressin affect the urine concentration and excretion of water.

4. In case of sodium depletion, the renin-angiotensin-aldosterone system is activated, which consequently reduces the sodium in urine.

5. However, the body’s response to excess sodium becomes slow, and in normal individuals also, excretion of excess sodium is slow.

Hypervolemia Causes

Excessive sodium or fluid intake

1. Therapy, especially postoperatively. This affects the fluid balance and renal functions due to physiological responses taking place as a result of injury.
2. High sodium intake
3. Transfusion reaction by blood transfusions
4. Responses to physiological stress:

Whenever an organ is stressed, it greatly affects the functioning of several other organs, and leads to fluid imbalance.

Sodium or water retention

1. Congestive heart failure – As heart doesn't function efficiently, blood regurgitates in the vein, thereby causing fluid overload.
2. Nephrotic syndrome
3. Glomerulonephritis
4. Liver cirrhosis
5. Hyperaldosteronism
6. Corticosteroid therapy
7. Chemotherapy drugs
8. Low protein intake (malnutrition)

Fluid shift into the intravascular space:

1. Fluid remobilization following burn treatment
2. Administration of plasma proteins like albumin
3. Administration of hypertonic saline solution or hypertonic fluids like Mannitol

Others Causes

1. Preeclampsia
2. Pregnancy
3. Hormonal disturbances
4. Head injury

Hypervolemia Symptoms

1. Ascites (fluid buildup in the abdomen)
2. Edema (swelling), especially hands, feet, and ankles
3. Strong and rapid pulse, Crackles on auscultation
4. Dyspnea (shortness of breath) – The excess fluid enters the lung's air spaces, and reducing the oxygen entering the blood, thereby leading to dyspnea.
5. Orthopnea (Difficulty breathing on lying down) – Here fluid gets collected in the lungs, causing breathing difficulty and Paroxysmal nocturnal dyspnea
6. High blood pressure and jugular vein distension, Increased central venous (CVP) and pulmonary artery pressure (PAP),Third heart sound (S3)
7. Decreased hemoglobin or hematocrit
8. Irritated cough
9. Restlessness and anxiety
10. Weight gain
11. Intake > output
12. Oliguria

Hypervolemia Complications

1. Congestive heart failure (most common)
2. Hyponatremia (hypervolemic hyponatremia)

Possible investigations

1. B-type natriuretic peptide (BNP): To diagnose heart failure.
2. Arterial blood gases – In case of unclear cause of dyspnea.
3. Fluid balance charts and serial weights – For monitoring treatment improvement.
4. Further investigations if necessary according to suspected cause.

Hypervolemia Differential diagnosis

Other causes of dyspnea

1) Pneumonia,Bronchospasm (asthma or chronic obstructive pulmonary disease)
2) Acute anaphylaxis may lead to wheezing, thereby resulting in swollen tongue or lips.
3) Pulmonary embolism (no added lung sounds)
4) Poor inspiratory effort may lead to basal lung crackles that may resolve after some deep breaths.
5) Fibrosing alveolitis may also cause fine inspiratory crackles

Other causes of raised jugular venous pressure (JVP):

1. Cardiac tamponade or constrictive pericarditis may cause raised JVP, which increases on inspiration.
2. Pulmonary embolism.
3. Superior vena cava obstruction (veins of neck and upper limb gets distended and non-pulsatile)

Other causes of peripheral edema:

1. Preeclampsia (always check urine protein in unwell 20 + weeks of pregnant women).
2. Hypothyroidism.
3. Lymphedema (non-pitting edema).
4. Hypoproteinaemia – malnutrition, nephrotic syndrome, malabsorption or liver disease.
5. Other causes of Venous obstruction (unilateral).
6. Severe varicose veins, deep venous thrombosis (DVT).
7. Pelvic mass (including pregnancy).
8. Obstruction of inferior vena cava (may not redistribute with posture).

Other causes of ascites:

1. Portal hypertension.
2. Cirrhosis.
3. Malignancy.

Hypervolemia Treatment

Hypervolemia treatment varies depending on its cause, which needs to be treated, and the patient's condition. Hospitalization is not mandatory, but in some cases, close monitoring is essential.

Medications-diuretics and inotropes, low salt in diet to decrease the load on the kidneys, to make it function better.

Isolated ultrafiltration

Examination of the blood is central to the diagnosis and management of hematologic diseases. Assessment of the prevalence of red cells, of the several types of leukocytes, and of platelets, usually from automated particle counters, and examination of the blood film for qualitative changes in the appearance of red cells, leukocytes, and platelets, and the presence of marrow precursors, malignant cells, and intracellular parasites can be used to diagnose specific diseases, gain insight into pathophysiology, and measure the response to treatment.

Quantitative measures routinely available from automated cell counters are generally reliable and provide a rapid and cost-effective way to screen for major disturbances of hematopoiesis. The complete blood count is a necessary part of the diagnostic workup in a broad variety of clinical conditions.

PRODUCTION AND DESTRUCTION OF ERYTHROCYTES

The volume of red cells in the body (red cell mass) can be measured by labeling a sample of erythrocytes and estimating their dilution in the circulation. The red cell mass of normal women ranges from 23 to 29 ml/kg body weight; that of normal men from 26 to 32 ml/kg. The red cell mass is maintained by the production of erythrocytes in the marrow and, after they age, their destruction by the macrophages in the spleen, liver, and marrow.

THE RED CELL MASS

The red cell mass is maintained and regulated by the marrow, which under steady-state conditions precisely replaces cells lost by senescence, bleeding, or destruction. The red cell mass defines anemias and polycythemias, and the kinetics of red cell production and destruction helps to establish their pathogenesis. A number of tests have been developed to measure the three main components of red cell kinetics: the red cell mass, the rate of red cell production, and the rate of red cell destruction. Some of these are simple but indirect, such as the hematocrit, reticulocyte count, haptoglobin, lactic dehydrogenase and unconjugated bilirubin concentration. Examination of the marrow allows one to assess total cellularity and the relative erythroid contribution, but it is limited in that one cannot infer the kinetics of cell production from a single static image. These tests are very useful in the aggregate, but can be supplemented by more complex but direct quantitation made possible by the use of radioisotopes.

HEMATOCRIT

The hematocrit is the fractional volume of the blood that the erythrocytes occupy. It can be measured on a sample of blood, expressed either as a percentage or as a fraction, viz., the volume occupied by the erythrocytes in a ml of blood. The total body hematocrit is the volume of red cells in the body divided by the total blood volume. The blood hematocrit is the simplest and most widely used test by which to estimate the size of the red cell mass. In most anemic patients it gives an excellent approximation of the total red cell mass and a functional estimation of the oxygen-carrying capacity and whole blood viscosity. Its main drawback is that it is an indirect measure that is influenced by changes in the plasma volume and may not reflect the size of the red cell mass in dehydrated or polycythemic patients. Dehydration is usually clinically apparent and can in most cases be taken into account when evaluating the significance of a specific hematocrit determination. When the hematocrit is moderately elevated it may also not reflect the total red cell mass, and only the direct measurement of the red cell mass can differentiate between relative and absolute polycythemia. However, when the hematocrit is above 60 percent, virtually all patients have an increase in total red cell mass.

STRUCTURE AND FUNCTION OF HEMOGLOBIN

As a gas transport protein hemoglobin has remarkable properties, reflecting structural changes in tetrameric deoxyhemoglobin as its heme groups bind four oxygen molecules.

Hemoglobin functions are to carry oxygen from the lungs to the tissues and transport carbon dioxide from the tissues to the lungs, and it also destroys the physiologically important nitric oxide molecule.

It has evolved to perform its transport functions in a highly efficient manner:

(1) The oxygen affinity of hemoglobin permits nearly complete saturation with oxygen in the lungs, as well as efficient oxygen unloading in the tissues;

(2) Its affinity increases with oxygenation, resulting in the sigmoid shape of the oxygen dissociation curve;

(3) deoxyhemoglobin binds protons and oxyhemoglobin releases protons.

The last property, expressed as the alkaline Bohr effect, also facilitates oxygen loading in the lungs and unloading in the tissues. The Perutz models of oxygenated and deoxygenated hemoglobin provide important insights into the structural basis of these three major features of the equilibria of oxygen with hemoglobin. The reader is referred to two of the many excellent sources for a detailed analysis of structure-function relationships.

The roles of different parts of the hemoglobin molecule in its equilibria have been deduced from its amino acid sequence, its helical conformation, models derived from x-ray crystallography, studies of the kinetics of reactions of hemoglobin with ligands, and observations utilizing nuclear magnetic resonance. The concentration of hemoglobin within human red cells is extraordinarily high (34 g/dl), and its efficiency as an oxygen carrier is enhanced by its packaging in flexible cells of optimal shape for the diffusion of gases.

Hemoglobin is the most important component of red blood cells. It is composed of a protein called heme, which binds oxygen. In the lungs, oxygen is exchanged for carbon dioxide.

Abnormalities of an individual's hemoglobin value can indicate defects in the normal balance between red blood cell production and destruction. Both low and high values can indicate disease states.

THE RETICULOCYTE

Birth. Prior to enucleation, intermediate filaments and the marginal band of microtubules disappear. Vimentin decreases in quantity throughout the cytoplasm. However, tubulin and actin concentrate at the point where the nucleus will exit. These changes, accompanied by microtubular rearrangements, play a role in nuclear expulsion. Two proposals have been advanced to explain how the reticulocyte exits the marrow; the precise mechanism is still unknown. The reticulocyte may actively traverse the sinus epithelium or more likely, since it appears incapable of directed amoeboid motion, it may be driven across by a pressure differential.

Maturation. If the clot is lysed, the macrophages present in the culture immediately recognize and phagocytose the expelled nuclei. Maturation of the circulating reticulocyte requires from 24 to 48 h. During this period some 20 percent of the ultimate hemoglobin content will be synthesized and the final assembly of the submembrane skeleton completed. In "young" reticulocytes the vast majority of ribosomes dispersed throughout the cytoplasm are in the form of polyribosomes. As protein synthesis diminishes during maturation these are gradually transformed into monoribosomes. Simultaneously, there is loss of transferrin receptors, and eventually the capacity for endocytosis disappears as well.

PATHOLOGY OF THE RETICULOCYTE AND ERYTHROCYTE

The reticulocyte may show pathologic alterations in size or staining properties. It may also contain inclusions visible by light microscopy or identifiable only on ultrastructural analysis. The majority of pathologic inclusions usually attributed to erythrocytes are actually found in reticulocytes and are nuclear or cytoplasmic remnants derived from the late-stage normoblasts.

ERYTHROCYTE AND RETICULOCYTE INCLUSIONS

Howell-Jolly bodies

Howell-Jolly bodies are small nuclear remnants that have the color of a pyknotic nucleus on Wright-stained films and give a positive Feulgen reaction for DNA. They are spherical in shape, usually no larger than 0.5 μm in diameter. Generally only one is present, but they may be numerous. In pathologic situations they appear to represent chromosomes that have been separated from the mitotic spindle during abnormal mitosis. More commonly, during normal maturation they arise from nuclear fragmentation (karyorrhexis) or incomplete expulsion of the nucleus. Howell-Jolly bodies are pitted from the reticulocytes in their passage through the interendothelial slits of the splenic sinus. They are characteristically present in the blood of splenectomized persons and in those suffering from hemolytic anemia, megaloblastic anemia, and hyposplenic states.

Pocked (or pitted) red cells

When viewed under interference-phase microscopy, pocked red cells (described by Koyama in 1962) appear to have surface membrane "pits" or craters. The vesicles or indentations that characterize these cells represent autophagic vacuoles adjacent to the cell membrane. These vacuoles appear to be instrumental in the disposal of cellular debris as the erythrocyte passes through the microcirculation of the spleen. Within one week following splenectomy, pocked red cell counts begin to rise, reaching a plateau at 2–3 months. Pocked red blood cell (RBC) counts are being increasingly utilized as a test of splenic function.Characteristic pitted erythrocytes. A pitted erythrocyte is recognisable on phase-interference microscopy by the characteristic "pit" on the cell membrane (arrows).

Cabot rings

The ringlike or figure-of-eight structures sometimes seen in megaloblastic anemia within reticulocytes and in an occasional, heavily stippled, late intermediate megaloblast are designated Cabot rings. Their exact composition is still open to question. Some have suggested that they originate from spindle material that has been mishandled during an abnormal mitosis. Others have found no indication of DNA or spindle filaments but have shown the rings to be associated with adherent granular material containing both arginine-rich histone and nonhemo-globin iron. Since both histone biosynthesis and iron metabolism/mobilization are abnormal in pernicious anemia, these structures is a marker of "cytoplasmic currents" within the cell.

Basophilic stippling

Basophilic stippling consists of granulations of variable size and number that stain deep blue with Wright stain. Electron microscope studies have shown that punctate basophilia represents aggregated ribosomes. The clumped ribosomes may include degenerating mitochondria and siderosomes. In conditions such as lead intoxication and thalassemia, the altered reticulocyte ribosomes have a greater propensity to aggregate. As a result, the basophilic granulation appears larger and is referred to as coarse basophilic stippling.

Heinz bodies

Heinz bodies are composed of denatured proteins, primarily hemoglobin, that form in red cells as a result of chemical insult; in hereditary defects of the hexose monophosphate shunt; the thalassemias; unstable hemoglobin syndromes; or sickle cell disease. They tend to adhere to the interior of the red cell membrane, protruding into the cytoplasm. Their position in dried and stained blood films is characteristically about one-third of the distance in from the edge of the disc, where membrane curvature is at a minimum, presumably because of the membrane stiffening that they cause. Membrane stiffening also results in their removal from red cells as the cells traverse the interepithelial slits of the splenic sinus.

Hemoglobin H inclusions

Hemoglobin H is composed of b4 tetramers, indicating that b chains are present in excess as a result of impaired a-chain production. Exposure to redox dyes such as brilliant cresyl blue, methylene blue, or new methylene blue results in denaturization and precipitation of the abnormal hemoglobin. Brilliant cresyl blue causes the formation of a large number of small membrane-bound inclusions, giving the cell a characteristic "golf-ball-like" appearance when viewed by light microscopy. Methylene blue and new methylene blue generate a smaller number of variably sized membrane-bound and floating inclusions. Most frequently seen in b-thalassemia, these changes may also be found in patients with unstable hemoglobin and in rare cases of erythroleukemia.

SIDEROSOMES AND PAPPENHEIMER BODIES

Normal or pathologic cells containing siderosomes ("iron bodies") are usually reticulocytes. In the pathologic state the iron granulations are larger and more numerous, and electron microscopy has shown that many of these are mitochondria containing ferruginous micelles rather than the ferritin aggregates that characterize the normal siderocyte. Siderosomes are usually found in the periphery of the cell, whereas basophilic stippling tends to be distributed homogeneously throughout the cell. Pappenheimer bodies are siderosomes that stain with Wright stain. Electron microscopy of these bodies shows that the iron is often contained within a lysosome, as confirmed by the presence of acid phosphate. Siderosomes may also contain degenerating mitochondria, ribosomes, and other cellular remnants.

MACRORETICULOCYTES

In the presence of an intense erythropoietin response to acute anemia, or experimentally in response to large doses of exogenously administered erythropoietin, "stress" reticulocytes are released into the circulation. These cells may be up to twice the normal volume, with a corresponding increase in hemoglobin content. Whether this increase results from one less mitotic division during maturation or from some other process is not yet clear. In contrast, even under moderate erythropoietic stress some of the reticulocytes in the marrow pool are shifted to the circulating pool. These "shift" reticulocytes contain a higher RNA content than normal and can now be quantified.

STRUCTURE AND SHAPE OF THE ERYTHROCYTE

The normal resting shape of the erythrocyte is a biconcave disc. Variations in the shape and dimensions of the red cell are useful in the differential diagnosis of anemias. Normal human red cells have a diameter of 7.5 to 8.7 μm, which decreases slightly with cell age. The membrane is present in sufficient excess to allow the cell to swell to a sphere of approximately 150 fl or to enter a capillary of 2.8 μm in diameter. The central one-third of the cell appears relatively pale compared with the periphery, reflecting its biconcave shape. Red cells on dried blood films are 0.6 μm thick, having lost about two-thirds of their normal thickness. Friction and surface tension involved in the preparation of the blood film produce fragmentation, "doughnut cells" or annulocytes, crescent-shaped cells, etc.

RED CELL SHAPE AND SURVIVAL IN THE CIRCULATION

The red cell spends most of its circulatory life within the capillary channels of the microcirculation. During its 100- to 120-day life span it travels a distance of approximately 250 km. That it survives this long is at least partially due to the unique capacity of its membrane to

“tank-tread”—rotate around the red cell contents. This arrangement transmits shocks from wall contact through the membrane to the viscous hemoglobin solution in the interior rather than concentrating the energy of contact in the membrane. Physical arrangement of membrane skeletal proteins in a uniform shell of highly folded hexagonal/pentagonal units permits this unusual behavior and is also responsible for the characteristic biconcave shape of the resting cell. Subtle differences in the discoid shape that resting cells assume are probably related to variations in the elastic properties of the submembrane skeleton. A deficiency in the amount of spectrin or the presence of mutant spectrin in the submembrane skeleton results in the abnormal discoid cells in hereditary spherocytosis, elliptocytosis, and pyropoikilocytosis. In regions of circulatory standstill or very slow flow, red cells travel in aggregates of two to a dozen cells, forming rouleaux. Within large vessels, aggregation is disrupted by the increased shear forces.

NOMENCLATURE OF COMMON RED CELL SHAPES

1. An international terminology using uniform Greek word stems has been introduced to describe cells on the basis of their three-dimensional morphology.
2. **Hypochromic microcyticerythrocytes:** occur in certain types of anaemia including iron deficiency anaemia and thalassemia.
3. **Macrocytes:** are larger than normal erythrocytes occurring in certain types of anaemia including those caused by B_{12} or folate deficiency.
4. **Normoblasts(or erythroblasts):** are the immediate precursors of erythrocytes - at this stage the nucleus is retained as can be seen in the illustration.
5. **Spherocytes:** are red cells with a loss of membrane leading to reduced diameter and decreased surface area but normal volume. They are seen in hereditary spherocytosis, erythroblastosis fetalis and acquired hemolytic anemias.
6. **Stomatocytes:** erythrocytes with a loosely folded, mouth-like pale area across the cell. They are seen in hereditary stomatocytosis, lead poisoning and thalassemia trait.
7. **Target cells (or codocytes):** have the hemoglobin concentrated in the middle and the periphery of the cell, and thereby resemble targets. They can be seen in hemoglobinopathies, e.g. thalassemias, and iron deficiency anemia.
8. **Teardrop erythrocytes (or dacryocytes):** are seen when there is extramedullary erythropoiesis or with marrow disorders or marrow infiltration, such as myelofibrosis or metastatic carcinoma
9. **Elliptocytes:** occur with several inherited disorders predisposing to haemolytic anaemia. They can also be seen in acquired disorders, such as iron deficiency anemia, infectious anemias, thalassemia, and in new-born babies.
10. **Sickle cells (**drepanocyte)**:** are seen in sickle cell anaemia - inherited disorder.
11. **Acanthocytes:** are spherocytical cells with large irregularly placed protrusions.
12. **Echinocytes:** are red blood cells distorted by exposure to a hypertonic medium.
13. **Schizocytes (schistocytes or helmet cells):** are fragmented cells showing bizarre poikilocytosis. They can be seen in various forms of microangiopathic haemolytic anemia as well as after injury by mechanical means, e.g. through cardiac valve prostheses.
14. **Bite cells:** are indicative of some haemolytic anemias (e.g. G6DP deficiency). They occur when there is a precipitation of haemoglobin against a portion of the inner membrane (known as a Heinz Body). This is later removed in the spleen leaving a 'bite mark'. Other causes of Heinz bodies (and thus Bite cells) are oxidant drugs and haemolytic anemia associated with severe liver disease.
15. **Howell-Jolly bodies:** are the small dark bodies in the illustration. They are nuclear remnants present in some normal red cells in the bone marrow but are removed by the spleen during the first few hours the cells spend in the circulatation. This appearance results from absence of splenic function, either following splenectomy, or due to splenic atrophy.
16. **Basophilic stippling:** of erythrocytes occurs with lead poisoning or megaloblastic anaemia.

17. **Leptocyte** is a wafer-thin cell which is generally large in diameter and displays a thin rim of hemoglobin at the periphery with a large area of central pallor. Such a cell reflects an increased surface/volume ratio.

18. **Keratocytes** are red cells with a relatively normal cell volume that have been deformed by removal of a region of apposed and sealed membranes so that they present with two or more points.

If necessary, any shape variation of the red cell may be described precisely by the use of compound terms such as spherostomatocyte. The addition of modifiers such as micro to denote a changed volume may add to descriptive precision, as in microspherocyte or macroleptocyte.

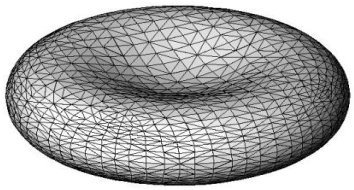
Variability in the size of red cells is designated anisocytosis, and any type of shape abnormality is designated as poikilocytosis.

THE NORMAL PHYSIOLOGY AND THE PATHOPHYSIOLOGY OF RED CELL SHAPE

The biconcave disc

The means by which a healthy red blood cell maintains its normal biconcave shape are still in dispute. However, most proposals can be subsumed under two headings: (1) The red cell is a reference shape into which the membrane is cast, much as a latex rubber glove is cast in the shape of a human hand, or (2) it is a dynamic equilibrium form controlled by the minimization of bending energy in the membrane. Among the observations that undermine the reference-shape hypothesis is the ability of the discocyte to withstand the relocation of the biconcavities anywhere on the membrane surface without significantly changing its shape. Against the minimization-of-bending-energy hypothesis are the measured values of the membrane-bending modulus. All estimates thus far are too low by one-half an order of magnitude to account for the observed membrane behavior.

Proposals that the submembrane skeleton behaves as an ionic gel and that the spectrin network functions as an entropic spring have served notice that the mechanical properties of the red blood cell membrane are exceedingly complex and still far from being completely understood.



This photomicrograph shows normal red blood cells (RBCs) as seen in the microscope after staining.

The Stomatocyte-Echinocyte-Discocyte Equilibrium At physiologic pH and in the presence of normal levels of plasma proteins (particularly albumin), healthy red cells will always be smooth, biconcave discs. As the pH raises or the albumin concentration lowers, or in the presence of lysolecithin or anionic phenothiazine derivatives, the rim of the disc becomes bumpy. These bumps are low, are widely spaced, and involve only the membrane of the red cell rim. This form is an echinocyte I. Further environmental stress will result in transformation to echinocytes II and III.

Environmental stress caused by low pH, excess albumin, or cationic phenothiazine derivatives will transform the discocyte into an intermediate form with deeper biconcavities, and then into a cup-shaped cell with only a single concavity, a stomatocyte. Thus far the changes are readily reversible, but if the single deep depression on the stomatocyte surface is obliterated by membrane loss, the transformation becomes irreversible and a spherostomatocyte is the result.

The aged cell

While there is a general agreement that the reticulocyte loses membrane as it matures into a discocyte, it is less certain that membrane loss continues throughout the erythrocyte life span. The notion that erythrocyte aging is synonymous with membrane loss, increasing MCHC, and decreasing deformability is largely the result of studies on density-separated cells and the equating of dense cells with aged cells. Indeed, dense cells are dense because their MCHC is elevated, and an elevated MCHC exerts a profoundly depressant effect on red cell deformability. Thus dense cells will always be relatively nondeformable—but whether they are aged, is still not settled. One thing is clear: unlike the reticulocyte, the aged red cell is not easily distinguished morphologically.

Osmotic behavior

The red cell behaves as an osmometer. When placed into a hypertonic solution it shrinks, and the inner surfaces of the biconcavities touch over a progressively larger central region. When red cells in hypotonic solutions reach their critical hemolytic volume, holes greater than 10 nm (100 Å) in size appear and the hemoglobin exits. Alternatively, a large tear may develop in the red cell membrane. Following hemolysis (exit of the hemoglobin), the holes or tears close and the cell resumes its original biconcave shape.

Deformability

The deformability of the intact cell is made up of contributions from the intrinsic deformability of the membrane itself, the internal viscosity, and the surface/volume ratio of the cell. The deformability of the intact cell can be measured by the time it takes a red cell suspension to traverse a filter of known pore size; or the cells may be suspended in a viscous medium and exposed to a shear force, and the change in shape observed microscopically.

In the circulation the primary cause of decreased red cell deformability is likely to be insufficient membrane (spherocytosis) rather than stiffening of the membrane. The interendothelial slits of the splenic sinus stress cells with a normal surface/volume ratio, and splenic phagocytes remove those with a ratio that is lower than normal. It is self-evident that a perfectly spherical red cell will be rigid no matter how low the MCHC or how flexible the isolated membrane might be.

ERYTHROCYTOSIS

Anemias and polycythemias are characterized, respectively by a decreased or increased size of the red cell mass. The anemias are associated with a decrease in the oxygen-carrying capacity of blood, they are usually expressed in terms of hemoglobin concentration and cause symptoms because of tissue hypoxia. The clinical manifestations are primarily due to hypoxia-induced compensatory features designed to prevent or ameliorate dangerous anoxia. Among these, the most important is an increase in the renal erythroid growth factor; however, almost all appear to be initiated by a single hypoxia-inducible transcription factor (HIF).

Erythrocyte disorders are traditionally divided into two groups:

(1) anemia;

(2) polycythemia.

Although this division is based on the presence of too few red cells **(erythrocytopenia)** and too many red cells **(erythrocytosis)**, anemia is functionally best characterized by a hemoglobin concentration below normal and polycythemia by a hematocrit above normal. Anemia is a disorder in which the patient suffers from tissue hypoxia, the consequence of a low oxygen-carrying capacity of the blood. Polycythemia, on the other hand, is a disorder in which the clinical manifestations are related to increased whole blood viscosity and increased blood volume, both consequences of a high hematocrit.

POLYCYTHEMIA (ERYTHROCYTOSIS)

The term polycythemia, denoting an increased amount of blood, has been applied to those conditions in which the number of erythrocytes is increased.

Primary polycythemia, polycythemia rubra vera (polycythemia vera), is an abnormality of the hematopoietic stem cell characterized by uncontrolled proliferation of erythroid, granulocytic, and megakaryocytic cells.

Secondary polycythemia, more appropriately – secondary erythrocytosis, refers to the conditions in which only the erythrocytesincreased in number and volume. Although the term secondary erythrocytosis is more descriptive of this group of disorders, secondary polycythemia is a time-honored name and will be used interchangeably with secondary erythrocytosis.

Polycythemia ("many cells") describes **an increase in the total quantity or volume (mass) of red blood cells in the body**, without any implication regarding leukocytes or platelets.

Erythrocytosis refers to **an increase in the concentration of erythrocytes**, however, whether measured as number of cells, hemoglobin, or packed cell volume (hematocrit).

Erythrocytosis may be the result of

1. An increase in the red cell volume or mass (polycythemia, called **absolute erythrocytosis**).

2. A reduced plasma volume (called **relative or spurious polycythemia or erythrocytosis**), which produces an increase in red cell concentration that does not reflect an increase in the quantity of red cells in the body.

Polycythemia (rubra) vera is **a myeloproliferative disorder associated with trilineage marrow hyperplasia characterized by an increased red cell mass**, usually in association with leukocytosis and thrombocytosis.

Pathophysiology and manifestations

The production and presence of an increased number of red cells are associated with certain general and specific effects generated by changes in blood viscosity and blood volume.

At hematocrit readings higher than 50 percent, the viscosity of blood increases steeply. The resulting decrease in blood flow will reduce the transport of oxygen, with optimal values found at hematocrit readings between 40 and 45 percent. In a study of the red cells from a number of animal species, it was found that the optimal value of oxygen transport corresponds closely to their normal hematocrits and may explain the evolutionary choice of certain hematocrit levels as optimal. However, before concluding that polycythemia always is a suboptimal condition, it is important to realize that it may be premature to translate viscosity readings, derived from blood tested in a rigid glass viscosimeter (Ostwald) or even in a cone-plate viscometer into blood flow through tiny distensible vessels in vivo. **First,** the flow through these narrow channels is rapid (high shear rate), which in a non-Newtonian fluid such as blood causes a marked decrease in viscosity. **Second,** blood flowing through narrow channels in vivo is axial with a central core of packed red cells sliding over a peripheral layer of lubricating low-viscosity plasma. **Finally** and most importantly, absolute polycythemia is not normovolemic but is accompanied by an increase in blood volume, which in turn enlarges the vascular bed and decreases the peripheral resistance. Since the blood pressure remains stable, the increase in blood volume must be associated with an increase in cardiac output and an increase in oxygen transport (cardiac output times hematocrit).

Observations in humans and experimental animals indicate that high viscosity causes a reduction in blood flow to most tissues and may be responsible for the cerebral and cardiovascular impairment experienced occasionally by high-altitude dwellers and patients with severe polycythemia, as well as in athletes self-administering overdoses of erythropoietin.

Under normal conditions, the rate of red cell production is adjusted to maintain the red cell mass at about 30 ml per kilogram of body weight. Since the lifespan of the red cells in polycythemia is normal, a mere doubling of the daily rate of red cell production would be adequate to maintain a red cell mass of 60 ml/kg or, in other words, to maintain a very substantial erythrocytosis. Consequently, the morphology and volume of the marrow are only moderately altered in polycythemia in comparison with the changes observed in some types of hemolytic anemia, in which the rate of red cell production may be 6 to 10 times normal. In erythrocytosis, the number of red cells destroyed daily would merely cause a slight increase in bilirubin levels and the presence of secondary gout and splenomegaly are usually signs of a myeloproliferative disorder rather than of erythrocytosis alone.

The increase in viscosity and vascular space are responsible for many of the signs and symptoms of polycythemia. The characteristic “ruddy cyanosis” in patients with polycythemia vera is caused by excessive deoxygenation of blood flowing sluggishly through dilated cutaneous vessels. Nonspecific symptoms such as headaches, dizziness, tinnitus, and a feeling of fullness of the face and head are probably also caused by a combination of increased viscosity and vascular dilatation.

Hemorrhages from the nose or stomach in patients with normal platelets and coagulation proteins can be attributed to capillary distention, but circulatory stagnation causing ischemia and necrosis may be contributory. Thromboses are common in polycythemia vera, but they also occur in erythrocytosis when aggravated by plasma loss (dehydration).

Classification of Erythrocytosis

1. Relative erythrocytosis or polycythemia (pseudoerythrocytosis)

1.1. Hemoconcentration

1.2. Spurious polycythemia (Gaisbock syndrome)

2. Polycythemia (absolute erythrocytosis)

3. Polycythemia vera

4. Secondary polycythemia

5. Secondary to decreased tissue oxygenation (physiologically appropriate polycythemia or hypoxic erythrocytosis)

5.1. High-altitude erythrocytosis (Monge disease)

5.2. Pulmonary disease: Chronic cor pulmonale, Ayerza syndrome, Cyanotic congenital heart disease

5.3. **Hypoventilation syndromes**:

5.4. Primary alveolar hypoventilation

5.5. Pickwickian syndrome, Ondine curse

5.6. Positional desaturation

5.7. Sleep apnea

6. Abnormal hemoglobins

6.1. Inherited

6.2. Acquired: drugs and chemicals, carboxyhemoglobin

7. Secondary to aberrant erythropoietin production or response

7.1. (Physiologically inappropriate polycythemia)

7.2. Tumors, cysts, hemangiomas

7.3. emsp; Androgen abuse

7.4. Erythropoietin abuse

8. Familial polycythemia

9. Idiopathic polycythemia

Polycythemia vera was first described in 1892 by Vaquez. In 1903 Osler reviewed four cases of his own and an additional five from the literature. The increased proliferation of granulocyte precursors and megakaryocytes was first described by Тьrk in 1904.

Secondary polycythemia is a term that describes a group of disorders characterized by an increased red cell mass brought about by enhanced stimulation of red cell production. Secondary polycythemia may be subdivided into appropriate polycythemia in which the erythron is responding normally to hypoxia and inappropriate polycythemia in which erythropoiesis is being stimulated by the aberrant production of or response to erythropoietin. In 1878, Paul Bert showed that the physiologic impairment observed at high altitude was due to a reduction in the oxygen content of air and at altitude 4570 m (15,000 ft) above sea level erythrocytosis was accepted as a compensatory adaptation to hypoxia.

At about the same time, it was observed that many patients with cyanosis were also polycythemic. Mechanical or neurogenic hypoventilation as a cause of cyanosis and polycythemia was first popularized in 1956 with the classic description of the Pickwickian syndrome by Burwell and colleagues. There has been an increasing interest in the polycythemia associated with arterial hypoxemia due to smoking and with tissue hypoxia due to inherited abnormal hemoglobins with high oxygen affinity. Inappropriate polycythemia may occur as a result of aberrant erythropoietin production by the kidney, by certain tumors, or by the ingestion of cobalt. Familial erythrocytosis is a rare autosomal dominant or a recessive form of inappropriate polycythemia.

In addition to appropriate and inappropriate secondary polycythemia there are some patients with mild erythrocytosis in which neither the cause or the clinical significance is clear. These patients do not have an increased red cell mass and their erythrocytosis is the result of a decreased plasma volume. The disorder is therefore not a true erythrocytosis and is designated apparent, spurious, or relative polycythemia. As long ago as 1905, Gaisbock reported that a number of hypertensive patients had plethora and an elevated red cell count but no splenomegaly, a condition

he termed polycythemia hypertonica and that is now sometimes called Gaisbock syndrome. In 1952 direct measurement of the blood volume in patients with polycythemia led Lawrence and Berlin to identify a subgroup of patients with a normal red cell volume but a reduced plasma volume. Although some members of this group were hypertensive, the authors were more impressed by their tense and anxious behavior and coined the term stress polycythemia.

ETIOLOGY AND PATHOGENESIS

Polycythemia vera arises from transformation of a single stem cell into a cell that has a selective growth advantage and that then gradually becomes the predominant source of marrow precursors. The clonal origin of polycythemia vera has been demonstrated in women heterozygous for a polymorphic X-chromosome marker, glucose-6-phosphate dehydrogenase. In each case all hematopoietic cell lineages express either the enzyme encoded by the maternal or paternal X chromosome, whereas nonhematopoietic cells are a mosaic of both enzyme types.

Examination of marrow-derived colonies from patients with polycythemia vera indicates that BFU-Es with normal EPO sensitivity coexist in the marrows of patients along with cells that are EPO-independent or hyperresponsive. The latter cells are the hallmark of the neoplastic change that results in uncontrolled production of erythrocytes. Other abnormalities that have been described include impaired thrombopoietin-mediated platelet tyrosine phosphorylation expression of Bcl-x, an inhibitor of apoptosis in an increased proportion of erythroid precursors, and increased expression of protein tyrosine phosphatase activity by red cell precursors. The fibroblasts that accumulate in the marrow of patients with polycythemia vera as the disease progresses are not a part of the abnormal clone.

Secondary polycythemia

Appropriate polycythemia High-Altitude Polycythemia.

The adaptive adjustments of humans living at high altitude involve a series of steps that reduce the steepness of the oxygen gradient between the atmosphere and the mitochondria. The initial oxygen gradient between atmospheric and alveolar air can be reduced by an increase in respiratory rate and volume. Since dead space and water vapor pressure are constant and acclimatized individuals do not ventilate excessively, the normal sea level gradient of about 60 torr is only reduced to about 40 torr at Morococha at 4540 m (14,900 ft) above sea level. Further reduction can be achieved, and at the top of Mount Everest extreme hyperventilation reduces the gradient to less than 10 torr. A shift in the oxygen dissociation curve to the right may be of benefit for short-term high-altitude acclimatization, but its usefulness for chronic acclimatization has probably been exaggerated. In the unacclimatized subject exposed acutely to high altitude, hyperventilation alkalosis leads initially to a shift of the oxygen dissociation curve to the left and to additional tissue hypoxia. The alkalosis and the hypoxia will in turn promote red cell synthesis of 2,3-bisphosphoglycerate (2,3-BPG) and ATP and cause the oxygen dissociation curve to shift back to a normal or even a right-shifted position. In chronic acclimatization, the blood pH slightly increased, and when this is taken into account the dissociation curve is shifted approximately normal. Smoker's Polycythemia Heavy smoking will result in the formation of carboxyhemoglobin, which does not transport oxygen and also causes an increase in oxygen affinity of the remaining normal hemoglobin. This leads to tissue hypoxia, erythropoietin production, and stimulation of red cell production. Smoking may also cause a reduction in plasma volume, and these two effects could easily explain the rise in the hematocrit without significant changes from normal in the red cell or plasma volumes. Chronic carbon monoxide poisoning is an important but generally unappreciated cause of mild polycythemia.

Polycythemia Secondary to Abnormal (High-Affinity) Hemoglobins. Hemoglobinopathies with certain amino acid substitutions may result in an increased affinity for oxygen, producing tissue hypoxia and a compensatory erythrocytosis. Mutations affecting the amino acids of the a1b2-globin chain contact affect normal rotation within the molecule and impair the rate of deoxygenation; however, most hemoglobins with mutations involving amino acids in the heme pocket are unstable and associated with hemolytic anemia and cyanosis. The inheritance of these hereditary disorders is autosomal dominant.

Polycythemia Secondary to Red Cell Enzyme Deficiencies. Deficiencies of red cell enzymes in early steps of glycolysis sometimes cause marked decreases in the levels of 2,3-BPG. This results in an increased oxygen affinity of hemoglobin and, in some cases, polycythemia. Polycythemia has also been observed in the "high ATP syndrome" associated with an abnormality of pyruvate kinase. Occasionally mild erythrocytosis occurs in patients with methemoglobinemia due to cytochrome b5 reductase (methemoglobin reductase) deficiency.

Chemically Induced Tissue Hypoxia. A number of chemicals have been suspected of causing histotoxic anoxia and secondary polycythemia, but the only chemical with a predictable capacity to cause erythrocytosis is cobalt; it seems likely that it acts by inhibiting oxidative metabolism. This erythropoietic effect has led to the therapeutic administration of 60 to 150 mg of cobalt chloride to patients with refractory anemias such as the anemias of chronic infection, cancer, or uremia.

Inappropriate polycythemia

Familial Erythrocytosis. Most patients with familial erythrocytosis have been shown to have mutations of the EPO receptor. The mutations are usually ones that cause truncations of the carboxy terminal of the receptor, resulting in constitutive activity of the receptor or hypersensitivity to EPO. The disorder is inherited in an autosomal dominant manner.

Renal Polycythemia. Absolute erythrocytosis has been observed in a considerable number of patients with solitary renal cysts, polycystic renal disease, or hydronephrosis. In most of these cases erythropoietin assays on cyst fluid, serum, or urine have disclosed the presence of erythropoietin. In general, it appears that patients with polycystic disease have a hematocrit value slightly higher than normal and definitely higher than would have been expected of patients with uremia. The presence of erythropoietin mRNA in tumor cells. Wilms' tumors and metanephric adenomas are also occasionally associated with an erythrocytosis.

Post–renal transplantation erythrocytosis occurs in about 10 percent. In some cases this erythrocytosis is associated with an increase in erythropoietin production and has been treated successfully in a few patients with theophylline or captopril. A role of insulin growth factor-1 has also been proposed in the erythrocytosis that occurs after transplantation, and the effect of angiotensin-activating enzyme in controlling the erythrocytosis may be due to suppression of this growth factor.

Brain Tumors. Erythrocytosis and inappropriate secretions of erythropoietin may be found in about 15 percent of patients with cerebellar hemangiomas. In adequately studied patients the arterial gas tensions have been normal. That the tumors are directly responsible for the polycythemia can be surmised from the identification of erythropoietin in cyst fluid and stromal cells and from a case in which erythropoietin mRNA was present in the tumor.

Endocrine Disorders. Pheochromocytomas, aldosterone-producing adenomas, Bartter syndrome, and dermoid cyst of the ovary have been described in association with erythrocytosis. Erythropoietin levels were found elevated in the serum and returned to normal after extirpation of the tumors. A number of pathogenetic mechanisms have been suggested, including mechanical interference with renal blood supply; hypertensive damage to renal parenchyma; functional interaction between aldosterone, renin, and erythropoietin; and inappropriate secretion of erythropoietin by the tumors. The mild polycythemia frequently observed in patients with Cushing syndrome may be caused by an excessive release of glucocorticoids.

The erythropoietic effect of androgens is of considerable practical importance. For many years, it was assumed that the higher red cell count in males was caused by androgens, but it was not until pharmacologic doses of testosterone were administered to women with carcinoma of the breast that the erythropoietic potency of androgens was appreciated.

Neonatal Erythrocytosis. Erythrocytosis at birth is a normal physiologic response to intrauterine hypoxia and to the high oxygen affinity of fetal red cells. However, it may become excessive and even symptomatic, especially in infants of diabetic mothers or if the clamping of the cord is delayed, permitting placental blood to boost the blood volume of the infant. Since it is difficult to recognize symptoms of hyperviscosity in the neonate, many pediatricians perform a partial exchange transfusion if the venous hematocrit is above 65 percent at birth.

Apparent polycythemia

The main clinical associations with apparent polycythemia are obesity, hypertension, and smoking. In obese patients the finding of a normal red cell volume may be spurious, since if the volume is expressed in terms of lean body weight, some of these patients would have a significant increase in red cell mass. In hypertensive patients there is no adequate explanation for the apparent increase in red cell production or decrease in plasma volume.

CLINICAL FEATURESOF POLYCYTHEMIA VERA

Onset. Polycythemia vera usually has an insidious onset, most commonly during the sixth decade of life, although the onset may occur in childhood or in old age. Presenting symptoms include headache, plethora, pruritus, thrombosis, and gastrointestinal bleeding, but some patients are diagnosed simply because abnormal blood counts are found on routine screening.

Thrombosis and haemorrhag. Thrombotic episodes are the most common complications of polycythemia vera, occurring in about one-third of the patients. These can be very serious, including episodes of hepatic vein thrombosis (Budd-Chiari syndrome), occurring in 10 percent of 140 patients in one series. The most common serious complication is a cerebrovascular accident, which accounts for about one-third of the thrombotic events, followed in frequency by myocardial infarction, deep-vein thrombosis, and pulmonary embolism. Bleeding and bruising, too, are common complications, being observed in about one-quarter of the patients.

Cutaneous. Pruritus occurs in approximately 40 percent of patients. It is usually aggravated by bathing or showering and may be so severe as to markedly compromise the quality of life of the patient. Its cause is unclear, and it has been attributed to increased numbers of mast cells in the skin and to elevated histamine levels.

Cardiovascular. Cardiovascular symptoms include angina, myocardial infarction, and congestive heart failure.

Neurological. Neurological symptoms, such as dizziness are very common. Neurological complications such as chorea or the POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome have been reported in single cases. Spinal cord compression secondary to extramedullary hematopoiesis has been documented

Surgery. Over 75 percent of patients with uncontrolled polycythemia vera develop complications during or after major surgery because both bleeding and thrombosis are common.

Association with other diseases. Patients with both polycythemia vera and chronic lymphocytic leukemia appear to have a relatively mild clinical course. An increased incidence of lymphocytic lymphomas has been documented.

Secondary polycythemia

Appropriate polycythemia. Tolerance to high altitudes varies greatly, but most normal individuals have no discomfort at altitudes of up to 2130 m (7000 ft). Above this level and especially if the ascent is rapid, some manifestations of cerebral hypoxia are common. Headaches, sleeplessness, and palpitations are frequently encountered, and weakness, nausea, vomiting, and mental dullness may be present. More severe manifestations include pulmonary and cerebral edema. Cheyne-Stokes respiration commonly occurs, especially during sleep. These symptoms constitute the syndrome of acute mountain sickness.

Ruddy cyanosis and physiologic emphysema are the two characteristic features of humans living at high altitudes. Venous and capillary engorgement can be observed readily in the conjunctiva, mucous membranes, and skin and may contribute to the remarkable capacity of Sherpas to walk barefoot and sleep on ice and snow. Asymptomatic retinal hemorrhages are seen frequently at high altitudes but rarely at altitudes of 3000 m (9000 ft) or less.

Inappropriate polycythemia. Familial erythrocytosis may be very severe with hemoglobin levels of more than 20 g/dl. Hypertension, coronary artery disease, and strokes have been reported to occur but are not a constant feature of the disorder.

Renal Polycythemia. The erythrocytosis that occurs with renal polycythemia can be very severe with red counts as high as 8×10^{12}/l having been reported and associated with hypertension and congestive failure.

Neonatal. Of 55 infants with neonatal polycythemia, 85 percent had signs and symptoms attributed to this disorder. These included "feeding problems" (21.8 %), plethora (20.0 %), lethargy (14.5 %), cyanosis (14.5 %), respiratory distress (9.1 %), jitteriness (7.3 %), and hypotonia (7.3 %). Other findings included hypoglycemia (40.0 %) and hyperbilirubinemia (21.8 %). In a larger group of nearly 1000 infants, 6 had an intracranial hemorrhage.

LABORATORY FEATURES OF POLYCYTHEMIA VERA

Marrow. The marrow is characteristically hypercellular, with involvement of all lineages.

Erythrocytes. The erythrocyte count is usually increased, and in patients who have undergone phlebotomy or had gastrointestinal bleeding episodes it may be increased out of proportion to the increase in the hemoglobin and hematocrit, since there will be marked hypochromia and microcytosis. The plasma iron in such patients is decreased, the iron binding capacity increased, and plasma ferritin levels are low. In late stages of the disease, the morphologic changes are characteristic of myelofibrosis, aniso- and poikilocytosis and abundant teardrop cells (dacrocytes). The PO_2 of the arterial blood is often lower than normal. The saturation with oxygen – reduced.

Leukocytes. An absolute neutrophilia occurs in about two-thirds of the patients. Occasional myelocytes and metamyelocytes are often present in the blood, and considerable degrees of immaturity are often present in patients with long-standing, advanced disease. Basophilia occurs in about two-thirds of patients with uncontrolled disease. Serum lysozyme levels are slightly increased in some patients, and because of the increased leukocyte turnover, levels of vitamin B_{12} are usually increased. The leukocyte alkaline phosphate level is elevated in about 70 percent of patients with polycythemia vera.

Platelets. The platelet count is increased in about one-half of patients at the time of diagnosis. In contrast to normal individuals, where phlebotomy results in an increase in the platelet count, platelet levels are not affected by phlebotomy of patients with polycythemia vera. There are no consistent abnormalities of thrombopoietin levels.

Patients with polycythemia vera, essential thrombocythemia, and other myeloproliferative disorders have a very unusual, nearly pathognomic defect in the primary wave of platelet aggregation induced by epinephrine. In contrast there is increased platelet thromboxane A2 generation and increased excretion of thromboxane metabolites. Platelet factor 4 levels are elevated. Fibrinogen binding after stimulation with platelet activating factor is diminished. The prothrombin time, partial prothrombin time, and fibrinogen level are normal, but fibrinogen turnover may be increased.

Secondary polycythemia. Characteristically, only the numbers of erythrocytes in the blood are increased. Increase in the leukocyte count may be present as another feature of the underlying disease, e.g., the pulmonary infection in chronic obstructive lung disease. In patients with appropriate polycythemia the underlying defect is usually demonstrable. Arterial hypoxia can be demonstrated in most cases, cyanosis. In inappropriate polycythemia the laboratory findings will be those of the underlying defect.

Differential diagnosis. Polycythemia vera must be distinguished from secondary polycythemia and from apparent polycythemia.

Polycythemia vera. The most important diagnostic features of polycythemia vera are erythrocytosis, leukocytosis, thrombocytosis, and splenomegaly. Frequently only two or three of these features are found at presentation and if sufficiently pronounced suffice to establish the diagnosis. Some patients have only one of these features initially, most commonly the erythrocytosis, but occasionally we find only thrombocytosis, leukocytosis, or splenomegaly.

Studies of red cell precursors suggest that patients who have been diagnosed as having pure erythrocytosis can be divided into two groups of about equal size, those with EPO-independent BFU-E and those without such precursors. It is possible that pure erythrocy-tosis is a distinct entity but that some of the patients who meet the criteria for this diagnosis actually have polycythemia vera. Other clinical features – elevated vitamin B_{12} levels, elevated serum uric acid levels, normal or near-normal arterial oxygen saturations, and pruritus.

Since polycythemia is distinguished by the fact that erythroid cells proliferate even in the absence of substantial levels of EPO, one would expect that at high hematocrit levels the production of EPO would be inhibited and the serum levels consequently reduced.

The Polycythemia Vera Study Group directly determined the red cell mass as the sine qua none of the diagnosis of polycythemia vera in patients entered into their studies. The principal value of a red cell mass determination might then be to distinguish apparent or spurious polycythemia from polycythemia vera and secondary polycythemia.

Secondary polycythemia. Patients with secondary polycythemia, like those with polycythemia vera, have a genuine increase in the number of circulating erythrocytes and of the red cell mass. However, in secondary polycythemia the increase in the red cell mass is a response to the stimulation of the marrow by EPO or the abnormal functioning of a mutant EPO receptor.

Such patients do not have the increase in the platelet count and leukocyte count or the splenomegaly that is characteristic of polycythemia vera, and it is the lack of involvement of other formed elements in hematopoietic proliferation that should arouse suspicion that the patient may have secondary polycythemia. In patients in whom the cause of the secondary polycythemia is lung or cardiac disease, clubbing is often present.

Spurious polycythemia. The erythrocytosis observed in patients with spurious polycythemia (apparent polycythemia, stress polycythemia) is a consequence of a decrease in the plasma volume. The observed erythrocytosis does not represent a true increase in the red cell mass. Usually the increase in the hematocrit is very modest. Such patients do not have an increased white blood count, thrombocytosis, or splenomegaly. The arterial oxygen saturation is normal.

Prognosis. Polycythemia vera is a disease compatible with normal or near-normal life for many years. However, ultimately leukemia may develop or the disease enters the spent phase. Leukemia occurs even in patients treated only by phlebotomy, although its incidence increases by the various applied forms of cytotoxic therapy.

Secondary polycythemia. Clinical course of secondary polycythemia is largely a function of the severity of the erythrocytosis. The morbidity that attends marked erythrocytosis presumably relates to the increase in blood viscosity very rapidly as levels rise beyond 50 percent. Therefore, lowering the hematocrit to a normal or near-normal level by phlebotomy is the usual treatment. The appropriate level is that at which the patient becomes asymptomatic. The phlebotomy is preferred because of the leukemogenic risk of the agents that are used in polycythemia vera.

Date	Grade	Teacher`s signature

ANEMIA: GENERAL CLINICAL AND HEMATOLOGICAL APPEARANCE. POSTHEMORRHAGIC ANEMIAS. ANEMIAS CAUSED BY DECREASED ERYTHROPOESIS. HEMOLYTIC ANEMIA

Relevance of the topic. Anemia is a very frequent hematologic symptom at the diverse diseases (diseases of a digestive tract, kidneys, collagenoses, infectious and parasitic diseases, malignant tumors, obstetric and gynecologic pathology, a number of endocrine diseases, a number of congenital and acquired diseases of children of early age, various intoxications, etc.). Besides, anemia can be of primary character, act as an independent hematologic disease. Thus, pathophysiological mechanisms of development the anemic states are very difficult and various. The knowledge of the main hematologic manifestations of anemia, the causes and mechanisms of development in each case gives the chance to the doctor not only to make the diagnosis, but also to plan actions for prevention and rational pathogenetic therapy of this type of pathology.

General aim – to be able to define existing anemic state and character of anemias according to the available classifications, using data of quantitative and qualitative changes of erythrocytes.

The student should be able to (specific objectives):

1. Resolve an issue of existence of anemia according to number of erythrocytes, concentration of hemoglobin and a color indicator;

2. Characterize the possible qualitative changes of erythrocytes in anemias to find their existence at blood dab microscopy of an animal with experimental anemia;

3. Classify anemias by their etiology, pathogenesis, quantitative and qualitative changes of erythrocytes and an erythropoesis, dynamics of a current;

4. Generalize the obtained data on quantitative and qualitative changes of erythrocytes at an animal and on the basis of it to give a conclusion concerning character of anemia.

The student should be able to (reqired knowledge and skills):

1. Characterise the main stages of erythrocytes formation(dep. Normal physiology);

2. Know normal parameters of number of erythrocytes, concentration of hemoglobin, a color indicator and quantity of retikulocyte at the adult (dep. Normal physiology);

3. Define number of erythrocytes, concentration of hemoglobin, a color indicator and quantity of retikulocyte in blood (dep. Normal physiology);

4. Prepare and paint dab of blood according to romanovsky-geimsa and to distinguish at its microscopy cellular elements of an erythrocyte row (dep. normal physiology).

QUESTIONS FOR THE LESSON

1. Iron deficiency anemia. Etiology, pathogenesis, leading clinical syndromes.
2. B_{12}-and anemia of folic acid deficiency. Etiology, pathogenesis, leading clinical syndromes.
3. Hypoplastic (aplastic) anemias. Etiology, pathogenesis, leading clinical syndromes.
4. Haemolytic anemias. Classification. Main clinical syndromes.
5. Intravascular hemolysis of erythrocytes. Causes, mechanisms. The changes developing in an organism owing to an intravascular hemolysis. Clinical and laboratory signs of an intravascular hemolysis.
6. Intracellular hemolysis of erythrocytes. Reasons, mechanisms. The changes developing in an organism owing to an intracellular hemolysis. Clinical and laboratory signs of an intracellular hemolysis.
7. Hereditary haemolytic anemias. Fermentopathy. Hemoglobinopathy. Membranopathy.
8. The acquired haemolytic anemias. Causes and mechanisms of development.

EXPERIMENTAL PART OF LESSON

Experiment 1: calculation of the number of erythrocytes in experimental hemolytic anemia.

The object of the experiment: rabbits.

Apparatus and reactives: microscopes, Vidal's tubes, injectors, micropipets, 5,0 ml pipets, 10 sol. Natrium chloridum, calculating chamber.

Procedure: Take two rabbits before practical lesson daily. One of them under control of hemoglobin was injected 1 % sol. phenylhydrasin subcutaneously in increased dose: 1 injection – 0.25 ml; 2 – 0.5 ml; 3 – 0.75 ml; 4 – 1 ml. Take 0.02 ml of blood by micropipete from marginal vein of ear and blow off into Vidal's tube with 3.98 ml one per cent of hydrochloric natrium solution. After 3 times washing of pipete shake up mixture carefully. Get the drop of mixture into calculating chamber bythe pipete fordistill water from hemometer. Calculate erythrocytes in 5 big (that is in 80 small) squares of Goryajev' net. By number of erythrocytes in 5 big squares calculate their numbers in 1 mkl of blood. Use the formula for calculation.

$$X = \frac{A \times 4000 \times B}{C}$$

here, X – the number of erythrocytes;

A – the sum of erythrocytes, calculated in 5 big squares;

C – the number of calculated small squares (80);

B – the blood dilution (in 200 times);

4000 – multiplier, which brings the volium of the liquid in limits of small square (1/4000 mkl) to 1 mkl. Calculate the number of erythrocytes for 1 L. Compare the amount of erythrocytes of experimental and normal rabbits.

RESULTS: _____

_____

Experiment 2: definition of hemoglobin amount in experimental hemolytic anemia.

The object of the experiment: rabbits.

Apparatus and reactives: hemometers, injectors, micropipets, 0.1 % hydrochloric acid solution, distill water.

Procedure: investigate experimental and normal rabbits. Pour 0.1 N of hydrochloric acid into a middle tube of hemometer to the mark of 2 on the scale × 10 g/l. Then by the pipete from the hemometer fill 0.02 ml blood, wipe the end by cotton with great care, gently blow the blood into the tube, wash the pipete by solution twice. After 5 min. dilute the mixture by distill water till the color of solution in the tube corresponds with the colour of standart hydrochloric hematin solution.

Mark the figure on the lower level of meniskas on the tube which then must be multiplied by 10 to define hemoglobin in g/l. Define the colour index according to the formula:

$$\text{C.I.} = \frac{\text{found amount of hemoglobin}}{\text{normal amount of hemoglobin}} : \frac{\text{found amount of erythrocytes}}{\text{normal amount of erythrocytes}}$$

Compare the amount of hemoglobin and colour index in anemia and normal rabbits.

RESULTS:_____

_____

_____

_____

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

ANEMIA

Red blood cell (RBC) production **(erythropoiesis**) takes place in the bone marrow under the control of the hormone erythropoietin (EPO). Juxtaglomerular cells in the kidney produce EPO in response to decreased O_2 delivery (as in anemia and hypoxia) and increased levels of androgens.

In addition to EPO, RBC production requires adequate supplies of substrates, mainly iron, vitamin B_{12}, and folate. Vitamin B_{12} and folate are discussed in Vitamin Deficiency, Dependency, and Toxicity; iron is discussed in Mineral Deficiency and Toxicity: Iron and discussed in Anemias Caused by Deficient Erythropoiesis: Iron Deficiency Anemia.

RBCs become senescent after about 120 days. They then lose their cell membranes and are largely cleared from the circulation by the phagocytic cells of the spleen, liver, and bone marrow. Hb is broken down in these cells and in hepatocytes primarily by the heme oxygenase system with conservation (and subsequent reutilization) of iron, degradation of heme to bilirubin through a series of enzymatic steps, and reutilization of protein. Maintenance of a steady number of RBCs requires daily renewal of 1/120 of the cells; immature RBCs (reticulocytes) are continually released and constitute 0.5 to 1.5 % of the peripheral RBC population.

Low levels of androgens leading to decreased EPO levels in women and girls and in elderly patients can predispose to anemia, as does the decline in the capacity of bone marrow to produce RBCs. With aging, Hb and Hct decrease slightly, but not below normal values. In women, other factors that frequently contribute to lower levels of RBCs include cumulative menstrual blood loss and increased demand for iron due to multiple pregnancies.

Classification

Having determined the red cell mass, both anemia and polycythemia can be classified as **(1) relative or (2) absolute**. Relative anemia and relative polycythemia are both characterized by a normal total red cell mass. Such conditions are usually not thought of as hematologic disorders but rather as disturbances in the regulation of the plasma volume.

Classification of the absolute anemias with a decreased red cell mass is difficult, since it has to take into account kinetic, morphologic, and pathophysiologic interacting criteria. Initially, all anemias should be divided into anemias caused by decreased production and anemias caused by increased destruction of red cells. This differentiation is to a great extent based on the reticulocyte count

The morphologic classification subdivides anemia into
(1) macrocytic anemia,
(2) normocytic anemia,
(3) microcytic hypochromic anemia.

The main advantages of this classification are that it is simple, based on readily available red cell indices (MCV and MCHC), and it forces the physician always to consider the most important types of curable anemia: vitamin B_{12}, folic acid, and iron-deficiency anemias. Such practical considerations have led to a wide acceptance of this classification. However, pathophysiologic classification is best suited for relating disease processes to potential treatment.

Anemia is a decrease in the number of RBCs, Hct, or Hb content per unit volume of blood.

The RBC mass represents the balance between production and destruction or loss of RBCs. Thus, anemia can result from one or more of 3 basic mechanisms (see *Table 1*):

1. Blood loss
2. Deficient erythropoiesis
3. Excessive hemolysis (RBC destruction)

Table 1

Classification of Anemia by Cause

Mechanism	Examples
Blood loss	
Acute	GI bleeding, Injuries, Childbirth, Surgery
Chronic	Bladder tumors, Cancer or polyps in GI tract, Heavy menstrual bleeding, Kidney tumors, Ulcers in the stomach or small intestine
Deficient erythropoiesis*	
Microcytic	Iron deficiency, Iron-transport deficiency, Iron utilization defect, Iron reutilization defect, Thalassemias (also classified under excessive hemolysis due to intrinsic RBC defects)
Normochromic-normocytic	Aplastic anemia, Hypoproliferation, In kidney disease. In endocrine failure (thyroid, pituitary), In protein depletion Myelodysplasia, Myelophthisis
Macrocytic	Copper deficiency, Folate deficiency, Vitamin$_{12}$ deficiency. Vitamin C deficiency,
Excessive hemolysis due to extrinsic RBC defects	
Reticuloendothelial hyper-activity with splenomegaly	Hypersplenism
Immunologic abnormalities	Autoimmune hemolysis, Cold antibody hemolysis (paroxysmal cold hemoglobinuria), Warm antibody hemolysis, Isoimmune (isoagglutinin) hemolysis
Mechanical injury	Infection, Trauma
Excessive hemolysis due to intrinsic RBC defects	
Membrane alterations, acquired	Hypophosphatemia, Paroxysmal nocturnal hemoglobinuria Stomatocytosis
Membrane alterations, congenital	Hereditary elliptocytosis, Hereditary spherocytosis
Metabolic disorders (inherited enzyme deficiencies)	Embden-Meyerhof pathway defects, G6PD deficiency
Hemoglobinopathies	Hb C disease, Hb E disease, Hb S-C disease, Hb S–β-thalassemia disease, Sickle cell disease (Hb S), Thalassemias (β, β-δ, and α)
*Classified according to RBC indices	

PATHOPHYSIOLOGY AND MANIFESTATIONS

Clinical manifestations of anemia are to some extent determined by its etiology and pathogenesis. Certain signs and symptoms, however, are general and can be attributed to a reduction in oxygen-carrying capacity. Although the red cells also carry carbon dioxide from the tissues to the lungs and help distribute nitric oxide throughout the body, the transport of these gases does not appear to be dependent on the number of red cells available and stays normal in anemic patients. Tissue hypoxia occurs when the pressure head of oxygen in the capillaries is too low to provide distant cells with enough oxygen for their metabolic needs. In

anemia, the extraction of the same amount of oxygen would lead to greater hemoglobin desaturation and a lower oxygen tension at the venous end of the capillary. Since this would result in destructive cellular hypoxia or anoxia in the immediate vicinity, a number of compensatory and frequently symptomatic adjustments in the supply of blood and oxygen are initiated selectively throughout the body.

Many of these protective adjustments involve production and stabilization of a single protein complex, HIF-1. This protein was first identified as a transcriptional factor for the erythropoietin gene1. Subsequent studies have shown that it is also capable of activating other genes involved in protection against hypoxia. For example, HIF-1 transcribes genes coding for many glycolytic enzymes, for growth factors controlling vessel formation, and for proteins regulating vasomotor function.

However, in the absence of oxygen, it is also stable, and the HIF-1 complex becomes functional as a transcriptional protein. Although HIF-1 may be present and functional in all hypoxic cells, its action varies from cell to cell. Consequently, tissue-specific and still unknown interacting factors must be present to explain the mobilization of the many compensatory mechanisms listed below that permit survival under hypoxic conditions.

Decreased oxygen consumption

Activation of genes coding for glycolytic enzymes saves oxygen but at the expense of using less-efficient metabolic pathways. Actually anaerobic glycolysis is not employed extensively in chronic well-tolerated anemias, and the overall consumption of oxygen in anemia may actually be 10 to 15 percent higher than normal because of the metabolic cost of cardiac and pulmonary overactivity.

Decreased oxygen affinity

One of the earliest and least costly adjustments of oxygen delivery is a decrease in the affinity of hemoglobin for oxygen. This permits increased oxygen extraction without jeopardizing oxygen pressure. Since there is no consistent decrease in the pH of blood or evidence of impaired CO_2 removal from the tissues, the observed change in oxygen affinity cannot be accounted for by a simple Bohr shift to the right. However, the red cells of patients with anemia generate increased amounts of 2,3-bisphosphoglycerate, and this phosphate compound has the capacity to combine with deoxygenated hemoglobin and decrease its affinity for oxygen. Accumulation of 2,3-bisphospho-glycerate has also been demon-strated in red cells of individuals with high-altitude hypoxemia.

Increased tissue perfusion

The effect of a decreased oxygen-carrying capacity on the tissue tension of oxygen can be offset if, by using all potential capillary channels, the distance from tissue cells to oxygen supply is reduced. This can be accomplished via HIF-1 activation of genes regulating both vasomotor activity and angiogenesis. Since in most anemias the blood volume is not changed significantly increased tissue perfusion has to be performed selectively with blood shunted from presumably nonvital donor areas to oxygen-sensitive recipient organs.

Although the kidney can hardly be thought of as a nonvital area, oxygen supply under normal conditions is in excess of oxygen demands. The arteriovenous oxygen difference in the kidney indicates that even a severe reduction in the kidney perfusion does not limit oxidative cellular metabolism. Nevertheless, enough renal hypoxia must be present to activate HIF-1 and generate increased amounts of erythropoietin and in turn new red cells). The effect on renal excretory mechanisms is slight, since the reduction in renal blood flow is offset by the high plasmacrit and, even in severe anemia with the renal blood flow reduced by almost 50 percent, the renal plasma flow is only moderately curtailed.

Increased cardiac output

An increase in cardiac output is an excellent but metabolically expensive compensatory device. It will decrease the fraction of oxygen that needs to be extracted during each circulation and thereby keep the oxygen pressure high. Since the viscosity of blood in anemic patients is lower than normal, and since selective vascular dilatation will decrease peripheral resistance, a high cardiac output can be maintained without any increase in blood pressure.

Signs of cardiac hyperactivity include tachycardia, increased arterial and capillary pulsation, and many hemodynamic murmurs. The cardiac murmurs are usually systolic and are heard best at the apex or at the pulmonary valve area. Diastolic murmurs are unusual, but all murmurs in an ane-mic patient should be considered hemodynamic until proved otherwise. Their characteristic feature is that they disappear promptly after the hemoglobin concentration has been restored to normal.

Increased pulmonary function

Since at sea level blood, regardless of oxygen-carrying capacity, is nearly completely oxygenated in the lungs, the oxygen pressure of arterial blood in an anemic patient should be the same as that in a normal individual, about 100 mmHg. Nevertheless, an increase in respiratory rate or vital capacity will decrease the oxygen gradient from ambient air to alveolar air and will increase the amount of oxygen available to oxygenate a greater than normal cardiac output. Consequently, exertional dyspnea and orthopnea are characteristic clinical manifestations of severe anemia.

Increased red cell production

The most appropriate response to anemia is a compensatory increase in the rate of red cell production. The change in erythropoietin levels ensures that in most cases red cell production will balance red cell destruction or red cell loss at a hemoglobin concentration much higher than that which would be found if the rate of red cell production had stayed the same. The administration of exogenous human recombinant erythropoietin augments or replaces endogenous synthesis. Using pharmacologic amounts, the effect on hemoglobin concentration will be most noticeable if endogenous production is subnormal due to renal failure or systemic illnesses. An increase in the number of circulating reticulocytes is the most significant laboratory reflection of accelerated red cell production.

Uncorrected tissue hypoxia

Despite mobilization of compensatory mechanisms, a certain residual degree of tissue hypoxia remains. Some of this contributes to the necessary driving force to sustain cardiovascular and erythropoietic adjustments, but tissue hypoxia per se may cause disturbing and even disabling symptoms. Angina pectoris, intermittent claudication, and night cramps are muscular signs of tissue hypoxia; headache, light-headedness, and faintness are cerebral signs. A number of diffuse gastrointestinal and genitourinary symptoms have been associated with anemia, but it is uncertain whether they should be attributed to tissue hypoxia, compensatory redistribution of blood, or the underlying cause of anemia.

A number of systemic symptoms result from this lifesaving maneuver.

1. Kidneys: Decreased blood flow is sensed by the kidneys, causing the renal renin-angiotensin response to activate, resulting in salt and water retention.
2. Skin: Decreased oxygen delivery to the skin results in impaired healing and loss of elasticity.
3. Hair: Decreased oxygen delivery to the hair results in thinning and early graying.
4. Nervous system: myelin degeneration may occur with loss of nerve fibers in the spinal cord. Numbness (paresthesias), gait disturbances, extreme weakness, spasticity.
5. Gastrointestinal tract: Decreased oxygen supply to the gastrointestinal tract often produces abdominal pain, nausea, vomiting, and anorexia.
6. Other areas: The skin, mucous membranes, lips, nailbeds, and conjunctiva become either pale as a result of reduced hemoglobin concentration, or yellowish as a result of the presence of products of red blood cell breakdown (hemolysis).

EVALUATION OF ANEMIA

Anemia is not a diagnosis; it is a manifestation of an underlying disorder. Thus, even mild, asymptomatic anemia should be investigated so that the primary problem can be diagnosed and treated.

History should address risk factors for particular anemias, symptoms of anemia itself, and symptoms that reflect the underlying disorder.

Anemia has many risk factors. For example, a vegan diet predisposes to vitamin B_{12} deficiency anemia, whereas alcoholism increases the risk of folate deficiency anemia. A number of hemoglobinopathies are inherited, and certain drugs predispose to hemolysis. Cancer, rheumatism and chronic inflammatory disorders can suppress bone marrow activity or enlarge the spleen.

Symptoms reflect compensatory responses to tissue hypoxia and usually develop when Hb falls to < 7 g/dL. However, they may develop at higher Hb levels in patients with limited cardiopulmonary reserve or in whom the anemia developed very rapidly. Symptoms such as weakness, seeing spots, fatigue, drowsiness, angina, syncope, and dyspnea on exertion can indicate anemia. Vertigo, headache, pulsatile tinnitus, amenorrhea, loss of libido, and GI complaints may also occur. Certain symptoms may suggest the cause of the anemia. For example, melena, epistaxis, hematochezia, hematemesis, or menorrhagia indicates bleeding. Jaundice and dark urine, in the absence of liver disease, suggest hemolysis. Diffuse severe bone or chest pain may suggest sickle cell disease, and stocking-glove paresthesias may suggest vitamin B_{12} or folate deficiency.

Physical Examination

Complete physical examination is necessary. Signs of anemia itself are neither sensitive nor specific; however, pallor is common with severe anemia.

Signs of underlying disorders are often more diagnostically accurate than are signs of anemia. **Heme-positive stool** identifies GI bleeding. **Hemorrhagic shock** (e.g., hypotension, tachycardia, pallor, tachypnea, diaphoresis) may result from acute bleeding. **Jaundice** may suggest hemolysis. **Splenomegaly** may occur with hemolysis, hemoglobinopathy, connective tissue disease, myeloproliferative disorder, infection, or cancer. **Peripheral neuropathy** suggests vitamin B_{12} deficiency. **Abdominal distention** in a patient with blunt trauma suggests acute hemorrhage. **Petechiae** develop in thrombocytopenia or platelet dysfunction. **Fever and heart murmurs** suggest infectious endocarditis, a possible cause of hemolysis. Rarely, high-output heart failure develops as a compensatory response to anemia-induced **tissue hypoxia**.

Laboratory evaluation begins with a CBC, including WBC and platelet counts, RBC indices and morphology (MCV, MCH, MCHC, RBC volume distribution width [RDW]), and examination of the peripheral smear. Reticulocyte count demonstrates how well the bone marrow compensates for the anemia. Recognition of general diagnostic patterns can expedite the diagnosis (see *Table 2*).

Table 2

Characteristics of Common Anemias

Etiology or Type	Morphologic Changes	Special Features
Blood loss, acute	Normochromic-normocytic, with polychromatophilia Hyperplastic marrow	If severe, possible nucleated RBCs and left shift of WBCs. Leukocytosis, Thrombocytosis
Blood loss, chronic	Same as iron deficiency	Same as iron deficiency
Folate deficiency	Same as vitamin B_{12} deficiency	Serum folate < 5 ng/mL (<11 nmol/L). RBC folate < 225 ng/mL RBCs (< 510 nmol/L), Nutritional deficiency and malabsorption (pregnancy, infancy, or alcoholism)
Hereditary spherocytosis	Spheroidal microcytes. Normoblastic erythroid hyperplasia	Increased mean RBC Hb level. Increased RBC fragility. Shortened survival of labeled RBCs. Increased radioactivity of spleen
Hemolysis, acute	Normochromic-normocytic. Reticulocytosis. Marrow erythroid hyperplasia	Increased serum bilirubin and LDH. Increased stool and urine urobilinogen. Hemoglobinuria in fulminating cases. Hemosiderinuria
Hemolysis, chronic	Normochromic-normocytic. Reticulocytosis. Marrow erythroid hyperplasia, Basophilic stippling	Increased serum bilirubin and LDH. Shortened RBC life span. Increased radioiron turnover. Hemosiderinuria
Infection or chronic inflammation	Normochromic-normocytic early, then microcytic. Normoblastic marrow. Normal iron stores	Decreased serum iron. Decreased total iron-binding capacity. Normal serum ferritin. Normal marrow iron content

Etiology or Type	Morphologic Changes	Special Features
Iron deficiency	Microcytic, with anisocytosis and poikilocytosis. Reticulocytopenia. Hyperplastic marrow, with delayed hemoglobination	Possible achlorhydria, smooth tongue, and spoon nails, Absent stainable marrow iron. Low serum iron, Increased total iron-binding capacity, Low serum ferritin
Marrow failure	Normochromic-normocytic (may be macrocytic). Reticulocytopenia. Failed marrow aspiration or evident hypo-plasia of eryth roid series or of all elements	Idiopathic (> 50 %) or secondary to exposure to toxic drugs or chemicals (eg, chloramphenicol, quinacrine, hydantoins, insecticides)
Marrow replacement (myelophthisis)	Anisocytosis and poikilocytosis, Nucleated RBCs. Early granulocyte precursors. Marrow aspiration possibly failing or showing leukemia, myeloma, metastatic cells	Marrow infiltration with infectious granulomas, tumors, fibrosis, or lipid histiocytosis. Possible hepatomegaly and splenomegaly. Possible bone changes. Radioiron uptake greater over spleen and liver than over sacrum
Paroxysmal cold hemoglobinuria	Normochromic-normocytic	Follows exposure to cold. Results from a cold agglutinin or hemolysin. Often associated with syphilis or other infections
Paroxysmal nocturnal hemoglobinuria	Normocytic (may be hypochromic because of iron deficiency), Marrow may be hyper- or hypocellular	Dark morning urine, Hemosiderin. Positive acid hemolysis (Ham's test) and sugar-water tests (mostly replaced by flow cytometric testing)
Sickle cell anemia	Anisocytosis and poikilocytosis, Some sickle cells in peripheral smear. Sickling of all RBCs in preparation with hypoxia	Largely limited to blacks. Urinary isosthenuria. Hb S detected during electrophoresis. Possibly painful vaso-occlusive crises and leg ulcers, Bone changes on x-ray
Sideroblastic anemia	Usually hypochromic but dimorphic with normocytes and macrocytes, Hyperplastic marrow, with delayed hemoglobination, Ringed sideroblasts	Inborn or acquired metabolic defect. Stainable marrow iron (plentiful). Response to vitamin B_6 administration (rare). Commonly part of myelodysplastic syndrome
Thalassemia	Microcytic. Thin cells. Target cells. Basophilic stippling. Anisocytosis and poikilocytosis. Nucleated RBCs in homozygotes	Decreased RBC fragility. Elevated Hb A_2 and Hb F (often). Mediterranean ancestry (common). In homozygotes, anemia from infancy. Splenomegaly. Bone changes on x-ray
Vitamin B_{12} deficiency	Oval macrocytes. Anisocytosis. Reticulocytopenia. Hypersegmented WBCs. Megaloblastic marrow	Serum B_{12} < 180 pg/mL (< 130 pmol/L). Frequent GI and CNS involvement. Positive Schilling test (although no longer done), Elevated serum bilirubin, Increased LDH, Antibodies to intrinsic factor in serum, Absent gastric intrinsic factor secretion

The automated CBC directly measures Hb, RBC count, and MCV (a measure of RBC size). The diagnostic criterion for anemia in men is Hb < 14 g/dL, Hct < 42 %, or RBC < 4.5 million/L; for women, Hb < 12 g/dL, Hct < 37 %, or RBC < 4 million/L. For infants, normal values vary with age, necessitating use of age-related tables. RBC populations are termed microcytic (small cells) if MCV is < 80 fL, and macrocytic (large cells) if MCV is > 100 fL. However, because reticulocytes are also larger than mature red cells, large numbers of reticulocytes can elevate the MCV and not represent an alteration of RBC production.

The RBC indices can help indicate the mechanism of anemia and narrow the number of possible causes. Microcytic indices occur with altered hemorglobin synthesis. The most common causes are iron deficiency, thalassemia, and related Hb-synthesis defects. In some patients with anemia of chronic disease, the MCV is microcytic or borderline microcytic. Macrocytic indices occur with impaired DNA synthesis (e.g., due to vitamin B_{12} or folate deficiencies or chemotherapeutic drugs such as hydroxyurea and antifolate agents) and in alcoholism because of abnormalities of the cell membrane. Acute bleeding may briefly

produce macrocytic indices because of the release of large young reticulocytes. Normocytic indices occur in anemias resulting from deficient EPO or inadequate response to it (hypoproliferative anemias). Hemorrhage, before iron deficiency develops, usually results in normocytic and normochromic anemia unless the number of large reticulocytes is excessive.

The peripheral smear is highly sensitive for excessive RBC production and hemolysis. It is more accurate than automated technologies for recognition of altered RBC structure, thrombocytopenia, nucleated RBCs, or immature granulocytes and can detect other abnormalities (e.g., malaria and other parasites, intracellular RBC or granulocyte inclusions) that can occur despite normal automated blood cell counts. RBC injury may be identified by finding RBC fragments, portions of disrupted cells **(schistocytes)**, or evidence of significant membrane alterations from oval-shaped cells **(ovalocytes)** or spherocytic cells. Target cells (thin RBCs with a central dot of Hb) are RBCs with insufficient Hb or excess cell membrane (e.g., due to hemoglobinopathies or liver disorders). The peripheral smear can also reveal variation in RBC shape (**poikilocytosis)** and size (**anisocytosis)**.

The reticulocyte count is expressed as the percentage of reticulocytes (normal range, 0.5 to 1.5 %) or as the absolute reticulocyte count (normal range, 50.000 to 150.000/мL). Higher values indicate excessive production, or reticulocytosis; in the presence of anemia, reticulocytosis suggests excessive RBC destruction. Low numbers in the presence of anemia indicate decreased RBC production. The reticulocyte response can usually be estimated based on the number of blue-stained cells found when the peripheral smear is stained with a supravital stain; this estimate makes a reticulocyte count, which requires flow cytometry or a large amount of time, unnecessary.

Bone marrow aspiration and biopsy provide direct observation and assessment of RBC precursors. Presence of abnormal maturation (dyspoiesis) of blood cells and the amount, distribution, and cellular pattern of iron content can be assessed. Serum bilirubin and LDH can sometimes help differentiate between haemolysis and blood loss; both are elevated in hemolysis and normal in blood loss.

TREATMENT OF ANEMIA

When the Hb falls dangerously low (eg, < 7 g/dL for patients without cardiopulmonary insufficiency or higher for patients with it), RBC transfusion temporarily increases O_2-carrying capacity. RBC transfusion should be reserved for patients.

POSTHEMORRHAGIC ANEMIA

Posthemorrhagic anemia refers to a reduced number of red blood cells in the body due to bleeding.

There are two types of anemias of this group according to the character of hemorrhage:

1) acute posthemorrhagic

2) chronic posthemorrhagic anemia.

Symptoms of Posthemorrhagic anemia. Reduced red blood cell count, asymptomatic in mild cases, loss of appetite, pale lips, pale eyelids, weakness, fatigue, lightheadedness, tiredness, headache, early symptoms are mild, shortness of breath on exertion, pallor, concentration problems, rapid heartbeat, irregular heartbeat, chest pain, dizziness, impaired cognitive ability, cold skin, shock – severe acute cases, lactic acidosis – severe acute cases

Treatment List for Posthemorrhagic anemia

The list of treatments: blood transfusion in more severe cases; albumin, dextran or plasma in milder cases, identification and control of bleeding source, iron supplementation – used in a stable patient to return haemoglobin levels and iron stores to normal, dietary advice – to ensure adequate intake of iron in the diet.

ANEMIAS DUE TO DECREASED ERYTHROPOIESIS

Anemia (a decrease in the number of RBCs, Hb content, or Hct) can result from decreased RBC production (erythropoiesis), increased RBC destruction, or blood loss.

Anemias due to decreased erythropoiesis are recognized by reticulocytopenia, which is usually evident on the peripheral smear. The RBC indices, mainly the MCV, narrow the differential diagnosis of deficient erythropoiesis and determine what further testing is necessary.

Microcytic anemias result from deficient or defective heme or globin synthesis. Microcytic anemias include iron deficiency anemias, iron-transport deficiency anemias, iron-utilization anemias (including some sideroblastic anemias and lead poisoning), and thalassemias. Patients with microcytic anemias typically require testing of iron stores.

Normocytic anemias result from primary bone marrow failure. They are usually characterized by a normal RBC distribution width (RDW) and normochromic indices. The mechanisms involved are hypoproliferation (deficiency of or inadequate response to erythropoietin [EPO]), hypoplasia (in aplastic anemia), myelophthisis, and myelodysplasia.

Macrocytic anemias result most often from impaired DNA synthesis, as occurs with deficiencies of vitamin B_{12} or folate.

Some anemias have variable findings on the peripheral smear. Anemia of chronic disease may be microcytic or normocytic. Anemias due to myelodysplastic syndromes may be microcytic, normocytic, or macrocytic. Treatment of deficient RBC production depends on the cause; however, stimulation of erythropoiesis with human recombinant EPO often is helpful in the anemia due to renal failure. Because erythropoiesis increases the iron requirement, supplemental iron is helpful when administering any treatment that aims to increase erythropoiesis.

IRON DEFICIENCY ANEMIA *(Anemia of Chronic Blood Loss; Chlorosis)*

Basic Iron Metabolism Most of the iron within the body is found in hemoglobin within erythrocytes (about 1800 mg of iron). Iron is stored in macrophages (and to a lesser extent in hepatocytes), which represents the storage pool of iron (about 1600 mg of iron). Small amounts of iron are found in myoglobin and in plasma (bound to transferrin). Iron is conserved within the body. The typical adult human body contains about 3000–4000 mg of iron. Only about 1 mg of iron is lost from the body per day (through blood loss or sloughed mucosal epithelial cells) and must be replaced through the diet and by recycling iron from senescent red cells.

Iron absorption in gastrointestinal tract. Dietary iron is obtained either from inorganic sources or animal sources (in heme from breakdown of hemoglobin or myoglobin). Dietary iron enters intestinal cells via specific transporters.

The iron is then used by the cell (incorporated into enzymes), stored as ferritin (excreted in the feces when the intestinal epithelial cell sloughs) or is transferred to the plasma (see figure below). Plasma transfer of iron from enterocytes to the transport protein, apotransferrin, occurs through specific iron channels, called ferroportins, and is facilitated by a protein (with ferroxidase activity) called hephaestin.

When apotransferrin binds iron, it is called transferrin. Hephaestin contains copper, so copper deficiency will decrease iron absorption (as the iron absorbed from the diet cannot be transferred to plasma). Hepcidin, a main iron regulating protein, decreases ferroportin and thus decreases iron absorption.

Iron transfer/recycling Iron is not free in the circulation but exists as transferrin (bound to apotransferrin). Most of the iron used for red blood cell hemoglobin production is obtained from hemoglobin breakdown of senescent RBCs (called recycling). When red blood cells reach the end of their lifespan (senescent), they are phagocytized by macrophages (in the spleen, liver, bone marrow). Proteolytic digestion of hemoglobin liberates heme and globins. Globins are broken down to amino acids which can be used for protein production. Iron is released from heme, leaving a porphyrin ring which is converted to bilirubin. Once iron is released from the heme, it is utilized by the cell (iron is an essential component of many enzymes), exported (via ferroportin), or stored as ferritin (like enterocytes – see figure). In macrophages, ceruloplasmin (which like hephaestin in intestinal cells also requires copper) is a ferroxidase and facilitates the transfer of macrophage iron to transferrin. So copper deficiency decreases iron release from macrophages and affects iron absorption.

Iron absorbed from the intestine is stored as ferritin in intestinal epithelium or transported in plasma as transferrin. Erythroid progenitors obtain iron for hemoglobin synthesis from plasma transferrin or from recycling of senescent erythrocytes by macrophages in bone marrow, spleen and liver. Iron that is in excess for that required for hemoglobin production is stored in macrophages as ferritin, which is oxidized to hemosiderin. These stores can be released from macrophages in times of need (increased erythropoiesis).

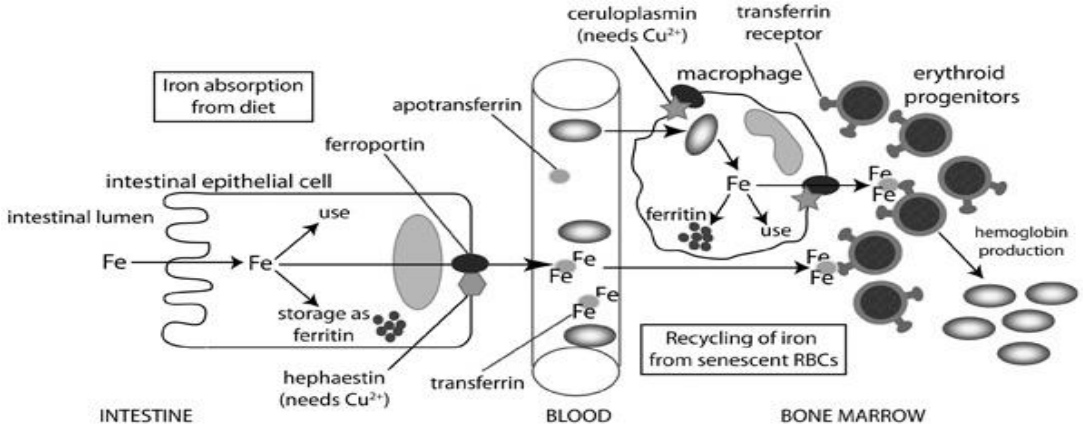


Fig. 1. Iron transfer/recycling

Iron deficiency is the most common cause of anemia and usually results from blood loss. Symptoms are usually nonspecific. RBCs tend to be microcytic and hypochromic, and iron stores are low as shown by low serum ferritin and low serum iron levels with high serum total iron binding capacity. If the diagnosis is made, occult blood loss is suspected. Treatment involves iron replacement and treatment of the cause of blood loss.

Pathophysiology Iron is distributed in active metabolic and storage pools. Total body iron is about 3.5 g in healthy men and 2.5 g in women; the difference relates to women's smaller body size, lower androgen levels, and dearth of stored iron because of iron loss due to menses and pregnancy. The distribution of body iron in an average man is Hb, 2100 mg; ferritin, 700 mg (in cells and plasma); hemosiderin, 300 mg (in cells); myoglobin, 200 mg; tissue (heme and nonheme) enzymes, 150 mg; and transport-iron compartment, 3 mg.

Iron absorption. Iron is absorbed in the duodenum and upper jejunum. Absorption of iron is determined by the type of iron molecule and by what other substances are ingested. Iron absorption is best when food contains heme iron (meat). Dietary nonheme iron must be reduced to the ferrous state and released from food binders by gastric secretions. Nonheme iron absorption is reduced by other food items (eg, vegetable fiber phytates and polyphenols; tea tannates, including phosphoproteins; bran) and certain antibiotics (eg, tetracycline). Ascorbic acid is the only common food element known to increase nonheme iron absorption.

Iron transport and usage. Iron from intestinal mucosal cells is transferred to transferrin, an iron-transport protein synthesized in the liver; transferrin can transport iron from cells (intestinal, macrophages) to specific receptors on erythroblasts, placental cells, and liver cells. For heme synthesis, transferrin transports iron to the erythroblast mitochondria, which insert the iron into protoporphyrin for it to become heme. Transferrin is extruded for reutilization. Synthesis of transferrin increases with iron deficiency but decreases with any type of chronic disease.

Iron storage and recycling. Iron not used for erythropoiesis is transferred by transferrin, an iron-transporting protein, to the storage pool; iron is stored in 2 forms, ferritin and hemosiderin. The most important is ferritin, which is a soluble and active storage fraction located in the liver (in hepatocytes), bone marrow, and spleen (in macrophages); in RBCs; and in serum. Iron stored in ferritin is readily available for any body requirement. Circulating (serum) ferritin level parallels the size of the body stores (1 ng/mL = 8 mg of iron in the storage pool). The 2 nd storage pool of iron is stored primarily in the liver (in Kupffer cells) and in bone marrow (in macrophages).

Because iron absorption is so limited, the body recycles and conserves iron. Transferrin grasps and recycles available iron from aging RBCs undergoing phagocytosis by mononuclear phagocytes. With aging, iron stores tend to increase because iron elimination is slow.

Iron deficiency: Deficiency develops in stages. In the first stage, iron requirement exceeds intake, causing progressive depletion of bone marrow iron stores. As stores decrease, absorption of dietary iron increases in compensation. During later stages, deficiency impairs RBC synthesis, ultimately causing anemia.

Etiology. Because iron is poorly absorbed, dietary iron barely meets the daily requirement for most people. Even so, people who eat a typical Western diet are unlikely to become iron deficient solely as a result of dietary deficiency.

Blood loss is almost always the cause. In men, the frequent cause is chronic occult bleeding, usually from the GI tract. In premenopausal women, cumulative menstrual blood loss (0.5 mg iron/day) is a common cause. Another cause of blood loss in men and women is chronic intravascular hemolysis. Vitamin C deficiency can contribute to iron deficiency anemia by causing capillary fragility, hemolysis, and bleeding.

Increased iron requirement may contribute to iron deficiency. From birth to age 2 and during adolescence, when rapid growth requires a large iron intake, dietary iron often is inadequate. During pregnancy, the fetal iron requirement increases the maternal iron requirement despite the absence of menses. Lactation also increases the iron requirement (mean, 0.4 mg/day).

Decreased iron absorption can result from gastrectomy and upper small-bowel malabsorption syndromes. Rarely, absorption is decreased by dietary deprivation from undernutrition.

Symptoms and Signs. Such symptoms include fatigue, loss of stamina, shortness of breath, weakness, dizziness, and pallor. Fatigue also may result from dysfunction of iron-containing cellular enzymes. Patients may have abnormal craving to eat substances (eg, ice, dirt, paint). Other symptoms include glossitis, cheilosis, concave nails (koilonychia), dysphagia caused by a postcricoid esophageal web (Plummer-Vinson syndrome).

Diagnosis. Iron deficiency anemia is suspected in patients with chronic blood loss or micro-cytic anemia, particularly if pica is present. In such patients, CBC, serum iron and ironbinding capacity, and serum ferritin are obtained.

Iron and iron-binding capacity (or transferrin) are usually both measured because their relationship is important. In general, normal serum iron is 75 to 150 μg/dL (13 to 27 μmol/L) for men and 60 to 140 μg/dL (11 to 25 μmol/L) for women; total iron-binding capacity is 250 to 450 μg/dL (45 to 81 μmol/L). Serum iron level is low in iron deficiency and in many chronic diseases and is elevated in hemolytic disorders and in iron-overload syndromes**.** The iron-binding capacity increases in iron deficiency. Serum transferrin receptor levels reflect the amount of RBC precursors available for active proliferation; levels are sensitive and specific. The range of normal is 3.0 to 8.5 μg/mL. Serum ferritin levels closely correlate with total body iron stores. The range of normal in most laboratories is 30 to 300 ng/mL, and the mean is 88 ng/mL in men and 49 ng/mL in women. Low levels (< 12 ng/mL) are specific for iron deficiency. However, ferritin is an acute-phase reactant, and levels increase in inflammatory and neoplastic disorders in cases of liver injury (e.g., hepatitis) and in some tumors (acute leukemia, Hodgkin lymphoma, and GI tract tumors).

The most sensitive and specific criterion for iron-deficient erythropoiesis is absent bone marrow stores of iron, although a bone marrow examination is rarely needed.

Stages of iron deficiency. Laboratory test results help stage iron deficiency anemia.

Stage 1 is characterized by decreased bone marrow iron stores; Hb and serum iron remain normal, but serum ferritin level falls to < 20 ng/mL. The compensatory increase in iron absorption causes an increase in iron-binding capacity (transferrin level).

Stage 2, erythropoiesis is impaired. Although the transferrin level is increased, the serum iron level decreases; transferrin saturation decreases. Erythropoiesis is impaired when serum iron falls to < 50 μg/dL (< 9 μmol/L) and transferrin saturation to < 16 %. The serum ferritin receptor level rises (> 8.5 mg/L).

Stage 3, anemia with normal-appearing RBCs and indices develops.

Stage 4, microcytosis and then hypochromia develop.

Stage 5, iron deficiency affects tissues, resulting in symptoms and signs.

To dignose iron deficiency anemia, we should consider its cause, usually bleeding. Patients with obvious blood loss (e.g., women with menorrhagia) may require no further testing. Men and postmenopausal women without obvious blood loss should undergo evaluation of the GI tract, because anemia may be the only indication of an occult GI cancer.

Other microcytic anemias. Iron deficiency anemia must be differentiated from other microcytic anemias (see *Table 1*). If tests exclude iron deficiency in patients with microcytic anemia, then anemia of chronic disease, structural Hb abnormalities (e.g., hemoglobinopathies), and congeni-tal RBC membrane abnormalities are considered.

Treatment

Iron therapy without pursuit of the cause is poor practice; the bleeding site should be sought even in cases of mild anemia. Iron can be provided by various iron salts (e.g., ferrous sulfate, gluconate, fumarate) or saccharated iron po 30 min before meals (food or antacids may reduce absorption). Ascorbic acid either as a pill (500 mg) or as orange juice when taken with iron enhances iron absorption without increasing gastric distress.

SIDEROBLASTIC ANEMIAS

Sideroblastic anemias are iron-utilization anemias that are usually part of a myelodysplastic syndrome, causing a normocytic-normochromic anemia with high RBC distribution width or a microcytic-hypochromic anemia, particularly with increased serum iron and ferritin and transferrin saturation.

Sideroblastic anemias are among the anemias characterized by inadequate marrow utilization of iron for Hb synthesis despite the present adequate or increased amounts of iron. Other iron-utilization anemias include some hemoglobinopathies, primarily thalassemias. Sideroblastic anemias are characterized by the presence of polychromatophilic, stippled, targeted RBCs (siderocytes). Sideroblastic anemias are generally part of a myelodysplastic syndrome but may be hereditary or may occur secondary to drugs (eg, chloramphenicol cycloserine, isoniazid, pyrazinamide) or toxins (including ethanol and lead). Pyridoxine deficiency can lead to sideroblastic anemia. Deficient reticulocyte production, intramedullary death of RBCs, and bone marrow erythroid hyperplasia (and dysplasia) occur. Although hypochromic RBCs are produced, other RBCs may be large producing normochromic indices; if so, variation in RBC size (dimorphism) usually produces.

Sideroblastic anemia is suspected in patients with microcytic anemia or a high RDW anemia, particularly with increased serum iron, serum ferritin, and transferrin saturation. The peripheral smear shows RBC dimorphism. RBCs may appear stippled. Bone marrow examination is necessary and reveals erythroid hyperplasia. Other features of myelodysplasia, such as chromosomal abnormalities, are frequently evident. Serum lead is measured if sideroblastic anemia has an unknown cause Elimination of a toxin or drug (especially alcohol) can lead to recovery. Rarely, congenital cases respond to pyridoxine 50 mg po tid, but incompletely. Pyridoxine deficiency is corrected by vitamin B_6 supplementation. Ring Sideroblasts in Sideroblastic Anemia.

ANEMIA OF CHRONIC DISEASE (Iron-Reutilization Anemia)

Anemia of chronic disease is a multifactorial anemia often coexistent with iron deficiency. Diagnosis generally requires the presence of chronic infection, inflammation, or cancer; microcytic or marginal normocytic anemia; and values for serum transferrin receptor and serum ferritin that are between those typical for iron deficiency and sideroblastic anemia. Treatment is to reverse the underlying disorder or, if the disorder is irreversible, to give erythropoietin.

Worldwide, anemia of chronic disease is the 2nd most common anemia. Early on, the RBCs are normocytic; with time they become microcytic. The major issue is that the marrow erythroid mass fails to expand appropriately in response to anemia.

Etiology. This type of anemia was thought to occur as part of a chronic disorder, most often infection, inflammatory disease (especially RA), or cancer; however, the same process appears to begin acutely during virtually any infection or inflammation. Three pathophysiologic mechanisms have been identified: Reticuloendothelial cells retain iron from senescent RBCs, making iron unavailable for Hb synthesis. There is thus a failure to compensate for the anemia with increased RBC production. Macrophage-derived cytokines (eg, IL-1β, tumor necrosis factor-α, interferon-β) in patients with infections, inflammatory states, and cancer cause or contribute to the decrease in EPO production and the impaired iron metabolism.

Diagnosis. Clinical findings are usually those of the underlying disorder (infection, inflammation, or cancer). Anemia of chronic disease is suspected in patients with microcytic or marginal normocytic anemia with chronic infection, inflammation, or cancer. If anemia of chronic disease is suspected, serum iron, transferrin, transferrin receptor, and serum ferritin are measured. Hb usually is > 8 g/dL unless an additional mechanism contributes to anemia. If iron deficiency is present in addition to anemia of chronic disease, serum ferritin generally remains < 100 ng/mL, and, if there is infection, inflammation, or cancer, a ferritin level of slightly < 100 ng/mL suggests that iron deficiency is superimposed on anemia of chronic disease.

HYPOPROLIFERATIVE ANEMIAS

Hypoproliferative anemias result from deficient erythropoietin (EPO) or a diminished response to it; they tend to be normocytic and normochromic. Renal, metabolic, and endocrine disorders are common causes. Treatment includes measures to correct the underlying disorder and sometimes EPO.

Hypoproliferation is a common mechanism in anemias of renal disease, hypometabolic or endocrine deficiency states (eg, hypothyroidism, hypopituitarism), and protein deprivation. The mechanism appears to be a relative or absolute decreased production of EPO. In hypometabolic states, the bone marrow may also fail to respond to EPO.

Anemia of renal disease. The deficiency in renal production of EPO and the severity of anemia correlate with the extent of renal dysfunction; anemia occurs when creatinine clearance is < 45 mL/min. Renal glomerular lesions (eg, from amyloidosis, diabetic nephropathy) generally result in the most severe anemia for their degree of excretory failure.

The term anemia of renal disease refers only to that caused by decreased EPO, but other mechanisms may increase its severity. In uremia, mild hemolysis is common; its basis is uncertain. Less common is RBC fragmentation (traumatic hemolytic anemia), which occurs when the renovascular endothelium is injured (eg, in malignant hypertension, membranoproliferative glomerulonephritis, polyarteritis nodosa, or acute cortical necrosis).

Other hypoproliferative anemias. Clinical and laboratory findings of other hypoproliferative normochromic-normocytic anemias are milder but otherwise mimic those of the anemia of renal disease. The mechanism of the anemia of protein depletion may be general hypometabolism. Hypometabolism may diminish the marrow response to EPO. Protein's role in hematopoiesis is unclear.

APLASTIC ANEMIA (Hypoplastic Anemia)

Aplastic anemia is a normocytic-normochromic anemia that results from a loss of blood cell precursors, causing hypoplasia of bone marrow, RBCs, WBCs, and platelets. Symptoms result from severe anemia, thrombocytopenia (petechiae, bleeding), or leukopenia (infections). Diagnosis requires demonstration of peripheral pancytopenia and the absence of cell precursors in bone marrow. Treatment is equine antithymocyte globulin and cyclosporine. Erythropoietin, granulocyte-macrophage colony-stimulating factor, and bone marrow transplantation may also be useful.

The term aplastic anemia commonly implies a panhypoplasia of the marrow with associated leukopenia and thrombocytopenia. In contrast, pure RBC aplasia is restricted to the erythroid cell line. Although both disorders are uncommon, aplastic anemia is more common.

Etiology. True aplastic anemia (most common in adolescents and young adults) is idiopathic in about ½ of cases. Recognized causes are chemicals (eg, benzene, inorganic arsenic),

radiation, and drugs (eg, antineoplastic drugs, antibiotics, NSAIDs, anticonvulsants, acetazolamide, gold salts, penicillamine, quinacrine). The mechanism is unknown, but selective (perhaps genetic) hypersensitivity appears to be the basis.

Fanconi's anemia is a very rare, familial form of aplastic anemia with bone abnormalities, microcephaly, hypogonadism, and brown pigmentation of skin. It occurs in children with abnormal chromosomes. Fanconi's anemia is often inapparent until some illness (especially an acute infection or inflammatory disorder) supervenes, causing peripheral cytopenias. With clearing of the supervening illness, peripheral values return to normal despite reduced marrow mass.

Pure RBC aplasia may be acute and reversible. Acute erythroblastopenia is a brief disappearance of RBC precursors from the bone marrow during various acute viral illnesses (particularly human parvovirus infection), especially in children. The anemia lasts longer than the acute infection. Chronic pure RBC aplasia has been associated with hemolytic disorders, thymomas, and autoimmune mechanisms and, less often, with drugs (eg, tranquilizers, anticonvulsants), toxins (organic phosphates), riboflavin deficiency, and chronic lymphocytic leukemia. A rare congenital form, Diamond-Blackfan anemia, usually occurs during infancy but has also been reported in adulthood.

Symptoms and Signs. Although onset of aplastic anemia usually is insidious, often occurring over weeks or months after exposure to a toxin, occasionally it is acute. Signs vary with the severity of the pancytopenia. Symptoms and signs of anemia (e.g., pallor) usually are severe.

Severe thrombocytopenia may cause petechiae, ecchymosis, and bleeding from the gums, into the conjunctivae, or other tissues. Agranulocytosis commonly causes life-threatening infections. Splenomegaly is absent unless induced by transfusion hemosiderosis. Symptoms of pure RBC + aplasia are generally milder and relate to the degree of the anemia or to the underlying disorder.

Diagnosis. Aplastic anemia is suspected in patients, particularly young patients, with pancytopenia. In aplastic anemia, RBCs are normochromic-normocytic. The WBC count reduction occurs chiefly in the granulocytes. Platelets are often far below 50,000/μL. Reticulocytes are decreased or absent. Serum iron is elevated. The bone marrow is acellular. In pure RBC aplasia, normocytic anemia, reticulocytopenia, and elevated serum iron are present, but WBC and platelet counts are normal. Bone marrow cellu-larity and maturation may be normal except for absence of erythroid precursors.

Treatment. In aplastic anemia, treatment of choice is equine antithymocyte globulin (ATG). Combined ATG and cyclosporine is also effective. Hematopoietic stem cell transplantation may help younger patients (particularly patients < 30) but requires an identical twin or an HLA-compatible sibling.

Pure RBC aplasia has been successfully managed with immunosuppressants (prednisone, cyclosporine, or cyclophosphamide), especially when an autoimmune mechanism is suspected. Because patients with thymoma-associated pure RBC aplasia improve after thymectomy, CT is used to seek the presence of such a lesion, and surgery is considered.

MYELOPHTHISIC ANEMIA

Myelophthisic anemia is a normocytic-normochromic anemia that occurs when normal marrow space is infiltrated and replaced by nonhematopoietic or abnormal cells. Causes include tumors, granulomatous disorders, and lipid storage diseases. Marrow fibrosis often occurs. Splenomegaly may develop. Characteristic changes in peripheral blood include anisocytosis, poikilocytosis, and excessive numbers of RBC and WBC precursors. Diagnosis usually requires bone marrow biopsy. Treatment is supportive and includes measures directed at the underlying disorder.

Descriptive terms used in this anemia can be confusing. Myelofibrosis, which is replacement of marrow by fibrous tissue bands, may be idiopathic (primary) or secondary. True myelofibrosis is a stem cell defect in which the fibrosis is secondary to other hematopoietic intramedullary events. Myelosclerosis is new bone formation that sometimes accompanies myelofibrosis. Myeloid metaplasia refers to extramedullary hematopoiesis in the liver, spleen, or lymph nodes that may accompany myelophthisis due to any cause. An old term, agnogenic myeloid metaplasia, indicates primary myelofibrosis with or without myeloid metaplasia.

Etiology. The most common cause is replacement of bone marrow by metastatic cancer (most often, breast or prostate; less often, kidney, lung, adrenal, or thyroid); extramedullary hematopoiesis tends to be modest. Other causes include myeloproliferative disorders (especially late-stage or spent polycythemia vera), granulomatous diseases, and (lipid) storage diseases. Myelofibrosis can occur in all of these.

Symptoms and Signs. Myeloid metaplasia may result in splenomegaly, particularly in patients with storage diseases. In severe cases, symptoms of anemia and of the underlying disorder may be present. Massive splenomegaly can cause abdominal pressure, early satiety, and left upper quadrant abdominal pain; hepatomegaly may be present. Hepatosplenomegaly is rare with myelofibrosis from malignant tumors.

Diagnosis. Myelophthisic anemia is suspected in patients with normocytic anemia, particularly when splenomegaly or a potential underlying disorder is present. If it is suspected, a peripheral smear should be obtained, because a leukoerythroblastic pattern (immature myeloid cells and nucleated RBCs, such as normoblasts in the smear) suggests myelophthisic anemia. Anemia, usually moder-ately severe, is characteristically normocytic but may be slightly macrocytic. RBC morphology may show extreme variation (anisocytosis and poikilocytosis) in size and shape. The WBC count may vary. The platelet count is often low, and platelets are often large and bizarre in shape. Reticulocytosis often occurs; it may be caused by premature release of reticulocytes from the marrow or extramedullary sites and thus does not always indicate increased blood regeneration.

X-rays, if obtained incidentally, may disclose bony lesions (myelosclerosis) characteristic of long-standing myelofibrosis or other osseous changes (ie, osteoblastic or lytic lesions of a tumor), suggesting the cause of anemia.

Treatment. The underlying disorder is treated. In idiopathic cases, management is supportive. Erythropoietin and corticosteroids (have been used, but only modest responses have been observed. Hydroxyurea (500 mg po once/day or once every other day) decreases spleen size and normalizes RBC values in many patients, but the response requires 6 to 12 mo of treatment.

MEGALOBLASTIC MACROCYTIC ANEMIAS

Megaloblastic anemias result most often from deficiencies of vitamin B_{12} and folate. Ineffective hematopoiesis affects all cell lines but particularly RBCs. Diagnosis is usually based on a CBC and peripheral smear, which may show a macrocytic anemia with anisocytosis and poikilocytosis, large oval RBCs (macro-ovalocytes), hypersegmented neutrophils, and reticulocytopenia. Treatment is directed at the underlying disorder.

Macrocytes are enlarged RBCs (ie, MCV > 100 fL/cell). Macrocytic RBCs occur in a variety of clinical circumstances, many unrelated to the megaloblastosis and the resultant anemia. Macrocytosis may be due to megaloblasts or other enlarged RBCs (*see Vitamin B_{12} Deficiency*). Megaloblasts are large nucleated RBC precursors with noncondensed chromatin. Megaloblastosis precedes macrocytic anemia.

Etiology. The most common cause of megaloblastic states is deficiency or defective utilization of vitamin B_{12} or folate.

Most macrocytic (i.e., MCV >100 fL/cell) anemias are megaloblastic. Nonmegaloblastic macrocytosis occurs in various clinical states, not all of which are understood. Anemia commonly occurs in patients with macrocytosis but usually results from mechanisms independent of macrocytosis.

Macrocytosis due to excess RBC membrane occurs in patients with chronic liver disease when cholesterol esterification is defective. Macrocytosis with an MCV of about 100 to 105 fL/cell can occur with chronic alcohol use in the absence of folate deficiency. Mild macrocytosis can occur in aplastic anemia, especially as recovery occurs. Macrocytosis is also common in myelodysplasia. Because RBC membrane molding occurs in the spleen after cell release from the marrow, RBCs may be slightly macrocytic after splenectomy, although these changes are not associated with anemia.

Nonmegaloblastic macrocytosis is suspected in patients with macrocytic anemias when testing excludes vitamin B_{12} and folate deficiencies. The macroovalocytes on peripheral smear

and the increased RBC distribution width that are typical of classic megaloblastic anemia may be absent. If nonmegaloblastic macrocytosis is unexplained or if myelodysplasia is suspected, bone marrow examination and cytogenetic analysis are done to exclude myelodysplasia. In nonmegaloblastic macrocytosis, the marrow is not megaloblastic, but in myelodysplasia and advanced liver disease there are megaloblastoid RBC precursors with dense nuclear chromatin that differ from the usual fine fibrillar pattern in anemias.

Pathophysiology. Megaloblastic states result from defective DNA synthesis. RNA synthesis continues, resulting in a large cell with a large nucleus. All cell lines have dyspoiesis, in which cytoplasmic maturity is greater than nuclear maturity; this dyspoiesis produces megaloblasts in the marrow before they appear in the peripheral blood. Dyspoiesis results in intramedullary cell death, making erythropoiesis ineffective and causing indirect hyperbilirubinemia and hyperuricemia. Because dyspoiesis affects all cell lines, reticulocytopenia and, during later stages, leukopenia and thrombocytopenia develop. Hypersegmentation of polymorphonuclear neutrophils is common; the mechanism of their production is unknown.

Symptoms and Signs. Anemia develops insidiously and may not cause symptoms until it is severe. Deficiencies of vitamin B_{12} may cause neurologic manifestations, including peripheral neuropathy, dementia, and subacute combined degeneration. Folate deficiency may also cause diarrhea and glossitis. Many patients with folate deficiency appear wasted, particularly with temporal wasting.

Diagnosis. Megaloblastic anemia is suspected in anemic patients with macrocytic indices. Diagnosis is usually based on peripheral smear. When fully developed, the anemia is macrocytic, with MCV > 100 fL/cell. The smear shows macro-ovalocytosis, anisocytosis, and poikilocytosis. The RBC distribution width (RDW) is high. Howell-Jolly bodies (residual fragments of the nucleus) are common. Reticulocytopenia is present.

MYELODYSPLASIA AND IRON-TRANSPORT DEFICIENCY ANEMIA

In myelodysplastic syndrome, anemia is commonly prominent. The anemia can be microcytic or normochromic-normocytic, usually with a dimorphic (large and small) population of circulating cells. Bone marrow examination shows decreased erythroid activity, megaloblastoid and dysplastic changes, and, sometimes, increased numbers of ringed sideroblasts. Treatment is the same as for sideroblastic anemias. Iron-transport deficiency anemia (atransferrinemia) is exceedingly rare. It occurs when iron cannot move from storage to the erythropoietic precursors. The presumed mechanism is absence of transferrin or presence of a defective transferrin molecule. In addition to anemia, hemosiderosis of lymphoid tissue, especially along the GI tract, is prominent.

ANEMIAS CAUSED BY HEMOLYSIS

At the end of their normal life span (about 120 days), RBCs are removed from the circulation. Hemolysis involves premature destruction and hence a shortened RBC life span (< 120 days). Anemia occurs when bone marrow production can no longer compensate for the shortened RBC survival; this condition is termed hemolytic anemia. If the marrow can compensate, the condition is termed compensated hemolytic anemia.

Etiology. Hemolysis can result from disorders extrinsic to the RBC or from intrinsic RBC abnormalities (*see Table 3*).

Table 3

Hemolytic Anemias

Mechanism	Disorder or Agent
Disorders Extrinsic to the RBC	
Reticuloendothelial hyperactivity	Hypersplenism
Immunologic abnormalities	Autoimmune hemolytic anemias: Cold antibody. Paroxysmal cold hemoglobinuria, Warm antibody
Infectious organisms	Babesia sp, Bartonella bacilliformis. Plasmodium falciparum, P. malariae, P. vivax
Toxin production by infectious organisms	Clostridium perfringens α- and β-Hemolytic streptococci, Meningococci

Mechanism	Disorder or Agent
Mechanical trauma	March hemoglobinuria, Skeletal trauma. Thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, Valvular heart disorders
Toxins	Compounds with oxidant potential (eg, dapsone, phenazopyridine), Copper (Wilson's disease). Lead, Insect venom, Snake venom
Intrinsic RBC abnormalities	
Congenital RBC membrane disorders	Hereditary elliptocytosis. Hereditary spherocytosis
Acquired RBC membrane disorders	Hypophosphatemia. Paroxysmal nocturnal hemoglobinuria. Stomatocytosis
Disorders of RBC metabolism	Embden-Meyerhof pathway defects (eg, pyruvate kinase deficiency), Hexose monophosphate shunt defects (eg, G6PD deficiency)
Disorders of Hb synthesis	Hb C disease, Hb S-C disease, Hb E disease. Sickle cell diseases, Thalassemias

Disorders extrinsic to the RBC. Most extrinsic disorders are acquired; the RBCs are normal and transfused cells as well as autologous cells are destroyed. Disorders extrinsic to the RBC include reticuloendothelial hyperactivity (hypersplenism), immunologic abnormalities (eg, autoimmune hemolytic anemia, isoimmune hemolytic anemia), mechanical injury (traumatic hemolytic anemia), and certain infections. Infectious organisms may cause hemolytic anemia through the direct action of toxins (e.g., from Clostridium perfringens, α- or β-hemolytic streptococci, meningococci) or by invasion and destruction of the RBC by the organism (Plasmodium sp, Bartonella sp).

Intrinsic RBC abnormalities. Defects intrinsic to the RBC that can cause hemolysis involve one or more components or functions of the RBC: the membrane, cell metabolism, and the Hb. Abnormalities include hereditary and acquired cell membrane disorders (eg, spherocytosis), disorders of RBC metabolism (G6PD deficiency), and hemoglobinopathies (sickle cell diseases, thalassemias). Quantitative and functional abnormalities of certain RBC membrane proteins (α- and β-spectrin, protein 4.1, F-actin, ankyrin) cause hemolytic anemias.

Pathophysiology. Hemolysis may be acute, chronic, or episodic. Chronic hemolysis may be complicated by aplastic crisis (temporary failure of erythropoiesis), usually caused by an infection, often parvovirus. Hemolysis can be extravascular, intravascular, or both.

Normal RBC processing. Senescent RBCs lose membrane and are cleared from the circulation largely by the phagocytic cells of the spleen, liver, bone marrow, and reticuloendothelial system. Hb is broken down in these cells primarily by the heme oxygenase system. The iron is conserved and reutilized, and heme is degraded to bilirubin, which is conjugated in the liver to bilirubin glucuronide and excreted in the bile.

Extravascular hemolysis. Most pathologic hemolysis is extravascular and occurs when damaged or abnormal RBCs are cleared from the circulation by cells of the spleen, liver, and bone marrow similar to the process by which senescent RBCs are removed. The spleen usually contributes to hemolysis by destroying mildly abnormal RBCs or cells coated with warm antibodies. An enlarged spleen may sequester even normal RBCs. Severely abnormal RBCs or RBCs coated with cold antibodies or complement (C3) are destroyed within the circulation and in the liver, which can remove damaged cells efficiently.

Intravascular hemolysis. Intravascular hemolysis is an important reason for premature RBC destruction and usually occurs when the cell membrane has been severely damaged by any of a number of different mechanisms, including autoimmune phenomena, direct trauma (march hemoglobinuria), shear stress (defective mechanical heart valves), and toxins (clostridial toxins, venomous snake bite).

Consequences of hemolysis. Unconjugated (indirect) hyperbilirubinemia and jaundice occur when the conversion of Hb to bilirubin exceeds the liver's capacity to conjugate and excrete bilirubin. Bilirubin catabolism causes increased stercobilin in the stool and urobilinogen

in the urine and sometimes cholelithiasis. The bone marrow responds to the excess loss of RBCs by accelerating production and release of RBCs, resulting in a reticulocytosis.

Symptoms and Signs Systemic manifestations resemble those of other anemias and include pallor, fatigue, dizziness, and possible hypotension. Hemolytic crisis (acute, severe hemolysis) is uncommon; it may be accompanied by chills, fever, pain in the back and abdomen, prostration, and shock. Severe hemolysis can cause jaundice and splenomegaly. Hemoglobinuria causes red or reddish-brown urine.

DiagnosisHemolysis is suspected in patients with anemia and reticulocytosis, particularly if splenomegaly or another possible cause is recognized. If hemolysis is suspected, we examine peripheral smear and measure serum bilirubin, LDH, and ALT. If results of these tests are inconclusive, urinary hemosiderin and serum haptoglobin are measured. One approach to narrowing the differential diagnosis in hemolytic anemias is to consider risk factors (e.g., geographic location, genetics, underlying disorder), examine the patient for splenomegaly, and do a direct antiglobulin (Coombs') test and peripheral smear.

The direct Coombs' test is used to determine whether RBC-binding antibody (IgG) or complement (C3) is present on RBC membranes. The patient's RBCs are incubated with antibodies to human IgG and C3. If IgG or C3 is bound to RBC membranes, agglutination occurs–a positive result. A positive result suggests the presence of autoantibodies to RBCs if the patient has not received a transfusion in the last 3 mo, alloantibodies to transfused RBCs (usually seen in acute or delayed hemolytic reaction), or drug-dependent or drug-induced antibodies against RBCs.

The indirect Coombs' test is used to detect IgG antibodies against RBCs in a patient's serum. The patient's serum is incubated with reagent RBCs; then Coombs' serum (antibodies to human IgG, or human anti-IgG) is added. If agglutination occurs, IgG antibodies (autoantibodies or alloantibodies) against RBCs are present. This test is also used to determine the specificity of an alloantibody.

Although some tests can help differentiate intravascular from extravascular hemolysis, sometimes it is difficult to differentiate them. During increased RBC destruction, both types are commonly involved, although to differing degrees.

Table 4

RBC Morphologic Changes in Hemolytic Anemias

RBC Morphology	Causes
Spherocytes	Transfused blood, Warm antibody hemolytic anemia. Hereditary spherocytosis
Schistocytes	Microangiopathy,Intravascular prostheses
Target cells	Hemoglobinopathies (sickle cell disease, Hb C disease, thalassemias)
Sickled cells	Sickle cell diseases
Agglutinated cells	Cold agglutinin disease
Heinz bodies or bite cells	G6PD deficiency, Oxidant stress, Unstable Hb
Nucleated erythroblasts and basophilia	Thalassemia major
Acanthocytes	Spur cell anemia

AUTOIMMUNE HEMOLYTIC ANEMIA

Autoimmune hemolytic anemia is caused by autoantibodies that react with RBCs at temperatures ≥ 37° C (warm antibody hemolytic anemia) or < 37° C (cold agglutinin disease). Hemolysis is usually extravascular. The direct antiglobulin (Coombs') test establishes the diagnosis and may suggest the cause. Treatment depends on the cause and may include corticosteroids, splenectomy, IV immune globulin, immunosuppressants, avoidance of blood transfusions, and withdrawal of drugs.

Etiology of Warm antibody hemolytic anemia: Warm antibody hemolytic anemia is the most common form of autoimmune hemolytic anemia (AIHA); it is more common among women. Autoantibodies in warm antibody hemolytic anemia generally react at temperatures ≥ 37° C. They may occur spontaneously or in association with certain disorders (SLE, lymphoma, chronic lymphocytic leukemia). Some drugs stimulate production of autoantibodies against Rh antigens (α-methyldopa-type of AIHA). Other drugs stimulate production of autoantibodies against the antibiotic–RBC-membrane complex as part of a transient hapten mechanism; the hapten may be stable (eg, high-dose penicillin, cephalosporins) or unstable (eg, quinidine, sulfonamides). In warm antibody hemolytic anemia, hemolysis occurs primarily in the spleen. It is often severe and can be fatal. Most of the autoantibodies in warm antibody hemolytic anemia are IgG.

Cold agglutinin disease: Cold agglutinin disease (cold antibody disease) is caused by autoantibodies that react at temperatures < 37 °C. It sometimes occurs with infections (especially mycoplasmal pneumonias or infectious mononucleosis) and lymphoproliferative states; about ½ of cases are idiopathic, which is the common form in older adults. Infections tend to cause acute disease, whereas idiopathic disease tends to be chronic. The hemolysis occurs largely in the extravascular mononuclear phagocyte system of the liver. The anemia is usually mild (Hb > 7.5 g/dL). Autoantibodies in cold agglutinin disease are usually IgM. The higher the temperature at which these antibodies react with the RBC, the greater the hemolysis is.

Paroxysmal cold hemoglobinuria: Paroxysmal cold hemoglobinuria (PCH; Donath-Landsteiner syndrome) is a rare type of cold agglutinin disease. Hemolysis results from exposure to cold, which may even be localized (from drinking cold water, from washing hands in cold water). An IgG autohemolysin binds to RBCs at low temperatures and causes intravascular hemolysis after warming. It occurs most often after a nonspecific viral illness or in otherwise healthy patients, although it occurs in some patients with congenital or acquired syphilis. The severity and rapidity of development of the anemia varies and may be fulminant.

Symptoms and Signs

Symptoms of warm antibody hemolytic anemia tend to be due to the anemia. If the disorder is severe, fever, chest pain, syncope, or heart failure may occur. Mild splenomegaly is typical.

Cold agglutinin disease manifests as an acute or chronic hemolytic anemia. Other cryopathic symptoms or signs may be present (e.g., acrocyanoses, Raynaud's syndrome, cold-associated occlusive changes). Symptoms of PCH may include severe pain in the back and legs, headache, vomiting, diarrhea, and passage of dark brown urine; hepatosplenomegaly may be present.

Table 5

Drugs That Cause Warm Antibody Hemolytic Anemia

Mechanism	Drugs
Autoantibody to Rh antigens	Cephalosporins, Diclofenac, Ibuprofen, Interferon alfa, Levodopa, Mefenamic acid, α-Methyldopa, Pro□ainamide, Teniposide, Thioridazin□, Tolmeti
Stable hapten	Cephalosporins, Fluorescein sodium, Penicillins, Tetracycline, Tolbutamide
Unstable hapten or□ unknown mechanism	p-Aminosalicylic acid, Amphotericin B, Antazoline, Cephalosporins, Chlorpropamide, Diclofenac, Diethylstilbestrol, Doxepin, Isoniazid, Quinine, Hydrochlorothiazide, Probenecid, Quinidine, Rifampin, Sulfonamides, Thiopental,

Diagnosis

AIHA is suspected in patients with hemolytic anemia, particularly if symptoms are severe or other suggestive symptoms are present. Routine laboratory tests generally suggest extravascular hemolysis (e.g., hemosiderinuria is absent; haptoglobin levels are near normal) unless anemia is sudden and severe or PCH is the cause. Spherocytosis and a high MCHC are typical.

AIHA is diagnosed by detection of autoantibodies with the direct antiglobulin (direct Coombs') test. Antiglobulin serum is added to washed RBCs from the patient; agglutination indicates the presence of immunoglobulin or complement (C) bound to the RBCs. Generally IgG is present in warm antibody hemolytic anemia, and C3 (C3b and C3d) in cold antibody disease. The test is ≤98 % sensitive for AIHA; false-negative results can occur if antibody density is very low or if the autoantibodies are IgA or IgM. In general, the intensity of the direct antiglobulin test correlates with the number of molecules of IgG or C3 bound to the RBC and, roughly, with the rate of hemolysis. A complementary test consists of mixing the patient's plasma with normal RBCs to determine whether such antibodies are free in the plasma (the indirect antiglobulin [indirect Coombs'] test). A positive indirect antiglobulin test and a negative direct test generally indicate an alloantibody caused by pregnancy, prior transfusions, or lectin cross-reactivity rather than immune hemolysis.

Direct Coombs' Test.The test is used to determine whether RBC-binding antibody (IgG) or complement (C3) is present on RBC membranes. The patient's RBCs are incubated with antibodies to human IgG and C3. If IgG or C3 is bound to RBC membranes, agglutination occurs–a positive result. A positive result suggests the presence of autoantibodies to RBCs if the patient has not received a transfusion in the last 3 mo, alloantibodies to transfused RBCs (usually seen in acute or delayed hemolytic reaction), or drug-dependent or drug-induced antibodies against RBCs

Once AIHA has been identified by the Coombs' test, testing should differentiate between warm antibody hemolytic anemia and cold agglutinin disease as well as the mechanism responsible for warm antibody hemolytic anemia. This determination can often be made by observing the pattern of the direct antiglobulin reaction. Three patterns are possible:

1. The reaction is positive with anti-IgG and negative with anti-C3. This pattern is common in idiopathic AIHA and in the drug-associated or α-methyldopa-type of AIHA, usually warm antibody hemolytic anemia.

2. The reaction is positive with anti-IgG and anti-C3. This pattern is common in patients with SLE and idiopathic AIHA, usually warm antibody hemolytic anemia, and is rare in drug-associated cases.

3. The reaction is positive with anti-C3 but negative with anti-IgG. This pattern occurs in cold agglutinin disease. It is uncommon in idiopathic AIHA, warm antibody hemolytic anemia, when the IgG antibody is of low affinity, in some drug-associated cases, and in PCH.

Warm antibody hemolytic anemias. In drug-induced warm antibody hemolytic anemias, drug withdrawal decreases the rate of hemolysis. With hapten-mediated AIHA, hemolysis ceases when the drug is cleared from the plasma. Corticosteroids have only little effect in drug-induced hemolysis; infusions of immune globulin may be more effective.

Cold agglutinin disease. Treatment is largely supportive in acute cases. In chronic cases, treatment of the underlying disorder often controls the anemia. However, in idiopathic chronic cases, mild anemia (Hb, 9 to 10 g/dL) may persist for life. Avoidance of cold exposure is often helpful. Splenectomy is of no value. Immunosuppressants have only modest effectiveness. Transfusions should be given sparingly, with the blood warmed through an on-line warmer. Because the autologous RBCs have already survived the autoantibodies, autologous cell survival is better than that of transfused cells.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder characterized by intravascular hemolysis and hemoglobinuria, the latter accentuated during sleep. Leukopenia, thrombocytopenia, and episodic crises are common.

PNH is most common among men in their 20s, but it occurs in both sexes and at any age.

Etiology. PNH is an acquired genetic mutation resulting in a membrane defect in stem cells and their progeny, including RBCs, WBCs, and platelets. It results in unusual sensitivity to normal C3 in the plasma, leading to ongoing intravascular hemolysis of RBCs and diminished marrow production of WBCs and platelets. The defect is a missing glycosyl-phosphatidyl-inositol anchor for membrane proteins caused by an abnormality of the PIG-A gene, which is located on the X chromosome.

Pathophysiology. Protracted urinary Hb loss may result in iron deficiency. Patients are strongly predisposed to both venous and arterial thrombi, including the Budd-Chiari syndrome. Thrombi are commonly fatal. Some patients with PNH develop aplastic anemia, and some with aplastic anemia develop PNH.

Crises may be precipitated by infection, iron use, vaccination, or menstruation. Abdominal and lumbar pain and symptoms of severe anemia may occur; gross hemoglobinuria and splenomegaly are common.

Diagnosis. PNH is suspected in patients who have typical symptoms of anemia or unexplained normocytic anemia with intravascular hemolysis, particularly if leukopenia or thrombocytopenia is present. The sensitive and specific test is determination of the absence of specific RBC or WBC membrane proteins (CD59 and CD55) by flow cytometry. An alternative is the acid hemolysis test (Ham's test). Hemolysis usually occurs if blood is acidified with HCl, incubated for 1 h, and centrifuged. Gross hemoglobinuria is common during crises, and the urine may contain hemosiderin.

Treatment is largely symptomatic. However, a new monoclonal antibody that is a terminal complement inhibitor, eculizumab, has reduced transfusion requirements, thromboembolism, and symptoms. Supportive measures include corticosteroids, androgen hormones, iron and folate supplementation, and sometimes transfusions and stem cell transplantation.

TRAUMATIC HEMOLYTIC ANEMIA (Microangiopathic Hemolytic Anemia)

Traumatic hemolytic anemia is intravascular hemolysis caused by excessive shear or turbulence in the circulation.

Trauma may originate outside the vessel, as in skeletal impact, e.g, repetitive foot striking (march hemoglobinuria) or from karate or bongo playing; within the heart across a pressure gradient, as in calcific aortic stenosis or with faulty aortic valve prostheses; in arterioles, as in severe (especially malignant) hypertension, some malignant tumors, or polyarteritis nodosa; or in end arterioles, often across fibrin deposits, as in thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. The trauma causes odd-shaped RBC fragments (triangles, helmet shapes) called schistocytes in the peripheral blood; their appearance on the peripheral smear is diagnostic. The small schistocytes cause low MCV and high RBC distribution width (the latter reflecting the anisocytosis).

Treatment addresses the underlying process. Iron deficiency anemia occasionally is superimposed on the hemolysis as a result of chronic hemosiderinuria and, when present, responds to iron-replacement therapy.

HEREDITARY SPHEROCYTOSIS AND HEREDITARY ELLIPTOCYTOSIS

Hereditary spherocytosis and hereditary elliptocytosis are congenital RBC membrane disorders. Symptoms, generally milder in hereditary elliptocytosis, include variable degrees of anemia, jaundice, and splenomegaly. Diagnosis requires demonstration of increased RBC osmotic fragility and a negative direct antiglobulin test. Rarely, patients < 45 yr with symptomatic disease require splenectomy.

Hereditary spherocytosis (chronic familial icterus; congenital hemolytic jaundice; familial spherocytosis; spherocytic anemia) is an autosomal dominant disease with variable gene penetrance. It is characterized by hemolysis of spheroidal RBCs and anemia.

Hereditary elliptocytosis (ovalocytosis) is a rare autosomal dominant disorder in which RBCs are oval or elliptical. Hemolysis is usually absent or slight, with little or no anemia; splenomegaly is often present.

Pathophysiology. Alterations in membrane proteins cause the RBC abnormalities in both disorders. In hereditary spherocytosis, the cell membrane surface area decreases disproportionately to the intracellular content. The decreased surface area of the cell impairs the flexibility needed for the cell to traverse the spleen's microcirculation, causing intrasplenic hemolysis. In hereditary elliptocytosis, genetic mutations result in weakness of the cytoskeleton of the cell, leading to deformation of the cell. The abnormally shaped RBCs are taken up and destroyed by the spleen.

Symptoms and signs of hereditary spherocytosis are usually mild, and the anemia may be so well compensated that it is not recognized until an intercurrent viral illness transiently decreases RBC production, simulating an aplastic crisis. However, these episodes are self-limited, resolving with resolution of the infection. Moderate jaundice and symptoms of anemia are present in severe cases. Splenomegaly is almost invariable but only rarely causes abdominal discomfort. Hepatomegaly may be present. Cholelithiasis (pigment stones) is common and may be the presenting symptom. Congenital skeletal abnormalities (tower-shaped skull, polydactylism) occasionally occur. Although usually one or more family members have had symptoms, several generations may be skipped because of variations in the degree of gene penetrance. Clinical features of hereditary elliptocytosis are similar to those of hereditary spherocytosis but tend to be milder.

Diagnosis. These disorders are suspected in patients with unexplained hemolysis, particularly if splenomegaly, a family history of similar manifestations, or suggestive RBC indices are present. Because RBCs are spheroidal and the MCV is normal, the mean corpuscular diameter is below normal, and RBCs resemble microspherocytes. Reticulocytosis of 15 to 30 % and leukocytosis are common. If these disorders are suspected, the RBC osmotic fragility test, the RBC autohemolysis test (which measures the amount of spontaneous hemolysis occurring after 48 h of sterile incubation), and, to rule out spherocytosis due to autoimmune hemolytic anemia, the direct antiglobulin (Coombs') test are done. RBC fragility is characteristically increased, but in mild cases, it may be normal unless sterile defibrinated blood is first incubated at 37° C for 24 h. RBC autohemolysis is increased. The direct antiglobulin test results are negative.

Treatment. Splenectomy, after appropriate vaccination, is the only specific treatment for either disorder but is rarely needed. It is indicated in patients < 45 yr with Hb persistently < 10 g/dL, jaundice or biliary colic, or persistent aplastic crisis. Although spherocytosis persists after splenectomy, the cells survive longer in the circulation. Usually, symptoms resolve and anemia and reticulocytosis decrease. However, RBC fragility remains high.

STOMATOCYTOSIS AND ANEMIA CAUSED BY HYPOPHOSPHATEMIA

Stomatocytosis (presence of cup- or bowl-shaped RBCs) and hypophosphatemia are RBC membrane abnormalities causing hemolytic anemia.

Stomatocytosis. Stomatocytosis is a rare condition of RBCs in which a mouthlike or slitlike pattern replaces the normal central zone of pallor. These cells are associated with congenital and acquired hemolytic anemia. The symptoms result from the anemia.

The rare congenital stomatocytosis, which shows autosomal dominant inheritance, causes a severe hemolytic anemia presenting very early in life. The RBC membrane is hyperpermeable to monovalent cations (Na and K); movement of divalent cations and anions is normal. About 20 to 30 % of circulating RBCs are stomatocytic; RBC fragility is increased, as is autohemolysis with inconstant correction with glucose. Splenectomy ameliorates anemia in some cases.

Acquired stomatocytosis with hemolytic anemia occurs primarily with recent excessive alcohol ingestion (hemolysis disappear within 2 wk of alcohol withdrawal).

Anemia caused by hypophosphatemia. RBC pliability varies according to intracellular ATP levels. Because the serum phosphate concentration affects RBC ATP levels, serum phosphate level < 0.5 mg/dL (< 0.16 mmol/L) depletes RBC ATP; the complex metabolic sequelae of hypophosphatemia also include 2,3-diphosphoglyceric acid depletion, a shift to the left in the O_2 dissociation curve, decreased glucose utilization, and increased lactate production. The resultant rigid, nonyielding RBCs are susceptible to injury in the capillary circulatory bed, leading to hemolysis and small, sphereshaped RBCs (microspherocytosis).

Severe hypophosphatemia may occur in alcohol withdrawal, diabetes mellitus, refeeding after starvation, the recovery (diuretic) phase after severe burns, hyperalimentation, severe respiratory alkalosis, and in uremic patients receiving dialysis who are taking antacids.

EMBDEN-MEYERHOF PATHWAY DEFECTS

Embden-Meyerhof pathway defects are autosomal recessive RBC metabolic disorders that cause hemolytic anemia.

Pyruvate kinase deficiency is one such enzyme defect. In all of these pathway defects, hemolytic anemia occurs only in homozygotes, and the exact mechanism of hemolysis is unknown. Spherocytes are absent, but small numbers of irregularly shaped spheres may be present. In general, assays of ATP and diphosphoglycerate help identify any metabolic defect and localize the defective sites for further analysis. There is no specific therapy for these hemolytic anemias, although most patients require no treatment other than supplemental folate 1 mg po once/day during acute hemolysis. Hemolysis and anemia persist after splenectomy.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked enzymatic defect common in blacks that can result in hemolysis after acute illnesses or intake of oxidant drugs (including salicylates and sulfonamides). Diagnosis is based on assay for G6PD, although tests are often falsely negative during acute hemolysis. Treatment is supportive.

The only important defect in the hexose monophosphate shunt pathway is caused by G6PD deficiency. Clinically, the most common form is the drug-sensitive variety. This X-linked disorder is fully expressed in males and homozygous females and is variably expressed in heterozygous females. This defect occurs in about 10 % of black males and females in the US and in lower frequencies among people with ancestors from the Mediterranean basin (Italians, Arabs, Sephardic Jews).

Pathophysiology. G6PD deficiency reduces energy available to maintain the integrity of the red cell membrane, which shortens RBC survival.

Hemolysis selectively affects older RBCs among affected blacks and among most affected whites. Hemolysis occurs commonly after fever, acute viral and bacterial infections, and diabetic acidosis. Less commonly, hemolysis occurs after exposure to drugs or to other substances that produce peroxide and cause oxidation of Hb and RBC membranes. These drugs and substances include primaquine, salicylates, sulfonamides, nitrofurans, phenacetin, naphthalene, some vitamin K derivatives, dapsone, phenazopyridine, nalidixic acid, methylene blue, and fava beans. Whether continued use of the offending drug leads to a compensated hemolytic state or lethal hemolysis depends on the degree of G6PD deficiency and the oxidant potential of the drug.

Chronic congenital hemolysis (without drug) occurs in some whites. Because older cells are selectively destroyed in blacks, hemolysis is usually self-limited, affecting < 25 % of RBC mass; in whites, the deficiency is more severe, and profound hemolysis may lead to hemoglobinuria and acute renal failure.

Diagnosis. The diagnosis is considered in patients with acute hemolysis, particularly black males. G6PD assay is done. Anemia, jaundice, and reticulocytosis develop during hemolysis. Heinz bodies, possibly particles of dead cytoplasm or denatured Hb, may be visible early during the hemolytic episode but do not persist in patients with an intact spleen because they are removed by it. A specific diagnostic clue is the presence in the peripheral blood of RBCs that appear to have had one or more bites (1-мм wide) taken from the cell periphery (bite cells), possibly as a result of Heinz body removal by the spleen.

Treatment. During acute hemolysis, treatment is supportive; transfusions are rarely needed. Patients are advised to avoid drugs or substances that initiate hemolysis.

SICKLE CELL DISEASE (Hb S Disease)

Sickle cell disease (Hb C disease, thalassemias)) causes a chronic hemolytic anemia occurring almost exclusively in blacks, caused by homozygous inheritance of Hb S. Sickle-shaped RBCs clog capillaries, causing organ ischemia. Acute exacerbations (crises) may develop frequently. Infection, bone marrow aplasia, or lung involvement (acute chest syndrome) can develop acutely and be fatal. Normocytic hemolytic anemia is characteristic. Diagnosis requires Hb electrophoresis. Crises are treated with analgesics and other supportive measures. Transfusions are occasionally required. Vaccines against bacterial infections, prophylactic antibiotics, and aggressive treatment of infections prolong survival. Hydroxyurea may decrease the frequency of crises.

Hemoglobinopathies

Hb molecules consist of polypeptide chains whose chemical structure is genetically controlled. The normal adult Hb molecule (Hb A) consists of 2 pairs of chains designated α and β. Normal blood also contains a $\leq$ 2.5 % concentration of Hb A2 (composed of α and δ chains). Fetal Hb (Hb F, which has γ chains in the place of βchains) gradually decreases, particularly in the first months of life, until it makes up <2 % of total Hb in adults. Hb F concentration increases in certain disorders of Hb synthesis and in aplastic and myeloproliferative states.

Some hemoglobinopathies result in anemias that are severe in patients who are homozygous but mild in those who are heterozygous. Some patients are heterozygous for 2 such abnormalities and have anemia with characteristics of both traits.

Different Hbs, as distinguished by electrophoretic mobility, are alphabetically designated in order of discovery (A, B, C), although the first abnormal Hb, sickle cell Hb, was designated Hb S. Structurally different Hbs with the same electrophoretic mobility are named for the city or location in which they were discovered. Standard description of a patient's Hb composition places the Hb of greatest concentration first (AS in sickle cell trait).

In the US, important anemias are caused by defective synthesis of Hb S or Hb C and the thalassemias, and immigration of Southeast Asians has made Hb E disease common

Pathophysiology. In Hb S, valine is substituted for glutamic acid in the 6th amino acid of the β chain. Oxygenated Hb S is much less soluble than oxygenated Hb A; it forms a semisolid gel that causes RBCs to deform in a sickle shape at sites of low PO_2. Distorted, inflexible RBCs adhere to vascular endothelium and plug small arterioles and capillaries, which leads to infarction. Venous plugging predisposes to thromboses. Because sickled RBCs are fragile, the mechanical trauma of circulation causes hemolysis. Chronic compensatory marrow hyperactivity deforms the bones.

Acute exacerbations. Acute exacerbations (crises) occur intermittently, often for no known reason. In some cases, fever, viral infection, or local trauma appears to precipitate a crisis.

Painful crisis is the most common type; it is caused by ischemia and infarction, typically of the bones, but also of the spleen, lung, or kidney. Aplastic crisis occurs when marrow erythropoiesis slows during acute infection (especially viral), during which an acute erythroblastopenia may occur.

Acute chest syndrome results from pulmonary microvascular occlusion and is a common cause of death, with mortality rates of up to 10 %. It occurs in all age groups but is most common in childhood. Repeated episodes predispose to chronic pulmonary hypertension.

In children, acute sequestration of sickled cells in the spleen may occur, exacerbating anemia. Complications:

Long-term consequences include impaired growth and development. Increased susceptibility to infection, particularly pneumococcal and Salmonella infections (includ-ing Salmonella osteomyelitis),

also results. Other consequences include ischemic stroke, CNS vasculitis, avascular necrosis of the hips, renal concentrating defects, renal failure, heart failure, and pulmonary fibrosis.

Symptoms and Signs. Patients may be poorly developed and often have a relatively short trunk with long extremities and a tower-shaped skull. Hepatosplenomegaly is common in children, but because of repeated infarctions and subsequent fibrosis (autosplenectomy), the spleen in adults is commonly very small. Cardiomegaly and systolic ejection (flow) murmurs are common. Cholelithiasis and chronic ulcers around the ankles are common.

Painful crisis causes severe pain in long bones (e.g, pretibial pain), the hands and feet (e.g, hand-foot syndrome), and joints. Joint pain may result from hemarthrosis or avascular necrosis of the femoral head. Severe abdominal pain may develop with or without vomiting and, when due to sickling itself, is usually accompanied by back and joint pain.

Acute chest syndrome is characterized by sudden onset of fever, chest pain, and pulmonary infiltrates. The infiltrates begin in the lower lobes, are bilateral in 1/3 of cases, and may be accompanied by pleural effusion. It may follow bacterial pneumonia. Hypoxemia may develop rapidly, causing dyspnea.

Heterozygotes. Patients who are heterozygous (Hb AS) do not experience hemolysis, painful crises, or thrombotic complications except possibly during hypoxic conditions (eg, at high altitudes, during sudden de-compression in airplanes). However, rhabdomyolysis and sudden death may occur during sustained, exhausting exercise. Impaired ability to concentrate urine (hyposthenuria) is common. Unilateral hematuria (by unknown mechanisms and usually from the left kidney) can occur but is selflimited.

Diagnosis. The type of testing done depends on the age of the patient. DNA testing can be used for prenatal diagnosis or to confirm a diagnosis of the sickle cell genotype. Screening of neonates is available in most US states and involves Hb electrophoresis. Screening and diagnosis in children and adults involve examination of the peripheral smear, Hb solubility testing, and Hb electrophoresis.

Prenatal screening. The sensitivity of prenatal diagnosis has been greatly improved with the availability of the PCR technique. It is recommended for families at risk for sickle cell (couples with medical or family histories of anemia). DNA samples can be obtained by chorionic villus sampling at 8 to 10 wk gestation. Amniotic fluid can be tested at 14–16 wk. Diagnosis is important for genetic counseling.

Newborn screening: Universal testing is currently recommended and is frequently one of a battery of newborn screening tests. To distinguish between Hbs F, S, A, and C, the recommended tests are Hb electrophoresis using cellulose acetate or acid citrate agar or Hb fractionation by high performance liquid chromatography (HPLC). Repeat testing at age 3 to 6 mo may be necessary for confirmation.

Screening and diagnosis of children and adults. Patients with a family history of sickle cell disease or trait should be screened with peripheral smear, Hb solubility testing, and Hb electrophoresis.

Patients with symptoms or signs suggesting the disorder or its complications (poor growth, acute and unexplained bone pain, aseptic necrosis of the femoral head, hematuria), and black patients with normocytic anemia (if hemolysis is present) require laboratory tests for hemolytic anemia, Hb electrophoresis, and examination of RBCs for sickling. If sickle cell disease is present, RBC count is usually between 2 and 3 million/μL with Hb reduced proportionately; cells are normocytic (microcytosis suggests a concomitant α-thalassemia).

The homozygous state is differentiated from other sickle hemoglobinopathies by electrophoresis showing only Hb S with a variable amount of Hb F. The heterozygote is differentiated by the presence of more Hb A than Hb S on electrophoresis. Hb S must be distinguished from other Hb with a similar electrophoretic pattern by showing the pathognomonic RBC morphology.

Bone marrow examination is not used for diagnosis. Incidental findings on skeletal x-rays may include widening of the diploic spaces of the skull and a sunray appearance of the diploic trabeculations. The long bones often show cortical thinning, irregular densities, and new bone formation within the medullary canal. Unexplained hematuria, even among patients not suspected of having sickle cell disease, should prompt consideration of sickle cell trait.

Treatment. Treatment includes regular health maintenance measures as well as specific treatment of the complications as they arise. Complications are treated supportively. No effective in vivo anti-sickling drug is available. Splenectomy is valueless. Stem cell transplantation has been curative in a small number of patients but has a 5 to 10 % mortality rate and so is not commonly done. Gene therapy offers hope for a cure, but it is still under study. Transfusion is given in many situations in which its efficacy has not been demonstrated. However, routine transfusion therapy is indicated for prevention of recurrent cerebral thrombosis, especially in children. Transfusion may be needed in pregnancy.

HEMOGLOBIN C DISEASE

Hemoglobin C disease is a hemoglobinopathy that causes symptoms similar to those of sickle cell disease, but milder.

Of blacks in the US, 2 to 3 % have the trait, which is asymptomatic. Symptoms in homozygotes are usually similar to those of sickle cell disease, but milder. However, the abdominal crises of sickle cell disease do not occur, and the spleen is usually enlarged.

Hemoglobin C disease is suspected in all patients with a family history and in black patients with clinical features suggesting sickle cell disease, particularly in adults with splenomegaly. The anemia is usually mild but can be moderately severe. The smear is normocytic, with 30 to 100 % target cells, spherocytes, and, rarely, crystal-containing RBCs. Nucleated RBCs may be present. The RBCs do not sickle. On electrophoresis, the Hb is type C. In heterozygotes, the only laboratory abnormality is centrally targeted RBCs. No specific treatment is recommended. Anemia usually is not severe enough to require blood transfusion.

HEMOGLOBIN S-C DISEASE

Hemoglobin S-C disease is a hemoglobinopathy that causes symptoms similar to those of sickle cell disease, but milder.

Because 10 % of blacks carry the Hb S trait, the heterozygous S-C combination is more common than homozygous Hb C disease. The anemia in Hb S-C disease is milder than the anemia in sickle cell disease; some patients even have normal Hb levels. Most symptoms are those of sickle cell disease, but symptoms are usually less frequent and less severe. However, gross hematuria, retinal hemorrhages, and aseptic necrosis of the femoral head are common. Hb S-C disease is suspected in patients whose clinical features suggest sickle cell disease or whose RBCs demonstrate sickling. Stained blood smears show target cells and a rare sickle cell. Sickling is identified in a sickling preparation, and Hb electrophoresis establishes the diagnosis. Treatment can be similar to that of sickle cell disease but is determined by severity of symptoms.

HEMOGLOBIN E DISEASE

Homozygous Hb E disease causes a mild hemolytic anemia, usually without splenomegaly.

Hb E is the 3rd most prevalent Hb worldwide (after Hb A and Hb S), primarily in black and Southeast Asian (> 15 % incidence of homozygous disease) populations, although rarely in Chinese populations. Heterozygotes (Hb E) are asymptomatic. Patients heterozygous for Hb E and в-thalassemia have a hemolytic disease more severe than S-thalassemia or homozygous Hb E disease and usually have splenomegaly.

In heterozygotes (Hb AE), routine laboratory test results of peripheral blood are normal. In homozygotes, a mild microcytic anemia with prominent target cells exists. Diagnosis of Hb E disorders is by Hb electrophoresis. Treatment in homozygous patients with severe disease usually involves chronic transfusions.

THALASSEMIAS

Thalassemias are a group of inherited microcytic, hemolytic anemias characterized by defective Hb synthesis. They are particularly common in people of Mediterranean, African, and Southeast Asian ancestry. Symptoms and signs result from anemia, hemolysis, splenomegaly, bone marrow hyperplasia, and, if there have been multiple transfusions, iron overload. Diagnosis is based on genetic tests and quantitative Hb analysis. Treatment for severe forms may include transfusion, splenectomy, chelation, and stem cell transplantation.

Pathophysiology. Thalassemia is among the most common inherited disorders of Hb production. It results from unbalanced Hb synthesis caused by decreased production of at least one globin polypeptide chain (α, β, δ, γ).

β-Thalassemia results from decreased production of β-polypeptide chains. Inheritance is autosomal: Heterozygotes are carriers and have asymptomatic mild to moderate microcytic anemia (thalassemia minor); homozygotes (β-thalassemia major, or Cooley's anemia) develop severe anemia and bone marrow hyperactivity. β-δ-Thalassemia is a less common form of β-thalassemia in which δ-chain as well as β-chain production is impaired and which also has heterozygous and homozygous states.

α-Thalassemia, which results from decreased production of α-polypeptide chains, has a more complex inheritance pattern, because genetic control of α-chain synthesis involves 2 pairs of genes (4 genes). Heterozygotes for a single gene defect (α-thalassemia-2) are usually clinically normal. Heterozygotes with defects in 2 of the 4 genes (α-thalassemia-1) tend to develop mild to moderate microcytic anemia but no symptoms. Defects in 3 of the 4 genes more severely impairs α-chain production, resulting in the formation of tetramers of excess βchains (Hb H) or, in infancy, γ-chains (Bart's Hb). Defects in all 4 genes are a lethal condition in utero, because Hb that lacks α-chains does not transport O_2.

Symptoms and Signs. Clinical features of thalassemias are similar but vary in severity. в-Thalassemia major manifests by age 1 to 2 yr with symptoms of severe anemia and transfusional and absorptive iron overload. Patients are jaundiced, and leg ulcers and cholelithiasis occur (as in sickle cell anemia). Splenomegaly, often massive, is common. Splenic sequestration may develop, accelerating destruction of transfused normal RBCs. Bone marrow hyperactivity causes thickening of the cranial bones and malar eminences. Long bone involvement predisposes to pathologic fractures and impairs growth, possibly delaying or preventing puberty. Iron deposits in heart muscle may cause heart failure. Hepatic siderosis is typical, leading to functional impairment and cirrhosis.

Diagnosis. Thalassemias are suspected in patients with a family history, suggestive symptoms or signs, or microcytic hemolytic anemia. If thalassemias are suspected, laboratory tests for microcytic and hemolytic anemias and quantitative Hb studies are done. Serum bilirubin, iron, and ferritin levels are increased. In в-thalassemia major, anemia is severe, often with Hb ≤ 6 g/dL. RBC count is elevated relative to Hb because the cells are very microcytic. The blood smear is virtually diagnostic, with many nucleated erythroblasts; target cells; small, pale RBCs; and punctate and diffuse basophilia.

In quantitative Hb studies, elevation of Hb A2 is diagnostic for в-thalassemia minor. In в-thalassemia major, Hb F is usually increased. The percentages of Hb F and Hb A2 are generally normal in б-thalassemias, and the diagnosis of single or double gene defect thalassemias may be carried out with newer genetic tests and often is one of exclusion of other causes of microcytic anemia. Hb H disease can be diagnosed by demonstrating the fast-migrating Hb H or Bart's fractions on Hb electrophoresis. Recombinant DNA approaches of gene mapping (particularly the PCR) have become standard for prenatal diagnosis and genetic counseling.

Target cells

If bone marrow examination is done for anemia (e.g, to exclude other causes), it shows marked erythroid hyperplasia. X-rays done for other reasons in patients with в-thalassemia

major show changes due to chronic bone marrow hyperactivity. The skull may show cortical thinning, widened diploic space, a sun-ray appearance of the trabeculae. The long bones may show cortical thinning, marrow space widening, and areas of osteoporosis. The vertebral bodies may have a granular or groundglass appearance.

Thalassemia major is an inherited form of hemolytic anemia, characterized by red blood cell (hemoglobin) production abnormalities. This is the most severe form of anemia, and the oxygen depletion in the body becomes apparent within the first 6 months of life. If left untreated, death usually results within a few years. Note the small, pale (hypochromic), abnormally-shaped red blood cells associated with thalassemia major. The darker cells likely represent normal RBCs from a blood transfusion.

Thalassemia minor is an inherited form of hemolytic anemia that is less severe than thalassemia major. This blood smear from an individual with thalassemia shows small (microcytic), pale (hypochromic), variously-shaped (poikilocytosis) red blood cells. These small red blood cells (RBCs) are able to carry less oxygen than normal RBCs.

Treatment. Children with в-thalassemia major should receive as few transfusions as possible to avoid iron overload. However, suppression of abnormal hematopoiesis by periodic RBC transfusion may be valuable in severely affected patients. To prevent or delay iron overload, excess (transfusional) iron must be removed. Splenectomy may help decrease transfusion requirements for patients with splenomegaly. Allogeneic stem cell transplantation has been successful, but the requirement for a histocompatible match, mortality and morbidity of the procedure, and lifelong requirement for immunosuppression have limited its usefulness.

HEMOGLOBIN S–B-THALASSEMIA DISEASE

Hemoglobin S–в-thalassemia disease is a hemoglobinopathy that causes symptoms similar to those of sickle cell disease, but milder.

Because of the increased frequency of both Hb S and в-thalassemia genes in similar population groups, inheritance of both defects is relatively common. Clinically, the disorder causes symptoms of moderate anemia and signs of sickle cell anemia, which are usually less frequent and less severe than those of sickle cell disease. Mild to moderate microcytic anemia is usually present along with some sickled RBCs on stained blood smears. Diagnosis requires quantitative Hb studies. The Hb A_2 is > 3 %. Hb S predominates on electrophoresis, and Hb A is decreased or absent. Hb F increase is variable. Treatment, if necessary, is the same as for sickle cell disease.

CONTROL TESTS

Which sign of the following is required for anemia? 1. Decrease of erythrocyte quantity in blood volume unit. 2. Decrease of hemoglobin content in blood. 3. Decrease of color index of blood.
Answer _____

Indicate the variants of anemia pathogenesis: 1. Decrease of the volume of blood plasma part, 2. Increased erythrocyte hemolysis. 3. Decrease of hemoglobin saturation by oxygen. 4. Proportional decrease of plasma volume and blood cells. 5. Disorder of hemoglobin synthesis or erythrocyte formation.
Answer _____

Erythrocyte content in blood is $3{,}5 \times 10^{12}$/l, hemoglobin content is 86 g/l: 1. What is the name of this phenomena? 2. Calculate the color parameter. 3. What does color parameter testify?
Answer _____

Erythrocyte content in blood is $3{,}0 \times 10^{12}$/l, hemoglobin content is 125 g/l: 1. Analyse these data. 2. Calculate the color parameter. 3. What disease is it typical for?
Answer _____

Date	Grade	Teacher`s signature

LEUKOCYTOSIS. LEUKOPENIA

Relevance of the topic. The idea of leukocytes quantity, a ratio of their separate forms in peripheral blood, and features of their qualitative changes has huge diagnostic value for the doctor of any profile. Primarily, it concerns the symptomatic changes of leucocyte composition of peripheral blood studying of which is an integral part of laboratory researches at any pathology. The accounting of these indicators in dynamics of a disease development and its treatment very often plays an important role in determination of treatment efficiency and the forecast of a disease. Thus, knowledge of the causes, mechanisms of emergence and development of symptomatic changes of leucocyte composition of blood, their features in different pathological processes and diseases are necessary for the doctor of any specialty.

General aim is to be able to understand the main symptomatic quantitative and qualitative changes of leucocyte composition of blood in the conditions of pathology, to know the possible causes and mechanisms of their emergence and development, to interpret changes of these data in diagnostic and predictive aspects of different types of pathology.

The student should be able to (specific objectives):

1) distinguish symptomatic changes of leucocyte composition of peripheral blood from pathological positions in system forms of its pathology;

2) characterize changes in leucocyte composition of blood of symptomatic character, to explain their causes, the mechanism of development and to give their classification;

3) estimate data on leukocytes quantity changes and a leucocyte formula in various pathological processes and diseases, to be able to prove their diagnostic and predictive value.

The student should be able to (the required knowledge and skills):

1) know the main stages in leucopoesis and to have idea about normal leukocyte formula (dep. of histology, dep. of normal physiology);

2) calculate quantity of leucocytes and to know limits of normal fluctuations of this indicator in human blood (dep. normal physiology);

3) prepare and paint blood dab according to Romanovsky-Giemsa, to know and distinguish (at its microscopy) different forms of leukocytes, to be able to count them and absolute number of each type of leucocytes (dep. of normal physiology).

QUESTIONS FOR THE LESSON

1. Leukocytosis. Emergence mechanisms, classification.
2. Physiological leukocytosis.
3. Pathological leukocytosis. Causes and mechanisms of development.
4. Jet and redistributive leukocytosis. Causes and mechanisms of development.
5. Types of a leukocytosis depending on a type of leucocytes.
6. Leucocyte formula. Relative and absolute leukocytosis and leucopenia.
7. Nuclear shift of neutrophile leucocytes. Types, causes, their predictive value.
8. Leucemoid reactions, their causes and hematologic characteristic.
9. Leucopenia, principles of classification.
10. Pathogenesis of the main clinical manifestations of leucopenia.
11. Leucopenia owing to the time reduction of leukocytes stay in peripheral blood and redistributive leucopenia. Causes and mechanisms of development.
12. Leucopenia due to violation of receipt of leukocytes from red bone marrow in blood. Causes, development mechanisms. Agranulocytosis. Causes and mechanisms of development.

EXPERIMENTAL PART OF THE LESSON

Experiment 1. Differential Leukocyte count (Leukocyte formula)

Apparatus and reactives. Blood smears of sick people with different types of leukocytosis, microscopes with immersion objectives, immersion oil.

Procedure. Collect a numbered blood smear from your teacher with the amount of leukocytes in a unit volume indicated. Determine the differential leucocyte count and cross-check with the standard figures. Determine the kind of leukocytosis.

Total of leucocytes	Basophils	Eosinophils	Neutrophils				Lymphocytes	Monocytes
			Mielocytes	Young	Band neutrophils	Segment neutrophils		

RESULTS: _____
_____
_____
_____

Experiment 2. Count the number of white blood cells during experimental postradiational leukopenia.

The object of the experiment: white rat

Apparatus and reactives: micropipette (capilary tube) from haemometer, test-tubes, injection needles, pipettes, counting cameras, microscopes, 5 % solution of acetic acid.

Procedure. Take two rats, one of which is five days old. Before the experiment it was subjected to general X-ray radiation in doses of 600 roentgen. Study the external signs of radiation syndrome, noting haemorrhage of the eyes, nose, changes in the fur, diarrhea, weight loss, change in general state (languitidy). Count the number of white blood cells in the experimental and intact rats. Place the rat in a camera, lower the tail in water with a temperature of 38 °C, thereby causing hyperemy. Wipe the tail with cotton balls, place. Pierce one of the tail veins with an injection needle. Wipe away the first drop of blood, the second one collect to the marked point in a measuring pipette from a haemometer. Blow the blood from the pipette to the bottom of the test-tube, where 0.38 ml of a 3 % solution of acetic acid, dyed in hencianvioletwas poured. Rinse the pipette three times. Shake the mixture energetically for 3 minutes, transfer to the counting camera with the pipette for distilled water from a haemometer. Count the white blood cells in 100 big squares of Gorev's camera. Calculate the amount of white blood cells in 1 mkl of blood by the formula:

$$X = \frac{A \times 4000 \times B}{C},$$

where: X – unknown number of white blood cells; A – sum of white blood cells, counted in 100 big squares; B – sum of counted small squares (1600); C – dilution of the blood (20 times) The volume of the small square = 1/4000 mcl (microlitre), therefore to transfer to 1 mkl, the formula has a multiplier of 4000. The amount of white blood cells calculate in 1l. Compare the amount of white blood cells of the radiated rat and the control rat.

RESULTS:_____
_____
_____
_____

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

White Blood Cell Disorders

The white blood cells and lymphoid tissue where these cells originate, mature, and function protect the body against invasion by foreign agents. Disorders of the white blood cells include a deficiency of leukocytes (leukopenia) and proliferative disorders. The proliferative disorders may be reactive, such as occurs with infection, or neoplastic, such as with the leukemias and lymphomas.

Leukocytes (white blood cells)

The white blood cells include the granulocytes (i.e., neutrophils, eosinophils, and basophils), the monocyte and macrophage lineage, and the lymphocytes. Granulocytes and monocytes are derived from the myeloid stem cell in the bone marrow and circulate in the blood. T lymphocytes (T cells) and B lymphocytes (B cells) originate in the bone marrow and migrate between the blood and the lymph. T lymphocytes mature in the thymus, and the B lymphocytes mature in the bone marro the mammalian equivalent of the avian bursa of Fabricius.

The T lymphocytes differentiate to form helper T cells, which serve to orchestrate the immune response, and cytotoxic T cells, which provide for cell-mediated immune responses. The B lymphocytes differentiate to form immunoglobulin-producing plasma cells. Another population of lymphocytes includes the large granular lymphocytes, or natural killer cells, which do not share the specificity or characteristics of the T lymphocytes or the B lymphocytes, but have the ability to lyse target cells.

The number of leukocytes, or white blood cells, in the peripheral circulation normally ranges from **5000 to 10,000/µL** of blood. **The term leukopenia describes an absolute decrease in white blood cell numbers.** The disorder may affect any of the specific types of white blood cells, but most often it affects the neutrophils, which are the predominant type of granulocyte.

Leukocytes

The leukocytes, or white blood cells, constitute only 1 % of the total blood volume. They originate in the bone marrow and circulate throughout the lymphoid tissues of the body. There they function in the inflammatory and immune processes. They include the granulocytes, the lymphocytes, and the monocytes.

Granulocytes. The granulocytes are all phagocytic cells and are identifiable because of their cytoplasmic granules. These white blood cells are spherical and have distinctive multilobar nuclei. The granulocytes are divided into three types (neutrophils, eosinophils, and basophils) according to the staining properties of the granules. Functionally, all granulocytes are phagocytes.

Neutrophils. The neutrophils, which constitute 55 % to 65 % of the total number of white blood cells, have granules that are neutral and hence do not stain with an acidic or a basic dye. Because these white cells have nuclei that are divided into three to five lobes, they are often called polymorphonuclear leukocytes.

The neutrophils are primarily responsible for maintaining normal host defenses against invading bacteria and fungi, cell remains, and a variety of foreign substances. The cytoplasm of mature neutrophils contains fine granules. These granules contain degrading enzymes that are used in destroying foreign substances and correspond to lysosomes found in other cells. Enzymes and oxidizing agents associated with these granules are capable of degrading a variety of natural and synthetic substances, including complex polysaccharides, proteins, and lipids. These enzymes are important in maintaining normal host defences and in mediating inflammation. The neutrophils have their origin in the myeloblasts that are found in the bone marrow.

The myeloblasts are the committed precursors of the granulocyte pathway and do not normally appear in the peripheral circulation. When they are present, it suggests a disorder of blood cell proliferation and differentiation. The myeloblasts differentiate into promyelocytes and then myelocytes. Usually, a cell is not called a myelocyte until it has at least 12 granules.

The myelocytes mature to become metamyelocytes (Greek meta, “beyond”), at which point they lose their capacity for mitosis. Subsequent development of the neutrophil involves reduction in size, with transformation from an indented to an oval to a horseshoe-shaped nucleus (i.e., band cell) and then to a mature cell with a segmented nucleus.

These mature neutrophils are often referred to as segs because of their segmented nucleus. Development from stem cell to mature neutrophil takes approximately 2 weeks. It is at this point that the neutrophil enters the bloodstream. After release from the marrow, the neutrophils spend only approximately 4 to 8 hours in the circulation before moving into the tissues. Their survival in the tissues lasts approximately 4 to 5 days. They die in the tissues in discharging their phagocytic function or they die of senescence.

The pool of circulating neutrophils (i.e., those that appear in the blood count) is in closely maintained equilibrium with a similar-sized pool of cells marginating along the walls of small blood vessels. These are the neutrophils that respond to chemotactic factors and migrate into the tissues toward the offending agent. Epinephrine, exercise, stress, and corticosteroid drug therapy can cause rapid increases in the circulating neutrophil count by shifting cells from the marginating to the circulating pool. Endotoxins or microbes have the opposite effect, producing a transient decrease in neutrophils by attracting neutrophils into the tissues.

Eosinophils. The cytoplasmic granules of the eosinophils stain red with the acidic dye eosin. These leukocytes constitute 1 to 3 % of the total number of white blood cells and increase in number during allergic reactions and parasitic infections. In allergic reactions, it is thought that they release enzymes or chemical mediators that detoxify the agents associated with allergic reactions. In parasitic infections, the eosinophils use surface markers to attach themselves to the parasite and then release hydrolytic enzymes that kill it.

Basophils. The granules of the basophils stain blue with a basic dye. These cells constitute only approximately 0.3 to 0.5 % of the white blood cells. The granules in the basophils contain heparin, an anticoagulant, and histamine, a vasodilator. The basophils share properties of mast cells and are thought to be involved in allergic and stress responses.

Lymphocytes. The lymphocytes constitute 20 to 30 % of the white blood cell count. They originate in the bone marrow from lymphoid stem cells. They have no identifiable granules in the cytoplasm and are also called agranulocytes. The lymphocytes play an important role in the immune response. They move between blood and lymph tissue, where they may be stored for hours or years. Their function in the lymph nodes or spleen is to defend against microorganisms in the immune response.

Blood Cell Counts

Blood Cells	Number of Cells/μL	Percentage of White Blood Cells
Red blood cell count	$4.2–5.4 \times 10^6$, $3.6–5.0 \times 10^6$ *	
White blood cell count	$4.40–11.3 \times 10^3$	
Differential count		
Granulocytes		
Neutrophils		
Segs		47–63
Bands		0–4
Eosinophils		0–3
Basophils		0–2
Lymphocytes		24–40
Monocytes		4–9
Platelet count	$150–400 \times 10^3$	

There are two types of lymphocytes: B lymphocytes and T lymphocytes. The B lymphocytes differentiate to form antibody-producing plasma cells and are involved in humoral-mediated immunity. The T lymphocytes activate other cells of the immune system and are involved in cell-mediated immunity.

Monocytes and Macrophages. Monocytes are the largest of the white blood cells and constitute approximately 3 to 8 % of the total leukocyte count. The life span of the circulating monocyte is approximately 1 to 3 days, three to four times longer than that of the granulocytes. These cells survive for months to years in the tissues.

The monocytes, which are phagocytic cells, are often referred to as macrophages when they enter the tissues. The monocytes engulf larger and greater quantities of foreign material than the neutrophils. These leukocytes play an important role in chronic inflammation and are also involved in the immune response by activating lymphocytes and by presenting antigen to T cells. When the monocyte leaves the vascular system and enters the tissues, it functions as a macrophage with specific activity.

The macrophages are known as histiocytes in loose connective tissue, microglial cells in the brain, and Kupffer cells in the liver. Some macrophages function in the alveoli.

Granulomatous inflammation is a distinctive pattern of chronic inflammation in which the macrophages form a capsule around insoluble materials that cannot be digested. Foreign-body granulomas are incited by relatively inert foreign bodies, such as talc or surgical sutures. Immune granulomas are caused by insoluble particles that are capable of inciting a cell-mediated immune response. The tubercle that forms in primary tuberculosis infections is an example of an immune granuloma.

The white blood cells and lymphoid tissue where these cells originate, mature, and function protect the body against invasion by foreign agents.

Disorders of the white blood cells **include a deficiency of leukocytes (leukopenia) and proliferative disorders.** The proliferative disorders may be reactive, such as occurs with infection, or neoplastic, such as with the leukemias and lymphomas. This chapter focuses on leukopenia, infectious mononucleosis, malignant lymphomas, leukemias, and plasma cell dyscrasias (multiple myeloma).

The hematopoietic system encompasses all the blood cells, their precursors, and their derivatives: the red blood cells, the thrombocytes or platelets, and the white blood cells. It includes the myeloid or bone marrow tissue in which the white blood cells are formed and the lymphoid tissues of the lymph nodes, thymus, and spleen, in which the white blood cells circulate and mature. The development of different cell lineages depends on cellular interactions and exposure to cytokines.

Nonneoplastic Disorders of White Blood Cells (Quantitative WBC Disorders)

Neutropenia (agranulocytosis)

Neutropenia refers specifically to a decrease in neutrophils. We commonly define it as a circulating neutrophil count of less than 1500 cells/μL. Agranulocytosis, which denotes a severe neutropenia, is characterized by a circulating neutrophil count of less than 200 cells/μL. The reduction in granulocytes can occur because there is reduced or ineffective production of neutrophils or because there is excessive removal of neutrophils from the blood. The causes of neutropenia are summarized in *Table 6*.

Table 6

Cause of neutropenia	Mechanism
Accelerated removal (e.g., inflammation and infection)	Removal of neutrophils from the circulation exceeds production
Drug-induced granulocytopenia	Predictable damage to precursor cells, usually dose dependent
Defective production	Idiosyncratic depression of bone marrow function
Cytotoxic drugs used in cancer therapy. Phenothiazine, thiouracil, chloram-phenicol, phenylbutazone and others	Intramedullary destruction of granulocytes
Immune destruction. Aminopyrine and others	Immunologic mechanisms with cytolysis or leukoagglutination
Periodic or cyclic neutropenia. (occurs during infancy and later)	Unknown
Neoplasms involving bone marrow (e.g., leukemias and lymphomas)	Overgrowth of neoplastic cells, which crowd out granulopoietic precursors
Idiopathic neutropenia that occurs in the absence of other disease or provoking influence	Autoimmune reaction
Felty's syndrome	Intrasplenic destruction of neutrophils

Acquired Neutropenia

Granulopoiesis may be impaired caused by a variety of bone marrow disorders, such as aplastic anemia or bone marrow depression due to cancer chemotherapy and irradiation, which interfere with the formation of all blood cells. Overgrowth of neoplastic cells in cases of nonmyelogenous leukemia and lymphoma also may suppress the function of neutrophil precursors. Infections by viruses or bacteria may drain neutrophils from the blood faster than they can be replaced, thereby depleting the neutrophil storage pool in the bone marrow. Because of the neutrophil's short life span of approximately 1 day in the peripheral blood, neutropenia occurs rapidly when granulopoiesis is impaired. Under these conditions, neutropenia usually is accompanied by thrombocytopenia (i.e., platelet deficiency).

In aplastic anemia, all of the myeloid stem cells are affected, resulting in anemia, thrombocytopenia, and agranulocytosis (*Table 7*). Autoimmune disorders or idiosyncratic drug reactions may cause increased and premature destruction of neutrophils. In splenomegaly, neutrophils may be trapped in the spleen along with other blood cells. In Felty's syndrome, a

variant of rheumatoid arthritis, there is increased destruction of neutrophils in the spleen. Most cases of neutropenia are drug related. Chemotherapeutic drugs used in the treatment of cancer (e.g., alkylating agents, antimetabolites) cause predictable dose dependent suppression of bone marrow function. The term idiosyncratic is used to describe drug reactions that are different from the effects obtained in most persons and that cannot be explained in terms of allergy.

Table 7

Classification of Neutropenias

Classification	Etiology
Neutropenia due to intrinsic defects in myeloid cells or their precursors	Aplastic anemia. Chronic idiopathic neutropenia, including benign neutropenia. Cyclic neutropenia, Myelodysplasia. Neutropenia associated with dysgammaglobulinemia. Paroxysmal nocturnal hemoglobinuria. Severe congenital neutropenia (Kostmann syndrome). Syndrome-associated neutropenias (eg, cartilage-hair hypoplasia syndrome, dyskeratosis congenita, glycogen storage disease type IB, Shwachman-Diamond syndrome)
Secondary neutropenias	Alcoholism. Autoimmune neutropenia, including chronic secondary neutropenia in AIDS. Bone marrow replacement by cancer, myelofibrosis (eg, due to granuloma), or Gaucher cells. Cytotoxic chemotherapy or radiation therapy. Drug-induced neutropenia. Folate or vitamin B_{12}-deficiency. Hypersplenism. Infection, Tγ lymphoproliferative disease

A number of drugs, such as chloramphenicol (an antibiotic), phenothiazine tranquilizers, sulfonamides, propylthiouracil (used in the treatment of hyperthyroidism), and phenylbutazone (used in the treatment of arthritis), may cause idiosyncratic depression of bone marrow function. Some drugs, such as hydantoin derivatives and primidone (used in the treatment of seizure disorders), can cause intramedullary destruction of granulocytes and thereby impair production. Many idiosyncratic cases of drug-induced neutropenia are thought to be caused by immunologic mechanisms, with the drug or its metabolites acting as antigens (i.e., haptens) to incite the production of antibodies reactive against the neutrophils. Neutrophils possess human leukocyte antigens (HLA) and other antigens specific to a given leukocyte line. Antibodies to these specific antigens have been identified in some cases of drug-induced neutropenia.

Congenital Neutropenia

A decreased production of granulocytes is a feature of a group of hereditary hematologic disorders, including cyclic neutropenia and Kostmann's syndrome. Periodic or cyclic neutropenia is an autosomal dominant disorder with variable expression that begins in infancy and persists for decades. It is characterized by periodic neutropenia that develops every 21 to 30 days and lasts approximately 3 to 6 days. Although the cause is undetermined, it is thought to result from impaired feedback regulation of granulocyte production and release.

Kostmann's syndrome, which occurs sporadically or as an autosomal recessive disorder, causes severe neutropenia while preserving the erythroid and megakaryocyte cell lineages that result in red blood cell and platelet production. The total white blood cell count may be within normal limits, but the neutrophil count is less than 200/μL. Monocyte and eosinophil levels may be elevated. Treatment includes the administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF).

A transient neutropenia may occur in neonates whose mothers have hypertension. It usually lasts from 1 to 60 hours but can persist for 3 to 30 days. This type of neutropenia, which is associated with increased risk for nosocomial infection, is thought to result from transiently reduced neutrophil production.

LYMPHOCYTOPENIA

Lymphocytopenia is a total lymphocyte count of < 1000/μL in adults or < 3000/μL in children < 2 yr. Sequelae include opportunistic infections and an increased risk of malignant and autoimmune disorders. If the CBC reveals lymphocytopenia, testing for immunodeficiency and analysis of lymphocyte subpopulations should follow. Treatment is directed at the underlying disorder.

The normal lymphocyte count in adults is 1000 to 4800/μL; in children < 2 yr, 3000 to 9500/μL. At age 6 yr, the lower limit of normal is 1500/μL. Both B and T cells are present in the peripheral blood; about 75 % of the lymphocytes are T cells and 25 % B cells. Because lymphocytes account for only 20 to 40 % of the total WBC count, lymphocytopenia may go unnoticed when WBC count is checked without a differential. Almost 65 % of blood T cells are CD4+ (helper) T cells. Most patients with lymphocytopenia have a reduced absolute number of T cells, particularly in the number of CD4+ T cells. The average number of CD4+ T cells in adult blood is 1100/μL (300 to 1300/μL), and the average number of cells of the other major T-cell subgroup, CD8+ (suppressor) T cells, is 600/μL (range, 100 to 900/μL).

Etiology. Lymphocytopenia can be acquired or inherited.

Acquired lymphocytopenia can occur with a number of other disorders (see *Table 8*). The most common causes include.

Table 8

Causes of Lymphocytopenia

Mechanism	Examples
Acquired	AIDS. Other infectious disorders, including hepatitis, influenza, TB, typhoid fever, and sepsis. Dietary deficiency in patients with ethanol abuse, protein-energy undernutrition, or zinc deficiency Iatrogenic after use of cytotoxic chemotherapy, glucocorticoids, high-dose psoralen and ultraviolet A radiation therapy, immunosuppressants, radiation therapy, or thoracic duct drainage. Systemic disorders with autoimmune features (eg, aplastic anemia, Hodgkin lymphoma, myasthenia gravis, protein-losing enteropathy, RA, renal failure, sarcoidosis, SLE, thermal injury)
Hereditary	Aplasia of lymphopoietic stem cells. Ataxia-telangiectasia. Cartilage-hair hypoplasia syndrome. Idiopathic CD4+ T lymphocytopenia. Immunodeficiency with thymoma. Severe combined immunodeficiency associated with a defect in the IL-2 receptor γ-chain, deficiency of ADA or PNP, or an unknown defect. Wiskott-Aldrich syndrome
ADA = adenosine deaminase; PNP = purine nucleoside phosphorylase	

Protein-energy malnutrition is the most common cause worldwide. AIDS is the most common infectious disease causing lymphocytopenia, which arises from destruction of CD4+ T cells infected with HIV. Lymphocytopenia may also reflect impaired lymphocyte production arising from destruction of thymic or lymphoid architecture. In acute viremia due to HIV or other viruses, lymphocytes may undergo accelerated destruction from active infections with the virus, may be trapped in the spleen or lymph nodes, or may migrate to the respiratory tract.

Iatrogenic lymphocytopenia is caused by cytotoxic chemotherapy, radiation therapy, or the administration of antilymphocyte globulin (or other lymphocyte antibodies). Long-term treatment for psoriasis using psoralen and ultraviolet A irradiation may destroy T cells. Glucocorticoids can induce lymphocyte destruction.

Lymphocytopenia may occur with autoimmune diseases such as SLE, RA, myasthenia gravis, and protein-losing enteropathy.

Inherited lymphocytopenia (see *Table 8*)

It may occur with inherited immunodeficiency and disorders that involve impaired lymphocyte production. Other inherited disorders, such as Wiskott-Aldrich syndrome, adenosine deaminase deficiency, and purine nucleoside phosphorylase deficiency, may involve accelerated T-cell destruction. In many disorders, antibody production is also deficient.

Lymphocytosis

I. <u>Lymphocytosis</u>

A. Absolute lymphocyte count over 4000/μL in adults or over 8000/μL in children

B. **Etiology**

1. Viral (e.g., mononucleosis) or bacterial (e.g., whooping cough)
2. Drugs (e.g., phenytoin)
3. Graves' disease

C. **Pathogenesis**

1. Increased production
2. Decreased entry into lymph nodes
   (e.g. lymphocytosis-promoting factor produced by *Bordetella pertussis)*

II. <u>Atypical lymphocytosis</u>

A. **Etiology**

1. Infection (e.g. mononucleosis, viral hepatitis, cytomegalovirus infection, toxoplasmosis)
2. Drugs (e.g., phenytoin)

B. **Pathogenesis**

1. Antigenically stimulated lymphocytes
2. Prominent nucleoli and abundant blue cytoplasm

III. <u>Infectious mononucleosis</u>

A. Caused by Epstein-Barr virus (EBV)

B. **Pathogenesis**

1. Primarily transmitted by kissing
   - EBV initially replicates in the salivary glands and then disseminates.
2. EBV attaches to CD21 receptors on B cells.
   - Causes B-cell proliferation and increased synthesis of antibodies
3. Virus remains dormant in B cells.
   - Recurrences may occur.

C. **Clinical findings**

1. Fatigue, tonsillitis
2. Hepatosplenomegaly, generalized lymphadenopathy
   - Danger of splenic rupture in contact sports
3. Rash develops if treated with ampicillin .

D. **Laboratory findings**

1. Atypical lymphocytosis
   - Usually more than 20 % of the total WBC count
   - Atypical lymphocytes are antigenically stimulated T- cells.
2. Positive heterophil antibody test
   - Detects IgM antibodies against horse (most common), sheep, and bovine RBCs
3. Positive antiviral capsid antigen test
   - Most sensitive test
4. Increased serum transaminases from hepatitis
   - Jaundice is rare.

Infectious mononucleosis is a self-limiting lymphoproliferative disorder caused by the Epstein-Barr virus (EBV), a member of the herpesvirus family. EBV is commonly present in all human populations. Infectious mononucleosis is most prevalent in adolescents and young adults in the upper socioeconomic classes in developed countries. This is probably because the disease, which is relatively asymptomatic when it occurs during childhood, confers complete immunity to the virus. In families from upper socioeconomic classes, exposure to the virus may be delayed until late adolescence or early adulthood. In such persons, mode of infection, size of the viral pool, and physiologic and immunologic condition of the host may determine whether the infection occurs.

Pathogenesis. Infectious mononucleosis is largely transmitted through oral contact with EBV-contaminated saliva. The virus initially penetrates the nasopharyngeal, oropharyngeal, and salivary epithelial cells. It then spreads to the underlying oropharyngeal lymphoid tissue and, more specifically, to B lymphocytes, all of which have receptors for EBV. Infection of the B cells may take one of two forms—it may kill the infected B cell, or it may become incorporated into its genome. A small number of infected B cells are killed and in the process release the virions. In most cells, however, the virus associates with the B-cell genome. The B cells that harbor the EBV genome proliferate in the circulation and produce the well-known heterophil antibodies that are used for the diagnosis of infectious mononeucleosis. A heterophil antibody is an immunoglobulin that reacts with antigens from another species, in this case, sheep red blood cells. The normal immune response is important in controlling the proliferation of the EBV-infected B cells and cell-free virus. Most important in controlling the proliferation of EBV-infected B cells are the cytotoxic CD8+ T cells and natural killer (NK) cells. The virus-specific T cells appear as large atypical lymphocytes that are characteristic of the infection. In otherwise healthy persons, the humoral and cellular immune responses control viral shedding by limiting the number of infected B cells rather than eliminating them. Although infectious B cells and free virions disappear from the blood following recovery from the disease, the virus remains in a few transformed B cells in the oropharyngeal region and is shed in the saliva. Once infected with the virus, persons remain asymptomatically infected for life, and a few intermittently shed EBV. Immunosuppressed persons shed the virus more frequently. Asymptomatic shedding of EBV by healthy persons accounts for most of the spread of infectious mononucleosis, despite the fact that it is not a highly contagious disease.

Monocytosis

1. Absolute monocyte count over 800/μL
2. Etiology
   A. Chronic infection (e.g., tuberculosis)
   B. Autoimmune disease (e.g., rheumatoid arthritis)
   C. Malignancy (e.g., carcinoma, malignant lymphoma)
3. Pathogenesis – Response to chronic inflammation or malignancy

Eosinophilic disorders

Eosinophils are granulocytes derived from the same progenitor cells as monocytes-macrophages, neutrophils, and basophils. Although they are phagocytic, eosinophils are less efficient than neutrophils in killing intracellular bacteria. And although eosinophilia commonly accompanies helminthic infections and eosinophils are toxic to helminths in vitro, there is no direct evidence that they kill parasites in vivo. Eosinophils may modulate immediate hypersensitivity reactions by degrading or inactivating mediators released by mast cells, such as histamine, leukotrienes (which may cause vasoconstriction and bronchoconstriction), lysophospholipids, and heparin. Prolonged eosinophilia may result in tissue damage.

Eosinophil granules contain major basic protein and eosinophil cationic protein; these proteins are toxic to several parasites and to mammalian cells. These proteins bind heparin and neutralize its anticoagulant activity. Eosinophil-derived neurotoxin can severely damage myelinated neurons. Eosinophil peroxidase, which differs significantly from peroxidase of other granulocytes, generates oxidizing radicals in the presence of hydrogen peroxide and a halide. Charcot-Leyden crystals are primarily composed of phospholipase B and are located in sputum, tissues, and stool in disorders in which there is eosinophilia (e.g, asthma, eosinophilic pneumonia).

Eosinophil production appears to be regulated by T cells through the secretion of the hematopoietic growth factors granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and interleukin-5 (IL-5). Although GM-CSF and IL-3 also increase the production of other myeloid cells, IL-5 increases eosinophil production exclusively.

Eosinophilia

Eosinophilia is defined as a peripheral blood eosinophil count > 450/μL. Causes and associated disorders are myriad but often represent an allergic reaction or parasitic infection. Diagnosis involves selective testing directed at clinically suspected causes. Treatment is directed at the cause.

Eosinophilia has features of an immune response: an agent such as Trichinella spiralisinvokes a primary response with relatively low levels of eosinophils, whereas repeated exposures result in an augmented or secondary eosinophilic response. Several compounds released by mast cells and basophils induce IgE-mediated eosinophil production. Such substances include eosinophil chemotactic factor of anaphylaxis, leukotriene B_4, complement complex (C5-C6-C7), and histamine (over a narrow range of concentration). Eosinophilia itself does not cause symptoms. However, occasionally patients with very severe eosinophilia (eg, eosinophil counts of > 100,000/μL), usually with eosinophilic leukemia, develop complications of hyperleukocytosis

Eosinophilia itself does not cause symptoms. However, occasionally patients with very severe eosinophilia (e.g, eosinophil counts of > 100,000/μL), usually with eosinophilic leukemia, develop complications of hyperleukocytosis

Etiology. Eosinophilia may be primary (i.e, clonal proliferation of eosinophils associated with hematologic disorders such as leukemias and myeloproliferative disorders), secondary to (or associated with) numerous nonhematologic disorders (see *Table 9*), or idiopathic (if other causes cannot be identified).

Table 9

Important Disorders and Treatments Associated With Eosinophilia

Cause or Associated Disorder	Examples
Allergic or atopic disorders	AsthmaAllergic bronchopulmonary aspergillosis Allergic rhinitis, Atopic dermatitis Drug reactions (eg, to antibiotics or NSAIDs) Eczema, Episodic angioedema with eosinophilia Milk-protein allergy, Occupational lung disease, Urticaria
Connective tissue, vasculitic, or granulomatous disorders (especially those involving the lungs)	Dressler's syndrome, Eosinophilic fasciitis Idiopathic eosinophilic synovitis Inflammatory bowel disease, Polyarteritis nodosa Progressive systemic sclerosis (scleroderma) RA, Sarcoidosis, Sjögren's syndrome, SLE
Endocrine disorders	Adrenal hypofunction
Immune disorders (often with eczema)	Congenital immunodeficiency syndrome (eg, IgA deficiency, hyper-IgE syndrome, Wiskott-Aldrich syndrome) Graft-vs-host disease
Myeloproliferative disorders	Acute or chronic eosinophilic leukemia Acute lymphoblastic leukemia (certain types) Chronic myelocytic leukemia, Hypereosinophilic syndrome
Nonparasitic infections	Aspergillosis, Brucellosis, Cat-scratch fever Chlamydial pneumonia of infancy Coccidioidomycosis (acute), Infectious lymphocytosis, Infectious mononucleosis, Mycobacterial disease, Scarlet fever
Parasitic infections (especially due to tissue-invasive metazoans)	Ascariasis, Clonorchiasis, Cysticercosis (caused by Taenia solium) Echinococcosis, Fascioliasis, Filariasis Hookworm infection, Paragonimiasis Schistosomiasis, Strongyloidiasis
Skin disorders	Dermatitis herpetiformis, Exfoliative dermatitis Pemphigus, Psoriasis

Cause or Associated Disorder	Examples
Syndromes of pulmonary infiltration with eosinophilia	Allergic bronchopulmonary aspergillosis Chronic eosinophilic pneumonia Churg-Strauss syndrome Simple pulmonary eosinophilia (Löffler's syndrome) Tropical pulmonary eosinophilia
Tumors	Carcinomas and sarcomas of the lung, pancreas, colon, cervix, or ovary, Hodgkin lymphoma Immunoblastic lymphadenopathy, Non-Hodgkin lymphomas
Miscellaneous	Cirrhosis, Familial eosinophilia Peritoneal dialysis, Radiation therapy, l-Tryptophan use

The **most common cause** is allergic or atopic disorders (typically respiratory or dermatologic)**.**

Other common causes include

Infections (typically parasitic), certain tumors (hematologic or solid, benign or malignant).

Almost any parasitic invasion of tissues can elicit eosinophilia, but protozoa and noninvasive metazoa usually do not.

Of the tumors, Hodgkin lymphoma may elicit marked eosinophilia, whereas eosinophilia is less common in non-Hodgkin lymphoma, chronic myelocytic leukemia, and acute lymphoblastic leukemia. Ovarian cancer is the most commonly associated solid tumor.

The pulmonary infiltrates with eosinophilia syndrome comprises a spectrum of clinical manifestations characterized by peripheral eosinophilia and eosinophilic pulmonary infiltrates but is usually of unknown cause.

Patients with eosinophilic drug reactions may be asymptomatic or have various syndromes, including interstitial nephritis, serum sickness, cholestatic jaundice, hypersensitivity vasculitis, and immunoblastic lymphadenopathy.

Several hundred patients were reported to have developed an eosinophilia-myalgia syndrome after taking l-tryptophan for sedation or psychotropic support. The symptoms (severe muscle pain, tenosynovitis, muscle edema, rash) lasted weeks to months, and several deaths occurred.

Date	Grade	Teacher’s signature

LEUKEMIA

Relevance of the topic. Being a kind of hemoblastoses, leukosis represents the group of diseases of blood system of tumor character and they are, as well as malignant tumors of other localization, one of the most dangerous forms of pathology of the human, agricultural animals and pets. Despite the fact that for the last decades the medical science has made the significant contribution to the solution of questions of an etiology, pathogenesis, diagnostics and treatment of leukosis, they continue to lead in the list among the most difficult diseases of the human, having big mortality percentage, in particular at children's and young age.

At the beginning of leukosis, patients can address to the doctor of any profile. Therefore, the knowledge of symptoms of these diseases, mechanisms of their development, features of a hematologic state at their different forms is necessary for each doctor.

General aim is to be able to characterize leukosis as kinds of hemoblastoses, to classify them, to explain destructive mechanisms of blood formation, quantitative and qualitative changes in composition of peripheral blood, to characterize leukosis in different forms. To be able to interpret the modern ideas of an etiology and pathogenesis of leukosis.

The students should be able to (specific objectives):

1) characterize a leucosis as a system disease of the hematogenic system;
2) give modern classification of leukosis by the hystogenetic principle, a course and a state of peripheral blood;

3) characterize the main techniques of the hematologic researches used in diagnosis of leukosis;

4) decide the possibility of leucosis occurrence by hematograms data;

5) understand changes in peripheral blood in leucosis and to distinguish its different forms;

6) name the main cytochemical indicators used for differential diagnosis of leukosis and to characterize the main forms of leukosis;

7) explain the mechanisms of erythrocyte changes and platelet composition of blood in leukosis;

8) explain the mechanisms of disfunctions of organs and systems in leukosis.

The students should be able to (required knowledge and skills):

1) characterize the main stages of a haemopoesis (dep. of normal physiology);

2) distinguish forming elements of granulocyte, lymphocyte, monocyte and erythrocyte ranks in blood dab microscopy (dep. of normal physiology).

QUESTIONS FOR THE LESSON

1. Leucosis. Etiology and pathogenesis.
2. Modern classification of leukosis.
3. Acute leucosis. Clinical manifestations. Pathogenesis of the main clinical syndromes.
4. Chronic leucosis. Clinical manifestations.
5. Stages of an acute and chronic leucosis. Principles of diagnostics and treatment.
6. Changes in a hemogram and a myelogram in leukosis.

EXPERIMENTAL PART OF THE LESSON

Experiment 1. Microscopy of blood preparations during aqute myeloid (myeloblastic) leukemia.

Apparatus and reactives. Blood smears of the sick, microscopes with immersion objectives, immersion oil.

Procedure. Count different forms of leukocytes. Pay attention to the absence of transition forms between young (blastic) and matured neutrophils.

RESULTS:_____
_____
_____
_____

Experiment 2. Microscopy of preparations of blood during chronic myeloid (myelocytic) leukemia.

Apparatus and reactives. Blood smears of the sick, microscopes with immersion objectives, immersion oil.

Procedure. Count different forms of leukocytes.

RESULTS: _____
_____

Experiment 3. Microscopy of blood preparations during chronic lymphoid leukemia.

Apparatus and reactives. Blood smears of the sick, microscopes with immersion objectives, immersion oil.

Procedure. While counting different forms of leukocytes, pay attention to the predominance of young lymphocyte forms (prolymphocytes, lymphoblasts).

RESULTS: _____
_____
_____

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

Neoplastic Disorders of Hematopoietic and Lymphoid Origin

The neoplastic disorders of hematopoietic and lymphoid origin represent the most important of the white cell disorders. They include somewhat overlapping categories: the lymphomas (Hodgkin's disease and non-Hodgkin's lymphoma), the leukemias, and the plasma cell dyscrasias (multiple myeloma). Clinical features of these neoplasms are largely determined by their site of origin, the progenitor cell from which they originated, and the molecular events involved in their transformation into a malignant neoplasm. Leukemias, arising from hematopoietic precursors in the bone marrow, can involve lymphocytes, granulocytes, and other blood cells. Because blood cells circulate throughout the body, these neoplasms are disseminated from the onset. The lymphomas originate in peripheral lymphoid structures such as the lymph nodes where B and T lymphocytes undergo further differentiation and proliferation as they interact with antigens. The plasma cell dyscrasias originate in the bone marrow where B cells differentiate into plasma cells.

Malignant lymphomas

The lymphomas, Hodgkin's disease and non-Hodgkin's lymphoma, represent solid tumors derived from neoplastic lymphoid tissue cells (i.e., lymphocytes or histiocytes) and their precursors or derivatives. The sixth most common cancer in the United States, the lymphomas are among the most studied human tumors and among the most curable.

Hodgkin's Diseaseis a specialized form of lymphoma that features the presence of an abnormal cell called a Reed–Sternberg cell. In 2003, there were an estimated 7600 newly diagnosed cases and 1300 deaths from Hodgkin's disease. Distribution of the disease is bimodal; the incidence rises sharply after 10 years of age, peaks in the early 20s, and then declines until 50 years of age. After 50 years of age, the incidence again increases steadily with age. The younger adult group consists equally of men and women, but after age 50 years, the incidence is higher among men. The overall incidence of Hodgkin's disease has declined significantly since the late 1980s at a rate of 0.9 % per year. The cause of Hodgkin's disease is unknown. There is a long-standing suspicion that the disease may begin as an inflammatory reaction to an infectious agent, possibly a virus. This belief is supported by epidemiologic data that include the clustering of the disease among family members and among students who have attended the same school. A suspected etiologic agent is EBV because a significant percentage of biopsy specimens have exhibited EBV DNA. In a number of studies that assessed the relationship between Hodgkin's disease and an infectious etiology, a threefold increased incidence of Hodgkin's disease was found in patients with a previous history of mononucleosis. Findings contradictory to the proposed viral hypothesis include an absence of occurrence in marital partners. There also seems to be an association between the presence of the disease and a deficient immune state. Although

exposure to carcinogens or viruses, as well as genetic and immune mechanisms, have been proposed as causes, none have proved to be involved in the pathogenesis of Hodgkin's disease.

Manifestations. Hodgkin's disease is characterized by painless and progressive enlargement of a single node or group of nodes. It is believed to originate in one area of the lymphatic system, and if unchecked, it spreads throughout the lymphatic network. The initial lymph node involvement typically is above the level of the diaphragm. An exception is in elderly persons, in whom the subdiaphragmatic lymph nodes may be the first to be involved. Involvement of the liver, spleen, and bone marrow occurs after the disease becomes generalized. The Reed-Sternberg cell, a distinctive tumor cell, is considered to be the true neoplastic element in Hodgkin's disease. The classic Reed-Sternberg cell is a binucleated cell with mirror-image nuclei that contain clear chromatin and a large eosinophilic nucleolus in each lobe. These malignant proliferating cells may invade almost any area of the body and may produce a wide variety of signs and symptoms. The spleen is involved in one third of the cases at the time of diagnosis. A common finding in Hodgkin's disease is the presence of painless lymph node enlargement, involving a single lymph node or groups of lymph nodes. The cervical and mediastinal nodes are involved most frequently. Less commonly, the axillary, inguinal, and retroperitoneal nodes are initially involved. Additional symptoms that suggest Hodgkin's disease include fevers, chills, night sweats, and weight loss. Persons with Hodgkin's disease are commonly designated as stage A if they lack constitutional symptoms and stage B if significant weight loss, fevers, pruritus, or night sweats are present. Approximately 40 % of persons with Hodgkin's disease exhibit the stage B symptoms. Other symptoms, such as fatigue and anemia, are indicative of disease spread. In the advanced stages of Hodgkin's disease, the liver, lungs, digestive tract, and, occasionally, CNS may be involved. As the disease progresses, the rapid proliferation of abnormal lymphocytes leads to an immunologic defect, particularly in cell-mediated responses, rendering the person more susceptible to viral, fungal, and protozoal infections. Anergy, or the failure to develop a positive response to skin tests, such as the tuberculin test, is common early in the course of the disease. An increased neutrophil count and mild anemia are often noted.

Non-Hodgkin's Lymphomas

The non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of solid tumors composed of neoplastic lymphoid cells. The heterogeneity reflects the potential for malignant transformation at any stage of B- and T-lymphocyte differentiation. Non-Hodgkin's occurs three times more frequently than Hodgkin's disease. In 2003, approximately 53,400 new cases of NHL were diagnosed in the United States, and approximately 23,400 deaths resulted from these disorders. Non-Hodgkin's lymphomas are the sixth most common malignancy in both men and women. Since the early 1970s, the incidence rates for NHL have nearly doubled, then stabilized in the 1990s as a result of the decline in NHLs related to acquired immunodeficiency disease (AIDS). The etiology of most of the NHLs is unknown. A viral cause is suspected in at least some of the lymphomas. There is evidence of EBV infection in 95 % of people with Burkitt's lymphoma, which is endemic to some parts of Africa. A second virus, the human T-cell lymphoma virus (HTLV-1), which is endemic in the south western islands of Japan, has been associated with adult T-cell leukemia-lymphoma. Non-Hodgkin's lymphoma is also seen with increased frequency in persons infected with human immunodeficiency virus (HIV), in those who have received chronic immunosuppressive therapy after organ transplantation, and in individuals with acquired or congenital immunodeficiencies. There is also a reported association between chronic Helicobacter pylori infection and low-grade, mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach.15 Other possible risk factors include occupational exposures to herbicides and chemical carcinogens.

Pathogenesis. Non-Hodgkin's lymphomas result from the malignant transformation of normal lymphoid tissue at specific stages of differentiation. Lymphoid tissues can be divided into two major categories: central and peripheral lymphoid tissues. The peripheral lymphoid

structures, which are the site of origin for the lymphomas, consist of the lymph nodes, spleen, and mucosa-associated lymphoid tissue of the gastrointestinal and respiratory tracts. The lymph nodes, which are located at strategic sites throughout the body, process nodes have a capsule, a cortex, a medulla, and sinuses. The cortex is divided into the follicular and diffuse (paracortical) regions, and the medulla is separated into medullary cords and sinuses. The T lymphocytes are more abundant in the paracortex, and the B lymphocytes are more abundant in the follicles and germinal centers located in the outer cortex.

The T lymphocytes proliferate on antigenic stimulation and migrate to the follicles, where they interact with B lymphocytes. These activated follicles become germinal centers, containing macrophages, follicular dendritic cells, and maturing T- and B-cells. Non-Hodgkin's lymphomas can originate from malignant transformation of either the T- or B-cells during their differentiation in the peripheral lymphoid tissues. Most (80 to 85 %) are of B-cell origin, with the remainder being largely of T-cell origin. Although NHLs can develop in any of the lymphoid tissues, they most commonly originate in the lymph nodes and are classified as follicular, diffuse, or centrocytic. Approximately 35 % of NHLs in the United States and 22 % in Europe are classified as follicular lymphomas. Non-Hodgkin's lymphomas have the potential to spread to various lymphoid tissues throughout the body, especially the liver, spleen, and bone marrow. The non-Hodgkin's lymphomas commonly are divided into three groups, depending on the grade of the tumor: low-grade lymphomas, which are predominantly B-cell tumors; intermediate-grade lymphomas, which include B-cell and some T-cell lymphomas; and high-grade lymphomas, which are largely immunoblastic (B-cell), lymphoblastic (T-cell), Burkitt's, and non-Burkitt's lymphomas.

LEUKEMIAS

The leukemias are malignant neoplasms of cells originally derived from hematopoietic stem cells. They are characterized by diffuse replacement of bone marrow with unregulated, proliferating, immature neoplastic cells. In most cases, the leukemic cells spill out into the blood, where they are seen in large numbers. The term leukemia (i.e., "white blood") was first used by Virchow to describe a reversal of the usual ratio of red blood cells to white blood cells. The leukemic cells may also infiltrate the liver, spleen, lymph nodes, and other tissues throughout the body, causing enlargement of these organs. Approximately 30,600 new cases of leukemia were diagnosed in 2010, and approximately 21,900 persons died of the disease. More children are stricken with leukemia than with any other form of cancer, and it is the leading cause of death in children between the ages of 1 and 14 years. Although leukemia commonly is thought of as a childhood disease, it strikes more adults than children. The overall trend in the 1990s has been a decrease in the incidence of leukemia in both men and women, with a slower decrease in deaths from leukemia.

Classification. The leukemias commonly are classified according to their predominant cell type (i.e., lymphocytic or myelogenous) and whether the condition is acute or chronic. Biphenotypic leukemias demonstrate characteristics of both lymphoid and myeloid lineages. A rudimentary classification system divides leukemia into four types: acute lymphocytic (lymphoblastic) leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous (myeloblastic) leukemia (AML), and chronic myelogenous leukemia (CML).

The lymphocytic leukemias, involve immature lymphocytes and their progenitors that originate in the bone marrow but infiltrate the spleen, lymph nodes, CNS, and other tissues.

The myelogenous leukemias, which involve the pluripotent myeloid stem cells in bone marrow, interfere with the maturation of all blood cells, including the granulocytes, erythrocytes, and thrombocytes.

Etiology and Molecular Biology. The causes of leukemia are largely unknown. The incidence of leukemia among persons who have been exposed to high levels of radiation is unusually high. The number of cases of leukemia reported in the most heavily exposed survivors of the atomic blasts at Hiroshima and Nagasaki during the 20-year period from 1950 to 1970 was nearly 30 times the expected rate. An increased incidence of leukemia also is

associated with exposure to benzene and the use of antitumor drugs (i.e., mechlorethamine, procarbazine, cyclophosphamide, chloramphenicol). Leukemia may occur as a second cancer after aggressive chemotherapy for other cancers, such as Hodgkin's disease. The existence of a genetic predisposition to develop acute leukemia is suggested by the increased leukemia incidence among a number of congenital disorders, including Down syndrome, von Reckinghausen's disease, and Fanconi's anemia. In individuals with Down syndrome, the incidence of acute leukemia is 10 times that of the general population. Also, there are numerous reports of multiple cases of acute leukemia occurring within the same family. Some T-cell leukemias, hairy cell leukemia, and lymphoma are caused by retroviruses, HTLV-1 and HTLV-2. The molecular biology of leukemia suggests that the event or events causing the disorders exert their effects through disruption or dysregulation of genes that normally regulate blood cell development, blood cell homeostasis, or both. Cytogenetic studies have shown that recurrent chromosomal changes occur in over one half of all cases of leukemia. Most commonly, these are structural changes classified as translocations, inversions, or deletions. It is the disruption or dysregulation of specific genes and gene products occurring at the site of these chromosome aberrations that contribute to the development of leukemia. In many instances, these genes have also been found to be directly or indirectly involved in the normal development or maintenance of the hematopoietic system. Thus, it would appear that leukemia results, at least in part, from disruption in the activity of genes that normally regulate blood cell development. Currently, more than 500 recurring translocations have been described in hematologic malignancies. One of the more studied is the reciprocal translocation from the long arm of chromosome 22 to the long arm of chromosome 9 that occurs in the Philadelphia (Ph′) chromosome. Almost all cases of CML and 22 to 25 % of adult ALL are associated with the Ph′ chromosome karyotype. Advances in the understanding of the molecular biology of leukemia are beginning to provide a more complete understanding of the molecular complexity of leukemia for the diagnosis, classification, treatment, and monitoring of clinical outcomes (*Table 10*).

Table 10

French-American-British (FAB) Classification of Acute Leukemias

FAB Classification	Description
Acute lymphocytic leukemia	
L1	Lymphoblasts with uniform, round nuclei and scant cytoplasm
L2	More variability of lymphoblasts, Sometimes irregular nuclei with more cytoplasm than L1
L3	Lymphoblasts with finer nuclear chromatin and blue to deep blue cytoplasm that contains vacuoles
Acute myelocytic leukemia	
M1	Undifferentiated myeloblastic, No cytoplasmic granulation
M2	Differentiated myeloblastic Sparse granulation in few to many cells
M3	Promyelocytic, Granulation typical of promyelocytic morphology
M4	Myelomonoblastic, Mixed myeloblastic and monocytoid morphology
M5	Monoblastic, Pure monoblastic morphology
M6	Erythroleukemic Predominantly immature erythroblastic morphology, sometimes megaloblastic appearance
M7	Megakaryoblastic, Cells with shaggy borders that may show some budding

Pathogenesis

1. Block in stem cell differentiation
   1.1. Monoclonal proliferation of neoplastic leukocytes behind the block
2. Leukemic cells
   A. Replace the bone marrow
   B. Replace normal hematopoietic cells
   C. Enter the peripheral blood
   D. Metastasize throughout the body

Manifestations of leukemia are due to suppression of normal blood cell formation and organ infiltration by leukemic cells. Inhibitory factors produced by leukemic cells and replacement

of marrow space may suppress normal hematopoiesis, with ensuing anemia, thrombocytopenia, and granulocytopenia. Organ infiltration results in enlargement of the liver, spleen, and lymph nodes, and occasional kidney and gonadal involvement. Meningeal infiltration results in clinical features associated with increasing intracranial pressure (eg, cranial nerve palsies).

Classification. Leukemias were originally termed acute or chronic based on life expectancy but now are classified according to cellular maturity.

Acute leukemias consist of predominantly immature, poorly differentiated cells (usually blast forms). Acute leukemias are divided into lymphocytic (ALL) and myelocytic (AML) types, which may be further subdivided by the French-American-British (FAB) classification.

Chronic leukemias have more mature cells than do acute leukemias. Chronic leukemias are described as lymphocytic (CLL) or myelocytic (CML).

Myelodysplastic syndromes involve progressive bone marrow failure but with an insufficient proportion of blast cells (< 30 %) for making a definite diagnosis of AML; 40 to 60 % of cases evolve into AML.

A leukemoid reaction is marked granulocytic leukocytosis (ie, WBC > 30,000/μL) produced by normal bone marrow in response to systemic infection or cancer. Although not a neoplastic disorder, a leukemoid reaction with a very high WBC count may require testing to distinguish it from CML.

Leukemoid reaction

A. Absolute leukocyte count usually above 50,000/μL.
  1A. May involve neutrophils, lymphocytes, or eosinophils
B. Etiology
  1B. Perforating appendicitis (neutrophils)
  2B. Whooping cough (lymphocytes)
  3B. Cutaneous larva migrans (eosinophils)
C. Pathogenesis
  1C. Exaggerated response to infection
  2C. Leukoerythroblastic reaction
D. Immature bone marrow cells enter the peripheral blood
E. Pathogenesis
  1E. Bone marrow infiltrative disease
  2E. Examples-fibrosis, metastatic breast cancer
    G. Peripheral blood findings (myeloblasts, progranulocytes)

Acute Leukemias is a cancer of the hematopoietic progenitor cells. It usually has a sudden and stormy onset with signs and symptoms related to depressed bone marrow function. Acute lymphocytic leukemia (ALL) is the most common leukemia in childhood, constituting 80 to 85 % of leukemia cases. The peak incidence occurs between 2 and 4 years of age. Acute myelogenous leukemia (AML) is chiefly an adult disease; however, it is also seen in children and young adults. The incidence steadily increases after middle age, with the median age of 60 to 65 years for adult AML. ALL encompasses a group of neoplasms composed of immature precursor B or T lymphocytes. Most cases (about 85 %) of ALL are of pre–B-cell origin. The AMLs are an extremely heterogeneous group of disorders. Some arise from the pluripotent stem cells in which myeloblasts predominate, and others arise from the monocyte-granulocyte precursor, which is the cell of origin for myelomonocytic leukemia. Of all the leukemias, AML is most strongly linked with toxins and underlying congenital and hematologic disorders. It is the type of leukemia associated with Down syndrome.

Acute myelocytic leukemia (aml) (Acute Myelogenous Leukemia; Acute Myeloid Leukemia)

In AML, malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived myeloid progenitor cell results in high circulating numbers of immature blood forms and replacement of normal marrow by malignant cells. Symptoms include fatigue, pallor, easy bruising and bleeding, fever, and infection; symptoms of

extramedullary leukemic infiltration are present in only about 5 % of patients (often as skin manifestations). Examination of peripheral blood smear and bone marrow is diagnostic. Treatment includes induction chemotherapy to achieve remission and postremission chemotherapy (with or without stem cell transplantation) to avoid relapse.

The incidence of AML increases with age; it is the more common acute leukemia in adults, with a median age of onset of 50 yr. AML may occur as a secondary cancer after chemotherapy or radiation therapy for a different type of cancer.

AML has a number of subtypes that are distinguished from each other by morphology, immunophenotype, and cytochemistry. Five classes are described, based on predominant cell type, including myeloid, myeloid-monocytic, monocytic, erythroid, and megakaryocytic.

Acute promyelocytic leukemia (APL) is a particularly important subtype, representing 10 to 15 % of all cases of AML, striking a younger age group (median age 31 yr) and particular ethnicity (Hispanics), in which the patient commonly presents with a coagulation disorder.

Chronic leukemias usually manifests as abnormal leukocytosis with or without cytopenia in an otherwise asymptomatic person.

In contrast to acute leukemias, chronic leukemias are malignancies involving the proliferation of well-differentiated myeloid and lymphoid cells. The two major types of chronic leukemia are chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). CLL is mainly a disorder of older persons; fewer than 10 % of those who develop the disease are younger than 50 years of age.

Men are affected twice as frequently as women. CML accounts for 15 % of all leukemias in adults. It is predominantly a disorder of adults between the ages of 30 and 50 years, but it can affect children as well. The incidence is slightly higher in men than women. Lymphocytic leukemia is a lymphoproliferative disorder characterized by lymphocytosis, lymphadenopathy, and splenomegaly. Most cases (95 %) result from the malignant transformation of relatively mature B lymphocytes that are immunologically incompetent.

The leukemic B cells fail to respond to antigenic stimulation; hence, persons with CLL have hypogammaglobulinemia. Infections remain a major cause of morbidity and mortality. Immunologic abnormalities, including autoimmune hemolytic anemia and immune-mediated thrombocytopenia, are also common, reflecting the abnormal immunoregulation inherent in the lymphocytic origin of the disorder.

Chronic myelogenous leukemia is a myeloproliferative disorder that results from the malignant transformation of a pluripotent hematopoetic stem cell. CML is associated with the presence of the Philadelphia (Ph) chromosome, representing a reciprocal translocation between the long arm of chromosome 22 and the long arm of chromosome.

The portion of the translocated long arm of chromosome 9 contains the ABL proto-oncogene that is the cellular homolog of the Abelson's murine leukemia virus. The ABL gene is received at a specific site on the long arm of chromosome 22, the break point cluster region (BCR).

The resulting BCR-ABL fusion gene codes for the BCR-ABL fusion protein, which is a constitutively active cytoplasmic tyrosine kinase that can phosphorylate several substrates, resulting in cell growth and proliferation. It is generally believed that CML develops when a single pluripotential hematopoietic stem cell acquires a Ph chromosome carrying the BCR-ABL fusion gene. Because the tyrosine kinase generated by the BCR-ABL gene is constitutively active, the affected cells bypass the regulated signals that control normal cell growth and differentiation and instead undergo malignant transformation to become leukemic cells.

The mechanism by which the Ph chromosome is firstly formed and the time required for progression to overt disease is unknown. It has been proposed that the close proximity of the BCR and ABL genes in the hematopoietic cells during interphase may favor translocation between the two chromosomes. In about 95 % of persons with CML, the Ph chromosome can be identified in granulocytic, erythroid, and megakaryocytic precursors as well as B cells, and in some cases, T cells. Although CML originates in the pluripotent stem cells, granulocyte precursors remain the dominant leukemic cell type.

CHRONIC MYELOCYTIC LEUKEMIA (CML)

(Chronic Granulocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloid Leukemia)

CML occurs when a pluripotent stem cell undergoes malignant transformation and clonal myeloproliferation, leading to a striking overproduction of immature granulocytes. Initially asymptomatic, CML progression is insidious, with a nonspecific "benign" stage (malaise, anorexia, weight loss) eventually giving way to accelerated or blast phases with more ominous signs, such as splenomegaly, pallor, easy bruising and bleeding, fever, lymphadenopathy, and skin changes. Peripheral blood smear, bone marrow aspirate, and demonstration of Philadelphia chromosome are diagnostic. Treatment is with imatinib, which significantly improves response and prolongs survival. The curative potential of imatinib is undefined. Myelosuppressive drugs (eg, hydroxyurea), stem cell transplantation, and interferon alfa are also used.

CML accounts for about 15 % of all adult leukemias. CML can strike at any age, although it is uncommon before age 10, and the median age at diagnosis is 45 to 55. CML may occur in either sex.

Pathophysiology

Most cases of CML appear to be induced by a translocation known as the Philadelphia (Ph) chromosome, which is demonstrable in 95 % of patients. It is a reciprocal translocation t (9; 22) in which a piece of chromosome 9 containing the oncogene c-abl is translocated to chromosome 22 and fused to the gene BCR. The fusion gene BCR-ABL is important in the pathogenesis and expression of CML and results in the production of a specific tyrosine kinase. CML ensues when an abnormal pluripotent hematopoietic progenitor cell initiates excessive production of granulocytes, primarily in the bone marrow but also in extramedullary sites (eg, spleen, liver). Although granulocyte production predominates, the neoplastic clone includes RBCs, megakaryocytes, monocytes, and even some T- and B-cells. Normal stem cells are retained and can emerge after drug suppression of the CML clone.

CML has 3 phases:

1. **Chronic phase**: An initial indolent period that may last months to years.
2. **Accelerated phase**: Treatment failure, worsening anemia, progressive thrombocytopenia or thrombocytosis, persistent or worsening splenomegaly, clonal evolution, increasing blood basophils, and increasing marrow or blood blasts.
3. **Blast phase**: Accumulation of blasts in extramedullary sites (e.g, bone, CNS, lymph nodes, skin), blasts in blood or marrow increased to > 20 %.

The blast phase leads to fulminant complications resembling those of acute leukemia, including sepsis and bleeding. Some patients progress directly from the chronic to the blast phase.

CML is most frequently diagnosed by a CBC obtained incidentally or during evaluation of splenomegaly. Granulocyte count is elevated, usually < 50,000/μL in asymptomatic patients and 200,000/μL to 1,000,000/μL in symptomatic patients. Platelet count is normal or moderately increased. Hb level is usually > 10 g/dL.

Peripheral smear may help differentiate CML from leukocytosis of other etiology. In CML, peripheral smear frequently shows immature granulocytes as well as absolute eosinophilia and basophilia, although in patients with WBC counts < 50,000/μL, immature granulocytes may not be seen. Leukocytosis in patients with myelofibrosis is usually associated with nucleated RBCs, teardrop-shaped RBCs, anemia, and thrombocytopenia. Leukemoid reactions resulting from cancer or infection are not often associated with absolute eosinophilia and basophilia.

The leukocyte alkaline phosphatase score is usually low in CML and increased in leukemoid reactions. Bone marrow examination should be done to evaluate the karyotype as well as cellularity and extent of myelofibrosis.

Diagnosis is confirmed by finding the Ph chromosome in samples examined with cytogenetic or molecular studies, although it is absent in 5 % of patients.

During the accelerated phase of disease, anemia and thrombocytopenia usually develop. Basophils may increase, and granulocyte maturation may be defective. The proportion of

immature cells and the leukocyte alkaline phosphatase score may increase. In the bone marrow, myelofibrosis may develop and sideroblasts may be seen on microscopy. Evolution of the neoplastic clone may be associated with development of new abnormal karyotypes, often an extra chromosome 8 or isochromosome 17.

Further evolution may lead to a blast phase with myeloblasts (60 % of patients), lymphoblasts (30 %), and megakaryoblasts (10 %). In 80 % of these patients, additional chromosomal abnormalities occur.

PLASMA CELL DYSCRASIAS

Plasma cell dyscrasias are characterized by expansion of a single clone of immuneglobulin-producing plasma cells and a resultant increase in serum levels of a single monoclonal immunoglobulin or its fragments. The plasma cell dyscrasias include multiple myeloma; localized plasmacytoma (solitary myeloma); lymphoplasmacytic lymphoma; primary or immunocyte amyloidosis due to excessive production of light chains; and monoclonal gammopathy of undetermined significance. Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the presence of the M proteins in the serum without other findings of multiple myeloma. M proteins can be detected in the serum of 1 to 3 % of healthy persons older than 50 years of age. MGUS is considered a premalignant condition. Approximately 20 % of persons with MGUS go on to develop a plasma cell dyscrasia (multiple myeloma, lymphoplasmacytic lymphoma, or amyloidosis) over a period of 10 to 15 years.

Multiple Myeloma. Multiple myeloma is by far the most frequent of the malignant plasma cell dyscrasias, accounting for 1 % of all cancers and 10 % of all hematologic malignancies in Caucasians and 20 % in African Americans. It occurs most frequently in persons older than 60 years of age with the median age of patients with multiple myeloma being 71 years. The occurrence of the disease tends to be more frequent in men than in women.

The cause of multiple myeloma is unknown. Risk factors are thought to include chronic immune stimulation, autoimmune disorders, exposure to ionizing radiation, and occupational exposure to pesticides or herbicides (e.g., dioxin). Myeloma has been associated with exposure to Agent Orange during the Vietnam War. A number of viruses have been associated with the pathogenesis of myeloma. There is a 4.5-fold increase in the likelihood of developing myeloma for persons with HIV. Hereditary and genetic factors may predispose to myeloma development. From family studies, researchers have identified 20 families in France where the risk for developing myeloma is as high as 5 %.

Pathogenesis.

Multiple myeloma is characterized by proliferation of malignant plasma cells in the bone marrow and osteolytic bone lesions throughout the skeletal system. As with other hematopoietic malignancies, it is now recognized that multiple myeloma is associated with chromosomal translocations, specifically those involving the immunoglobulin G (IgG) locus on chromosome 14. One fusion partner is a fibroblast growth factor receptor gene on chromosome 4, which is truncated to produce a constitutively active receptor.

There is also a reported overexpression by myeloma cells of a gene, called the dickkopf 1 (DKK1) gene, which codes for a protein product that inhibits differentiation of osteoblast precursor cells, thereby contributing to the osteolytic lesions that occur with the disease. One of the characteristics of multiple myelomas is the unregulated production of a monoclonal antibody referred to as the M protein because it is detected as an M spike on protein electrophoresis. In most cases, the M protein is either IgG (60 %) or IgA (20 to 25 %). In the remaining 15 to 20 % of cases, the plasma cells produce only abnormal proteins, termed Bence Jones proteins, that consist of light chains of the immunoglobulin molecule. Because of their low molecular weight, the Bence Jones proteins are readily excreted in the urine. Persons with this form of the disease (light-chain disease) have Bence Jones proteins in their serum but lack the M component.

However, up to 80 % of myeloma cells produce both complete immunoglobulins as well as excess light chains; therefore, both M proteins and Bence Jones proteins are present. Many

of the light chain proteins are directly toxic to renal tubular structures, which may lead to tubular destruction and, eventually, to renal failure.

Cytokines are important in the pathogenesis of the disorder. The multiple myeloma cell has a surface-membrane receptor for IL-6, which is known to be a growth factor for the disorder. Another important growth factor for the myeloma cell is IL-1, which has important osteoclast activity.

Other growth factors that are implicated in multiple myeloma include granulocyte-colony stimulating factor, interferon-alfa, and IL-10. Replacement of the bone marrow (and perhaps humoral suppression of myelopoiesis) leads initially to anemia and later to general bone marrow failure. The proliferation of neoplastic myeloma cells is supported by the cytokine IL-6 produced by fibroblasts and macrophages in the bone marrow stroma.

MYELOPROLIFERATIVE DISORDERS

OVERVIEW OF MYELOPROLIFERATIVE DISORDERS

The myeloproliferative disorders are characterized by abnormal proliferation of one or more hematopoietic cell lines or connective tissue elements. They include

1. **Essential thrombocythemia**
2. **Primary myelofibrosis**
3. **Polycythemia vera**
4. **Chronic myelocytic leukemia**

Essential thrombocythemia, primary myelofibrosis, and polycythemia vera are Philadelphia chromosome–negative myeloproliferative disorders. Myeloproliferative disorders, particularly chronic myelocytic leukemia, sometimes lead to acute leukemia; some hematologists also classify hypereosinophilic syndrome and mastocytosis as myeloproliferative disorders. However, most experts argue that these disorders are sufficiently different and omit them.

Each disorder is identified according to its predominant feature or site of proliferation (*Table 11*). Despite overlap, each disorder has a somewhat typical constellation of clinical features, laboratory findings, and course. Although proliferation of one cell line may dominate the clinical picture, each disorder is typically caused by clonal proliferation of a pluripotent stem cell, causing varying degrees of abnormal proliferation of RBC, WBC, and platelet precursors in the bone marrow. This abnormal clone does not, however, produce bone marrow fibroblasts, which can proliferate in polyclonal reactive fashion.

Table 11

Classification of Myeloproliferative Disorders

Disorder	Predominant Feature
Polycythemia vera	Erythrocytosis
Primary myelofibrosis (or myelosclerosis)	Bone marrow fibrosis with extramedullary hematopoiesis
Essential thrombocythemia	Thrombocytosis
Chronic myelocytic leukemia	Granulocytosis

An abnormality of a tyrosine kinase called JAK2, involved in the bone marrow response to erythropoietin, contributes to the cause of polycythemia vera and causes a high proportion of cases of essential thrombocythemia and myelofibrosis.

ESSENTIAL THROMBOCYTHEMIA

(Essential Thrombocytosis; Primary Thrombocythemia)

Essential thrombocythemia (ET) is characterized by an increased platelet count, megakaryocytic hyperplasia, and a hemorrhagic or thrombotic tendency. Symptoms and signs may include weakness, headaches, paresthesias, bleeding, splenomegaly, and erythromelalgia with digital ischemia. Diagnosis is based on a platelet count > 450,000/μL, normal RBC mass or normal Hct in the presence of adequate iron stores, absence of myelofibrosis, the Philadelphia chromosome (or BCR-ABL rearrangement), and any other disorder that could cause thrombocytosis.

Treatment is controversial but may include aspirin. Patients > 60 yr and those with previous thromboses and transient ischemic attacks require cytotoxic drugs to decrease risk of thromboses. Data suggest that risk of thrombosis does not correlate with platelet count, although anecdotal experience suggests otherwise.

Pathophysiology ET is a typically clonal abnormality of a multipotent hematopoietic stem cell. However, some women who fulfill diagnostic criteria for ET have polyclonal hematopoiesis. ET usually occurs with bimodal peaks of between ages 50 and 70 yr and a separate peak among young females. Platelet production is increased. Platelet survival is usually normal, although it may decrease due to splenic sequestration and in patients with erythromelalgia with digital ischemia.

In elderly patients with atherosclerosis, increased platelets may lead to serious bleeding or, more commonly, thrombosis.

Thrombosis is the major cause of morbidity and mortality. Recent studies indicate that an elevated leukocyte count is a major independent risk factor for thromboses. Although anecdotally (and intuitively), elevated platelet count may increase the risk of thrombosis, one study found an inverse relationship between absolute platelet count and thrombotic risk. Bleeding is more likely with extreme thrombocytosis (ie, > 1.5 million platelets/μL) due to an acquired von Willebrand's factor deficiency.

THROMBOCYTOSIS (Secondary Thrombocythemia)

Thrombocytosis can develop secondary to:

Chronic inflammatory disorders, e.g, RA, inflammatory bowel disease, TB, sarcoidosis, Wegener's granulomatosis, acute infection, hemorrhage, iron deficiency, hemolysis, cancer (particularly Hodgkin lymphoma, non-Hodgkin lymphoma), splenectomy, myeloproliferative and hematologic disorders (e.g, polycythemia vera, chronic myelocytic leukemia, sideroblastic anemia, myelodysplasia [5q-syndrome], idiopathic myelodysplasia)

There are also congenital familial thrombocytoses such as those due to thrombopoietin and thrombopoietin receptor gene mutations.

Platelet function is usually normal. Unlike ET, thrombocytosis does not increase the risk of thrombotic or hemorrhagic complications unless patients have severe arterial disease or prolonged immobility. With secondary thrombocytosis, the platelet count is usually < 1,000,000/μL, and the cause may be obvious from the history and physical examination (perhaps with confirmatory testing).

CBC and peripheral blood smear should help suggest iron deficiency or hemolysis. If a cause is not obvious, evaluation for a myeloproliferative disorder should be considered.

Treatment of the underlying disorder usually returns the platelet count to normal.

PRIMARY MYELOFIBROSIS
(Agnogenic Myeloid Metaplasia; Myelofibrosis with Myeloid Metaplasia)

Primary myelofibrosis (PMF) is a chronic, usually idiopathic disorder characterized by bone marrow fibrosis, splenomegaly, and anemia with immature and teardrop-shaped RBCs.

Diagnosis requires bone marrow examination and exclusion of other conditions that can cause myelofibrosis (secondary myelofibrosis). Treatment is usually supportive.

Pathophysiology

Myelofibrosis is excessive bone marrow fibrosis and loss of hematopoietic cells, with subsequent marked increase in extramedullary hematopoiesis (primarily in the liver and spleen, which enlarge significantly).

Myelofibrosis may be primary or secondary to a number of hematologic, malignant, and nonmalignant conditions (*Table 12*).

Table 12

Conditions Associated with Myelofibrosis

Condition	Examples
Cancers	Cancer with bone marrow metastases, Hodgkin lymphoma. Leukemias (particularly chronic myelocytic and hairy cell). Multiple myeloma, Non-Hodgkin lymphoma. Polycythemia vera (15 to 30 % of patients in the spent phase)
Infections	Osteomyelitis, TB
Primary pulmonary hypertension	–
Toxins	Benzene, Thorium dioxide, X- or γ-radiation
Autoimmune disorders (rarely)	SLE, Systemic sclerosis

PMF is more common than secondary myelofibrosis and results from neoplastic transformation of a multipotent bone marrow stem cell. These PMF progeny cells stimulate bone marrow fibroblasts (which are not part of the neoplastic transformation) to secrete excessive collagen. The peak incidence of PMF is between 50 and 70 yr.

In PMF, large numbers of nucleated RBCs (normoblasts) and granulocytes are released into the circulation (leukoerythroblastosis). Serum LDH level is often elevated.

Bone marrow failure eventually occurs, with consequent anemia and thrombocytopenia. Rapidly progressive, chemotherapy-incurable acute leukemia develops in about 10 % of patients. Malignant or acute myelofibrosis, an unusual variant, has a more rapidly progressive downhill course; this variant may actually be a true megakaryocytic leukemia.

Date	Grade	Teacher's signature

DISTURBANCES IN HEMOSTASIS. CHANGES IN THE PHYSICAL-CHEMICAL PROPERTIES OF BLOOD

Relevance of the topic. The aggregation is one of the most ancient and extremely important manifestations of a homeostasis and represents the sum of the processes leading to a thrombogenesis. Trombogenesis can have double value in activity of an organism. On the one hand, formation of blood clot protects an organism from blood loss, on the other hand- leads to blood-groove disorder and trophic of organs and tissues that is the important mechanism in pathogenesis of many diseases. In clinic, doctors of almost all specialties face disorders of an aggregation (because they complicate the course of surgical, obstetric and gynecologic, therapeutic, oncological, stomatologic, infectious and other diseases). Thus, the range of manifestations of coagulapatias is extremely wide, from the hidden latent forms to life-threatening manifestations.

It is difficult to name a pathological state, process or a disease, which wouldn't be followed by changes in physical and chemical properties of blood. Because changes in different indicators of physical and chemical properties of blood have nonspecific character, data on some of them, along with data of other laboratory researches, help a doctor make a diagnose, and judgement about efficiency of the treatment. In some cases detailed study of changes in some of these indicators is obligatory for statement of the correct diagnosis (some types of disproteinemia and the anemia, coagulopathy). One of the most widespread indicators of changes in physical and chemical properties of whole blood is the speed of subsidence of erythrocytes (SSE), and in hematologic practice and toxicology – osmotic resistance of erythrocytes.

General aim is to be able to characterize a condition of the coagulation system of blood by coagulogram indicators. To be able to interpret changes of SSE and osmotic resistance of erythrocytes in different pathological processes and diseases as the data of additional methods in diagnosis of diseases and criterion of treatment efficiency.

The student should be able to (specific objectives):

1) define the term "system of a hemostasis";

2) characterize the mechanisms to stop bleeding and restore the integrity of the vascular course;

3) define changes of SSE and osmotic resistance of erythrocytes;

4) connect these changes with possible disorders in physical and chemical properties of blood in pathology;

5) explain mechanisms of SSE change and osmotic resistance of erythrocytes in different pathological processes and diseases.

The student should be able to (required knowledge and skills):

1) characterize coagulation mechanisms (dep. of normal physiology);

2) explain participation of a liver in coagulation mechanisms (dep. of biochemistry and normal physiology);

3) characterize the main physical and chemical properties of blood and erythrocytes, to explain, their causes (dep. normal physiology);

4) what shows the SSE indicator, what factors it depends on (dep. of normal physiology);

5) determine value of SSE and to know normal borders of its fluctuations (dep. of normal physiology);

6) characterize the cause of the osmotic and oncotic pressure of blood plasma (dep. of normal physiology);

7) know what represents iso-, hypo- and hypertensive solutions to characterize influence of these solutions on a cell (dep. of chemistry and normal physiology);

8) define the terms "maximum" and "minimum" resistance of erythrocytes, to specify normal borders of fluctuations of these sizes (dep. normal physiology);

9) explain, what properties of erythrocytes and plasma the size of osmotic resistance depends on (dep. of normal physiology);

10) perform and consider the determination reaction of osmotic resistance of erythrocytes (dep. of normal physiology).

QUESTIONS FOR THE LESSON

1. Hemostasis. Structurally functional components enabling the realization of mechanisms of a hemostasis.
2. Disorders of vascular platelet hemostasis. Causes, pathogenesis. Clinical manifestations, their pathogenesis.
3. Main mechanisms and pathological manifestations of vascular platelet hemostasis (primary hemostasis).
4. Main mechanisms and pathological manifestations of a plasma hemostasis (secondary hemostasis).
5. Groups of hemorrhagic diseases. Criteria of diagnostics of mechanisms of violation of a hemostasis.
6. Types of bleeding, their main manifestations.
7. Coagulopathy due to the excess of anticoagulants and acute stimulation of a fibrinolisys.
8. Hereditary coagulopathy. Pathogenesis, manifestations. Hemophilia. Clinical and laboratory criteria.
9. Thrombocytopenia. Etiology, pathogenesis.
10. Clinical and laboratory criteria idiopathic trombocytepenic purple.
11. Thrombocytopathy. Mechanism of violations of adhesion, aggregation of platelets, releases of platelets granules.
12. Vazopathy: types, Causes, development mechanisms, pathogenesis of the main clinical manifestations.
13. Hyper coagulation. Thtombocytic syndrome (trombophylia).
14. Syndrome of a disseminated intravascular coagulation (DIC-syndrome).
15. Osmotic and oncotic pressure of blood. Causes of disorders.
16. Osmotic resistance of erythrocytes. Causes of disorders.
17. Speed of subsidence of erythrocytes. Causes of disorders.
18. Disorders of proteinaceous composition of blood, their causes.

EXPERIMENTAL PART OF THE LESSON

Experiment 1. Determination of the osmotic resistance of erythrocytes in experimental haemolitic anemia.

The object of the experiment. Rabbits.

Apparatus and reactives. Sets of hypotonic solutions of table salt with different concentrations (from 0,60–0,32 %), 1 ml pipettes, micropipettes (capillary tubes), injection needles, centrifuge.

Procedure. Take two rabbits, in one of them haemolytic phenylhydrase anemiawas caused experimentally. With the help of a pipette, transfer different concentrations of 1 ml. solutions of table salt. Carry out the transfer, beginning with lower concentrations and ending

with the highest. Then add 0,02 ml. of blood taken from the marginal vein of the ear into the test-tubes. Addition of the blood should begin from the highest concentration to the lowest. The capillary for taking blood should be rinsed twice with the same solution to ensure complete removal of blood. In half an hour all the test-tubes should be centrifuged at a speed of 3000 RPM/min for 5 minutes. Estimate the degree of haemolysis. Note the maximum (complete haemolysis) and the minimum (traces of haemolysis) osmotic resistance of erythrocytes in the blood of the control rabbit and experimental rabbit.

RESULTS: _____

_____

_____

Experiment 2. Determining the Erythrocyte Sedimentation Rate (ESR) in experimental haemolytic anemia.

The object of the experiment. Rabbits.

Apparatus and reactives. Panchenkov's apparatus, porcelain (china) crucibles, injection needles, 5 %

Procedure. Rinse the capillary tube from Panchenkov's apparatus with 5 % solution of sodium citrate. Then fill the tube with the same solution to the point "P" (50 mm) and blow into the crucible. From the marginal ear vein take blood twice till point "K" (100 mm), blow into the crucible and mix throughly. By doing this, the blood becomes stabilized. Fill up the capillary tube with the stabilized blood till point "O" and place it strictly upright in Panchenkov's apparatus. In an hour's time count in ml the height of the formed column of plasma. Compare the ESR of the anemic and control rabbit.

RESULTS: _____

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_____

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

HEMOSTASIS

OVERVIEW OF HEMOSTASIS

Normal hemostasis is dependent upon the complex interaction of plasma coagulation and fibrinolytic proteins, platelets, and the blood vasculature. Hemostasis can be divided into three categories, which makes this complex process easier to understand. In addition, each of these categories usually produce different clinical signs, which can aid in narrowing down a differential diagnostic list in a bleeding animal. For example, a defect in primary hemostasis should be considered first in a dog presenting with epistaxis (as shown in the image on the right), whereas a defect in secondary hemostasis is likely in a dog with hemarthrosis. However, it must be realized that all three processes occur simultaneously and not sequentially in vivo.

The 3 categories are:

1. **Primary hemostasis.** This is defined as the formation of the platelet plug.

2. **Secondary hemostasis.** This is defined as the formation of fibrin through the coagulation cascade.

3. Tertiary hemostasis. This is defined as the formation of plasmin for the clot breakdown.

Hemostasis, the arrest of bleeding from an injured blood vessel, requires the combined activity of vascular, platelet, and plasma factors. Regulatory mechanisms counterbalance the tendency of clots to form. Hemostatic abnormalities can lead to excessive bleeding or thrombosis.

Vascular Factors. Vascular factors reduce blood loss from trauma through local vasoconstriction (an immediate reaction to injury) and compression of injured vessels by extravasation of blood into surrounding tissues. Vessel wall injury triggers the attachment and activation of platelets and production of fibrin; platelets and fibrin combine to form a clot.

Platelet Factors. Various mechanisms, including endothelial cell nitric oxide and prostacyclin, promote blood fluidity by preventing platelet stasis and dilating intact blood vessels. These

mediators are no longer produced when the vascular endothelium is disrupted. Under these conditions, platelets adhere to the damaged intima and form aggregates. Initial platelet adhesion is to von Willebrand's factor (VWF), previously secreted by endothelial cells into the subendothelium. VWF binds to receptors on the platelet surface membrane (glycoprotein Ib/IX).

Platelets anchored to the vessel wall undergo activation. During activation, platelets release mediators from storage granules, including adenosine diphosphate (ADP). Other biochemical changes resulting from activation include hydrolysis of membrane phospholipids, inhibition of adenylate cyclase, mobilization of intracellular Ca, and phosphorylation of intracellular proteins.

Arachidonic acid is converted to thromboxane A_2; this reaction requires cyclooxygenase and is inhibited irreversibly by aspirin and reversibly by many NSAIDs. ADP, thromboxane A_2, and other mediators induce activation and aggregation of additional platelets on the injured endothelium. Another receptor is assembled on the platelet surface membrane from glycoproteins IIb and IIIa. Fibrinogen binds to the glycoprotein IIb/IIIa complexes of adjacent platelets, connecting them into aggregates.

Platelets provide surfaces for the assembly and activation of coagulation complexes and the generation of thrombin. Thrombin converts fibrinogen to fibrin. Fibrin strands bind aggregated platelets to help secure the platelet-fibrin hemostatic plug.

Plasma Factors. Plasma coagulation factors interact to produce thrombin, which converts fibrinogen to fibrin. Radiating from and anchoring the hemostatic plug, fibrin strengthens the clot.

In the intrinsic pathway, factor XII, high molecular weight kininogen, prekallikrein, and activated factor XI (factor XIa) interact to produce factor IXa from factor IX.

Factor IXa then combines with factor VIIIa and procoagulant phospholipid (present on the surface of activated platelets and tissue cells) to form a complex that activates factor X. In the extrinsic pathway, factor VIIa and tissue factor directly activate factor X (the factor VIIa/tissue factor complex also activates factor IX.

Activation of the intrinsic or extrinsic pathway activates the common pathway, resulting in formation of the fibrin clot. Three steps are involved in common pathway activation:

1. A prothrombin activator is produced on the surface of activated platelets and tissue cells. The activator is a complex of an enzyme, factor Xa, and 2 cofactors, factor Va and procoagulant phospholipid.

2. The prothrombin activator cleaves prothrombin into thrombin and another fragment.

3. Thrombin induces the generation of fibrin polymers from fibrinogen. Thrombin also activates factor XIII, an enzyme that catalyzes formation of stronger bonds between adjacent fibrin monomers, as well as factor VIII and factor XI.

Ca^{2+} ions are needed in most thrombin-generating reactions (Ca^{2+}-chelating agents [eg, citrate, ethylenediaminetetraacetic acid] are used in vitro as anticoagulants). Vitamin K–dependent clotting factors (factors II, VII, IX, and X) cannot bind normally to phospholipid surfaces through Ca^{2+} bridges and function in blood coagulation when the factors are synthesized in the absence of vitamin K.

Table 13

Components of Blood Coagulation Reactions

Factor Number or Name	Synonym	Purpose
Plasma factors		
I	Fibrinogen	A precursor of fibrin
II	Prothrombin	A precursor of thrombin, which converts fibrinogen to fibrin; activates factors V, VIII, XI, and XIII; and binds to thrombomodulin to activate protein C Is vitamin K–dependent
V	Proaccelerin	Is activated to factor Va, which is a cofactor for the enzyme factor Xa in the factor Xa/Va/phospholipid complex, which cleaves prothrombin to thrombin Is present in α granules in platelets Factor Va inactivated by activated protein C in complex with free protein S

Factor Number or Name	Synonym	Purpose
VII	Proconvertin	Binds to tissue factor and is then activated to form the enzymatic component of the factor VIIa/tissue factor complex, which activates factors IX and X Is vitamin K–dependent
VIII	Antihemophilic globulin	Is activated to factor VIIIa, which is a cofactor for the enzyme factor IXa in the factor IXa/VIIIa/phospholipid complex, which activates factor X Is a large cofactor protein (as is factor V) Circulates in plasma bound to von Willebrand's factor multimers As factor VIIIa, is inactivated by activated protein C in complex with free protein S (as is factor Va)
IX	Christmas factor	Is activated to factor IXa, which is the enzyme of the factor IXa/VIIIa/phospholipid complex, which activates factor X Is vitamin K–dependent
X	Stuart-Prower factor	Is activated to factor Xa, which is the enzyme of the factor Xa/Va/phospholipid complex, which cleaves prothrombin to thrombin Is vitamin K–dependent
XI	Plasma thromboplastin antecedent	Is activated to factor XIa, which activates factor IX in a reaction requiring Ca^{2+} ions
Prekallikrein	Fletcher factor	Participates in a reciprocal reaction in which it is activated to kallikrein by factor XIIa As kallikrein, catalyzes further activation of factor XII to factor XIIa Circulates as a biomolecular complex with high molecular weight kininogen
High molecular weight kiningen	Fitzgerald factor	Circulates as a bimolecular complex with prekallikrein
XII	Hageman factor	When activated to factor XIIa by surface contact, kallikrein, or other factors, activates prekallikrein and factor XI, triggering the intrinsic coagulation pathway in vitro
XIII	Fibrin stabilizing factor	When activated by thrombin, catalyzes formation of peptide bonds between adjacent fibrin monomers, thus strengthening and stabilizing the fibrin clot
Protein C	—	Is activated by thrombin bound to thrombomodulin; then proteolyzes and inhibits (in the presence of free protein S and phospholipid) the cofactor activity of factors VIIIa and Va Is vitamin K–dependent
Protein S	—	Circulates in plasma as free protein S and as protein S bound to C4b-binding protein of the complement system Functions in its free form as a cofactor for activated protein C Is vitamin K–dependent
Cell surface factors		
Tissue factor	Tissue thromboplastin	Is a lipoprotein that is constitutively present on the membrane of certain tissue cells, including perivascular fibroblasts, boundary epithelial cells (eg, epithelial cells of the skin, amnion, and GI and GU tracts), and glial cells of the nervous system May also develop in pathologic states on activated monocytes and macrophages and on activated vascular endothelium Is present on some tumor cells Binds factor VIIa, which initiates the extrinsic coagulation pathway
Procoagulant phospholipid	—	Acidic phospholipid (primarily phosphatidyl serine) present on the surface of activated platelets and other tissue cells Is a component of the factor IXa/VIIIa/phospholipid complex which activates factor X and of the factor Xa/Va/phospholipid complex which activates prothrombin Functions as the lipid moiety of tissue factor
Thrombomodulin	—	Is an endothelial cell surface binding site for thrombin, which, when bound to thrombomodulin, activates protein C

Although the coagulation pathways are helpful in understanding mechanisms and laboratory evaluation of coagulation disorders, in vivo coagulation is predominantly via the extrinsic pathway. People with hereditary deficiencies of factor XII, high molecular weight kininogen, or prekallikrein have no bleeding abnormality. People with hereditary factor XI deficiency have a mild to moderate bleeding disorder. In vivo, factor XI (an intrinsic pathway

factor) is activated when a small amount of thrombin is generated. Factor IX can be activated both by factor XIa and factor VIIa/tissue factor complexes.

In vivo, initiation of the extrinsic pathway occurs when injury to blood vessels brings blood into contact with tissue factor on membranes of cells within and around the vessel walls. This contact with tissue factor generates factor VIIa/tissue factor complexes that activate factor X and factor IX. Factor IXa, combined with its cofactor, factor VIIIa, on phospholipid membrane surfaces generates additional factor Xa. Factor X activation by both factor VIIa/tissue factor and factor IXa/VIIIa complexes is required for normal hemostasis. This requirement for factors VIII and IX explains why hemophilia type A (deficiency of factor VIII) or type B (deficiency of factor IX) results in bleeding despite an intact extrinsic coagulation pathway initiated by factor VIIa/tissue factor complexes.

Regulatory Mechanisms

Several inhibitory mechanisms prevent activated coagulation reactions from amplifying uncontrollably, causing extensive local thrombosis or disseminated intravascular coagulation. These mechanisms include

1. Inactivation of procoagulant enzymes
2. Fibrinolysis
3. Hepatic clearance of activated clotting factors

Inactivation of coagulation factors. Plasma protease inhibitors (antithrombin, tissue factor pathway inhibitor, α_2-macroglobulin, heparin cofactor II) inactivate coagulation enzymes. Antithrombin inhibits thrombin, factor Xa, factor XIa, and factor IXa. Heparin enhances antithrombin activity.

Two vitamin K–dependent proteins, protein C and free protein S, form a complex that inactivates factors VIIIa and Va by proteolysis. Thrombin, when bound to a receptor on endothelial cells (thrombomodulin), activates protein C. Activated protein C, in combination with free protein S and phospholipid cofactors, proteolyzes and inactivates factors VIIIa and Va.

Fibrinolysis. Fibrin deposition and lysis must be balanced to maintain temporarily and subsequently remove the hemostatic seal during repair of an injured vessel wall. The fibrinolytic system dissolves fibrin by means of plasmin, a proteolytic enzyme. Fibrinolysis is activated by plasminogen activators released from vascular endothelial cells. Plasminogen activators and plasminogen (from plasma) bind to fibrin, and plasminogen activators cleave plasminogen into plasmin. Plasmin then proteolyzes fibrin into soluble fibrin degradation products that are swept away in the circulation.

There are several plasminogen activators:

1. Tissue plasminogen activator (tPA), from endothelial cells, is a poor activator when free in solution but an efficient activator when bound to fibrin in proximity to plasminogen.

2. Urokinase exists in single-chain and double-chain forms with different functional properties. Single-chain urokinase cannot activate free plasminogen but, like tPA, can readily activate plasminogen bound to fibrin. A trace concentration of plasmin cleaves single-chain to double-chain urokinase, which activates plasminogen in solution as well as plasminogen bound to fibrin. Epithelial cells that line excretory passages (eg, renal tubules, mammary ducts) secrete urokinase, which is the physiologic activator of fibrinolysis in these channels.

3. Streptokinase, a bacterial product not normally found in the body, is another potent plasminogen activator.

Streptokinase, urokinase, and recombinant tPA (alteplase) have all been used therapeutically to induce fibrinolysis in patients with acute thrombotic disorders.

Regulation of fibrinolysis. Fibrinolysis is regulated by plasminogen activator inhibitors (PAIs) and plasmin inhibitors that slow fibrinolysis. PAI-1, the most important PAI, inactivates tPA and urokinase and is released from vascular endothelial cells and activated platelets. The primary plasmin inhibitor is α_2-antiplasmin, which quickly inactivates any free plasmin escaping

from clots. Some α_2-antiplasmin is also cross-linked to fibrin polymers by the action of factor XIIIa during clotting. This cross-linking may prevent excessive plasmin activity within clots.

tPA and urokinase are rapidly cleared by the liver, which is another mechanism of preventing excessive fibrinolysis.

Excessive bleeding

Unusual or excessive bleeding may be indicated by several different signs and symptoms. Patients may present with unexplained nosebleeds (epistaxis), excessive or prolonged menstrual blood flow (menorrhagia), or prolonged bleeding after minor cuts, tooth brushing or flossing, or trauma. Other patients may have unexplained skin lesions, including petechiae (small intradermal or mucosal hemorrhages), purpura (areas of mucosal or skin hemorrhage larger than petechiae), ecchymoses (bruises), or telangiectasias (dilated small vessels visible on skin or mucosa). Some critically ill patients may suddenly bleed from vascular punctures or skin lesions and have severe hemorrhage from these sites or from the GI or GU tract. In some patients, the first sign is a laboratory test abnormality suggesting the susceptibility to excessive bleeding that is found incidentally.

Etiology. Excessive bleeding can result from several mechanisms (*see Table 14*).

Table 14

Some Causes of Excessive Bleeding

Category	Examples
Platelet disorders	
Decreased number of platelets (quantitative disorder)	Inadequate production (eg, in leukemias, aplastic anemia, and some myelodysplastic syndromes). Splenic sequestration (eg, in cirrhosis with congestive splenomegaly) Increased platelet destruction or consumption (eg, in idiopathic thrombocytopenic purpura, DIC, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, sepsis, and HIV infection) Drug-induced destruction (eg, by heparin, quinidine, quinine, sulfonamides, sulfonylureas, rifampin, or gold salts)
Increased number of platelets (quanti-tative disorder)	Essential thrombocythemia (thrombosis may be more common than bleeding)
Inadequate platelet function (qualitative disorder)	Von Willebrand's disease (inadequate VWF-mediated platelet adhesion) Drug-induced dysfunction (eg, byaspirin or NSAIDs) Systemic disorders (uremia; occasionally, myeloproliferative or myelodysplastic syndromes, multiple myeloma)
Coagulation disorders	
Acquired	Vitamin K deficiency Liver disease Anticoagulation with warfarin or heparin DIC
Hereditary	Hemophilia A (factor VIII deficiency) Hemophilia B (factor IX deficiency)
Vascular disorders	
Acquired	Vitamin C deficiency Henoch-Schönlein purpura
Hereditary	Connective tissue disorders (eg, Ehlers-Danlos syndrome, osteogenesis imperfecta, Marfan syndrome) Hereditary hemorrhagic telangiectasia
DIC = disseminated intravascular coagulation; VWF = von Willebrand's factor	

Platelet disorders may involve an abnormal number of platelets (typically too few platelets, although an extremely elevated platelet count may be associated either with thrombosis or with excessive bleeding), defective platelet function, or both. Coagulation disorders may be acquired or hereditary.

Overall, the most common causes of excessive bleeding include:

1. **Severe thrombocytopenia**
2. **Excessive anticoagulation with warfarin or heparin**
3. **Liver disease (inadequate production of coagulation factors)**

Review of systems should specifically query about bleeding from sites other than those volunteered (e.g, patients complaining of easy bruising should be questioned about frequent nosebleeds, gum bleeding while tooth brushing, melena, hemoptysis, blood in stool or urine). Patients should be asked about symptoms of possible causes, including abdominal pain and diarrhea (GI illness); joint pain (connective tissue disorders); and amenorrhea and morning sickness (pregnancy).

Past medical history should seek known systemic conditions associated with defects in platelets or coagulation, particularly (severe infection, cancer, cirrhosis, HIV infection, pregnancy, SLE, or uremia, prior excessive or unusual, bleeding or transfusions, family history of excessive bleeding).

Drug history should be reviewed, particularly use of heparin, warfarin, aspirin, and NSAIDs. Patients also should be questioned about intake of drugs and foods (including herbal supplements) that decrease the metabolism of warfarin and thus increase its anticoagulant effect.

Physical examination. Vital signs and general appearance can indicate hypovolemia (tachycardia, hypotension, pallor, diaphoresis) or infection (fever, tachycardia, hypotension with sepsis).

The skin and mucous membranes (nose, mouth, vagina) are examined for petechiae, purpura, and telangiectasias. GI bleeding can often be identified by digital rectal examination. Signs of bleeding in deeper tissues may include tenderness during movement and local swelling, muscle hematomas, and, for intracranial bleeding, confusion, stiff neck, focal neurologic abnormalities, or a combination of these findings.

Characteristic findings of alcohol abuse or liver disease are ascites, splenomegaly (secondary to portal hypertension), and jaundice.

Red flags: The following findings are of particular concern:

1. **Signs of hypovolemia or hemorrhagic shock**
2. **Pregnancy or recent delivery**
3. **Signs of infection or sepsis**

Interpretation of findings: Bleeding in a patient taking warfarin is especially likely if there has been a recent increase in dose or addition of a drug or food that may interfere with warfarin inactivation. Telangiectasias on the face, lips, oral or nasal mucosa, and tips of the fingers and toes in a patient with a positive family history of excessive bleeding is likely hereditary hemorrhagic telangiectasia.

Bleeding from superficial sites, including skin and mucous membranes, suggests a quantitative or qualitative defect in platelets or a defect in blood vessels (eg, amyloidosis).

Bleeding into deep tissues (eg, hemarthroses, muscle hematomas, retroperitoneal hemorrhage) suggests a defect in coagulation (coagulopathy).

A family history of excessive bleeding suggests an inherited coagulopathy (eg, hemophilia), a qualitative platelet disorder, a type of von Willebrand's disease (VWD), or hereditary hemorrhagic telangiectasia. Absence of a known family history does not, however, exclude an inherited disorder of hemostasis.

Bleeding in a patient who is pregnant or has recently delivered, who is in shock, or who has a serious infection suggests disseminated intravascular coagulation (DIC).

Bloody diarrhea and thrombocytopenia in a child with fever and GI symptoms suggest the hemolytic-uremic syndrome (HUS), which is often associated with infection by Escherichia coli O157:H7.

In a child, a palpable, purpuric rash on the extensor surfaces of the extremities suggests Henoch-Schönlein purpura, particularly if accompanied by fever, polyarthralgia, or GI symptoms.

Patients with known alcohol abuse or liver disease may have coagulopathy, splenomegaly, or thrombocytopenia.

In patients with a history of IV drug abuse, HIV infection should be considered.

Testing. Most patients require laboratory evaluation (*see Table 15*). The initial tests are Screening tests evaluate the components of hemostasis, including the number of circulating platelets and the plasma coagulation pathways. The most common screening tests for bleeding disorders are the platelet count, PT, and PTT. If results are abnormal, a specific test can usually pinpoint the defect. Determination of the level of fibrin degradation products measures in vivo activation of fibrinolysis.

Table 15

Laboratory Tests of Hemostasis by Phase

Test	Purpose
Formation of initial platelet plugs	
Platelet count	Quantifies platelet number
Platelet aggregation	Evaluates adequacy of platelet responsiveness to physiologic stimuli that activate platelets (eg, collagen, ADP, arachidonic acid) Detects abnormal patterns in hereditary or acquired platelet functional disoders
VWF antigen	Measures total concentration of plasma VWF protein
VWF multimer composition	Evaluates distribution of VWF multimers in plasma (eg, large multimers are missing in type 2 variants of VWD)
Ristocetin agglutination	Screens for large multimers of VWF in plasma (often done as part of routine laboratory evaluation for VWD—see Thrombocytopenia and Platelet Dysfunction: Diagnosis)
Ristocetin cofactor activity	Quantifies large multimers of VWF in plasma (see Thrombocytopenia and Platelet Dysfunction: Diagnosis)
Formation of fibrin	
PT	Screens for the factors in extrinsic and common pathways (factors VII, X, and V; prothrombin; and fibrinogen)
PTT	Screens for the factors in intrinsic and common pathways (prekallikrein; high molecular weight kininogen; factors XII, XI, IX, VIII, X, and V; prothrombin; and fibrinogen)
Specific functional assays for coagulation factors	Determines activity of the specific coagulant factor tested as a percentage of normal
Thrombin time	Evaluates the last step of coagulation (thrombin cleavage of fibrinogen to fibrin) Is prolonged by heparin activation of antithrombin and in conditions resulting in qualitative fibrinogen abnormalities or hypofibrinogenemia
Reptilase time	If it is normal and thrombin time is prolonged, provides presumptive evidence that a plasma sample contains heparin (eg, residual heparin after extracorporeal bypass or in a sample drawn from an IV line kept open with heparin flushes) because reptilase time is not affected by heparin activation of antithrombin
Fibrinogen level	Quantifies plasma fibrinogen, which is increased in acute phase reactions and decreased in severe liver disease and severe DIC
Fibrinolysis	
Clot stability during 24-h incubation in saline and in 5M urea	Causes lysis of clots in saline if fibrinolytic activity is excessive or in 5M urea if factor XIII is deficient. Should be done in patients with defective wound healing or frequent miscarriages
Plasminogen activity	Quantifies plasma plasminogen, which is decreased in patients with congenital early-onset venous thromboembolism (rare)
α_2-Antiplasmin	Quantifies plasma level of this fibrinolysis inhibitor, which is reduced in patients with excessive bleeding due to increased fibrinolysis (rare)
Serum fibrinogen andfibrin degradion products	Screens for DIC, Increased levels when plasmin has acted on fibrinogen or fibrin in vivo (eg, in DIC). Superseded by plasma D-dimer assay
Plasma D-dimer	Is measured with a monoclonal antibody latex agglutination test or with an ELISA If high, indicates that thrombin has been generated in vivo with resultant deposition of fibrin, activation of the cross-linking enzyme factor XIII, and secondary fibrinolysis Has the practical advantage that it can be done on citrate-treated plasma and thus, unlike the test for serum fibrin degradation products, does not require blood clotting in a special tube to prepare serum free of residual fibrinogen

ADP = adenosine diphosphate; DIC = disseminated intravascular coagulation; ELISA =enzyme-linked immunosorbent assay; VWD = von Willebrand's disease; VWF = von Willebrand's factor.

Prothrombin time (PT) screens for abnormalities in the extrinsic and common pathways of coagulation (plasma factors VII, X, V, prothrombin, and fibrinogen). The PT is reported as the international normalized ratio (INR), which reflects the ratio of the patient's PT to the laboratory's control value; the INR controls for differences in reagents among different laboratories. Because commercial reagents and instrumentation vary widely, each laboratory determines its own normal range for PT and PTT; a typical normal range for the PT is between 10 and 13 sec. An INR > 1.5 or a PT ≥ 3 sec longer than a laboratory's normal control value is usually abnormal and requires further evaluation. The INR is valuable in screening for abnormal coagulation in various acquired conditions (eg, vitamin K deficiency, liver disease, DIC). It is also used to monitor therapy with the oral vitamin K antagonist, warfarin.

Partial thromboplastin time (PTT) screens plasma for abnormalities in factors of the intrinsic and common pathways (prekallikrein; high molecular weight kininogen; factors XII, XI, IX, VIII, X, and V; prothrombin; fibrinogen). The PTT tests for deficiencies of all clotting factors except factor VII (measured by the PT) and factor XIII. A typical normal range is 28 to 34 sec. A normal result indicates that at least 30 % of all coagulation factors in the pathway are present in the plasma. Heparin prolongs the PTT, and the PTT is often used to monitor heparin therapy. Inhibitors that prolong the PTT include an autoantibody against factor VIII (see Coagulation Disorders: Hemophilia and see also Coagulation Disorders: Coagulation Disorders Caused by Circulating Anticoagulants) and antibodies against protein-phospholipid complexes (lupus anticoagulant—see also Thrombotic Disorders and see Coagulation Disorders: Coagulation Disorders Caused by Circulating Anticoagulants).

Prolongation of PT or PTT may reflect – Factor deficiency, presence of an inhibitor of a component of the coagulation pathway

The PT and PTT do not become prolonged until one or more of the clotting factors tested are about 70 % deficient. For determining whether prolongation reflects a deficiency of one or more clotting factor or the presence of an inhibitor, the test is repeated after mixing the patient's plasma with normal plasma in a 1 : 1 ratio. Because this mixture provides about 50 % of normal levels of all coagulation factors, failure of the mixture to correct almost completely the prolongation suggests the presence of an inhibitor in patient plasma.

Normal results on initial tests exclude many bleeding disorders. The main exceptions are VWD and hereditary hemorrhagic telangiectasia. VWD is a common entity in which the associated deficiency of factor VIII is frequently insufficient to prolong the PTT. Patients who have normal initial test results, along with symptoms or signs of bleeding and a positive family history, should be tested for VWD by measuring plasma von Willebrand's factor (VWF) antigen, ristocetin cofactor activity (an indirect test for large VWF multimers), VWF multimer pattern, and factor VIII levels.

If **thrombocytopenia** is present, the peripheral blood smear often suggests the cause (*see Table 15*). If the smear is normal, patients should be tested for HIV. If the result of the HIV test is negative and the patient is not pregnant and has not taken a drug known to cause platelet destruction, then idiopathic thrombocytopenic purpura is likely. If there are signs of hemolysis (fragmented RBCs on smear, decreasing Hb level), thrombotic thrombocytopenic purpura (TTP) or HUS is suspected, although sometimes other hemolytic disorders can cause these findings. HUS occurs in children with hemorrhagic colitis. The Coombs' test is negative in TTP and HUS. If the CBC and peripheral blood smear demonstrate other cytopenias or abnormal WBCs, a hematologic abnormality affecting multiple cell types is suspected, and a bone marrow aspiration or biopsy is necessary for diagnosis.

Prolonged PTT with normal platelets and PT suggests hemophilia A or B. Factor VIII and IX assays are indicated. Inhibitors that specifically prolong the PTT include an autoantibody against factor VIII and antibodies against protein-phospholipid complexes (lupus anticoagulant). Clinicians suspect one of these inhibitors when a prolonged PTT does not correct after 1 : 1 mixing with normal plasma.

Prolonged PT with normal platelets and PTT suggests factor VII deficiency. Congenital factor VII deficiency is rare; however, the short half-life of factor VII in plasma causes factor VII to decrease to low levels more rapidly than other vitamin K–dependent coagulation factors (eg, in patients given warfarin anticoagulation or in patients with incipient liver disease).

Prolonged PT and PTT with thrombocytopenia suggest DIC, especially in association with obstetric complications, sepsis, cancer, or shock. Confirmation is by finding elevated levels of D-dimers (or fibrin degradation products) and decreasing plasma fibrinogen levels on serial testing. Prolonged PT or PTT with normal platelet count occurs with liver disease or vitamin K deficiency or during anticoagulation with warfarin or unfractionated heparin. Liver disease is suspected based on history and is confirmed by finding elevation of serum aminotransferases and bilirubin; hepatitis testing is recommended.

Imaging tests are often required to detect occult bleeding in patients with bleeding disorders. For example, head CT should be done in patients with severe headaches, head injuries, or impairment of consciousness. Abdominal CT is needed in patients with abdominal pain or other findings compatible with intraperitoneal or retroperitoneal hemorrhage.

THROMBOTIC DISORDERS

In healthy people, homeostatic balance exists between procoagulant (clotting) forces and anticoagulant and fibrinolytic forces. Numerous genetic, acquired, and environmental factors can tip the balance in favor of coagulation, leading to the pathologic formation of thrombi in veins (deep venous thrombosis), arteries (MI, ischemic stroke), or cardiac chambers. Thrombi can obstruct blood flow at the site of formation or detach and embolize to block a distant blood vessel (pulmonary embolism, embolic stroke).

Etiology

Genetic defects that increase the propensity for venous thromboembolism include

1. Factor V Leiden mutation, which causes resistance to activated protein C (APC)
2. Prothrombin 20210 gene mutation
3. Deficiency of protein C, protein S, protein Z, or antithrombin

Acquired defects also predispose to venous and arterial thrombosis(*see Table 16*).

Other disorders and environmental factors can increase the risk of thrombosis, especially if a genetic abnormality is also present.

Table 16

Acquired Causes of Thromboembolism

Condition	Comments
Antiphospholipid antibodies	—
Atherosclerosis	Increases risk of arterial thrombi Higher risk in patients with preexisting stenosis When atherosclerotic plaques rupture, they release of tissue factor into the blood, activate coagulation, initiate local platelet adhesion and aggregation, and cause thrombosis
Cancer (promyelocytic leukemia; lung, breast, prostate, pancreas, stomach, and colon tumors)	May activate coagulation by secreting a factor X–activating protease, by expressing tissue factor on exposed membrane surfaces, or both
Heparin-induced thrombocytopenia	Associated with platelet aggregation and increased risk of thrombosis
Hyperhomocysteinemia	Possible cause. Due to folate, vitamin B_{12}, or vitamin B_6deficiency
Infection if severe (eg, sepsis)	Increases risk of venous thrombosis Increases expression of tissue factor by monocytes and macrophages
Oral contraceptives that contain estrogen	Low risk with low-dose regimens More frequent in patients who have a predisposing genetic abnormality for venous thromboembolism
Stasis	Due to surgery, orthopedic or paralytic immobilization, heart failure, pregnancy, or obesity
Tissue injury	Due to trauma or surgery

FACTOR V RESISTANCE TO ACTIVATED PROTEIN C (APC)

APC (in complex with protein S) degrades factors Va and VIIIa, thus inhibiting coagulation. Any of several mutations to factor V make it resistant to inactivation by APC, increasing the tendency for thrombosis. Factor V Leiden is the most common of these mutations. Homozygous mutations increase the risk of thrombosis more than do heterozygous mutations.

Factor V Leiden as a single gene defect in European populations is present in about 5 %, but it rarely occurs in native Asian or African populations. It is present in 20 to 60 % of patients with spontaneous venous thrombosis.

PROTEIN C DEFICIENCY

Protein C is a vitamin K–dependent protein, as are coagulation factors VII, IX, and X, prothrombin, and proteins S and Z. Because APC degrades factors Va and VIIIa, APC is a natural plasma anticoagulant. Decreased protein C from genetic or acquired causes promotes venous thrombosis. Heterozygous deficiency of plasma protein C has a prevalence of 0.2 to 0.5 %; about 75 % of people with this defect experience a venous thromboembolism (50 % by age 50). Homozygous or doubly heterozygous deficiency causes neonatal purpura fulminans, ie, severe neonatal disseminated intravascular coagulation (DIC). Acquired decreases occur in patients with liver disease or DIC, during cancer chemotherapy (including L-asparaginaseadministration), and during warfarin therapy. Diagnosis is based on antigenic and functional plasma assays.

Patients with symptomatic thrombosis require anticoagulation with heparin or low mol wtheparin, followed by warfarin; use of the vitamin K antagonist, warfarin, as initial therapy occasionally causes thrombotic skin infarction by lowering vitamin K–dependent protein C levels before a therapeutic decrease has occurred in most vitamin K–dependent clotting factors. Neonatal purpura fulminans is fatal without replacement of protein C and anticoagulation with heparin.

Protein S, a vitamin K–dependent protein, is a cofactor for APC-mediated cleavage of factors Va and VIIIa. Heterozygous deficiency of plasma protein S predisposes to venous thrombosis and is similar to protein C deficiency in genetic transmission, prevalence, laboratory testing, treatment, and precautions. Homozygous deficiency of protein S can cause neonatal purpura fulminans that is clinically indistinguishable from that caused by homozygous deficiency of protein C. Acquired deficiencies of protein S (and protein C) occur during DIC and warfarintherapy and after L-asparaginase administration. Diagnosis is based on antigenic assays of total or free plasma protein S. (Free protein S is the form unbound to C4 binding protein).

Protein Z, another vitamin K–dependent protein, functions as a cofactor to down-regulate coagulation by forming a complex with the plasma protein, Z-dependent protease inhibitor (ZPI). The complex inactivates factors Xa, XI, and IX on phospholipids surfaces. The consequence of either protein Z or ZPI deficiency in the pathophysiology of thrombosis and fetal loss is unresolved; however, either defect may make thrombosis more likely if an affected patient also has another congenital coagulation abnormality (factor V Leiden). Quantification of protein Z and ZPI is done in research laboratories by plasma electrophoresis and immunoblotting. It is not yet known whether anticoagulant therapy or prophylaxis is indicated in protein Z or ZPI deficiency.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME
(Anti-Cardiolipin Antibodies; Lupus Anticoagulant)

The antiphospholipid antibody syndrome consists of thrombosis and (in pregnancy) fetal demise associated with various autoimmune antibodies directed against one or more phospholipid-binding proteins (β_2-glycoprotein I, prothrombin, annexin). These proteins normally bind to phospholipid membrane constituents and protect them from excessive coagulation activation. The autoantibodies displace the protective proteins and, thus, produce procoagulant endothelial cell surfaces and cause arterial or venous thromboses. In vitro clotting tests may paradoxically be prolonged because the antiprotein/phospholipid antibodies interfere with coagulation factor assembly and activation on the phospholipid components added to plasma to initiate the tests. The lupus anticoagulant is an antiphospholipid autoantibody that binds to protein-phospholipid complexes. It was initially recognized in patients with SLE, but these patients now account for

a minority of patients with the autoantibody. The lupus anticoagulant is suspected if the PTT is prolonged and does not correct immediately upon 1 : 1 mixing with normal plasma but does return to normal upon the addition of an excessive quantity of phospholipids. Antiphospholipid antibodies in patient plasma are measured by immunoassays of IgG and IgM antibodies that bind to phospholipid-β_2-glycoprotein I complexes on microtiter plates.

Heparin, warfarin and aspirin have been used for prophylaxis and treatment.

HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia may predispose to arterial thrombosis and venous thromboembolism, possibly because of injury to vascular endothelial cells. Plasma homocysteine levels are elevated $\geq$ 10-fold in homozygous cystathionine β-synthase deficiency. Milder elevations occur in heterozygous deficiency and in other abnormalities of folate metabolism, including methyltetrahydrofolate dehydrogenase deficiency. However, by far the most common causes of hyperhomocysteinemia are acquired deficiencies of folate, vitamin B_{12}, or vitamin B_6.

The diagnosis is established by measuring plasma homocysteine levels.

Plasma homocysteine levels may be normalized by dietary supplementation with folic acid, vitamin B_{12}, or vitamin B_6 (pyridoxine) alone or in combination; however, it is not clear that this therapy reduces the risk of arterial or venous thrombosis.

COAGULATION DISORDERS

OVERVIEW OF COAGULATION DISORDERS

Abnormal bleeding can result from disorders of the coagulation system, of platelets, or of blood vessels. Disorders of coagulation can be acquired or hereditary. The major causes of acquired coagulation disorders are vitamin K deficiency, liver disease, disseminated intravascular coagulation, and development of circulating anticoagulants. Severe liver disease (cirrhosis, fulminant hepatitis, acute fatty liver of pregnancy) may disturb hemostasis by impairing clotting factor synthesis. Because all coagulation factors are made in the liver, both the PT and PTT are elevated in severe liver disorders. Occasionally, decompensated liver disease also causes excessive fibrinolysis and bleeding due to decreased hepatic synthesis of α_2-antiplasmin.

The most common hereditary disorder of hemostasis is von Willebrand The most common hereditary coagulation disorders are the hemophilias.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)
(Consumption Coagulopathy; Defibrination Syndrome)

Disseminated intravascular coagulation (DIC) involves abnormal, excessive generation of thrombin and fibrin in the circulating blood. During the process, increased platelet aggregation and coagulation factor consumption occur. DIC that evolves slowly (over weeks or months) causes primarily venous thrombotic and embolic manifestations; DIC that evolves rapidly (over hours or days) causes primarily bleeding. Severe, rapidly evolving DIC is diagnosed by demonstrating thrombocytopenia, an elevated PTT and PT, increased levels of plasma d-dimer (or serum fibrin degradation products), and a decreasing plasma fibrinogen level. Treatment includes correction of the cause and replacement of platelets, coagulation factors (in fresh frozen plasma), and fibrinogen (in cryoprecipitate) to control severe bleeding. Heparin is used as therapy (or prophylaxis) in patients with slowly evolving DIC who have (or are at risk of) venous thromboembolism.

Etiology

DIC usually results from exposure of tissue factor to blood, initiating the coagulation cascade. DIC occurs in the following clinical circumstances:

1. Complications of obstetrics (abruptio placentae, saline-induced therapeutic abortion, retained dead fetus or products of conception, amniotic fluid embolism): Placental tissue with tissue factor activity enters or is exposed to the maternal circulation.

2. Infection, particularly with gram-negative organisms: Gram-negative endotoxin causes generation or exposure of tissue factor activity in phagocytic, endothelial, and tissue cells.

3. Cancer, particularly mucin-secreting adenocarcinomas of the pancreas and prostate and acute promyelocytic leukemia: Tumor cells express or release tissue factor.

4. Shock due to any condition that causes ischemic tissue injury and release of tissue factor.

Less common causes of DIC include severe tissue damage from head trauma, burns, frostbite, or gunshot wounds; complications of prostate surgery that allow prostatic material with tissue factor activity (along with plasminogen activators) to enter the circulation; venomous snake bites in which enzymes enter the circulation, activate one or several coagulation factors, and either generate thrombin or directly convert fibrinogen to fibrin; profound intravascular hemolysis; and aortic aneurysms or cavernous hemangiomas (Kasabach-Merritt syndrome) associated with vessel wall damage and areas of blood stasis.

Pathophysiology

Slowly evolving DIC primarily causes venous thromboembolic manifestations (eg, deep venous thrombosis, pulmonary embolism), although occasionally cardiac valve vegetations occur; abnormal bleeding is uncommon.

Severe, rapidly evolving DIC, in contrast, causes thrombocytopenia and depletion of plasma clotting factors and fibrinogen, which cause bleeding. Bleeding into organs, along with microvascular thromboses, may cause dysfunction and failure in multiple organs. Delayed dissolution of fibrin polymers by fibrinolysis may result in the mechanical disruption of RBCs, producing schistocytes and mild intravascular hemolysis.

Symptoms and Signs In slowly evolving DIC, symptoms of venous thrombosis and pulmonary embolism may be present. In severe, rapidly evolving DIC, skin puncture sites (arterial punctures) bleed persistently, ecchymoses form at sites of parenteral injections, and serious GI bleeding may occur.

Hemophilia

Hemophilias are common hereditary bleeding disorders caused by deficiencies of either clotting factor VIII or IX. The extent of factor deficiency determines the probability and severity of bleeding. Bleeding into deep tissues or joints usually develops within hours of trauma. The diagnosis is suspected in a patient with an elevated PTT and normal PT and platelet count; it is confirmed by specific factor assays. Treatment includes replacement of the deficient factor if acute bleeding is suspected, confirmed, or likely to develop (eg, before surgery).

Hemophilia A (factor VIII deficiency), which affects about 80 % of patients with hemophilia, and hemophilia B (factor IX deficiency) have identical clinical manifestations, screening test abnormalities, and X-linked genetic transmission. Specific factor assays are required to distinguish the two.

Etiology. Hemophilia is an inherited disorder that results from mutations, deletions, or inversions affecting a factor VIII or factor IX gene. Because these genes are located on the X chromosome, hemophilia affects males almost exclusively. Daughters of men with hemophilia are obligate carriers, but sons are normal. Each son of a carrier has a 50 % chance of having hemophilia, and each daughter has a 50 % chance of being a carrier.

Pathophysiology. Normal hemostasis requires > 30 % of normal factor VIII and IX levels. Most patients with hemophilia have levels < 5 %. Carriers usually have levels of about 50 %; rarely, random inactivation of their normal X chromosome in early embryonic life results in a carrier having factor VIII or IX levels of < 30 %.

Most patients with hemophilia who were treated with plasma concentrates in the early 1980s were infected with HIV due to contaminated factor concentrates. Occasional patients developed immune thrombocytopenia secondary to HIV infection, which exacerbated bleeding.

COAGULATION DISORDERS CAUSED BY CIRCULATING ANTICOAGULANTS

Circulating anticoagulants are usually autoantibodies that neutralize specific clotting factors in vivo (autoantibody against factor VIII or factor V) or inhibit protein-bound phospholipid in vitro. Occasionally, the latter type of autoantibody causes bleeding in vivo by binding prothrombin.

Circulating anticoagulants should be suspected in patients with excessive bleeding combined with either a prolonged PTT or PT that does not correct when the test is repeated with a 1 : 1 mixture of normal plasma and the patient's plasma. Antiphospholipid antibodies typically cause thrombosis. However, in a subset of patients, the antibodies bind to prothrombin-phospholipid complexes and induce hypoprothrombinemia and bleeding.

FACTOR VIII ANTICOAGULANTS

Isoantibodies to factor VIII develop in about 15 to 35 % of patients with severe hemophilia A as a complication of repeated exposure to normal factor VIII molecules during replacement therapy. Factor VIII autoantibodies also arise occasionally in patients without hemophilia, eg, in postpartum women as a manifestation of an underlying systemic autoimmune disorder or of transiently disordered immune regulation, or in elderly patients without overt evidence of other underlying disorders. Patients with a factor VIII anticoagulant can develop life-threatening hemorrhage.

Plasma containing a factor VIII antibody has a prolonged PTT that does not correct when normal plasma or another source of factor VIII is added in a 1 : 1 mixture to the patient's plasma. Testing is done immediately after mixture and again after incubation.

Therapy with cyclophosphamide and corticosteroids may suppress autoantibody production in patients without hemophilia. In postpartum women, the autoantibodies may disappear spontaneously. Management of acute hemorrhage in patients with hemophilia who have factor VIII isoantibodies or autoantibodies is by recombinant factor VIIa.

UNCOMMON HEREDITARY COAGULATION DISORDERS

Most hereditary coagulation disorders other than hemophilia are rare autosomal recessive conditions that cause disease only in homozygous people (*Table 17*). Factor XI deficiency is uncommon in the general population but common in descendants of European Jews (gene frequency about 5 to 9 %). Bleeding typically occurs after significant injuries, including trauma or surgery, in people who are homozygotes or compound heterozygotes.

Table 17

Screening Laboratory Test Results in Inherited Defects in Blood Coagulation

Screening Test Results*	Defect	Comments
PTT long PT normal	Factor XII, high molecular weight kininogen, or prekallikrein	Laboratory test abnormality without clinical bleeing Must be distinguished from factor XI deficiency, in which posttraumatic and perioperative bleeding may occur, by specific assays
PTT long PT normal	Factor XI	Autosomal recessive, Increased frequency in Ashkenazi Jews, Posttraumatic and perioperative bleeding, For bleeding: Fresh frozen plasma 5–20 mL/kg/day to keep factor XI level > 30 %
PTT long PT normal	Factor VIII or IX	Factor VIII deficiency (hemophilia A) Factor IX deficiency (hemophilia B) X-linked transmission, Mild or severe bleeding in males, depending on factor VIII or IX level
PTT normal PT long	Factor VII	Autosomal recessive, Rare If deficiency is severe (< 2 %), serious bleeding If levels are > 5 %, mild or no bleeding Therapy of choice: Recombinant factor VIIa
PTT long PT long	Factor X, V, or prothrombin	Autosomal recessive, Rare, Mild to severe bleeding, Diagnosed by specific assays For bleeding episodes due to factor X or prothrombin deficiency: Fresh frozen plasma or prothrombin complex concentrate For treatment of factor V deficiency: Fresh frozen plasma with or without platelet concentrates (to supply platelet factor V)
In afibrinogenemia (fibrinogen < 10 mg/dL), no clotting in PTT or PT In hypofibrinogenemia (fibrinogen 70–100 mg/dL), PTT and PT often prolonged by several seconds and thrombin time long	Fibrinogen	Severe bleeding in afibrinogenemia (homozygous state) Posttraumatic and perioperative bleeding in hypofibrinogenemia (heterozygous state) For treatment: Cryoprecipitate (5–10 bags, with each containing about 250 mg fibrinogen)
PTT and PT long Thrombin time long	Dysfibrinogenemia	Various manifestations (no or only mild, posttraumatic and perioperative bleeding, tendency for thrombosis, wound dehiscence) Fibrinogen low in clotting assay but normal in immunologic assay

Screening Test Results*	Defect	Comments
PTT normal PT normal Thrombin time normal Clot lysis in 5M urea	Factor XIII	Autosomal recessive, Rare, Poor wound healing, Spontaneous abortions in women, Severe bleeding when levels are < 1 % of normal For treatment: Fresh frozen plasma (1–2 units q 4–6 wk is effective because half-life of factor XIII is about 10 days)
PTT and PT normal Clot lysis times in 5M urea or saline accelerated	α_2-Antiplasmin deficiency	Severe bleeding in homozygotes Posttraumatic and perioperative bleeding in heterozygotes Specific assay required for confirmation of diagnosis
*PT results are typically reported as INR		

Severe deficiency of α_2-antiplasmin (1 to 3 % of normal), the major physiologic inhibitor of plasmin, can also cause bleeding. Diagnosis is based on a specific α_2-antiplasmin assay. ε-Aminocaproic acid or tranexamic acid is used to control or prevent acute bleeding.

Heterozygous people with α_2-antiplasmin levels of 40 to 60 % of normal can occasionally experience excessive surgical bleeding if secondary fibrinolysis is extensive (in patients who have had open prostatectomy).

BLEEDING DUE TO ABNORMAL BLOOD VESSELS

OVERVIEW OF VASCULAR BLEEDING DISORDERS

Bleeding may result from abnormalities in platelets, coagulation factors, or blood vessels. Vascular bleeding disorders result from defects in blood vessels, typically causing petechiae, purpura, and bruising but, except for hereditary hemorrhagic telangiectasia, seldom leading to serious blood loss. Bleeding may result from deficiencies of vascular and perivascular collagen in Ehlers-Danlos syndrome and in other rare hereditary connective tissue disorders (pseudoxanthoma elasticum, osteogenesis imperfecta, Marfan syndrome). Hemorrhage may be a prominent feature of scurvy or of Henoch-Schцnlein purpura, a hypersensitivity vasculitis common during childhood. In vascular bleeding disorders, tests of hemostasis are usually normal. For most disorders, diagnosis is clinical; specific tests are available for some.

AUTOERYTHROCYTE SENSITIZATION (Gardner-Diamond Syndrome)

Autoerythrocyte sensitization is a rare disorder affecting women. It is characterized by local pain and burning preceding painful ecchymoses that occur primarily on the extremities.

Autoerythrocyte sensitization typically occurs in white women who are experiencing emotional stress or who have concomitant psychologic illness. Episodes of ecchymosis are painful and can occur spontaneously or after trauma or surgery. Bruising can occur on different sites of the body from where the trauma occurs. Tests of the coagulation system are normal.

In women with autoerythrocyte sensitization, intradermal injection of 0.1 mL of autologous RBCs or RBC stroma may result in pain, swelling, and induration at the injection site. This result suggests that escape of RBCs into the tissues is involved in the pathogenesis of the lesion. However, most patients also have associated severe psychoneurotic symptoms. In addition, psychogenic factors, such as self-induced purpura, seem related to the pathogenesis of the syndrome in some patients.

Diagnosis is based on examination of intradermal injection site of autologous RBCs and of a separate control injection site (without RBCs) 24 to 48 h after injection. Excoriation, which can complicate the test's interpretation, is prevented by making both sites difficult for the patient to reach.

Treatment is psychiatric intervention and therapy.

DYSPROTEINEMIAS CAUSING VASCULAR PURPURA

Conditions that cause an abnormal protein content in the blood, typically in the form of immunoglobulins, can affect vascular fragility and lead to purpura.

Amyloidosis causes amyloid deposition within vessels in the skin and subcutaneous tissues, which may increase vascular fragility, causing purpura. In some patients, coagulation factor X is adsorbed by amyloid and becomes deficient, but this deficiency is usually not the cause of bleeding. Periorbital purpura or a purpuric rash that develops in a nonthrombo-

cytopenic patient after gentle stroking of the skin suggests amyloidosis. Most patients have elevated serum levels of free light chains. The diagnosis is confirmed by tissue biopsy.

Cryoglobulinemia produces immunoglobulins that precipitate when plasma is cooled (i.e, cryoglobulins) while flowing through the skin and subcutaneous tissues of the extremities. Monoclonal immunoglobulins formed in Waldenstrцm macroglobulinemia or in multiple myeloma occasionally behave as cryoglobulins, as may mixed IgM-IgG immune complexes formed in some chronic infectious diseases, most commonly hepatitis C. Cryoglobulinemia can also lead to small-vessel vasculitis, which can cause purpura. Cryoglobulins can be detected by laboratory testing.

Hypergammaglobulinemic purpura is a vasculitic purpura that primarily affects women. Recurrent crops of small, palpable purpuric lesions develop on the lower legs. These lesions leave small residual brown spots. Many patients have manifestations of an underlying immunologic disorder (e.g, Sjцgren syndrome, SLE). The diagnostic finding is a polyclonal increase in IgG.

Hyperviscosity syndrome usually resulting from a markedly elevated plasma IgM concentration, may also result in purpura and other forms of abnormal bleeding (profuse epistaxis) in patients with Waldenstrцm macroglobulinemia. Marked elevations of other immunoglobulins (IgA and IgG3) can also be associated with hyperviscosity syndrome.

HEREDITARY HEMORRHAGIC TELANGIECTASIA (Rendu-Osler-Weber Syndrome)

Hereditary hemorrhagic telangiectasia is a hereditary disorder of vascular malformation transmitted as an autosomal dominant trait affecting men and women.

More than 80 of patients have mutations in the endoglin (ENG) gene, which encodes a receptor for transforming growth factor beta-1 (TGF-в1) and TGF-в3 or in the MADH4 gene, which encodes SMAD4, a protein active in the TGF-в signalling pathway.

PURPURA SIMPLEX (Easy Bruising)

Purpura simplex is increased bruising that results from vascular fragility.

Purpura simplex is extremely common. The cause and mechanism are unknown. Purpura simplex may represent a heterogeneous group of disorders or merely a variation of normal.

The disorder usually affects women. Bruises develop on the thighs, buttocks, and upper arms in people without known trauma. The history usually reveals no other abnormal bleeding, but easy bruising may be present in family members. Serious bleeding does not occur. The platelet count and tests of platelet function, blood coagulation, and fibrinolysis are normal.

No drug prevents the bruising; patients are often advised to avoid aspirin and aspirin-containing drugs, but there is no evidence that bruising is related to or worsened by their use. Patients should be reassured that the condition is not serious. All patients should be evaluated for the possibility of physical abuse.

SENILE PURPURA causes ecchymoses and results from increased vessel fragility due to connective tissue damage to the dermis caused by chronic sun exposure, aging, and drugs.

Senile purpura typically affects elderly patients as their dermal tissues atrophy and blood vessels become more fragile. Patients develop persistent dark purple ecchymoses, which are characteristically confined to the extensor surfaces of the hands and forearms. New lesions appear without known trauma and then resolve over several days, leaving a brownish discoloration caused by deposits of hemosiderin. This discoloration may clear over weeks to months or may be permanent. The skin and subcutaneous tissue of the involved area often appear thinned and atrophic. Drugs (corticosteroids, warfarin, aspirin, clopidogrel) may exacerbate the ecchymoses. No treatment hastens lesion resolution or is needed. Although cosmetically displeasing, the disorder has no health consequences and does not herald severe bleeding elsewhere.

THROMBOCYTOPENIA AND PLATELET DYSFUNCTION

OVERVIEW OF PLATELET DISORDERS

Platelets are cell fragments that function in the clotting system. Thrombopoietin, primarily produced in the liver in response to decreased numbers of bone marrow megakaryocytes and circulating platelets, stimulates the bone marrow to synthesize platelets from megakaryocytes. Platelets circulate for 7 to 10 days. About one third are always transiently sequestered in the spleen. The platelet count is normally 140,000 to 440,000/μL. However, the count can vary slightly according to menstrual cycle phase, decrease during near-term pregnancy (gestational thrombocytopenia), and increase in response to inflammatory cytokines (secondary, or reactive, thrombocytosis). Platelets are eventually destroyed by apoptosis, a process independent of the spleen.

Platelet disorder include

Any of these conditions, even those in which platelets are increased, may cause defective formation of hemostatic plugs and bleeding.

The risk of bleeding is inversely proportional to the platelet count and platelet function (*see Table 18)*. When platelet function is reduced (eg, as a result of uremia or aspirin use), the risk of bleeding increases.

Table 18

Platelet Count and Bleeding Risk

Platelet Count	Risk of Bleeding*
≥ 50,000/μL	Minimal
20,000–50,000/μL	Minor bleeding after trauma
< 20,000/μL	Spontaneous bleeding
< 5000/μL	Severe, possibly life-threatening spontaneous bleeding
*Reduced platelet function (eg, due to uremia o aspirin use) adds to risk of bleeding in each platelet count range	

Etiology

Thrombocythemia and thrombocytosis. Essential thrombocythemia is a myeloproliferative disorder involving overproduction of platelets because of a clonal abnormality of a hematopoietic stem cell. A markedly elevated platelet count typically leads to thrombosis, but some patients develop bleeding.

Reactive thrombocytosis is platelet overproduction in response to another disorder. There are many causes, including acute infection, chronic inflammatory disorders (RA, inflammatory bowel disease, TB, sarcoidosis), iron deficiency, and certain cancers.

Thrombocytopenia. Causes of thrombocytopenia can be classified by mechanism (*see Table 19*) and include failed platelet production, increased splenic sequestration of platelets with normal platelet survival, increased platelet destruction or consumption (both immunologic and nonimmunologic causes), dilution of platelets, and a combination of these mechanisms.

Increased splenic sequestration is suggested by splenomegaly.

Table 19

Classification of Thrombocytopenia

Cause	Conditions
Diminished or absent megakaryocytes in bone marrow	Aplastic anemia. Leukemia. Myelosuppressive drugs (eg, hydroxyurea, interferon alfa-2b, chemotherapy drugs). Paroxysmal nocturnal hemoglobinuria (some patients)
Diminished platelet production despite the presence of megakaryocytes in bone marrow	Alcohol-induced thrombocytopenia. HIV-associated thrombocytopenia. Myelodysplastic syndromes (some). Vitamin B_{12} or folate (folic acid) deficiency
Platelet sequestration in enlarged spleen	Cirrhosis with congestive splenomegaly Gaucher disease. Myelofibrosis with myeloid metaplasia

Cause	Conditions
Immunologic destruction	Connective tissue disorders Drug-induced thrombocytopenia HIV-associated thrombocytopenia Immune thrombocytopenia Lymphoproliferative disorders Neonatal alloimmune thrombocytopenia Posttransfusion purpura Pregnancy (gestational thrombocytopenia)
Nonimmunologic destruction	Disseminated intravascular coagulation. Sepsis. Certain systemic infections (eg, hepatitis, Epstein-Barr virus, cytomegalovirus, or dengue virus infection). Thrombocytopenia in acute respiratory distress syndrome. Thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome
Dilution	Massive red blood cell replacement or exchange transfusion (loss of platelet viability in stored blood)

A large number of drugs may cause thrombocytopenia (*see Thrombocytopenia and Platelet Dysfunction: Drug-induced immunologic destruction*), typically by triggering immunologic destruction. Overall, the most common specific causes of thrombocytopenia include: gestational thrombocytopenia, drug-induced thrombocytopenia due to immune-mediated platelet destruction (commonlyquinine, trimethoprim/sulfamethoxazole), drug-induced thrombocytopenia due to dose-dependent bone marrow suppression (by chemotherapeutic agents), thrombocytopenia accompanying systemic infection, immune thrombocytopenia (ITP, formerly called immune thrombocytopenic purpura)

Platelet dysfunction. Platelet dysfunction may stem from an intrinsic platelet defect or from an extrinsic factor that alters the function of normal platelets. Dysfunction may be hereditary or acquired. Hereditary disorders of platelet function consist of von Willebrand disease, the most common hereditary hemorrhagic disease, and hereditary intrinsic platelet, which are much less common. Acquired disorders of platelet are commonly due to diseases as well as toaspirinand other drugs.

Thrombocytopenia. In patients with thrombocytopenia, the peripheral smear may suggest the cause (*see Table 20*). If the smear shows abnormalities other than thrombocytopenia, such as nucleated RBCs or abnormal or immature WBCs, bone marrow aspiration is indicated.

Table 20

Peripheral Blood Findings in Thrombocytopenic Disorders

Findings	Conditions
Normal RBCs and WBCs	Drug-induced thrombocytopenia
Gestational thrombocytopenia, HIV-related thrombocytopenia	Immune thrombocytopenia, Posttransfusion purpura
RBC fragmentation (schistocytes)	Metastatic cancer, DIC
Preeclampsia with DIC	Thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome
WBC abnormalities	Hypersegmented polymorphonuclear leukocytes in megaloblastic anemias
Immature cells or increased mature lymphocytes in leukemia	Markedly diminished granulocytes in aplastic anemia
Frequent giant platelets (approaching the size of RBCs)	Bernard-Soulier syndrome
Disorders related to the myosin, heavy chain 9, non-muscle gene (MYH9)	Other congenital thrombocytopenias
RBC abnormalities, nucleated RBCs, and immature granulocytes	Myelodysplasia
DIC = disseminated intravascular coagulation.	

Bone marrow aspiration reveals the number and appearance of megakaryocytes and is the definitive test for many disorders causing bone marrow failure. However, normal number and appearance of megakaryocytes does not always indicate normal platelet production. For example, in patients with immune thrombocytopenia, platelet production may be decreased despite the normal appearance and increased number of megakaryocytes. If the bone marrow is

normal but the spleen is enlarged, increased splenic sequestration is the likely cause of thrombocytopenia; if the bone marrow is normal and the spleen is not enlarged, excess platelet destruction is the likely cause. Measurement of antiplatelet antibodies is not clinically useful. HIV testing is done in patients at risk of HIV infection.

Suspected platelet dysfunction. In patients with platelet dysfunction, a drug cause is suspected if symptoms began only after patients started taking a potentially causative drug. A hereditary cause is suspected if there is a lifelong history of easy bruising, bleeding after tooth extractions or surgery, or heavy menstruation. In the case of a suspected hereditary cause, von Willebrand antigen and factor activity studies are done. Platelet dysfunction caused by systemic disorders is typically mild and of minor clinical importance. In these patients, the causative systemic disorder is the clinical concern, and hematologic tests are unnecessary.

ACQUIRED PLATELET DYSFUNCTION

Acquired platelet dysfunction, which is common, may result from aspirin, other NSAIDs, or systemic disorders.

Acquired platelet dysfunction is suspected and diagnosed when an isolated prolongation of bleeding is observed and other possible diagnoses have been eliminated. Platelet aggregation studies are unnecessary.

Drugs. Aspirin, other NSAIDs, and inhibitors of the platelet P2Y12 ADP receptor (clopidogrel, prasugrel, ticagrelor) may induce platelet dysfunction.

Aspirin and NSAIDs prevent cyclooxygenase-mediated production of thromboxane A_2. This effect can last 5 to 7 days. Aspirin modestly increases bleeding in healthy people but may markedly increase bleeding in patients with underlying platelet dysfunction or a severe coagulation disturbance (patients receiving heparin, patients with severe hemophilia). Clopidogrel, prasugrel, and ticagrelor all can markedly reduce platelet function and increase bleeding.

Systemic disorders. Many disorders (myeloproliferative and myelodysplastic disorders, uremia, macroglobulinemia and multiple myeloma, cirrhosis, SLE) can impair platelet function.

Uremia prolongs bleeding via unknown mechanisms. If bleeding is observed clinically, bleeding may be reduced with vigorous dialysis, cryoprecipitate administration, or desmopressin infusion. If necessary, increasing the Hb concentration to > 10 g/dL by transfusion or by giving erythropoietin also reduces bleeding.

Cardiopulmonary bypass. Platelets may become dysfunctional, prolonging bleeding, as blood circulates through a pump oxygenator during cardiopulmonary bypass. The mechanism appears to be activation of fibrinolysis on the platelet surface with resultant loss of the glycoprotein Ib/IX binding site for von Willebrand factor. Regardless of platelet count, patients who bleed excessively after cardiopulmonary bypass are often transfused with platelets. Giving aprotinin (a protease inhibitor that neutralizes protease activity) during bypass may preserve platelet function and reduce the need for transfusion.

HEREDITARY INTRINSIC PLATELET DISORDERS

Hereditary intrinsic platelet disorders are rare and cause lifelong bleeding tendencies. Diagnosis is confirmed by platelet aggregation tests. Platelet transfusion is usually necessary to control serious bleeding.

Normal hemostasis requires platelet adhesion and activation.

Adhesion (i.e, of platelets to exposed vascular subendothelium) requires von Willebrand factor (VWF) and the platelet glycoprotein Ib/IX complex.

Activation promotes platelet aggregation and fibrinogen binding and requires the platelet glycoprotein IIb/IIIa complex. Activation involves release of adenosine diphosphate (ADP) from platelet storage granules and conversion of arachidonic acid to thromboxane A_2 via a cyclooxygenase-mediated reaction. ADP and thromboxane A_2 then promote changes in the platelet IIb/IIIa complex, which in turn increase fibrinogen binding, thereby allowing platelets to aggregate.

Hereditary intrinsic platelet disorders can involve defects in any of these substrates and steps. These disorders are suspected in patients with lifelong bleeding disorders who have normal platelet counts and coagulation study results. Diagnosis usually is based on platelet aggregation tests; however, platelet aggregation tests are not quantitative, and interpretation of results is often inconclusive (*see Table 21*).

Table 21

Aggregation Tests in Hereditary Disorders of Platelet Function

Disorder	Collagen, Epinephrine, and Low-Dose ADP	High-Dose ADP	Ristocetin
Disorders of amplification of platelet activation	Impaired	Normal	Normal
Thrombasthenia	Absent	Absent	Normal or impaired
Disorders of platelet adhesion (eg, Bernard-Soulier syndrome, von Willebrand disease)	Normal	Normal	Impaired
ADP = adenosine diphosphate			

Disorders of adhesion. Bernard-Soulier syndrome is a rare autosomal recessive disorder. It impairs platelet adhesion via a defect in the glycoprotein Ib/IX complex. Bleeding may be severe. Platelets are unusually large. They do not aggregate with ristocetin but aggregate normally with ADP, collagen, and epinephrine.

Large platelets associated with functional abnormalities also occur in the May-Hegglin anomaly, a thrombocytopenic disorder with abnormal WBCs, and in the Chédiak-Higashi sydrome. Platelet transfusion is necessary to control serious bleeding.

Von Willebrand disease is due to a deficiency or defect in the von Willebrand factor (VWF) that is needed to permit platelet adhesion. It is often treated with desmopressin or factor replacement with pasteurized intermediate-purity factor VIII concentrate.

Disorders of activation: Disorders of amplification of platelet activation are the most common hereditary intrinsic platelet disorders and produce mild bleeding. They may result from decreased ADP in the platelet granules (storage pool deficiency), from an inability to generate thromboxane A_2 from arachidonic acid, or from an inability of platelets to aggregate in response to thromboxane A_2. Platelet aggregation tests reveal impaired aggregation after exposure to collagen, epinephrine, and low levels of ADP and normal aggregation after exposure to high levels of ADP. The same pattern can result from use of NSAIDs or aspirin, the effect of which can persist for several days. Therefore, platelet aggregation tests should not be done in patients who have recently taken these drugs.

Thrombasthenia (Glanzmann disease) is a rare autosomal recessive disorder causing a defect in the platelet glycoprotein IIb/IIIa complex; platelets cannot aggregate. Patients may have severe mucosal bleeding (nosebleeds that stop only after nasal packing and transfusions of platelet concentrates). The diagnosis is confirmed by the finding that platelets fail to aggregate after exposure to epinephrine, collagen, or even high levels of ADP but do aggregate transiently after exposure to ristocetin. Platelet transfusion is necessary to control serious bleeding.

VON WILLEBRAND DISEASE

Von Willebrand disease (VWD) is a hereditary deficiency of von Willebrand factor (VWF), which causes platelet dysfunction. Bleeding tendency is usually mild. Screening tests show a normal platelet count and, possibly, a slightly prolonged PTT. Diagnosis is based on low levels of VWF antigen and abnormal ristocetin cofactor activity. Treatment involves control of bleeding with replacement therapy (pasteurized intermediate-purity factor VIII concentrate) or desmopressin.

VWF is synthesized and secreted by vascular endothelium to form part of the perivascular matrix. VWF promotes the platelet adhesion phase of hemostasis by binding with a receptor on the platelet surface membrane (glycoprotein Ib/IX), thus connecting the platelets to the vessel wall. VWF is also required to maintain normal plasma factor VIII levels. Levels of VWF can temporarily increase in response to stress, exercise, pregnancy, inflammation, or infection.

VWD is classified into 3 types:

Type 1. A quantitative deficiency of VWF, which is the most common form and is an autosomal dominant disorder.

Type 2. A qualitative impairment in synthesis of VWF that can result from various genetic abnormalities and is an autosomal dominant disorder.

Type 3. A rare autosomal recessive disorder in which homozygotes have no detectable VWF.

Although VWD, like hemophilia A, is a hereditary disorder that may, when severe, cause factor VIII deficiency, that deficiency is usually only moderate.

IMMUNE THROMBOCYTOPENIA (ITP)

Immune thrombocytopenia (ITP) is a bleeding disorder caused by thrombocytopenia not associated with a systemic disease. Typically, it is chronic in adults but is usually acute and self-limited in children. Spleen size is normal. Diagnosis requires that other disorders be excluded through selective tests. Treatment includes corticosteroids, splenectomy, immunosuppressants, and thrombopoietin agonist drugs. For life-threatening bleeding, platelet transfusions, IV corticosteroids, IV anti-D immune globulin, and IV immunoglobulin are required.

ITP usually results from development of an autoantibody directed against a structural platelet antigen. In childhood ITP, the autoantibody may be triggered by viral antigens. The trigger in adults is unknown.

THROMBOCYTOPENIA DUE TO SPLENIC SEQUESTRATION

Increased splenic platelet sequestration can occur in various disorders that cause splenomegaly. Although the thrombocytopenia in advanced cirrhosis is mostly due to reduced thrombopoietin production by the liver (and consequent reduced platelet production), platelets are sequestered in other forms of congestive splenomegaly.

The platelet count usually is > 30,000/мL unless the disorder causing splenomegaly also impairs platelet production (in myelofibrosis with myeloid metaplasia). Sequestered platelets are released from the spleen by epinephrine and thus may be available at a time of stress. Therefore, thrombocytopenia caused only by splenic sequestration rarely causes bleeding. In patients with normal hepatic function, splenectomy corrects the thrombocytopenia; but splenectomy is not indicated unless severe thrombocytopenia due to simultaneous marrow failure is present.

THROMBOCYTOPENIA: OTHER CAUSES

Platelet destruction can develop because of immunologic causes (viral infection, drugs, connective tissue or lymphoproliferative disorders, blood transfusions) or nonimmunologic causes (sepsis, acute respiratory distress syndrome). Manifestations are petechiae, purpura, and mucosal bleeding. Laboratory findings depend on the cause. The history may be the only suggestion of the diagnosis. Treatment is correction of the underlying disorder.

Acute respiratory distress syndrome. Patients with acute respiratory distress syndrome may develop nonimmunologic thrombocytopenia, possibly secondary to deposition of platelets in the pulmonary capillary bed.

Blood transfusions. Posttransfusion purpura causes immunologic platelet destruction indistinguishable from immune thrombocytopenia (ITP), except for a history of a blood transfusion within the preceding 7 to 10 days. The patient, usually a woman, lacks a platelet antigen (PLA-1) present in most people. Transfusion with PLA-1–positive platelets stimulates formation of anti–PLA-1 antibodies, which (by an unknown mechanism) can react with the patient's PLA-1–negative platelets. Severe thrombocytopenia results, taking 2 to 6 weeks to subside. Treatment with IV immunoglobulin (IVIG) is usually successful.

Connective tissue and lymphoproliferative disorders. Connective tissue (e.g, SLE) or lymphoproliferative disorders can cause immunologic thrombocytopenia. Corticosteroids and the usual treatments for ITP are effective; treating the underlying disorder does not always lengthen remission.

Drug-induced immunologic destruction. Commonly used drugs that occasionally induce thrombocytopenia include, quinine, trimethoprim/sulfamethoxazole, glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), hydrochlorothiazide, garbamazepine, acetaminophen, chlorpropamide, ranitidine, rifampin, vancomycin

Drug-induced thrombocytopenia occurs typically when a drug bound to the platelet creates a new an "foreign" antigen, causing an immune reaction. This disorder is indistinguishable from ITP except for the history of drug ingestion. When the drug is stopped, the platelet count typically begins to increase within 1 to 2 days and recovers to normal within 7 days.

Heparin-induced thrombocytopenia (HIT) occurs in up to 1 % of patients receiving unfractionated heparin. HIT may occur even when very-low-dose heparin (used in flushes to keep IV or arterial lines open) is used. The mechanism is usually immunologic. Bleeding rarely occurs, but more commonly platelets clump excessively, causing vessel obstruction, leading to paradoxical arterial and venous thromboses, which may be life threatening (thromboembolic occlusion of limb arteries, stroke, acute MI). Heparinshould be stopped in any patient who becomes thrombocytopenic or whose platelet count decreases by more than 50 %. Stopping heparin is mandatory, and tests are done to detect antibodies to heparin bound to platelet factor 4. Anticoagulation with nonheparin anticoagulants (argatroban, bivalirudin, fondaparinux) is necessary at least until platelet recovery. Low molecular weight heparin (LMWH) is less immunogenic than unfractionated heparin but cannot be used to anticoagulate patients with HIT because most HIT antibodies cross-react with LMWH.

Infections. HIV infection may cause immunologic thrombocytopenia indistinguishable from ITP except for the association with HIV. The platelet count may increase when glucocorticoids are given. However, glucocorticoids are often withheld unless the platelet count falls to < 20,000/mL, because these drugs may further depress immune function. The platelet count also usually increases after treatment with antiviral drugs.

Hepatitis C infection is commonly associated with thrombocytopenia. Active infection can create a thrombocytopenia that is indistinguishable from ITP with platelets < 10,000/μL. Lower degrees of thrombocytopenia (platelet count 40.000 to 70.000/μL) may be due to liver damage that reduced production of thrombopoietin, the hematopoietic growth factor that regulates megakaryocyte growth and platelet production. Hepatitis-induced thrombocytopenia responds to the same treatments as does ITP.

Other infections such as systemic viral infections (Epstein-Barr virus, cytomegalovirus), rickettsial infections (Rocky Mountain spotted fever), and bacterial sepsis are typically associated with thrombocytopenia.

Pregnancy. Mild thrombocytopenia, typically asymptomatic, occurs late in gestation in about 5 % of normal pregnancies (gestational thrombocytopenia); it is usually mild (platelet counts < 70,000/mL are rare), requires no treatment, and resolves after delivery. However, severe thrombocytopenia may develop in pregnant women with preeclampsia and the HELLP syndrome (hemolysis, elevated liver function tests, and low platelets—see Abnormalities of Pregnancy: Preeclampsia and Eclampsia); such women typically require immediate delivery, and platelet transfusion is considered if platelet count is < 20.000/mL (or < 50.000/mL if delivery is to be cesarean).

Sepsis. Sepsis often causes nonimmunologic thrombocytopenia that parallels the severity of the infection. The thrombocytopenia has multiple causes: disseminated intravascular coagulation, formation of immune complexes that can associate with platelets, activation of complement, deposition of platelets on damaged endothelial surfaces, and platelet apoptosis

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AND HEMOLYTIC-UREMIC SYNDROME (HUS)

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) are acute, fulminant disorders characterized by thrombocytopenia and microangiopathic hemolytic anemia. Other manifestations may include alterations in level of consciousness and kidney failure. Diagnosis requires demonstrating characteristic laboratory test abnormalities, including

Coombs-negative hemolytic anemia. Treatment is plasma exchange and corticosteroids in adults and supportive care (sometimes including hemodialysis) in children.

Pathophysiology

TTP and HUS involve nonimmunologic platelet destruction. Loose strands of platelets and fibrin are deposited in multiple small vessels and damage passing platelets and RBCs, causing significant thrombocytopenia and anemia. Platelets are also consumed within multiple small thrombi. Multiple organs develop bland platelet-von Willebrand factor (VWF) thrombi (without the vessel wall granulocytic infiltration characteristic of vasculitis) localized primarily to arterio-capillary junctions, described as thrombotic microangiopathy. The brain, heart, and kidneys are particularly likely to be affected. TTP and HUS differ mainly in the relative degree of kidney failure.

Typically, disorders in adults are described as TTP and are less likely to involve kidney failure. HUS is used to describe the disorder in children, which typically involves kidney failure.

CHANGES IN THE PHYSICOCHEMICAL PROPERTIES OF THE BLOOD

The **specific gravity of the blood** (normally 1.050–1.060) depends mainly on the number of erythrocytes, amount of proteins and content of sodium chloride. It increases as a result of hemoconcentration, erythremia and increased content of proteins, and decreases in blood dilution (hydremia), anemia and qualitative starvation.

The **surface tension of the blood** is reduced in accumulation of the capillary-stimulating substances (bile acids, soaps and certain metabolites). It also decreases in eclampsia, uremia and asphyxia when the amount of such substances noticeably increases. Contrariwise, protein deficiency and hydremia increase the surface tension.

The **osmotic pressure of the blood** (normally 7.7–8.1 atm.) increases **(hyperosmia)** in dehydration, consumption a lot of sodium, retention of sodium in the organism, increased content of carbon dioxide in the blood because of increased dissociation of salts. Hyperosmia results in **dehydration of cells and decomposition of cell proteins**. A decrease of the osmotic pressure **(hypoosmia)** can be connected with redundant consumption of water, retention of water in the organism, a loss of sodium. It is accompanied by redundant receipt of water into cells and leads to **water poisoning and hemolysis.**

The **colloid osmotic, or oncotic, pressure** depends on the content of albumins in the blood.

The osmotic and oncotic pressure are important in the pathogenesis of edemas.

The Viscosity of the Blood. If we assume the viscosity of water at 37^{o}C to be unity, the viscosity of the blood in relation to water will normally be 4.5–5. The viscosity depends on the amount and sizes of formed elements, the ratio of leukocytes and erythrocytes, carbon dioxide saturation, concentration of proteins and proportion of their various fractions in the blood and partly the mineral composition. In pathology it may vary between 2 and 20. The viscosity increases in anhydremia (polycythemia and leukemia), accumulation of carbon dioxide because of the increased viscosity of proteins, in hyperfunction of the thyroid owing to slight hemoconcentration, in hyperproteinemia and the increased content of globulins and fibrinogen (inflammation and certain infections). It decreases in anemias and hydremias, decreased hemocoagulation, myxedema, hypoproteinemia.

With the increased viscosity of the blood the peripheral resistance of the vessels increases, work of the heart and circulation are hindered. With the decreased viscosity circulation is accelerated.

The Erythrocyte Sedimentation Rate (ESR; normally 1–10 mm/h in man and 2–15 mm/h in women). It depends on the various factors:

1) the changed ratio between proteins of the blood. The increased content of the high dispersed proteins (globulins, fibrinogen) in inflammation and certain infections leads to acceleration of ESR, as far as these proteins absorbed on the negative charged erythrocytes reduce their surface charge and thus promote their agglutination and sedimentation;

2) the number of erythrocytes. The increased their number (polycythemia, shock) reduces ESR, and the decreased number (anemia) accelerates ESR;

3) the content of cholesterol and lecitine in blood. Cholesterol absorbed on erythrocytes accelerates and lecitine, on the contrary, decreases ESR;

4) the changed relative density of erythrocytes. In hypercapnia (asphyxia, cardiac insufficiency) ESR decreases owing to increased diameter of erythrocytes and reduced their relative density;

5) viscosity of the blood. Hydremia accelerates ESR and the increased viscosity (anhydremia) reduces ESR.

6) ESR also can be accelerated in intensive physical work.

The osmotic resistance of erythrocytes (ORE) is their stability in hypotonic solutions. There are **minimum and maximum ORE**. The normal minimum implies the hypotonicity of a solution in which the least resistant erythrocytes are hemolysed (0.42–0.44 % sodium chloride solution), and the normal maximum is the concentration of a solution in which the most resistant cells (i.e. all of the cells) are hemolysed (0.32–0.34 %). ORE depends on their maturity, form, and composition of plasma. The form of erythrocyte is characterized by a ratio between its thickness and diameter. This ratio is called index of sphericity (normally 0.27–0.28).

The reduced ORE (increase of parameters minimum and maximum) is observed in hereditary microspherocytic anemia by Minkovsky and Shoffar characterised by the increased index of sphericity of erythrocytes, in hemolytic jaundice, toxicoses, bronchopneumonias, leukemias, cirrhosis of the liver, etc.

The increased ORE takes place in mechanical jaundice; in several cases of polycythemia, massive hemorrhages and iron-deficiency anemia because of stimulated erythropoiesis (the less mature cells possessing the disk form and the small index of sphericity are more resistant).

CHANGES IN THE BIOCHEMICAL COMPOSITION OF THE BLOOD

Changes in protein content in the blood include hypoproteinemia, hyperproteinemia and dysproteinemia.

Hypoproteinemia is a decreased concentration of proteins in the blood plasma. It arises mainly at the expense of a decreased content of albumins and may be acquired and hereditary. Its causes are: starvation, cachexia, certain affections of the liver and digestive system, pathology of the kidneys accompanied by proteinuria, following hemorrhages, and formation of extensive transsudates and exudates. A content of fibrinogen is decreased in severe liver diseases.

One of the manifestations of hypoproteinemia is hydremia (diluted blood) and decreased colloid osmotic pressure of the plasma which is normally maintained mainly by albumins.

Hyperproteinemia is an increased concentration of proteins in the blood plasma. It may be absolute and relative. The relative one occurs more often and is a result of hemoconcentration (anhydremia), i.e. as a result of a loss of water. The absolute one is usually connected with hyperglobulinemia, as a rule, at the expense of γ-globulins in infectious diseases, allergy, and chronic liver diseases. An increased content of fibrinogen is observed in acute and chronic inflammations and infections, nephrosis, some tumours, stress.

It is very important to determine a ratio of albumins to globulins which in norm is equal 1.5–2.3. It is increased in acute and chronic infections, and decreased in liver, nervous and cardiac diseases, in cachexia.

Dysproteinemia is a changed ratio between the separate kinds of globulins. It may be acquired and hereditary and is divided into dysglobulinemias and dysgammaglobulinemias (dysimmunoglobulinemias).

Causes of **dysglobulinemias** are: acute inflammation, diffuse diseases of the connective tissue, autoimmune diseases, and hepatic dysfunctions. A deficit of haptoglobin (α_3-globulin) leads to disturbance of binding and transportation of hemoglobin which is released in normal hemolysis; a decreased synthesis of the antihemophilic globulin (β_2-globulin) leads to hemorrhages; a deficit of transferrin (β_1-globulin) leads to disturbance in iron metabolism.

Causes of **dysgammaglobulinemias** are: myeloma disease, when malignant cells produce abnormal globulins (M-protein and/or Bens-Johns' proteins), Waldenstrem's macroglobulinemia (tumour from B-lymphocytes which produce immunoglobulin M), diffuse diseases of the connective tissue with appearance of cryoglobulins [proteins which are observed in malignant and autoimmune diseases and can precipitate in action of cold (hypothermia)].

Dysproteinemia leads to immunity disorders.

Paraproteinemia is an appearance of qualitatively changed γ-globulinsin the blood plasma. Its causes are the same as the causes of dysgammaglobulinemias.

Other changes in the biochemical composition of the blood (for example, changes in the protein metabolites, pigments, glucose, lipids, and minerals) are considered in the chapters on the pathology of metabolism.

Date	Grade	Teacher's signature

PATHOPHYSIOLOGY OF THE SYSTEMIC BLOOD CIRCULATION. INSUFFICIENCY BLOOD CIRCULATION. PATHOPHYSIOLOGY OF HEART. CARDIAC INSUFFICIENCY

Relevance. Heart failure is one of the main causes of incapacitation, disability and death in patients suffering from diseases of the cardiovascular system. The study of the etiology and pathogenesis of these menacing forms of disease is necessary for a practice physician, as heart failure is due to different causes and mechanisms. This knowledge will promote the development of clinical, optionally rational approaches to treatment of each patient. Study in experiment animals' heart failure can reveal the mechanisms of its development.

The Overall Objective is to be able to characterize heart failure, to explain main causes and mechanisms of its development.

The student should be able to (specific objectives):

1) expand the essence of the notions «heart failure»;
2) classify the causes and mechanisms of heart failure;
3) distinguish the main manifestations of heart failure, to explain the mechanisms of their occurrence and development;
4) model acute heart failurein rats, to explain the mechanisms of compensation and decompensation during the experiment.

The student should be able to (required knowledge and skils):

1) explain the mechanism of heart rate (Depart. of normal physiology);
2) explain the role of cardiac and extracardiac mechanisms in the regulation of the heart (Depart. of normal physiology);
3) interpret the main indicators of the heart (Department. of normal physiology);
4) explain the effect of a changing heart rate and stroke volume values of the efficiency of the heart (Depart. of normal physiology).

QUESTIONS FOR THE LESSON

1. Typical forms of the cardiovascular system's pathology. Circulatory failure: definition, forms.
2. Heart failure. Definition of the notion. Causes. Classification.
3. Mechanisms of urgent and long-term compensation and compensatory mechanisms of reduced contractile function of the heart. Main mechanisms of hypertrophied heart decompensation.
4. The main mechanisms of reducing myocardial contractile function in heart failure.
5. Overload and myocardial forms of heart failure. Kinds. Causes. Signs. Compensatory mechanisms ensuring an adequate level of cardiac output.
6. The right and left ventricular heart failure. Causes. Manifestations and pathogenesis.
7. Acute and chronic heart failure. Kinds. Causes. Manifestations and pathogenesis.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

BLOOD FLOW THROUGH VESSELS IS EFFECTED BY PRESSURE AND RESISTANCE

The flow of blood through the vessels of the circulatory system is a function of the pressure in the system and the resistance to flow caused by the blood vessels. Blood flow is directly proportional to pressure and inversely proportional to resistance.

If the pressure in a vessel increases, the blood flow will increase. However, if the resistance in a vessel increases, the blood flow will decrease.

Resistance in the blood vessels is effected by three parameters:

1. **Length of the vessel. The longer the vessel, the greater the resistance is.**
2. **Viscosity of the blood. The greater the viscosity, the greater the resistance is.**
3. **Radius of the vessel. The smaller the radius, the greater the resistance.is**

Of all of the factors effecting blood flow, the radius of the blood vessel is the most potent. Blood flow is proportional to the 4th power of vessel radius. This means that if the radius of a blood vessel doubles (by vasodilation), the flow will increase 16 fold (2 to the 4th power is 16). On the other hand, if the radius of a vessel is reduced by half (by vasoconstriction), the blood flow will be reduced 16 fold. This is because small changes in the vessel radius make very large changes in blood flow.

Extrinsic Regulation of Blood Flow

Extrinsic regulation refers to a form of control that comes from an outside source. The extrinsic regulation of blood flow refers to the control of arteriolar radius by both the autonomic nervous system and the endocrine system.

Exercise and Blood Flow

Changes in blood flow that occur during the exercise provide an excellent illustration of intrinsic and extrinsic control of arteriolar radius. The vascular tone of arterioles found in skeletal muscle is relatively high, consequently blood flow to resting muscles is low (20–25 % of total blood flow). The increase in blood flow to skeletal muscles during exercise is mediated by three factors:

1. **An increase in cardiac output.** Exercise activates the sympathetic nervous system. Increased sympathetic output to the heart causes an increase in heart rate and stroke volume. Heavy exercise increases venous return of blood to the heart via the skeletal muscle pump and the respiratory pump. An increase in venous return leads to an increase in end-diastolic volume (EDV), which in turn, causes an increase in stroke volume.

2. **Vasodilation of skeletal muscle arterioles.** The most important factor governing flow of blood to exercising muscles is local metabolic control (active hyperemia). As muscular activity increases, metabolites build up and directly induce the vasodilation of local arterioles. Additionally, beta-adrenergic stimulation by epinephrine causes vasodilation of arterioles in skeletal muscle.

3. **Vasoconstriction of arterioles in the viscera and skin**. As a result of alpha-adrenergic sympathetic stimulation, arterioles in the viscera and skin vasoconstrict during exercise. However, as exercise progresses and body temperature rises, cutaneous arterioles dilate in order to radiate heat and reduce body temperature.

Blood volume is a measurement of the volume, or amount of space, that the blood takes up in a given person. This includes both red blood cells and plasma; it is not limited to one particular part of blood. Maintaining a normal volume of blood is very important as it carries oxygen and essential nutrients throughout the body. If a person loses too much blood because of a bleeding wound or because of inadequate blood cell synthesis, dangerously low blood pressure can result and may cause vital organs to receive inadequate amounts of oxygen and nutrients.

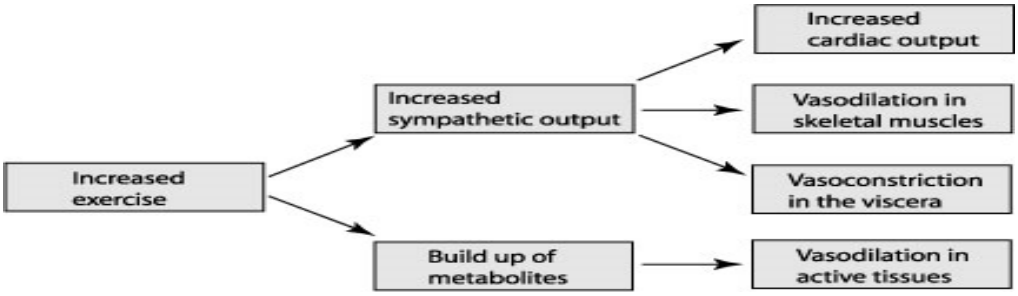


Fig. 2. Summary of Factors that Effect Blood Flow during Exercise

There are many different factors that affect blood volume from person to person. Females, on average, have less blood than males do, and the bodies of children tend to contain less than those of grown men or women. People who live at high altitudes tend to have a higher volume because there is less oxygen in the air.

Blood volume is regulated by the excretory system, particularly by the action of the kidneys. When the amount of blood in the body increases to a certain point, blood pressure increases and, through mechanisms involving nerves and hormones, a signal is sent to the kidneys. The kidneys then reabsorb less fluid, causing more water and other substances necessary to blood production to be lost through urination, decreasing the volume of blood. The opposite happens when there is too little blood; the kidneys reabsorb more water and other substances necessary for blood, causing less to be lost through urination. Through this and other mechanisms, blood pressure and volume are regulated and maintained at healthy levels.

Blood Volume

Blood volume is determined by the amount of water and sodium ingested, excreted by the kidneys into the urine, lost through the gastrointestinal tract, lungs and skin. The amounts of water and sodium ingested and lost are highly variable. To maintain blood volume within a normal range, the kidneys regulate the amount of water and sodium lost into the urine. For example, if excessive water and sodium are ingested, the kidneys normally respond by excreting more water and sodium into the urine.

Regulation of Blood Volume by Renal Excretion of Water and Sodium

The primary mechanism by which the kidneys regulate blood volume is by adjusting the ex-cretion of water and sodium into the urine. For example, increased blood volume increases arterial pressure, renal perfusion, and glomerular filtration rate. This leads to an increase in renal excretion of water and sodium that is termed pressure natriuresis. In certain types of renal disease, the pressure natriuresis relationship is altered so that the kidneys retain more sodium and water at a given pressure, thereby increasing blood volume. Activation of the renin-angiotensin-aldosterone system (*Fig. 3*) causes increased sodium retention which also leads to reduced water loss into the urine. Both angiotensin and aldosterone, although by different mechanisms, stimulate distal tubular sodium reabsorption and decreases sodium and water loss by the kidney. Activation of the renin-angiotensin-aldosterone system occurs in renal artery stenosis, which is one cause of secondary hypertension. Another important hormone in regulating water balance is vasopressin (antidiuretic hormone; ADH). This hormone is released by the posterior pituitary. One of its actions is to stimulate water reabsorption in the collecting duct of the kidney, thereby decreasing water loss and increasing blood volume.

How Blood Volume Affects Blood Pressure

Changes in blood volume affect arterial pressure by changing cardiac output. Increasing blood volume intesifies central venous pressure. This raises right atrial pressure, right ventricular and diastolic pressure and volume. This increase in ventricular preload intesifies ventricular stroke volume by the Frank-Starling mechanism. An increase in right ventricular stroke volume raises pulmonary venous blood flow to the left ventricular, thereby intensifying left ventricular preload and stroke volume. An increase in stroke volume then raises cardiac output and arterial blood pressure.

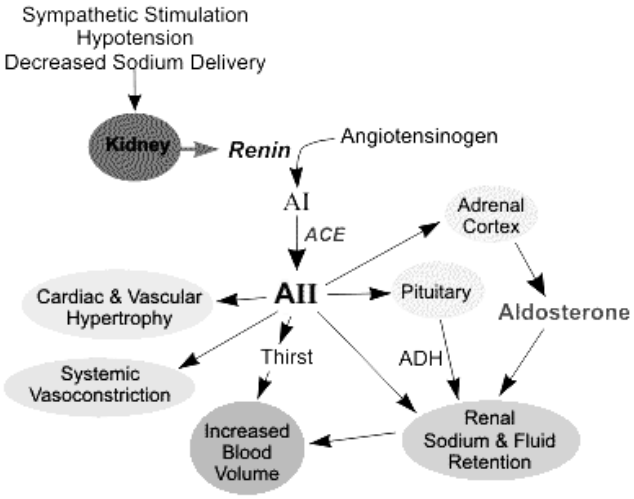


Fig. 3. Effects of angiotensin II

CARDIAC CYCLE

The term cardiac cycle is used to describe rhythmic pumping action of the heart. The cardiac cycle is divided into two parts: systole, the period during which the ventricles are contracting, and diastole, the period during which the ventricles are relaxed and filling with blood. Simultaneous changes occur in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram (ECG), and heart sounds during the cardiac cycle. Electrical activity, recorded on the ECG, precedes the mechanical events of the cardiac cycle. The small, rounded P wave of the ECG represents depolarization of the sinoatrial node (i.e., pacemaker of the heart), the atrial conduction tissue, and the atrial muscle mass. The QRS complex registers the depolarization of the ventricular conduction system and the ventricular muscle mass. The T wave on the ECG occurs during the last half of systole and represents repolarization of the ventricles. The cardiac conduction system and the ECG.

Ventricular Systole and Diastole Ventricular systole is divided into two periods: the isovolumetric contraction period and the ejection period. The isovolumetric contraction period, which begins with the closure of the AV valves and occurrence of the first heart sound, heralds the onset of systole. Immediately after closure of the AV valves, there is an additional 0.02 to 0.03 second during which the semilunar outlet (pulmonic and aortic) valves remain closed. During this period, the ventricular pressures rise abruptly because all of the valves are closed and no blood is leaving the heart. The ventricles continue to contract until left ventricular pressure is slightly higher than aortic pressure, and right ventricular pressure is higher than pulmonary artery pressure. At this point, the semilunar valves open, signaling the onset of the ejection period. At the end of systole, the ventricles relax, causing a precipitous fall in intraventricular pres-sures. As this occurs, blood from the large arteries flows back toward the ventricles, causing the aortic and pulmonic valves to snap shut an event that is marked by the second heart sound. After closure of the semilunar valves, the ventricles continue to relax for another 0.03 to 0.06 second (the isovolumetric relaxation period). During this time, both the semilunar and AV valves are closed, and the ventricular volume remains the same, as the ventricular pressure drops. Ventricular diastole is marked by ventricular filling. When ventricular pressure becomes less than atrial pressure, the AV valves open, and blood that has been accumulating in the atria during systole flows into the ventricles.

Aortic Pressure The aortic pressure reflects changes in the ejection of blood from the left ventricle. There is a rise in pressure and stretching of the elastic fibers in the aorta as blood is ejected into the aorta at the onset of systole. The aortic pressure continues to rise and then begins to fall during the last quarter of systole as blood flows out of the aorta into the peripheral vessels. The aorta is highly elastic and as such stretches during systole to accommodate the blood that is being ejected from the left heart during systole. During diastole, the recoil of the elastic fibers in the aorta serves to maintain the aortic pressure.

Atrial Filling and Contraction Atrial contraction occurs during the last third of diastole. There are three main atrial pressure waves that occur during the cardiac cycle. The a wave is caused by atrial contraction. The c wave occurs as the ventricles begin to contract, and their increased pressure causes the AV valves to bulge into the atria. The v wave results from a slow buildup of blood in the atria toward the end of systole when the AV valves are still closed. The right atrial pressure waves are transmitted to the internal jugular veins as pulsations. These pulsations can be observed visually and may be used to assess cardiac function. Right atrial pressure is regulated by a balance between the ability of the heart to move blood out of the right heart and through the left heart into the systemic circulation and the tendency of blood to flow from the peripheral circulation into the right atrium. Right atrial pressure is also affected by changes in intrathoracic pressure. It is decreased during inspiration when intrathoracic pressure becomes more negative, and it is increased during coughing or forced expiration when intrathoracic pressure becomes more positive. Venous return is a reflection of the amount of blood in the systemic circulation that is available for return to the right heart and the force that moves blood back to the right side of the heart Venous return is increased when the blood volume is expanded or when right atrial pressure falls, and it is decreased in hypovolemic shock or when right atrial pressure rises. Although the main function of the atria is to store blood as it enters the heart, these chambers also act as pumps that aid in ventricular filling

REGULATION OF CARDIAC PERFORMANCE

The efficiency of the heart as a pump often is measured in terms of cardiac output or the amount of blood the heart pumps each minute. The cardiac output (CO) is the product of the stroke volume (SV) and the heart rate (HR) and can be expressed by the equation: CO = SV Ч HR. The cardiac output varies with body size and the metabolic needs of the tissues. It increases with physical activity and decreases during rest and sleep. The average cardiac output in normal adults ranges from 3.5 to 8.0 L/min. In the highly trained athlete, this value can increase to levels as high as 32 L/min during maximum exercise. The cardiac reserve refers to the maximum percentage of incThe heart's ability to increase its output according to body needs mainly depends on four factors: the preload, or ventricular filling; the afterload, or resistance to ejection of blood from the heart; cardiac contractility; and the heart rate. Cardiac performance is influenced by the work demands of the heart and the ability of the coronary circulation to meet its metabolic needs.

Preload. The preload represents the volume work of the heart. It is called the preload because it is the work imposed on the heart before the contraction begins. Preload represents the amount of blood that the heart must pump with each beat and is largely determined by the venous return to the heart and the accompanying stretch of the muscle fibers. The anatomic arrangement of the actin and myosin filaments in the myocardial muscle fibers is such that the tension or force of contraction is greatest when the muscle fibers are stretched just before the heart begins to contract. The maximum force of contraction and cardiac output is achieved when venous return produces an increase in left ventricular end-diastolic filling (i.e., preload) such that the muscle fibers are stretched approximately two and one-half times their normal resting length. When the muscle fibers are stretched to this degree, there is optimal overlap of the actin and myosin filaments and number of cross-bridge at-tachments needed for maximal contraction. The increased force of contraction that accompanies an increase in ventricular end-diastolic volume is referred to as the **Frank-Starling** mechanism. The **Frank-Starling** mechanism allows the heart to adjust its pumping ability to accommodate various levels of venous return. Cardiac output is less when decreased filling causes excessive overlap of the actin and myosin filaments or when the filaments are pulled too far apart because of excessive filling.

Afterload. The afterload is the pressure or tension work of the heart. It is the pressure that the heart must generate to move blood into the aorta. It is called the afterload because it is the work presented to the heart after the contraction has commenced. The systemic arterial blood pressure is the main source of afterload work for the left heart, and the pulmonary arterial pressure is the main source of afterload work for the right heart. The afterload work of the left ventricle is increased with narrowing (i.e., stenosis) of the aortic valve.

Cardiac Contractility Cardiac contractility refers to the ability of the heart to change its force of contraction without changing its resting (i.e., diastolic) length. The contractile state of the myocardial muscle is determined by biochemical and biophysical properties that govern the actin and myosin interactions in the myocardial cells. It is strongly influenced by the number of calcium ions that are available to participate in the contractile process. An inotropic influence is one that modifies the contractile state of the myocardium independent of the Frank-Starling mechanism. For instance, sympathetic stimulation produces a positive inotropic effect by increasing the calcium that is available for inte-raction between the actin and myosin filaments. Hypoxia exerts a negative inotropic effect by interfering with the generation of adenosine triphosphate (ATP) needed for muscle contraction.

Heart Rate. The heart rate determines the frequency with which blood is ejected from the heart. Therefore, as heart rate increases, cardiac output tends to increase. As the heart rate increases, the time spent in diastole is reduced, and there is less time for the filling of the ventricles before the onset of systole. At a heart rate of 75 beats/minute, one cardiac cycle lasts 0.8 second, of which approximately 0.3 second is spent in systole and approximately 0.5 second in diastole. As the heart rate increases, the time spent in systole remains approximately the same, whereas that spent in diastole decreases. This leads to a decrease in stroke volume; at high heart rates, it may cause a decrease in cardiac output.

Blood Vessels and the Systemic Circulation. The vascular system functions in the delivery of oxygen and nutrients and removal of wastes from the tissues. It consists of arteries and arterioles, the capillaries, and the venules and veins. Blood vessels are dynamic structures that constrict and relax to adjust blood pressure and flow to meet the varying needs of the many different tissue types and organ systems. Structures such as the heart, brain, liver, and kidneys require a large and continuous flow to carry out their vital functions. For example, there is a need for increased blood flow to the skin during fever and for increased skeletal muscle blood flow during exercise.

HEART FAILURE

Heart Failure (HF) (Congestive Heart Failure)

Heart failure (HF) is a syndrome of ventricular dysfunction. Left ventricular failure causes shortness of breath and fatigue, and right ventricular failure causes peripheral and abdominal fluid accumulation; the ventricles can be involved together or separately.

Physiology

Cardiac contractility (force and velocity of contraction), ventricular performance, and myocardial O_2 requirements are determined by preload, afterload, substrate availability (e.g, O_2, fatty acids, glucose), heart rate and rhythm, and amount of viable myocardium. Cardiac output (CO) is the product of stroke volume and heart rate; it is also affected by venous return, peripheral vascular tone, and neurohumoral factors.

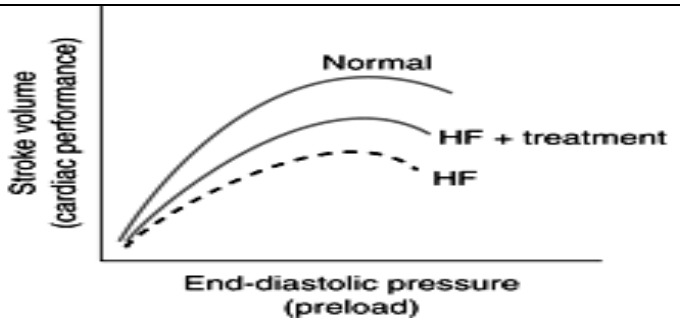
Preload is the loading condition of the heart at the end of its relaxation phase (diastole) just before contraction (systole). Preload represents the degree of end-diastolic fiber stretch and end-diastolic volume, which is influenced by ventricular diastolic pressure and the composition of the myocardial wall.

Afterload is the force resisting myocardial fiber contraction at the start of systole; it is de-termined by chamber pressure, volume, and wall thickness at the time the aortic valve opens.

The **Frank-Starling** principle describes the relationship between preload and cardiac performance. It states that, normally, systolic contractile performance (represented by stroke volume or CO) is proportional to preload within the normal physiologic range (*see Fig. 4: Heart Failure: Frank-Starling principle*).

Contractility is difficult to measure without cardiac catheterization but is reasonably reflected by the ejection fraction (EF), which is the percentage of end-diastolic volume ejected with each contraction; Cardiac reserve is the ability of the heart to increase its performance above resting levels in response to emotional or physical stress; body O_2 consumption may increase from 250 to ≥ 1500 mL/min during maximal exertion. Mechanisms include increasing

heart rate, systolic and diastolic volume, stroke volume, and tissue extraction of O_2 (the difference between O_2 content in arterial blood and mixed venous or pulmonary artery blood).



Normally, as preload increases, cardiac performance also increases. However at a certain point, performance plateaus, then declines. In heart failure (HF) due to systolic dysfunction (bottom curve), the overall curve shifts downward, reflecting reduced cardiac performance at a given preload, and as preload increases, cardiac performance increases less. With treatment (middle curve), performance is improved, although not normalized.

Fig. 4. Heart Failure: Frank-Starling principle

Pathophysiology. In HF, the heart may not provide tissues with adequate blood for metabolic needs, and cardiac-related elevation of pulmonary or systemic venous pressures may result in organ congestion. This condition can result from abnormalities of systolic or diastolic function or, commonly, both. Although a primary abnormality may be a change in myocyte function, there are also changes in collagen turnover of the extracellular matrix. Cardiac structural defects (e.g, congenital defects, valvular disorders), rhythm abnormalities (including persistently high heart rate), and high metabolic demands (e.g, from thyrotoxicosis) also can cause HF.

Systolic dysfunction. In systolic dysfunction, the ventricle contracts poorly and empties inadequately, leading initially to increased diastolic volume and pressure and decreased EF. Many defects in energy utilization, energy supply, electrophysiologic functions, and contractile element interaction occur, with abnormalities in intracellular Ca modulation and cAMP production.

Predominant systolic dysfunction is common in HF due to MI, myocarditis, and dilated cardiomyopathy. Systolic dysfunction may affect primarily the LV or the right ventricle (RV); LV failure often leads to RV failure.

Diastolic dysfunction. In diastolic dysfunction (also called HF with preserved systolic function or HF with preserved/normal EF), ventricular filling is impaired, resulting in reduced ventricular end-diastolic volume, increased end-diastolic pressure, or both. Contractility and hence EF remain normal; EF may even increase as the poorly filled LV empties more completely to maintain CO. Markedly reduced LV filling can cause low CO and systemic symptoms. Elevated left atrial pressures can cause pulmonary hypertension and pulmonary congestion.

Diastolic dysfunction usually results from impaired ventricular relaxation, increased ventricular stiffness, valvular disease, or constrictive pericarditis. Acute myocardial ischemia is also a cause of diastolic dysfunction. Resistance to filling increases with age, probably reflecting myocyte loss and increased interstitial collagen deposition; thus, diastolic dysfunction is particularly common among the elderly. Diastolic dysfunction predominates in hypertrophic cardiomyopathy, disorders with ventricular hypertrophy (e.g, hypertension, significant aortic stenosis), and amyloid infiltration of the myocardium.

LV failure. In failure due to LV dysfunction, CO decreases and pulmonary venous pressure increases. When pulmonary capillary pressure exceeds the oncotic pressure of plasma proteins (about 24 mm Hg), fluid extravasates from the capillaries into the interstitial space and alveoli, reducing pulmonary compliance and increasing the work of breathing. Lymphatic drainage increases but cannot compensate for the increase in pulmonary fluid. Marked fluid accumulation in alveoli (pulmonary edema) significantly alters ventilation-perfusion (V/Q) relationships: Deoxygenated pulmonary arterial blood passes through poorly ventilated alveoli,

decreasing systemic arterial oxygenation (PaO_2) and causing dyspnea, because of elevated pulmonary venous pressure and increased work of breathing;

RV failure. In failure due to RV dysfunction, systemic venous pressure increases, causing fluid extravasation and consequent edema, primarily in dependent tissues (feet and ankles of ambulatory patients) and abdominal viscera. The liver is affected most, but the stomach and intestine also become congested; fluid accumulation in the peritoneal cavity (ascites) can occur. RV failure commonly causes moderate hepatic dysfunction, with usually modest increases in conjugated and unconjugated bilirubin, PT, and hepatic enzymes (e.g, alkaline phosphatase, AST, ALT). The impaired liver breaks down less aldosterone, further contributing to fluid accumulation. Chronic venous congestion in the viscera can cause malabsorption of nutrients and drugs, protein-losing enteropathy (characterized by diarrhea and marked hypoalbuminemia).

Cardiac response. If ventricular function is impaired, a higher preload is required to maintain CO. As a result, the ventricles are remodeled over time: The LV becomes less ovoid and more spherical, dilates, and hypertrophies; the RV dilates and may hypertrophy. Initially compensatory, these changes eventually increase diastolic stiffness and wall tension (i.e, diastolic dysfunction develops), compromising cardiac performance, especially during physical stress. Increased wall stress raises O_2 demand and accelerates apoptosis (programmed cell death) of myocardial cells. Dilation of the ventricles can also cause mitral or tricuspid valve regurgitation with further increases in end-diastolic volumes.

Hemodynamic responses. With reduced CO, tissue O_2 delivery is maintained by increasing O_2 extraction and sometimes shifting the oxyhemoglobin dissociation curve. Reduced CO with lower systemic BP activates arterial baroreflexes, increasing sympathetic tone and decreasing parasympathetic tone. As a result, heart rate and myocardial contractility in-crease, arterioles in selected vascular beds constrict, venoconstriction occurs, and Na and water are retained. These changes compensate for reduced ventricular performance and help maintain hemo-dynamic homeostasis in the early stages of HF.

Renal responses: As cardiac function deteriorates, renal blood flow and GFR decrease, and blood flow within the kidneys is redistributed. The filtration fraction and filtered Na decrease, but tubular resorption increases, leading to Na and water retention. Blood flow is further redistributed away from the kidneys during exercise, but renal blood flow improves during rest, possibly contributing to nocturia.

Decreased perfusion of the kidneys activates the renin-angiotensin-aldosterone system, increasing Na and water retention and renal and peripheral vascular tone. These effects are amplified by the intense sympathetic activation accompanying HF.

The renin-angiotensin-aldosterone-vasopressin (ADH) system causes a cascade of potentially deleterious long-term effects. Angiotensin II worsens HF by causing vasoconstriction, including efferent renal vasoconstriction, and by increasing aldosterone production, which not only enhances Na reabsorption in the distal nephron but also causes myocardial and vascular collagen deposition and fibrosis. Angiotensin II increases norepinephrine release, stimulates release of ADH, and triggers apoptosis. Angiotensin II may be involved in vascular and myocardial hypertrophy, thus contributing to the remodeling of the heart and peripheral vasculature, potentially worsening HF. Aldosterone can be synthesized in the heart and vasculature independently of angiotensin II (perhaps mediated by corticotropin, nitric oxide, free radicals, and other stimuli) and may have deleterious effects in these organs.

Neurohumoral responses. In conditions of stress, neurohumoral responses help increase heart function and maintain BP and organ perfusion, but chronic activation of these responses is detrimental to the normal balance between myocardial-stimulating and vasoconstricting hormones and between myocardial-relaxing and vasodilating hormones.

The heart contains many neurohumoral receptors (б1, в1, в2, в3, angiotensin II type 1 [AT1] and type 2 [AT2], muscarinic, endothelin, serotonin, adenosine, cytokine); the role of

these receptors is not yet fully defined. In patients with HF, в1 receptors (70 % of cardiac в receptors) are downregulated, probably in response to intense sympathetic activation. The result of downregulation is impaired myocyte contractility and increased heart rate. Detrimental effects include vasoconstriction with increased preload and afterload, direct myocardial damage including apoptosis, reduced renal blood flow, and activation of other neurohumoral systems, including the renin-angiotensin-aldosterone-ADH system.

Increased ADH decreases renal excretion of free water, possibly contributing to hyponatremia in HF. Atrial natriuretic peptide is released in response to increased atrial volume and pressure; brain (B-type) natriuretic peptide (BNP) is released from the ventricle in response to ventricular stretching.

Because endothelial dysfunction occurs in HF, fewer endogenous vasodilators (e.g, nitric oxide, prostaglandins) are produced, and more endogenous vasoconstrictors (e.g, endothelin) are produced, thus increasing afterload.

EtiologyBoth cardiac and systemic factors can impair cardiac performance and cause or aggravate HF

Classification The traditional distinction of left and right ventricular failure is somewhat misleading because the heart is an integrated pump, and changes in one chamber ultimately affect the whole heart. However, these terms indicate the major site of pathology leading to HF and can be useful for initial evaluation and treatment. Other common descriptive terms include acute or chronic; congestive; high output or low output; systolic or diastolic; dilated or nondilated; and ischemic, hypertensive, or idiopathic dilated cardiomyopathy.

LV failure characteristically develops in ischemic heart disease, hypertension, mitral or aortic valvular regurgitation, aortic stenosis, most forms of cardiomyopathy, and congenital heart disorders (e.g, ventricular septal defect or patent ductus arteriosus with large shunts).

RV failure is most commonly caused by previous LV failure or by a severe lung disorder. Other causes are multiple pulmonary emboli, RV infarction, primary pulmonary hypertension, tricuspid regurgitation or stenosis, mitral stenosis, pulmonary artery or valve stenosis, pulmonary venous occlusive disease, or congenital disorders such as Ebstein's anomaly or Eisenmenger's syndrome. Some conditions mimic RV failure, except cardiac function may be normal; they include volume overload and increased systemic venous pressure in polycythemia or overtransfusion, acute renal failure with retention of Na and water, obstruction of either vena cava, and hypoproteinemia from any cause resulting in low plasma oncotic pressure and peripheral edema.

Biventricular failure results from disorders that affect the whole myocardium (e.g, viral myocarditis, amyloidosis, Chagas disease) or long-standing LV failure causing RV failure.

High-output HF results from a persistently high CO, which may eventually result in an inability of a normal heart to maintain adequate output. Conditions that may increase CO include severe anemia, beriberi, thyrotoxicosis, advanced Paget's disease, arteriovenous fistula, and persistent tachycardia. CO is high in various forms of cirrhosis, but much of the observed fluid retention is due to hepatic mechanisms.

Table 22

Causes of Heart Failure

CardiacType	Examples
Myocardial damage	MI, Myocarditis, Cardiomyopathy,Some chemotherapy drugs
Valvular disorders	Aortic stenosis, Mitral regurgitation
Arrhythmias	Bradyarrhythmias, Tachyarrhythmias
Conduction defects	AV node block, Left bundle branch block
Reduced substrate availability (eg, of free fatty acids or glucose)	Ischemia
Infiltrative or matrix disorders	Amyloidosis, Chronic fibrosis, Hemochromatosis
Systemic	
Disorders that increase demand for CO	Hyperthyroidism, Paget's disease
Disorders that increase resistance to output	Aortic stenosis, Hypertension

Cardiomyopathy is a general term reflecting disease of the myocardium. Most commonly, the term refers to a primary disorder of the ventricular myocardium that is not caused by congenital

anatomic defects; valvular, systemic, or pulmonary vascular disorders; isolated pericardial, nodal, or conduction system disorders; or epicardial coronary artery disease (CAD). The term is sometimes used to reflect etiology (e.g, ischemic vs hypertensive cardiomyopathy). Cardiomyopathy does not always lead to symptomatic HF. It is often idiopathic and is classified as dilated congestive, hypertrophic, infiltrative-restrictive, or apical-ballooning cardiomyopathy.

Symptoms and Signs Manifestations differ depending on the extent to which the LV and RV are initially affected. Clinical severity varies significantly and is usually classified according to the New York Heart Association system (*see Table 23: Heart Failure: New York Heart Association (NYHA) Classification of Heart Failure*); the examples of ordinary activity may be modified for elderly, debilitated patients. Severe LV failure may cause pulmonary edema or cardiogenic shock.

Table 23

New York Heart Association (NYHA) Classification of Heart Failure

NYHA Classifi-cation	Definition	Limita-tion	Example
I	Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations	None	Can complete any activity requiring ≤7 MET: 1. Carry 11 kg up 8 steps 2. Carry objects weighing 36 kg 3. Shovel snow 4. Spade soil, Ski 5. Play squash, handball, or baketball
II	Ordinary physical activity causes fatigue, dyspnea, palpitations, o angina	Slight	Can complete any activity requiring ≤5 MET: 1. Sexual intercourse without stopping 2. Garden, Roller skate 3. Walk 7 km/h on level ground 4. Climb one flight stairs at a normal pace without symptoms
III	Comfortable at rest; less than ordinary physical activity causes fatigue dyspnea, alpitations, or angina	Moderate	Can complete any activity requiring ≤2 MET: 1. Shower or dress without stopping 2. Strip and make a bed 3. Clean windows, Play golf 4. Walk 4 km/h
IV	Symptoms occur at rest; any physical activity icreases discomfort	Sever	Cannot do or cannot complete any activity requiring ≥ 2 MET; cannot do any ofthe above activities
MET = metabolic equivalent task			

In LV failure, the most common symptoms are dyspnea, reflecting pulmonary congestion, and fatigue, reflecting low CO. Dyspnea usually occurs during exertion and is relieved by rest. As HF worsens, dyspnea can occur during rest and at night, sometimes causing nocturnal cough. Dyspnea occurring immediately or soon after lying flat and relieved promptly by sitting up (orthopnea) is common as HF advances. In paroxysmal nocturnal dyspnea (PND), dyspnea awakens patients several hours after they lie down and is relieved only after they sit up for 15 to 20 min. In severe HF, periodic cycling of breathing can occur during the day or night; the sudden hyperpneic phase may awaken the patient from sleep. Sleep-related breathing disorders, such as sleep apnea, are common in HF and may aggravate HF. Severely reduced cerebral blood flow and hypoxemia can cause chronic irritability and impair mental performance.

In RV failure, the most common symptoms are ankle swelling and fatigue. Sometimes patients feel a sensation of fullness in the abdomen or neck. Hepatic congestion can cause right upper quadrant abdominal discomfort, intestinal congestion can cause anorexia and abdominal bloating.

Less specific HF symptoms include cool peripheries, postural light-headedness, nocturia, and decreased daytime micturition. Skeletal muscle wasting can occur in severe biventricular failure and may reflect some disuse but also increased catabolism associated with increased cytokine pro-duction. Significant weight loss (cardiac cachexia) is an ominous sign associated with high mortality.

Examination: General examination may detect signs of systemic disorders that cause or aggravate HF (e.g, anemia, hyperthyroidism, alcoholism, hemochromatosis).

In LV failure, tachycardia and tachypnea may occur. Patients with severe LV failure may appear visibly dyspneic or cyanotic, hypotensive, and confused or agitated because of hypoxia and poor cerebral perfusion. Some of these less specific symptoms are more common in the elderly.

Central cyanosis reflects hypoxemia. Peripheral cyanosis of the lips, fingers, and toes reflects low blood flow with increased O_2 extraction. If massage improves nail bed color, cyanosis may be peripheral; increasing local blood flow does not improve color if cyanosis is central.

Cardiac findings in LV systolic dysfunction include a diffuse, sustained, and laterally displaced apical impulse; pansystolic murmur of mitral regurgitation at the apex may occur. Pulmonary findings include inspiratory basilar crackles that do not clear with coughing and, if pleural effusion is present, dullness to percussion and diminished breath sounds at lung bases.

Signs of RV failure include nontender peripheral pitting edema (digital pressure leaves visible and palpable imprints, sometimes quite deep) in the feet and ankles; an enlarged and sometimes pulsatile liver palpable below the right costal margin; abdominal swelling and ascites; and visible elevation of the jugular venous pressure, sometimes with large a or vwaves that are visible even when the patient is seated or standing. In severe cases, peripheral edema can extend to the thighs or even the sacrum, scrotum, lower abdominal wall, and occasionally even higher. Severe edema in multiple areas is termed anasarca. Edema may be asymmetric if patients lie on one side.

With hepatic congestion, the liver may be palpably enlarged or tender, and hepatojugular or abdominal-jugular reflux may be detected. Precordial palpation may detect the left parasternal lift of RV enlargement, and auscultation may detect the murmur of tricuspid regurgitation or the RV S_3 along the left sternal border; both findings are augmented upon inspiration.

ECG findings are not diagnostic, but an abnormal ECG, especially showing previous MI, LV hypertrophy, left bundle branch block, or tachyarrhythmia (e.g, rapid atrial fibrillation), increases suspicion for HF and may help identify the cause. An entirely normal ECG is uncommon in chronic HF.

Imaging. Echocardiography can help evaluate chamber dimensions, valve function, EF, wall motion abnormalities, LV hypertrophy, and pericardial effusion. Intracardiac thrombi, tumors, and calcifications within the heart valves, mitral annulus, and aortic wall abnormalities can be detected. Doppler studies of mitral and pulmonary venous inflow often help identify and quantify LV diastolic dysfunction; tissue Doppler imaging is more accurate. Measuring LVEF can distinguish between predominant diastolic dysfunction (EF > 0.50) and systolic dysfunction (EF < 0.40).

Blood tests: erum BNP levels are high in HF; this finding may help when clinical findings are unclear or other diagnoses (e.g, COPD) need to be excluded. Recommended blood tests include CBC, creatinine, BUN, electrolytes (including Mg and Ca), glucose, albumin, and liver function tests. Thyroid function tests are recommended for patients with atrial fibrillation and for selected, especially elderly, patients.

Arrhythmias. It is important to identify and treat the cause of an arrhythmia

1. Electrolytes are normalized.
2. Atrial and ventricular rate are controlled.
3. Sometimes antiarrhythmic drugs are given.

Sinus tachycardia, a common compensatory change in HF, usually subsides when HF treat-ment is effective. If it does not, associated causes (e.g, hyperthyroidism, pulmonary emboli, fever, anemia) should be sought.

Atrial fibrillation with an uncontrolled ventricular rate must be treated; the target resting ventricular rate is typically < 80 beats/min.

Isolated ventricular premature beats, which are common in HF, do not require specific treatment. However, optimization of HF treatments and correction of electrolyte abnormalities (es-pecially K and Mg) reduce the risk of ventricular arrhythmias.

Pulmonary Edema is acute, severe left ventricular failure with pulmonary venous hypertension and alveolar flooding. Findings are severe dyspnea, diaphoresis, wheezing, and sometimes blood-tinged frothy sputum. Diagnosis is clinical and by chest x-ray.

If left ventricular (LV) filling pressure increases suddenly, plasma fluid moves rapidly from pulmonary capillaries into interstitial spaces and alveoli, causing pulmonary edema. Although precipitating causes vary by age and country, about one half of cases result from acute coronary ischemia; some from decompensation of significant underlying heart failure (HF), including diastolic dysfunction HF due to hypertension; and the rest from arrhythmia, an acute valvular disorder, or acute volume overload often due to IV fluids.

Symptoms and Signs Patients present with extreme dyspnea, restlessness, and anxiety with a sense of suffocation. Cough producing blood-tinged sputum, pallor, cyanosis, and marked diaphoresis are common; some patients froth at the mouth. The pulse is rapid and low volume, and BP is variable. Marked hypertension indicates significant cardiac reserve; hypotension with systolic BP < 100 mg Hg is ominous. Inspiratory fine crackles are widely dispersed anteriorly and posteriorly over both lung fields. Marked wheezing (cardiac asthma) may occur. Signs of right ventricular (RV) failure (eg, neck vein distention, peripheral edema) may be present.

Cor Pulmonale

Cor pulmonale is right ventricular enlargement secondary to a lung disorder that causes pulmonary artery hypertension. Right ventricular failure follows. Findings include peripheral edema, neck vein distention, hepatomegaly, and a parasternal lift. Diagnosis is clinical and by echocardiography.

Cor pulmonale results from a disorder of the lung or its vasculature; it does not refer to right ventricular (RV) enlargement secondary to left ventricular (LV) failure, a congenital heart disorder (eg, ventricular septal defect), or an acquired valvular disorder. Cor pulmonale is usually chronic but may be acute and reversible.

Pathophysiology

Lung disorders cause pulmonary hypertension by several mechanisms:

1. Loss of capillary beds (e.g, due to bullous changes in COPD or thrombosis in pulmonary embolism)
2. Vasoconstriction caused by hypoxia, hypercapnia, or both
3. Increased alveolar pressure (e.g, in COPD, during mechanical ventilation)
4. Medial hypertrophy in arterioles (often a response to pulmonary hypertension due to other mechanisms)

Pulmonary hypertension increases afterload on the RV, resulting in a cascade of events that is similar to what occurs in LV failure, including elevated end-diastolic and central venous pressure and ventricular hypertrophy and dilation. Demands on the RV may be intensified by increased blood viscosity due to hypoxia-induced polycythemia.

Etiology. Acute cor pulmonale has few causes. Chronic cor pulmonale is usually caused by COPD, but there are several less common causes. In patients with COPD, an acute exacerbation or pulmonary infection may trigger RV overload. In chronic cor pulmonale, risk of venous thromboembolism is increased.

Symptoms and Signs Initially, cor pulmonale is asymptomatic, although patients usually have significant symptoms due to the underlying lung disorder (eg, dyspnea, exertional fatigue). Later, as RV pressures increase, physical signs commonly include a left parasternal systolic lift, a loud pulmonic component of the 2nd heart sound (S2), and murmurs of functional tricuspid and pulmonic insufficiency. Later, an RV gallop rhythm augmented during inspiration, distended jugular veins, hepatomegaly, and lower-extremity edema may occur.

Table 24

Causes of Cor Pulmonale

Acuity	Condition
Acute	Massive pulmonary embolization Injury due to mechanical ventilation (most commonly for ARDS)
Chronic	COPD*,Extensive loss of lung tissue due to surgery or trauma Chronic, unresolved pulmonary emboli, Pulmonary veno-occlusive disorders Systemic sclerosis, Pulmonary interstitial fibrosis,Kyphoscoliosis Obesity, alveolar hypoventilation, Neuromuscular disorders involving respiratory muscles
ARDS = acute respiratory distress syndrome	

CARDIOMYOPATHIES

A cardiomyopathy is a primary disorder of the heart muscle. It is distinct from structural cardiac disorders such as coronary artery disease, valvular disorders, and congenital heart disorders.

A cardiomyopathy is a primary disorder of the heart muscle. It is distinct from structural cardiac disorders such as coronary artery disease, valvular disorders, and congenital heart disorders.

Cardiomyopathies are divided into 3 main types:

1) dilated,

2) hypertrophic,

3) restrictive

The term ischemic cardiomyopathy refers to the dilated, poorly contracting myocardium that sometimes occurs in patients with severe coronary artery disease. Manifestations of cardiomyopathies are usually those of heart failure and vary depending on whether there is systolic dysfunction, diastolic dysfunction, or both. Some cardiomyopathies may also cause chest pain, syncope, or sudden death.

Table 25

Diagnosis and Treatment of Cardiomyopathies

Feature or Method	Dilated	Hypertrophic	Restrictive
Pathophysiology	Systolic dysfunction	Diastolic dysfunction ± outflow obstruction	Diastolic dysfunction
Clinical findings	LV and RV failure. Cardiomegaly. Functional AV valve regurgitation S_3 and S_4	Exertional dyspnea, angina, syncope, sudden death. Ejection ± mitral regurgitation murmurs, S_4	Exertional dyspnea and fatigue. LV ± RV failure. Functional AV valve regurgitation
ECG	Nonspecific ST- and T-wave abnormalities, Q waves	LV hypertrophy and ischemia. Deep septal Q waves	LV hypertrophy or low voltage
Echocardiography	Dilated hypokinetic ventricles ±mural thrombus. Low EF and, frequently, functional AV valve regurgitation	Hypertrophied ventricle ± mitral systolic anterior motion ± asymmetric hypertrophy ± LV gradient	Increased wall thickness ± cavity obliteration. LV diastolic dysfunction
X-ray	Cardiomegaly Pulmonary venous congestion	No cardiomegaly	No or mild cardiomegaly
Hemodynamics	Normal or high EDP, low EF, diffusely dilated hypokinetic ventricles ± AV valve regurgitation. Low CO	High EDP, high EF± outflow subvalvular gradient ± mitral regurgitation. Normal or low CO	High EDP, dip and plateau diastolic LV pressure curve Normal or low CO
Prognosis	20 % mortality in first year, and about 10 %/yr thereafter	About 1 % annual risk of sudden death	70 % 5-yr mortality
AV – atrioventricular; BBB – bundle branch block; CO – cardiac output; EDP – end-diastolic pressure; EF – ection fraction; ICD – implantable cardioverter-defibrillator; LV – left ventricular; RV – right ventricular; S_3–3rd; S_4 = 4th heart sound			

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is myocardial dysfunction causing heart failure in which ventricular dilation and systolic dysfunction predominate. Symptoms include dyspnea, fatigue, and peripheral edema. Diagnosis is clinical and by chest x-ray and echocardiography.

Pathophysiology

In some patients, DCM is believed to start with acute myocarditis, followed by a variable latent phase, a phase with diffuse necrosis of myocardial myocytes (due to an autoimmune reaction to virus-altered myocytes), and chronic fibrosis. Regardless of the cause, the myocardium dilates, thins, and hypertrophies in compensation, often leading to functional mitral or tricuspid regurgitation and atrial dilation.

The disorder affects both ventricles in most patients, only the left ventricle (LV) in a few (unless with an ischemic etiology), and only the right ventricle (RV) rarely. Mural thrombi frequently form once chamber dilation is significant, especially during the acute myocarditis phase. Cardiac arrhythmias often complicate the acute myocarditis and late chronic dilated phases as may atrioventricular (AV) block. Atrial fibrillation commonly occurs as the left atrium dilates.

Etiology DCM has many known and probably many unidentified causes. The most common cause in temperate zones is diffuse coronary artery disease (CAD) with diffuse ischemic myopathy. More than 20 viruses can cause DCM; in temperate zones, coxsackievirus B is most common. In Central and South America, Chagas disease due to Trypanosoma cruzi is the most common infectious cause. DCM is becoming increasingly common among patients with HIV infection.

Other causes include toxoplasmosis, thyrotoxicosis, and beriberi. Many toxic substances, particularly alcohol, various organic solvents, and certain chemotherapeutic drugs, damage the heart. Stress and other hyperadrenergic states can trigger acute DCM that is typically reversible (episodes of tachycardia). Genetic factors play a role in 20 to 35 % of cases; several genes and loci have been implicated.

Symptoms and Signs

Onset is usually a gradual except in acute myocarditis, acute apical ballooning cardiomyopathy, and tachyarrhythmia-induced myopathy. Symptoms depend on which ventricle is affected. LV dysfunction causes exertional dyspnea and fatigue due to elevated LV diastolic pressure and low cardiac output. RV failure causes peripheral edema and neck vein distention. Infrequently the RV is predominantly affected in younger patients, and atrial arrhythmias and sudden death due to malignant ventricular tachyarrhythmias are typical. About 25 % of all patients with DCM have atypical chest pain.

The **ECG** may show sinus tachycardia and nonspecific ST-segment depression with low voltage or inverted T waves. Sometimes pathologic Q waves are present in the precordial leads, simulating previous MI. Left bundle branch block is common.

Echocardiography shows dilated, hypokinetic cardiac chambers and rules out primary valvular disorders. Segmental wall motion abnormalities, typical of MI, can also occur in DCM because the process may be patchy. May also show a mural thrombus MRI is not routinely done but may be useful when detailed imaging of myocardial structure or function is needed. In cardiomyopathy, MRI may show abnormal myocardial tissue texture.

Coronary angiography is required when the diagnosis is in doubt after noninvasive tests, particularly for patients with chest pain or several cardiovascular risk factors or for elderly patients, who are more likely to have CAD. However, nonobstructive coronary artery lesions detected by angiography may not be the cause of DCM.

Table 26

Causes of Dilated Cardiomyopathy

Cause	Examples
Myocardial ischemia	Coronary artery disease
Chronic tachycardia	Uncontrolled atrial fibrillation
Infections (acute or chronic)	Bacterial: Spirochetal, Rickettsial, Viral (including HIV infection), Fungal, Protozoan, Helminthic
Granulomatous disorders	Sarcoidosis, Granulomatous or giant cell myocarditis, Wegener's granulomatosis
Metabolic disorders	Nutritional disorders (eg, beriberi, selenium deficiency, carnitine deficiency, kwashiorkor), Familial storage disorders, Uremia, Hypokalemia, Hypomagnesemia, Hypophosphatemia, Diabetes mellitus, Hyperthyroidism, Hypothyroidism, Pheochromocytoma, Acromegaly, Morbid obesity

Cause	Examples
Drugs and toxins	Ethanol, Cocaine, Anthracyclines,Cobalt, Psychotherapeutic drugs (antidepressants, phenothiazine), Catecholamines, Cyclophosphamide, Radiation
Tumors	Certain endocrinologically active tumors (eg, pheochromocytoma, adrenal, tumors, thyroid tumors)
Connective tissue dist	SLE, Systemic sclerosis, RA
Genetic abnormality	Familial disease: autosomal dominant, X-linked, autosomal recessive, or mitochondrial inheritance
Hereditary disorders	Friedreich's ataxia
Pregnancy	(peripartum period)

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a congenital or acquired disorder characterized by marked ventricular hypertrophy with diastolic dysfunction but without increased afterload (eg, from valvular aortic stenosis, coarctation of the aorta, systemic hypertension).

Symptoms include dyspnea, chest pain, syncope, and sudden death. A systolic murmur, increased by Valsalva maneuver, is typically present in the hypertrophic obstructive type. Diagnosis is by echocardiography. HCM is a common cause of sudden death in young athletes.

Etiology. Most cases of HCM are inherited. At least 50 different mutations that are inherited in an autosomally dominant pattern have been identified; spontaneous mutations are common. Perhaps 1 in 500 people is affected; phenotypic expression varies markedly.

Pathophysiology The myocardium is abnormal with cellular and myofibrillar disarray, although this finding is not specific for HCM. In the most common form, the upper interventricular septum below the aortic valve is markedly hypertrophied and thickened, with little or no hypertrophy of the left ventricular (LV) posterior wall; this pattern is called asymmetric septal hypertrophy. During systole, the septum thickens, and sometimes the anterior leaflet of the mitral valve, already abnormally oriented because of the abnormally shaped ventricle, is sucked toward the septum by a **Venturi** effect of high velocity blood flow, further obstructing the outflow tract and decreasing cardiac output. The resulting disorder may be termed hypertrophic obstructive cardiomyopathy. Less commonly, midventricular hypertrophy leads to an intracavitary gradient at the papillary muscle level. In both forms, the distal LV may ultimately thin and dilate. Apical hypertrophy can also occur but does not obstruct outflow, although it may obliterate the apical portion of the LV during systole. Sometimes the hypertrophy is diffuse and symmetrical. Contractility is grossly normal, resulting in a normal ejection fraction (EF). Later, EF is elevated because the ventricle has a small volume and empties nearly completely to maintain cardiac output. Hypertrophy results in a stiff, noncompliant chamber (usually the LV) that resists diastolic filling, elevating end-diastolic pressure and thus increasing pulmonary venous pressure. As resistance to filling increases, cardiac output decreases, an effect worsened by any outflow tract gradient present. Because tachycardia allows less time for filling, symptoms tend to appear mainly during exercise or tachyarrhythmias.

Coronary blood flow may be impaired, causing angina pectoris, syncope, or arrhythmias in the absence of epicardial coronary artery disease (CAD). Flow may be impaired because capillary density relative to myocyte size is inadequate (capillary/myocyte imbalance) or lumen diameter of intramyocardial coronary arteries is narrowed by intimal and medial hyperplasia and hypertrophy. Also, exercise lowers peripheral vascular resistance and aortic root diastolic pressure, thus reducing coronary perfusion pressure. In some cases, myocytes gradually die, probably because capillary/myocyte imbalance causes chronic diffuse ischemia. As myocytes die, they are replaced by diffuse fibrosis. Then, the hypertrophied ventricle with diastolic dysfunction gradually dilates and systolic dysfunction also develops. Infective endocarditis can complicate HCM because of the mitral valve abnormality and because of rapid blood flow through the outflow tract during early systole. Atrioventricular block is sometimes a late complication.

Symptoms and Signs Typically, symptoms appear between ages 20 and 40 and are exertional. They include dyspnea, chest pain (usually resembling typical angina, palpitations, and syncope. Because systolic function is preserved, fatigability is seldom reported.

Syncope usually occurs without warning during exertion either because outflow obstruction worsens with the increased contractility or because of nonsustained ventricular or atrial arrhythmia. Syncope is a marker of increased risk of sudden death, which is thought to result from ventricular tachycardia or fibrillation.

BP and heart rate are usually normal, and signs of increased venous pressure are rare. When the outflow tract is obstructed, the carotid pulse has a brisk upstroke, bifid peak, and rapid down-stroke. The apex beat may have a sustained thrust due to LV hypertrophy.

Septal hypertrophy produces a systolic ejection-type murmur that does not radiate to the neck and may be heard at the left sternal edge in the 3rd or 4th intercostal space. A mitral regurgitation murmur due to distortion of the mitral apparatus may be heard at the apex.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is characterized by noncompliant ventricular walls that resist diastolic filling; one or both ventricles, most commonly the left, may be affected. Symptoms include fatigue and exertional dyspnea.

Diagnosis is by echocardiography and cardiac catheterization.

RCM is the least prevalent form of cardiomyopathy. It is classified as

1. Nonobliterative (myocardial infiltration by an abnormal substance)
2. Obliterative (fibrosis of the endocardium and subendocardium)

Either type may be diffuse or nondiffuse (when the disorder affects only one ventricle or part of one ventricle unevenly).

Etiology. Some disorders that cause RCM also affect other tissues (e.g, amyloidosis, hemochromatosis). Some myocardial infiltrative disorders also affect other cardiac tissue. Rarely, amyloidosis affects coronary arteries. Sarcoidosis and Fabry's disease may also affect nodal conduction tissue. Löffler's syndrome (a subcategory of hypereosinophilic syndrome with primary cardiac involvement), which occurs in the tropics, begins as an acute arteritis with eosinophilia, followed by thrombus formation on the endocardium and atrioventricular (AV) valves, progressing to fibrosis. Endocardial fibroelastosis, which occurs in temperate zones, affects only the left ventricle (*Table 27*).

Table 27

Causes of Restrictive Cardiomyopathy

Cause	Examples
Genetic abnormalities	Fabry's disease, Gaucher's disease, Hemochromatosis
Connective tissue disorders	Amyloidosis, Diffuse systemic sclerosis, Endocardial fibroelastosis
Other	Carcinoid tumors, Hypereosinophilic syndrom, Radiation, Sarcoidosis

Pathophysiology Endocardial thickening or myocardial infiltration (sometimes with death of myocytes, papillary muscle infiltration, compensatory myocardial hypertrophy, and fibrosis) may occur in one, typically the left, or both ventricles. As a result, the mitral or tricuspid valves may malfunction, leading to regurgitation. Functional AV valve regurgitation may result from myocardial infiltration or endocardial thickening. If nodal and conduction tissues are affected, the sinoatrial node malfunctions, sometimes causing various grades of AV block. The main hemodynamic consequence is diastolic with a rigid, noncompliant ventricle, impaired diastolic filling, and high filling pressure, leading to pulmonary venous hypertension. Systolic function may deteriorate if compensatory hypertrophy of infiltrated or fibrosed ventricles is inadequate. Mural thrombi can form, resulting in systemic emboli.

Symptoms and Signs are exertional dyspnea, orthopnea, and, when the right ventricle is affected, peripheral edema. Fatigue results from a fixed cardiac output due to resistance to ventricular filling. Atrial and ventricular arrhythmias and AV block are common; angina and syncope are uncommon. Symptoms and signs closely mimic those of constrictive pericarditis. Physical examination detects a quiet precordium, a low-volume and rapid carotid pulse, pulmonary crackles, and pronounced neck vein distention with a rapid y descent. In some cases, a murmur of functional mitral or tricuspid regurgitation results because myocardial or endocardial infiltration or fibrosis changes chordae or ventricular geometry.

VALVULAR DISORDERS

Overview of Cardiac Valvular Disorders Any heart valve can become stenotic or insufficient, causing hemodynamic changes long before symptoms. Most often, valvular stenosis or insufficiency occurs in isolation in individual valves, but multiple valvular disorders may coexist and a single valve may be both stenosed and insufficient.

Diagnosis involves echocardiography. Management of a valvular lesion commonly requires only periodic observation, with no active treatment for many years. Intervention is usually indicated only when a moderate or severe valvular lesion causes symptoms or cardiac dysfunction.

Aortic Regurgitation (AR) is incompetency of the aortic valve causing flow from the aorta into the left ventricle during diastole. Causes include idiopathic valvular degeneration, rheumatic fever, endocarditis, myxomatous degeneration, congenital bicuspid aortic valve, aortic root dilatation or dissection, and connective tissue or rheumatologic disorders. Symptoms include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, and chest pain. Signs include widened pulse pressure and an early diastolic murmur. Diagnosis is by physical examination and echocardiography.

Etiology AR may be acute or chronic.

The primary causes of acute AR are

1. Infective endocarditis
2. Dissection of the ascending aorta

Chronic AR in adults is most often caused by

1. Idiopathic degeneration of the aortic valves or root
2. Bicuspid aortic valve
3. Rheumatic fever
4. Infective endocarditis
5. Myxomatous degeneration
6. Trauma

In children, the most common cause is a ventricular septal defect with aortic valve prolapse. Rarely, AR is caused by seronegative spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis), RA, SLE, arthritis associated with ulcerative colitis, luetic (syphilitic) aortitis, osteogenesis imperfecta, thoracic aortic aneurysm, aortic dissection, supravalvular aortic stenosis, Takayasu arteritis, rupture of a sinus of Valsalva, acromegaly, and temporal (giant cell) arteritis. AR due to myxomatous degeneration may develop in patients with Marfan syndrome or Ehlers-Danlos syndrome.

Pathophysiology In chronic AR, left ventricular (LV) volume and stroke volume gradually increase because the LV receives aortic blood regurgitated in diastole in addition to blood from the pulmonary veins and left atrium. LV hypertrophy compensates for the increase in LV volume over years, but decompensation eventually develops. These changes may ultimately cause arrhythmias, LV impairment, and heart failure (HF).

Aortic Stenosis (AS) is narrowing of the aortic valve obstructing blood flow from the left ventricle to the ascending aorta during systole. Causes include a congenital bicuspid valve, idiopathic degenerative sclerosis with calcification, and rheumatic fever. Untreated AS progresses to become symptomatic with one or more of the classic triad of syncope, angina, and exertional dyspnea; heart failure and arrhythmias may develop. A carotid pulse with small amplitude and delayed upstroke and a crescendo-decrescendo ejection murmur are characteristic. Diagnosis is by physical examination and echocardiography. Asymptomatic AS in adults usually requires no treatment.

Etiology. Aortic sclerosis, a degenerative aortic valve disease with thickening of aortic valve structures by fibrosis and calcification initially without causing significant obstruction, is the most common cause of AS in elderly patients. Over years, aortic sclerosis progresses to stenosis in as many as 15 % of patients. Aortic sclerosis resembles atherosclerosis, with deposition of lipoproteins, inflammation and calcification of the valves; risk factors are similar.

The most common cause of AS in patients < 70 yr is a congenital bicuspid aortic valve. Congenital AS occurs in 3 to 5/1000 live births and affects more males; it is associated with coarctation and rapid dilatation of the ascending aorta. In developing countries, rheumatic fever is the most common cause in all age groups. Su-pravalvular AS caused by a discrete, congenital membrane or hypoplastic constriction just above the sinuses of Valsalva is uncommon. A sporadic form of supravalvular AS is associated with a characteristic facies (high and broad forehead, hypertelorism, strabismus, upturned nose, dental abnormalities, puffy cheeks, micrognathia, low-set ears). When associated with idiopathic hypercalcemia of infancy, this form is known as Williams syndrome. Subvalvular AS caused by a congenital membrane or fibrous ring just beneath the aortic valve is uncommon.

Pathophysiology

Aortic regurgitation may accompany AS, and about 60 % of patients > 60 yr with significant AS also have mitral annular calcification, which may lead to significant mitral regurgitation.

The increased pressure load imposed by AS results in compensatory hypertrophy of the left ventricle (LV) without cavity enlargement (concentric hypertrophy). As the pressure gradient across the aortic valve increases, wall stress (afterload) increases, causing LV cavity enlargement, reduced ejection fraction (EF) and a misleadingly low gradient across the aortic valve (low gradient severe AS). Elevated shear stress across the stenosed aortic valve degrades von Willebrand factor multimers. The resulting coagulopathy may cause GI bleeding in patients with angiodysplasia (Heyde syndrome).

Mitral Valve Prolapse (MVP) is a billowing of mitral valve leaflets into the left atrium during systole. The most common cause is idiopathic myxomatous degeneration. MVP is usually benign, but complications include mitral regurgitation, endocarditis, chordal rupture, and possibly thromboembolism. MVP is usually asymptomatic in the absence of important regurgitation, although there are reports that some patients experience chest pain, dyspnea, dizziness, and palpitations. Signs include a crisp mid-systolic click, followed by a late systolic murmur if regurgitation is present. Diagnosis is by physical examination and echocardiography. Prognosis is excellent in the absence of significant regurgitation, but chordal rupture and endocarditis may occur. No specific treatment is necessary unless significant mitral regurgitation is present.

Etiology MVP is most often caused by myxomatous degeneration of the mitral valve and chordae tendineae. Degeneration is usually idiopathic, although it may be inherited in an autosomal dominant or, rarely, in an X-linked recessive fashion. Myxomatous degeneration may also be caused by connective tissue disorders (e.g, Marfan syndrome, Ehlers-Danlos syndrome, adult polycystic kidney disease, osteogenesis imperfecta, pseudoxanthoma elasticum, SLE, polyarteritis nodosa) and muscular dystrophies. MVP is more common among patients with Graves disease, hypomastia, von Willebrand syndrome, sickle cell disease, and rheumatic heart disease. Myxomatous degeneration may also affect the aortic or tricuspid valve, resulting in aortic or tricuspid prolapse. Primary tricuspid regurgitation is much less common than secondary tricuspid regurgitation due to mitral regurgitation (MR).

MR due to MVP may occur in patients with apparently normal mitral valve leaflets (ie, nonmyxomatous) due to papillary muscle dysfunction or rheumatic chordal rupture. MR is the most common complication of MVP. **MR may be acute** (due to ruptured chordae tendineae causing flail mitral valve leaflets) **or chronic**. Sequelae of chronic MR include heart failure and atrial fibrillation (AF) with thromboembolism. Whether MVP causes stroke independent of MR and AF is unclear.

Mitral Regurgitation (MR) is incompetency of the mitral valve causing flow from the left ventricle (LV) into the left atrium during ventricular systole. Common causes include mitral valve prolapse, rheumatic fever, and functional regurgitation secondary to LV dilation or infarction. Complications include progressive heart failure, arrhythmias, and endocarditis. Symptoms and signs include palpitations, dyspnea, and a holosystolic apical murmur. Diagnosis is by physical examination and echocardiography. Prognosis depends on LV function and severity and duration of MR.

Causes of acute MR include

1. Ischemic papillary muscle dysfunction or rupture
2. Infective endocarditis and acute rheumatic fever
3. Myxomatous rupture of the chordae tendinae
4. Acute dilation of the LV due to myocarditis or ischemia
5. Mechanical failure of a prosthetic mitral valve

Common causes of chronic MR include those of acute MR plus

1. Myxomatous mitral valve prolapse (MVP)
2. Functional (distortion of normal valve apparatus by LV dilation or infarction)
3. Rheumatic fever and Infective endocarditis

Uncommon causes of chronic MR include a congenital endocardial cushion defect with a cleft anterior leaflet, SLE, acromegaly, myxoma involving the valve or chordae, and calcification of the mitral annulus (mainly in elderly women). Functional regurgitation occurs through a normal valve that is distorted by LV remodeling. Causes include dilated cardiomyopathy and regional or global myocardial ischemia.

In infants, the most likely causes of MR are papillary muscle dysfunction, endocardial fibroelastosis, acute myocarditis, cleft mitral valve with or without an endocardial cushion defect, and myxomatous degeneration of the mitral valve.

Pathophysiology of acute MR may cause acute pulmonary edema and cardiogenic shock or sudden cardiac death. Complications of chronic MR include gradual enlargement of the left atrium (LA); LV enlargement and eccentric hypertrophy, which initially compensates for regurgitant flow (preserving forward stroke volume) but eventually decompensates (reducing forward stroke volume); atrial fibrillation (AF), which may be further complicated by thromboembolism; and infective endocarditis.

Mitral Stenosis (MS) is narrowing of the mitral orifice that impedes blood flow from the left atrium to the left ventricle. The (almost) invariable cause is rheumatic fever. Common complications are pulmonary hypertension, atrial fibrillation, and thromboembolism. Symptoms are those of heart failure; signs include an opening snap and a diastolic murmur. Diagnosis is by physical examination and echocardiography. Prognosis is good.

In MS, mitral valve leaflets become thickened and immobile and the mitral orifice becomes narrowed due to fusion of the commissures and the presence of shortened, thickened and matted chordae. The most common cause is rheumatic fever, even though many patients do not recall the disorder. Very rare causes include mitral annular calcification, bacterial endocarditis, SLE, atrial myxoma, RA, malignant carcinoid syndrome with an atrial right-to-left shunt. Occasionally, MS is congenital. Left atrial (LA) size and pressure increase progressively to compensate for MS; pulmonary venous and capillary pressures also increase and may cause secondary pulmonary hypertension, leading to right ventricular (RV) heart failure and tricuspid and pulmonic regurgitation. Rate of progression varies. LA enlargement predisposes to atrial fibrillation (AF), a risk factor for thromboembolism. The faster heart rate and loss of atrial contraction with onset of AF often leads to sudden worsening of symptoms.

Pulmonary Regurgitation (PR) is incompetency of the pulmonic valve causing blood flow from the pulmonary artery into the right ventricle during diastole. The most common cause is pulmonary hypertension. PR is usually asymptomatic. Signs include a decrescendo diastolic murmur. Diagnosis is by echocardiography.

Secondary pulmonary hypertension is by far the most common cause of PR. Less common causes are infective endocarditis, surgical repair of tetralogy of Fallot, idiopathic pulmonary artery dilation, and congenital valvular heart disease. Carcinoid syndrome, rheumatic fever, and catheter-induced trauma are rare causes. Severe PR is rare and most often results from an isolated congenital defect involving dilation of the pulmonary artery and pulmonary valve annulus.

PR may contribute to development of right ventricular (RV) dilatation and eventually RV dysfunction–induced heart failure (HF), but in most cases, pulmonary hypertension contributes

to this complication much more significantly. Rarely, acute RV dysfunction–induced HF develops when endocarditis causes acute PR.

Pulmonic Stenosis (PS) is narrowing of the pulmonary outflow tract causing obstruction of blood flow from the right ventricle to the pulmonary artery during systole. Most cases are congenital; many remain asymptomatic until adulthood. Signs include a crescendo-decrescendo ejection murmur. Diagnosis is by echocardiography. Symptomatic patients and those with large gradients require balloon valvuloplasty.

Etiology – PS is most often congenital and affects predominantly children; stenosis may be valvular or just below the valve in the outflow tract (infundibular). It commonly is a component of tetralogy of Fallot. Less common causes are Noonan syndrome (a familial syndrome similar to Turner syndrome but with no chromosomal defect) and carcinoid syndrome in adults.

Tricuspid Regurgitation (TR) is insufficiency of the tricuspid valve causing blood flow from the right ventricle to the right atrium during systole. The most common cause is dilation of the right ventricle. Symptoms and signs are usually absent, but severe TR can cause neck pulsations, a holosystolic murmur, and right ventricular–induced heart failure or atrial fibrillation. Diagnosis is by physical examination and echocardiography. TR is usually benign and does not require treatment, but some patients require annuloplasty or valve repair or replacement.

Etiology. TR is most commonly secondary, caused by dilation of the right ventricle (RV) with malfunction of a normal valve, as occurs in pulmonary hypertension, RV dysfunction–induced heart failure (HF), and pulmonary outflow tract obstruction. TR is less commonly primary, due to valvular abnormalities from infective endocarditis in IV drug abusers, carcinoid syndrome, chest or abdominal injury, rheumatic fever, idiopathic myxomatous degeneration, ischemic papillary muscle dysfunction, congenital defects (eg, cleft tricuspid valve, endocardial cushion defects), Ebstein anomaly (downward displacement of a distorted tricuspid cusp into the RV), Marfan syndrome, and use of certain drugs (e.g, ergotamine, fenfluramine, phentermine). Long-standing severe TR may lead to RV dysfunction–induced HF and atrial fibrillation (AF).

Tricuspid Stenosis (TS) is narrowing of the tricuspid orifice that obstructs blood flow from the right atrium to the right ventricle. Almost all cases result from rheumatic fever. Symptoms include a fluttering discomfort in the neck, fatigue, cold skin, and right upper quadrant abdominal discomfort. Jugular pulsations are prominent, and a presystolic murmur is often heard at the left sternal edge in the 4th intercostal space and is increased during inspiration. Diagnosis is by echocardiography.

TS is almost always due to rheumatic fever; tricuspid regurgitation is almost always present, as is rheumatic mitral valvulopathy (usually mitral stenosis). Rare causes of TS include SLE, right atrial (RA) myxoma, congenital malformations, and metastatic tumors. The RA becomes hypertrophied and distended, and sequelae of right heart disease–induced heart failure develop but without right ventricular (RV) dysfunction; the RV remains underfilled and small. Uncommonly, atrial fibrillation occurs.

Date	Grade	Teacher's signature

CARDIAC ARRHYTHMIAS

Relevance. Diseases of the cardiovascular system, according to the World Health Organization, currently take the first place in the morbidity structure of the world' population and are the most frequent cause of death. Many of them are often accompanied by changes in heart rhythm, leading to important hemodynamic disorders in the body of patients, to disability, and sometimes to death. The doctor needs to know the etiology and pathogenesis of arrhythmias, ECG changes, the principles of etiologic and pathogenic therapy. Modelling of arrhythmias in animals allows us to study some of the etiological factors that cause arrhythmias, and find out some mechanisms of arrhythmias.

Overall Objective is to be able to reproduce the model of the main forms of cardiac rhythm disturbances caused by dysfunction of the pathways of the heart, to explain the causes and mechanisms of their occurrence in order to develop the ability to use etiotropic and pathogenetic treatment of arrhythmias.

The student should be able to (specific objectives):

1) give the definition of "cardiac arrhythmia" and classify them;

2) modulate violations of automatism, excitability and conduction of the heart in the experiment on the frog;

3) write down kymograms arrhythmias and compare them with the normal rhythm to determine the main features of arrhythmias;

4) explain the mechanisms of arrhythmias appearance, their main manifestations on ECG and hemodynamic disturbances in the organism during arrhythmia.

The student should be able to (required knowledge and skills):

1) explain the basic properties of the heart muscle (automatism, excitability, conductivity and contractility) (Depart. of normal physiology);

2) explain the ECG of a healthy person in the standard leads (Depart. of normal physiology);

3) explain the mechanisms of neural and humoral regulation of cardiac activity (Depart. of normal physiology).

QUESTIONS FOR THE LESSON

1. Definition of the concept "arrhythmia". Main causes of arrhythmia. Signs of functional and organic disorders of heart rhythm.
2. Arrhythmias as a result of violation of automatism. Causes. Kinds.
3. Silent sinus node syndrome. Reasons for electrophysiological mechanism, basic ECG signs.
4. Heterotopic cardiac arrhythmias. Types of ectopic rhythms.
5. Migration pacemaker. Reasons basic ECG signs.
6. Arrhythmia occurrence leading to conduction disturbances in the heart. Kinds.
7. Arrhythmia due to slowing down or blockade of impulse conduction in the heart. Causes. Kinds.
8. Syndrome of premature ventricular excitation. Causes. Manifestation. Main ECG signs.
9. Combined cardiac rhythm disorders. Causes, mechanisms, types.
10. Extrasystoles. Mechanism. Causes, types, basic ECG signs.
11. Paroxysmal tachycardia. Mechanism. Forms, Main ECG signs.
12. Flutter and atrial fibrillation. Mechanism. Main ECG signs.
13. Atrial and ventricular fibrillation. Main ECG signs.
14. Electrophysiological mechanisms of cardiac dysfunction.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

Cardiac Conduction and Rhythm Disorders

Heart muscle is unique among other muscles as it is capable of generating and rapidly conducting its own electrical impulses or action potentials. These action potentials result in excitation of muscle fibers throughout the myocardium. Impulse formation and conduction result in weak electrical currents that spread through the entire body. These impulses are recorded

on an electrocardiogram. Disorders of cardiac impulse generation and conduction range from benign arrhythmias that are merely annoying to those causing serious disruption of heart function and sudden cardiac death. Certain areas of the heart, the myocardial cells have been modified to form the specialized cells of the conduction system. Although most myocardial cells are capable of initiating and conducting impulses, it is the conduction system that maintains the pumping efficiency of the heart. Specialized pacemaker cells generate impulses at a faster rate than other types of heart tissue, and the conduction tissue transmits these impulses at a more rapid rate than other cardiac cell types. Because of these properties, the conduction system usually controls the rhythm of the heart. Blood reaches the conduction tissues by way of the coronary blood vessels. Coronary heart disease that interrupts blood flow through the vessels supplying tissues of the conduction system can induce serious and sometimes fatal disturbances in cardiac rhythm. The specialized excitatory and conduction system of the heart consists of the sinoatrial (SA) node, in which the normal rhythmic impulse is generated; the intermodal pathways between the atria and the ventricles; the atrioventricular (AV) node and bundle of His, which conduct the impulse from the atria to the ventricles; and the Purkinje fibers, which conduct the impulses to all parts of the ventricle.

The SA node, which has the fastest intrinsic rate of firing (60 to 100 beats per minute), normally serves as the pacemaker of the heart. It is a spindle-shaped strip of specialized muscle tissue, about 10 to 20 mm in length and 2 to 3 mm wide, located in the posterior wall of the right atrium just below of the opening of the superior vena cava and less than 1 mm from the epicardial surface. Blood supply to the SA node is provided by means of the circumflex artery. It has been suggested that no single cell in the SA node serves as the pacemaker, but rather that sinus nodal cells discharge synchronously because of mutual entrainment. As a result, the firing of faster-discharging cells is slowed down by slower-discharging cells, and the firing rate of slower-discharging cells is sped up by faster discharging cells, resulting in a synchronization of their firing rate. Impulses originating in the SA node travel through the atria to the AV node. Because of the anatomic location of the SA node, the progression of atrial depolarization occurs in an inferior, leftward, and somewhat posterior direction, and the right atrium is depolarized slightly before the left atrium.

There are three internodal pathways between the SA node and the AV node. These three tracts anastomose proximal to the AV node. Interatrial conduction appears to be accomplished through Bachmann's bundle. This large muscle bundle originates along the anterior border of the SA node and travels posteriorly around the aorta to the left atrium. The heart essentially has two conduction systems: one that controls atrial activity and one that controls ventricular activity. The AV node connects the two conduction systems and provides one-way conduction between the atria and ventricles. The AV node is a compact ovoid structure, which is located slightly beneath the right atrial endocardium, anterior to the opening of the coronary sinus, and immediately above the insertion of the septal leaflet of the tricuspid valve. The blood supply to the AV node is provided by the right coronary artery. AV node greatly delays transmission of the impulse. This delay provides a mechanical advantage whereby the atria complete their ejection of blood before ventricular contraction begins. Under normal circumstances, the AV node provides the only connection between the atrial and ventricular conduction systems. The atria and ventricles would beat independently of each other if the transmission of impulses through the AV node were blocked. The Purkinje system, which supplies the ventricles, has large fibers that allow for rapid conduction and almost simultaneous excitation of the entire right and left ventricles (0.06 second). This rapid rate of conduction throughout the Purkinje system is necessary for the swift and efficient ejection of blood from the heart. The fibers of the Purkinje system originate in the AV node and proceed to form the bundle of His, which extends through the fibrous tissue between the valves of the heart and into the ventricular system. Because of its proximity to the aortic valve and the mitral valve ring, the bundle of His is predisposed to inflammation and deposits of calcified debris that can interfere with impulse conduction. The bundle of His penetrates into the ventricles and almost immediately divides into right and left bundle branches that

straddle the interventricular septum. Branches from the anterior and posterior descending coronary arteries provide blood supply for the His bundle, making this conduction site less susceptible to ischemic damage, unless the damage is extensive. The bundle branches move through the subendocardial tissues toward the papillary muscles and then subdivide into the Purkinje fibers, which branch out and supply the outer walls of the ventricles. The main trunk of the left bundle branch extends for approximately 1 to 2 cm before fanning out as it enters the septal area and divides further into two segments: the left posterior and anterior fascicles. The left bundle branch is supplied with blood from both the left anterior descending artery and the posterior descending artery (formed from the right coronary artery), whereas the right bundle branch receives its blood from both the right and left anterior descending coronary arterial systems. The AV nodal fibers, when not stimulated, discharge at an intrinsic discharge rate of 40 to 60 times a minute, and the Purkinje fibers discharge at 15 to 40 times per minute. Although the AV node and Purkinje system have the ability to control the rhythm of the heart, they do not normally do so because the discharge rate of the SA node is considerably faster. Each time the SA node discharges, its impulses are conducted into the AV node and Purkinje fibers, causing them to fire. The AV node can assume the pacemaker function of the heart should the SA node fail to discharge, and the Purkinje system can assume the pacemaker function of the ventricles should the AV node fail to conduct impulses from the atria to the ventricles. Should this occur, the heart rate will reflect the intrinsic firing rate of these structures.

ACTION POTENTIALS. A stimulus delivered to excitable tissues (i.e., muscles, nerves) evokes an electrical event called an action potential. The electrical events that normally take place in the heart are responsible for initiating each cardiac contraction. An action potential can be divided into three phases: the resting or unexcited state, depolarization, and repolarization. The inside of a cardiac cell, like all living cells, contains a negative electrical charge compared with the outside of the cell. During the resting state, the membrane is relatively permeable to potassium but much less so to sodium and calcium. Charges of opposite polarity become aligned along the membrane (positive on the outside and negative on the inside). Depolarization occurs when the cell membrane suddenly becomes selectively permeable to current-carrying ions such as sodium. Sodium ions enter the cell and result in a sharp rise of the intracellular potential to positivity. Repolarization involves reestablishment of the resting membrane potential. It is a complex and somewhat slower process, involving the outward flow of electrical charges and the return of membrane potential to its resting state. During repolarization, the membrane conductance or permeability for potassium greatly increases, allowing the positively charged potassium ions to move outward across the membrane. This outward movement of potassium removes positive charges from inside the cell; thus, the membrane again becomes negative on the inside and positive on the outside. The sodium-potassium membrane pump also assists in repolarization by pumping positively charged sodium ions out across the cell membrane.

Cardiac Action Potential

The action potential in cardiac muscle is typically divided into five phases: phase 0 – upstroke or rapid depolarization, phase 1 – early repolarization period, phase 2 – plateau, phase 3 – final rapid repolarization period, and phase 4 – diastolic depolarization.

Cardiac muscle has three types of membrane ion channels that contribute to the voltage changes that occur during the phases of the cardiac action potential. They are the fast sodium channels, the slow calcium channels, and the potassium channels.

During phase 0, in atrial and ventricular muscle and in the Purkinje system, the fast sodium channels in the cell membrane are stimulated to open, resulting in the rapid influx of sodium. The action potentials in the normal SA and AV nodes have a much slower upstroke and are mediated predominantly by the slow calcium currents.

The point at which the sodium gates open is called the depolarization threshold. When the cell has reached this threshold, a rapid influx of sodium occurs. The exterior of the cell now is negatively charged in relation to the highly positive interior of the cell. This rapid

influx of sodium produces a rapid, positively directed change in the transmembrane potential, resulting in the electrical spike and overshoot during phase 0 of the action potential. The membrane potential shifts from a resting membrane potential of approximately -90 millivolts (mV) to +20 mV. The rapid depolarization that constitutes phase 0 is responsible for the QRS complex on the electrocardiogram (ECG).

Depolarization of a cardiac cell tends to cause adjacent cells to depolarize because the voltage spike of the cell's depolarization stimulates the sodium channels in nearby cells to open.

Therefore, when a cardiac cell is stimulated to depolarize, a wave of depolarization is propagated across the heart, cell by cell.

Phase 1 occurs at the peak of the action potential and signifies inactivation of the fast sodium channels with an abrupt decrease in sodium permeability. The slight downward slope is thought to be caused by the influx of a small amount of negatively charged chloride ions and efflux of potassium. The decrease in intracellular positivity reduces the membrane potential to a level near 0 mV, from which the plateau, or phase 2, arises.

Phase 2 represents the plateau of the action potential. If potassium permeability increased to its resting level at this time, as it does in nerve fibers or skeletal muscle, the cell would repolarize rapidly. Instead, potassium permeability is low, allowing the membrane to remain depolarized throughout the phase 2 plateau. A concomitant influx of calcium into the cell through slow channels contributes to the phase 2 plateau. Calcium ions entering the muscle during this phase also play a key role in the contractile process. These unique features of the phase 2 plateau in these cells cause the action potential of cardiac muscle (several hundred milliseconds) to last 3 to 15 times longer than that of skeletal muscle and cause a corresponding increased period of contraction. The phase 2 plateau coincides with the ST segment of the ECG.

During phase 3 repolarization period, the slow channels close, and the influx of calcium and sodium ceases. There is a sharp rise in potassium permeability, contributing to the rapid outward movement of potassium and reestablishment of the resting membrane potential (-90 mV). At the conclusion of phase 3, the distribution of potassium and sodium returns membrane to the normal resting state. The T wave on the ECG corresponds with phase 3 of the action potential.

Phase 4 represents the resting membrane potential. During phase 4, the activity of the sodium-potassium pump contributes to maintenance of the resting membrane potential by transporting sodium out of the cell and moving potassium back in. Phase 4 corresponds to diastole.

ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) is a graphic recording of the electrical activity of the heart. The electrical currents generated by the heart spread through the body to the skin, where they can be sensed by appropriately placed electrodes, amplified, and viewed on an oscilloscope or chart recorder. The deflection points of an ECG are designated by the letters P, Q, R, S, and T. Depicts the electrical activity of the conduction system on an ECG tracing. The P wave represents the SA node and atrial depolarization; the QRS complex (i.e., beginning of the Q wave to the end of the S wave) depicts ventricular depolarization; and the T wave portrays ventricular repolarization. The isoelectric line between the P wave and the Q wave represents depolarization of the AV node, bundle branches, and Purkinje system. Atrial repolarization occurs during ventricular depolarization and is hidden in the QRS complex. The ECG records the potential difference in charge (in millivolts) between two electrodes as depolarization and repolarization waves move through the heart and are conducted to the skin surface.

The shape of the recorder tracing is determined by the direction in which the impulse spreads through the heart muscle in relation to electrode placement. A depolarization wave that moves toward the recording electrode registers as a positive, or upward, deflection. Conversely, if the impulse moves away from the recording electrode, the deflection is downward, or negative.

When there is no flow of charge between electrodes, the potential is zero, and a straight line is recorded at the baseline of the chart. The ECG recorder is much like a camera in that it

can record different views of the electrical activity of the heart, depending on where the recording electrode is placed. The horizontal axis of the ECG measures time (seconds), and the vertical axis measures the amplitude of the impulse (millivolts). Each heavy vertical line represents 0.2 second, and each thin line represents 0.04 second.

The widths of ECG complexes are commonly referred to in terms of duration of time. On the vertical axis, each heavy horizontal line represents 0.5 mV. The connections of the ECG are arranged such that an upright deflection indicates a positive potential and a downward deflection indicates a negative potential. Although the vertical axis determines amplitude in terms of voltage, these values frequently are communicated as millimeters of positive or negative deflection rather than in millivolts.

Conventionally, 12 leads (6 limb leads and 6 chest leads) are recorded for a diagnostic ECG, each providing a unique view of the electrical forces of the heart from a different position on the body's surface. The six limb leads view the electrical forces as they pass through the heart on the frontal or vertical plane. The six chest leads provide a view of the electrical forces as they pass through the heart on the horizontal plane. The goals of continuous bedside cardiac monitoring have shifted from simple heart rate and arrhythmia monitoring to identification of ST-segment changes, advanced arrhythmia identification, diagnosis, and treatment. Many diagnostic criteria are lead specific. The selected monitoring leads must maximize the potential for accurately identifying anticipated arrhythmias and ischemic events according to the patient's underlying clinical situation.

Disorders of Cardiac Rhythm and Conduction

There are two types of disorders of the cardiac conduction system: disorders of rhythm and disorders of impulse conduction. The terms dysrhythmia and arrhythmia have sometimes been used interchangeably to describe disorders of cardiac rhythm. Marriott has pointed out that the term arrhythmia was originally based on the usage of the alpha privative (the prefix a-) to imply "imperfection in" as opposed to "absence of" cardiac rhythms. However, Marriott further pointed out that the term dysrhythmia has not been generally accepted, and conventional use of the term arrhythmia continues. Therefore, the term arrhythmia will be used throughout this chapter. There are many causes of cardiac arrhythmias and conductions disorders, including congenital defects or degenerative changes in the conduction system, myocardial ischemia and infarction, fluid and electrolyte imbalances, and the effects of drug ingestion. Arrhythmias are not necessarily pathologic; they can occur in both healthy and diseased hearts. Disturbances in cardiac rhythms exert their harmful effects by interfering with the heart's pumping ability. Excessively rapid heart rates (tachyarrhythmias) reduce the diastolic filling time, causing a subsequent decrease in the stroke volume output and in coronary perfusion while increasing the myocardial oxygen needs. Abnormally slow heart rates (bradyarrhythmias) may impair the blood flow to vital organs such as the brain.

Mechanisms of arrhythmias and conduction disorders

The specialized cells in the conduction system manifest four inherent properties that contribute to the genesis of all cardiac rhythms, both normal and abnormal. They are automaticity, excitability, conductivity, and refractoriness. An alteration in any of these four properties may produce arrhythmias or conduction defects. The ability of certain cells in the conduction system to initiate an impulse or action potential spontaneously is referred to as automaticity. The SA node has an inherent discharge rate of 60 to 100 times per minute. It normally acts as the pacemaker of the heart because it reaches the threshold for excitation before other parts of the conduction system have recovered sufficiently to be depolarized. If the SA node fires more slowly or SA node conduction is blocked, another site that is capable of automaticity takes over as pacemaker. Other regions that are capable of automaticity include the atrial fibers that have plateau-type action potentials, the AV node, the bundle of His, and the bundle branch Purkinje fibers. These pacemakers have a slower rate of discharge than the SA node. The AV node has an inherent firing rate of 40 to 60 times per minute, and the Purkinje system fires at a rate of 20 to 40 times

per minute. The SA node may be functioning properly, but because of additional precipitating factors, other cardiac cells can assume accelerated properties of automaticity and begin to initiate impulses. These additional factors might include injury, hypoxia, electrolyte disturbances, enlargement or hypertrophy of the atria or ventricles, and exposure to certain chemicals or drugs. An **ectopic pacemaker** is an excitable focus outside the normally functioning SA node. These pacemakers can reside in other parts of the conduction system or in muscle cells of the atria or ventricles. A premature contraction occurs when an ectopic pacemaker initiates a beat. Premature contractions do not follow the normal conduction pathways, they are not coupled with normal mechanical events, and they often render the heart refractory or incapable of responding to the next normal impulse arising in the SA node. They occur without incident in persons with healthy hearts in response to sympathetic nervous system stimulation or other stimulants such as caffeine. In the diseased heart, premature contractions may lead to more serious arrhythmias. **Excitability** describes the ability of a cell to respond to an impulse and generate an action potential. Myocardial cells that have been injured or replaced by scar tissue do not possess normal excitability. For example, during the acute phase of an ischemic event, involved cells become depolarized. These ischemic cells remain electrically coupled to the adjacent nonischemic area; current from the ischemic zone can induce reexcitation of cells in the nonischemic zone. **Conductivity** is the ability to conduct impulses, and **refractoriness** refers to the extent to which the cell is able to respond to an incoming stimulus. The refractory period of cardiac muscle is the interval in the repolarization period during which an excitable cell has not recovered sufficiently to be reexcited. Disturbances in conductivity or refractoriness predispose to arrhythmias. Almost all tachyarrhythmias are the result of a phenomenon known as **reentry.** Under normal conditions, an electrical impulse is conducted through the heart in an orderly, sequential manner. The electrical impulse then dies out and does not reenter adjacent tissue because that tissue has already been depolarized and is refractory to immediate stimulation. However, fibers that were not activated during the initial wave of depolarization can recover excitability before the initial impulse dies out, and they may serve as a link to reexcite areas of the heart that were just discharged and have recovered from the initial depolarization. This activity disrupts the normal conduction sequence. For reentry to occur, there must be areas of slow conduction and unidirectional conduction block. For previously depolarized areas to repolarize adequately to conduct an impulse again, slow conduction is necessary. Unidirectional block is necessary to provide a one-way route for the original impulse to reenter, thereby blocking other impulses entering from the opposite direction from extinguishing the reentrant circuit. Reentry requires a triggering stimulus such as an extrasystole. If sufficient time has elapsed for the refractory period in the reentered area to end, a self-perpetuating, circuitous movement can be initiated. Reentry may occur anywhere in the conduction system. The functional components of a reentry circuit can be large and include an entire specialized conduction system, or the circuit can be microscopic. It can include myocardial tissue, AV nodal cells, junctional tissue, or the ventricles. Factors contributing to the development of a reentrant circuit include ischemia, infarction, and elevated serum potassium levels. Scar tissue interrupts the normally low-resistance paths between viable myocardial cells, slowing conduction, promoting asynchronous myocardial activation, and predisposing to unidirectional conduction block. Specially filtered signal-averaged electrocardiography can be used to detect the resultant late potentials. There are several forms of reentry. The first is anatomic reentry. It consists of an excitation wave that travels in a set pathway. Arrhythmias that arise as a result of anatomic reentry are paroxysmal supraventricular tachycardias, as seen in Wolff-Parkinson-White syndrome, atrial fibrillation, atrial flutter, AV nodal reentry, and some ventricular tachycardias. Functional reentry does not rely on an anatomic structure to circle; rather, it depends on the local differences in conduction velocity. Spiral reentry is the most common form of this type of reentry. It is initiated by a wave of electrical current that does not propagate naturally in its normal plane after meeting refractory tissue. The broken end of the wave curls, forms a vortex, and permanently rotates. This phenomenon suppresses normal pacemaker activity and can result in atrial fibrillation.

Arrhythmias observed with functional reentry are likely to be polymorphic because of charging circuits. Reflection is sometimes considered another form of reentry that can occur in parallel pathways of myocardial tissue or the Purkinje network. With reflection, the cardiac impulse reaches the depressed segment, triggers the surrounding tissue, and then returns in a retrograde direction through the severely depressed region. Reflection differs from true reentry in that the impulse travels along the same pathway in both directions and does not require a circuit.

TYPES OF ARRHYTHMIAS

Sinus Node Arrhythmias. In a healthy heart driven by sinus node discharge, the heart rate ranges between 60 and 100 beats per minute. On the ECG, a P wave may be observed to precede every QRS complex. Historically, normal sinus rhythm has been considered the "normal" rhythm of a healthy heart. In normal sinus rhythm, a P wave precedes each QRS complex, and the RR intervals, which are used to measue heart rate, remain relatively constant over time. Alterations in the function of the SA node lead to changes in rate or rhythm of the heartbeat. Respiratory sinus arrhythmia is a cardiac rhythm characterized by gradual lengthening and shortening of RR intervals. This variation in cardiac cycles is related to intrathoracic pressure changes that occur with respiration and resultant alterations in autonomic control of the SA node. Inspiration causes acceleration of the heart rate, and expiration causes slowing. Respiratory sinus arrhythmia accounts for most heart rate variability in healthy individuals. Decreased heart rate variability has been associated with altered health states, including myocardial infarction, congestive heart failure, hypertension, diabetes mellitus, and prematurity in infants.

Sinus Bradycardia. Sinus bradycardia describes a slow (< 60 beats per minute) heart rate. In sinus bradycardia, a P wave precedes each QRS. A normal P wave and PR interval (0.12 to 0.20 second) indicate that the impulse originated in the SA node rather than in another area of the conduction system that has a slower inherent rate. Vagal stimulation decreases the firing rate of the SA node and conduction through the AV node to cause a decrease in heart rate. This rhythm may be normal in trained athletes, who maintain a large stroke volume, and during sleep. Sinus bradycardia may be an indicator of poor prognosis when it occurs in conjunction with acute myocardial infarction, particularly if associated with hypotension.

Sinus Tachycardia. Sinus tachycardia refers to a rapid heart rate (> 100 beats per minute) that has its origin in the SA node. A normal P wave and PR interval should precede each QRS complex. The mechanism of sinus tachycardia is enhanced automaticity related to sympathetic stimulation or withdrawal of vagal tone. Sinus tachycardia is a normal response during fever and exercise and in situations that incite sympathetic stimulation. It may be associated with congestive heart failure, myocardial infarction, and hyperthyroidism. Pharmacologic agents such as atropine, isoproterenol, epinephrine, and quinidine also can cause sinus tachycardia.

Sinus Arrest. Sinus arrest refers to failure of the SA node to discharge and results in an irregular pulse. An escape rhythm develops as another pacemaker takes over. Sinus arrest may result in prolonged periods of asystole and often predisposes to other arrhythmias.

Sick Sinus Syndrome. Sick sinus syndrome is a term that describes a number of forms of cardiac impulse formation and intra-atrial and AV conduction abnormalities. The syndrome most frequently is the result of total or subtotal destruction of the SA node, areas of nodal–atrial discontinuity, inflammatory or degenerative changes of the nerves and ganglia surrounding the node, or pathologic changes in the atrial wall. In addition, occlusion of the sinus node artery may be a significant contributing factor. The arrhythmias associated with sick sinus syndrome include spontaneous persistent sinus bradycardia that is not drug induced or appropriate for the physiologic circumstances, prolonged sinus pauses, combinations of SA and AV node conduction disturbances, or alternating paroxysms of rapid regular or irregular atrial tachyarrhythmias and periods of slow atrial and ventricular rates (bradycardia-tachycardia syndrome). Most commonly, the term **sick sinus syndrome**is used to refer to the bradycardia-tachycardia syndrome. The bradycardia is caused by disease of the sinus node, and the tachycardia is caused by paroxysmal atrial or junctional arrhythmias.

Arrhythmias of Atrial Origin. Impulses from the SA node pass through the conductive pathways in the atria to the AV node. Arrhythmias of atrial origin include premature atrial contractions, paroxysmal supraventricular tachycardia, atrial flutter, and atrial fibrillation.

Premature Atrial Contraction(PACs) are contractions that originate in the atrial conduction pathways or atrial muscle cells and occur before the next expected SA node impulse. This impulse to contract usually is transmitted to the ventricle and back to the SA node. The location of the ectopic focus determines the configuration of the P wave. In general, the closer the ectopic focus is to the SA node, the more the ectopic complex resembles a normal sinus complex. The retrograde transmission to the SA node often interrupts the timing of the next sinus beat, such that a pause occurs between the two normally conducted beats.

Paroxysmal Supraventricular Tachycardia is sometimes referred to as paroxysmal atrial tachycardia. This term includes all tachyarrhythmias that originate above the bifurcation of the bundle of His and have a sudden onset and termination. They may be the result of AV nodal reentry, Wolff- Parkinson-White syndrome (caused by an accessory conduction pathway between the atria and ventricles), or intraatrial or sinus node reentry. Paroxysmal supraventricular tachycardias tend to be recurrent and of short duration.

Reentry is the circular propagation of an impulse around 2 interconnected pathways with different conduction characteristics and refractory periods.

Atrioventricular nodal reentry is used here as an example. Two pathways connect the same points. Pathway A has slower conduction and a shorter refractory period. Pathway B conducts normally and has a longer refractory period.

I. A normal impulse arriving at 1 goes down both A and B pathways. Conduction through pathway A is slower and finds tissue at 2 already depolarized and thus refractory. A normal sinus beat results.

II. A premature impulse finds pathway B refractory and is blocked, but it can be conducted on pathway A because its refractory period is shorter. On arriving at 2, the impulse continues forward and retrograde up pathway B, where it is blocked by refractory tissue at 3. A premature supraventricular beat with an increased PR interval results.

III. If conduction over pathway A is sufficiently slow, a premature impulse may continue retrograde all the way up pathway B, which is now past its refractory period. If pathway A is also past its refractory period, the impulse may reenter pathway A and continue to circle, sending an impulse each cycle to the ventricle (4) and retrograde to the atrium (5), producing a sustained reentrant tachycardia (***Fig. 5*).**

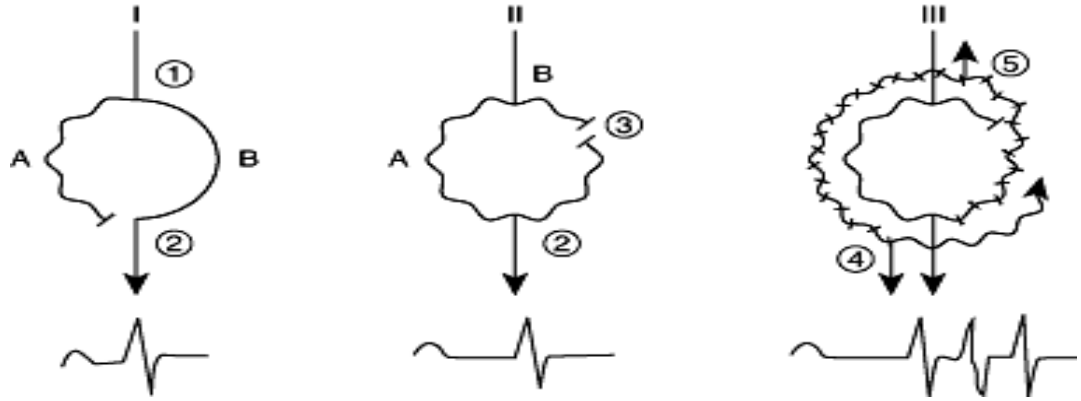


Fig. 5. Mechanism of typical reentry

Atrial Flutter

Atrial flutter is a rapid regular atrial rhythm due to an atrial macroreentrant circuit. Symptoms include palpitations and sometimes weakness, effort intolerance, dyspnea, and presyncope. Atrial thrombi may form and embolize. Diagnosis is by ECG.

Atrial flutter is much less common than atrial fibrillation, but its causes and hemodynamic consequences are similar. Many patients with atrial flutter also have periods of atrial fibrillation.

Typical atrial flutter is due to a large reentrant circuit involving most of the right atrium. The atria depolarize at a rate of 250 to 350 beats/min (typically 300 beats/min). Because the atrioventricular (AV) node cannot usually conduct at this rate, typically half of the impulses get through (2: block), resulting in a regular ventricular rate of 150 beats/min. Sometimes the block varies from moment to moment, causing an irregular ventricular rhythm. Less commonly, a fixed 3:1, 4:1, or 5:1 block may be present. The probability of a thromboembolic event, once considered rare in atrial flutter, is now thought to be about half of that in atrial fibrillation (unless atrial fibrillation is also occurring).

Symptoms and Signs depend primarily on ventricular rate and the nature of any underlying heart disorder. If ventricular rate is < 120 beats/min and regular, there are likely to be few or no symptoms. Faster rates and variable AV conduction usually cause palpitations, and decreased cardiac output may cause symptoms of hemodynamic compromise (e.g, chest discomfort, dyspnea, weakness, syncope). Close inspection of the jugular venous pulse reveals flutter a waves.

Diagnosis. The diagnosis is by ECG. In typical flutter, ECG shows continuous and regular atrial activation with a saw tooth pattern, most obvious in leads II, III, and aVF.

Carotid sinus massage can increase AV block and better expose the typical flutter waves. A similar response may follow pharmacologic AV nodal blockade (e.g, with adenosine), but such therapy does not terminate atrial flutter.

Junctional Arrhythmias

The AV node can act as a pacemaker in the event the SA node fails to initiate an impulse. Junctional rhythms can be transient or permanent, and they usually have a rate of 40 to 60 beats per minute. Junctional fibers in the AV node or bundle of His also can serve as ectopic pacemakers, producing premature junctional complexes. Another rhythm originating in the junctional tissues is nonparox-ysmal junctional tachycardia. This rhythm usually is of gradual onset and termination. However, it may occur abruptly if the dominant pacemaker slows sufficiently. The rate associated with junctional tachycardia ranges from 70 to 130 beats per minute, but it may be faster. The P waves may precede, be buried in, or follow the QRS complexes, depending on the site of the originating impulses. Clinical significance of non-paroxysmal junctional tachycardia is the same as for atrial tachycardias. Non- paroxysmal junctional tachycardia is observed most frequently in individuals with underlying heart disease, such as inferior wall myocardial infarction or myocarditis, or after open-heart surgery.

Disorders of Ventricular Conduction and Rhythm

Junctional fibers in the AV node join with the bundle of His, which divides to form the right and left bundle branches. The bundle branches continue to divide and form the Purkinje fibers, which supply the walls of the ventricles. As the cardiac impulse leaves the junctional fibers, it travels through the AV bundle. Next, the impulse moves down the right and left bundle branches that lie beneath the endocardium on either side of the septum. It then spreads out through the walls of the ventricles. Interruption of impulse conduction through the bundle branches is called bundle branch block. These blocks usually do not cause alterations in the rhythm of the heartbeat. Instead, a bundle branch block interrupts the normal progression of depolarization, causing the ventricles to depolarize one after the other because the impulses must travel through muscle tissue rather than through the specialized conduction tissue. 35 This prolonged conduction causes the QRS complex to be wider than the normal 0.04 to 0.10 second. The left bundle branch bifurcates into the left anterior and posterior fascicles. An interruption of one of these fascicles is referred to as a hemiblock.

Long QT Syndrome and Torsades de Pointes (LQTS) is characterized by prolongation of the QT interval that may result in a characteristic type of polymorphic ventricular tachycardia called torsades de pointes and sudden cardiac death. 36–38 Torsades de pointes (twisting or rotating around a point) is a specific type of ventricular tachycardia. The term refers to the polarity of the QRS complex, which swings from positive to negative and vice versa. The QRS abnormality is characterized by large, bizarre, polymorphic QRS complexes

that vary, often from beat to beat, in amplitude and direction, as well as in rotation of the complexes around the isoelectric line.

The rate of tachycardia is 100 to 180 beats per minute but can be as fast as 200 to 300 beats per minute. The rhythm is highly unstable and may terminate in ventricular fibrillation or revert to sinus rhythm. LQTS is caused by various agents and conditions that reduce the magnitude of outward repolarizing potassium currents, enhance the magnitude of the inward depolarizing sodium and calcium currents, or both. Thus, there is delayed repolarization of the ventricles with development of early depolarizing after potentials that initiate the arrhythmia. Typically, the QT interval is measured in a lead in which the T-wave is prominent and its end is easily distinguished, such as V2 or V3. Because the QT interval shortens with tachycardia and lengthens with bradycardia, it is typically corrected for heart rate and is noted as QTc. In addition, T-wave morphology frequently is abnormal in patients with LQTS. LQTS has been classified into hereditary and acquired forms, both of which are associated with the development of torsades de pointes and sudden cardiac death. The hereditary forms of LQTS are caused by disorders of membrane ion-channel proteins, with either potassium channel defects or sodium channel defects. In some cases, the disorder may result from a gene defect that alters the function of a single ion channel. The gene mutations that result in congenital LQTS have been identified on chromosomes 3, 4, 7, 11, and 21. The hereditary forms of LQTS are typically considered adrenergic dependent because they are generally triggered by increased activity of the sympathetic nervous system. Acquired LQTS has been linked to a variety of conditions, including cocaine use, exposure to organophosphorous compounds, electrolyte imbalances, marked bradycardia, myocardial infarction, subarachnoid hemorrhage, autonomic neuropathy, human immunodeficiency virus HIV infection, and protein-sparing fasting. Medications linked to LQTS include digitalis, anti-arrhythmic agents (e.g., amiodarone, procainamide, and quinidine), verapamil (calcium channel blocker), haloperidol (antipsychotic agent), and erythromycin (antibiotic). The acquired forms of LQTS are often classified as pause dependent because the torsades associated with them generally occurs at slow heart rates or in response to short-longshort RR-interval sequences.

Ventricular Arrhythmias that arise in the ventricles commonly are considered more serious than those that arise in the atria because they afford the potential for interfering with the pumping action of the heart.

Premature Ventricular Contractions. A premature ventricular contraction (PVC) is caused by a ventricular ectopic pacemaker. After a PVC, the ventricle usually is unable to repolarize sufficiently to respond to the next impulse that arises in the SA node. This delay is commonly referred to as a compensatory pause, which occurs while the ventricle waits to reestablish its previous rhythm. When a PVC occurs, the diastolic volume usually is insufficient for ejection of blood into the arterial system. As a result, PVCs usually do not produce a palpable pulse, or the pulse amplitude is significantly diminished. In the absence of heart disease, PVCs typically are not clinically significant. The incidence of PVCs is greatest with ischemia, acute myocardial infarction, history of myocardial infarction, ventricular hypertrophy, infection, increased sympathetic nervous system activity, or increased heart rate. PVCs also can be the result of electrolyte disturbances or medications. A special pattern of PVC called ventricular bigeminy is a condition in which each normal beat is followed by or paired with a PVC. The occurrence of frequent PVCs in the diseased heart predisposes the patient to the development of other, more serious arrhythmias, including ventricular tachycardia and ventricular fibrillation.

Ventricular Tachycardia. Ventricular tachycardia describes a cardiac rhythm originating distal to the bifurcation of the bundle of His, in the specialized conduction system in ventricular muscle, or both.

Ventricular tachycardia (middle tracing) is characterized by a rapid ventricular rate of 70 to 250 beats per minute and the absence of P waves. In ventricular fibrillation (bottom tracing), there are no regular or effective ventricular contractions, and the ECG tracing is totally disorganized. Ventricular rate of 70 to 250 beats per minute, and the onset can be sudden or

insidious. Usually, ventricular tachycardia is exhibited electrocardiographically by wide, tall, bizarre-looking QRS complexes that persist longer than 0.10 second. QRS complexes can be uniform in appearance, or they can vary randomly, in a repetitive manner (e.g., torsades de pointes), in an alternating pattern (e.g., bidirectional), or in a stable but changing fashion. Ventricular tachycardia can be sustained, lasting more than 30 seconds and requiring intervention, or it can be nonsustained and stop spontaneously. This rhythm is dangerous because it eliminates atrial kick and can cause a reduction in diastolic filling time to the point at which cardiac output is severely diminished or nonexistent.

Ventricular Flutter and Fibrillation. These arrhythmias represent severe derangements of cardiac rhythm that terminate fatally within minutes unless corrective measures are taken promptly. The ECG pattern in ventricular flutter has a sine wave appearance with large oscillations occurring at a rate of 150 to 300 per minute. In ventricular fibrillation, the ventricle quivers but does not contract. The classic ECG pattern of ventricular fibrillation is that of gross disorganization without identifiable waveforms or intervals. When the ventricles do not contract, there is no cardiac output, and there are no palpable or audible pulses. The immediate defibrillation using a nonsynchronized DC electrical shock is mandatory for ventricular fibrillation and for ventricular flutter that has caused loss of consciousness.

Disorders of Atrioventricular Conduction

Under normal conditions, the AV junction, which consists of the AV node with its connections to the entering atrial internodal pathways, the AV bundle, and the nonbranching portion of the bundle of His, provides the only connection for transmission of impulses between the atrial and ventricular conduction systems. Junctional fibers in the AV node have high-resistance characteristics that cause a delay in the transmission of impulses from the atria to the ventricles. This delay provides optimal timing for atrial contribution to ventricular filling and protects the ventricles from abnormally rapid rates that arise in the atria. Conduction defects of the AV node are most commonly associated with fibrosis or scar tissue in fibers of the conduction system. Conduction defects also may result from medications, including digoxin, в-adrenergic–blocking agents, calcium channel–blocking agents, and class 1A antiarrhythmic agents. Additional contributing factors include electrolyte imbalances, inflammatory disease, or cardiac surgery.

Heart block refers to abnormalities of impulse conduction. It may be normal, physiologic (e.g., vagal tone), or pathologic. It may occur in the AV nodal fibers or in the AV bundle, which is continuous with the Purkinje conduction system that supplies the ventricles. The PR interval on the ECG corresponds with the time it takes for the cardiac impulse to travel from the SA node to the ventricular pathways. Normally, the PR interval ranges from 0.12 to 0.20 second.

First-Degree AV Block. First-degree AV block is characterized by a prolonged PR interval (exceeds 0.20 second). The prolonged PR interval indicates delayed AV conduction, but all atrial impulses are conducted to the ventricles. This condition usually produces a regular atrial and ventricular rhythm. Clinically significant PR interval prolongation can result from conduction delays in the AV node itself, the His-Purkinje system, or both. When the QRS complex is normal in contour and duration, the AV delay almost always occurs in the AV node and rarely in the bundle of His. In contrast, when the QRS complex is prolonged, showing a bundle branch block pattern, conduction delays may be in the AV node or the His-Purkinje system. First-degree block may be the result of disease in he AV node such as ischemia or infarction, or of infections such as rheumatic fever or myocarditis. 48–50 Isolated first-degree heart block usually is not symptomatic, and temporary or permanent cardiac pacing is not indicated.

Second-Degree AV Block. Second-degree AV block is characterized by intermittent conduction failure n of one or more impulses from the atria to the ventricles. The nonconducted P wave can appear intermittently or frequently. A distinguishing feature of second-degree AV block is that conducted P waves relate to QRS complexes with recurring PR intervals; that is, the association of P waves with QRS complexes is not random. 1 Second-degree AV block has been divided into two types: type I (i.e., Mobitz type I or Wenckebach's

phenomenon) and type II (i.e., Mobitz type II). A Mobitz type I AV block is characterized by progressive lengthening of the PR interval until an impulse is blocked and the sequence begins again. It frequently occurs in persons with inferior wall myocardial infarction, particularly with concomitant right ventricular infarction. The condition is usually associated with an adequate ventricular rate and rarely is symptomatic. It is transient and does not require temporary pacing. In the Mobitz type II AV block, an intermittent block of atrial impulses occurs with a constant PR interval. It frequently accompanies anterior wall myocardial infarction and can require temporary or permanent pacing. This condition is associated with a high mortality rate. In addition, Mobitz type II AV block is associated with other types of organic heart disease and often progresses to complete heart block.

Third-Degree AV Block. Third-degree, or complete, AV block occurs when the conduction link for all impulses from the SA node and atria through the AV node is blocked, resulting in depolarization of the atria and ventricles being controlled by separate pacemakers. The atrial pacemaker can be sinus or ectopic in origin. The ventricular pacemaker usually is located just below the region of the block. The atria usually continue to beat at a normal rate, and the ventricles develop their own rate, which normally is slow (30 to 40 beats per minute). The atrial and ventricular rates are regular but dissociated. Third-degree AV block can result from an interruption at the level of the AV node, in the bundle of His, or in the Purkinje system. Third-degree blocks at the level of the AV node usually are congenital, whereas blocks in the Purkinje system usually are acquired. Normal QRS complexes, with rates ranging from 40 to 60 complexes per minute, usually are displayed on the ECG when the block occurs proximal to the bundle of His. Complete heart block causes a decrease in cardiac output with possible periods of syncope (fainting), known as a **Stokes-Adams attack**. Most persons with complete heart block require a cardiac pacemaker.

Reentrant Supraventricular Tachycardias (SVT, PSVT)

Reentrant supraventricular tachycardias (SVT) involve reentrant pathways with a component above the bifurcation of the His bundle. Patients have sudden episodes of palpitations that begin and terminate abruptly; some have dyspnea or chest discomfort. Diagnosis is clinical and by ECG. Treatment is with vagotonic maneuvers and, if they are ineffective, with IV adenosine or nondihydropyridine Ca channel blockers for narrow QRS rhythms or for wide QRS rhythms known to be a reentrant SVT with aberrant conduction that requires atrioventricular nodal conduction.

Pathophysiology. The reentry pathway in supraventricular tachycardia is within the atrioventricular (AV) node in about 50 %, involves an accessory bypass tract in 40 %, and is within the atria or sinoatrial (SA) node in 10 %. AV nodal reentrant tachycardia occurs most often in otherwise healthy patients. It is most commonly triggered by an atrial premature beat. Accessory pathway reentrant tachycardia involves tracts of conducting tissue that partially or totally bypass normal AV connections (bypass tracts). They run most commonly from the atria directly to the ventricles and less commonly from the atrium to a portion of the conduction system or from a portion of the conduction system to the ventricle. They can be triggered by atrial premature beats or ventricular premature beats.

Wolff-Parkinson-White (WPW) syndrome: WPW (preexcitation) syndrome is the most common accessory pathway SVT, occurring in about 1 to 3/1000 people. WPW syndrome is mainly idiopathic, although it is more common among patients with hypertrophic or other forms of cardiomyopathy, transposition of the great vessels, or Epstein's anomaly. In classic (or manifest) WPW syndrome, antegrade conduction occurs over both the accessory pathway and the normal conducting system during sinus rhythm. The accessory pathway, being faster, depolarizes some of the ventricle early, resulting in a short PR interval and a slurred upstroke to the QRS complex.

The delta wave prolongs QRS duration to > 0.12 sec, although the overall configuration, apart from the delta wave, may appear normal. Depending on the orientation of the delta wave, a pseudoinfarction pattern Q-wave may be present. Because the early depolarized parts of the ventricle also repolarize early, the T-wave vector may be abnormal.

In concealed WPW syndrome, the accessory pathway does not conduct in an antegrade direction; consequently, the above ECG abnormalities do not appear. However, it conducts in a retrograde direction and thus can participate in reentrant tachycardia.

In the most common form of reentrant tachycardia (called orthodromic reciprocating tachycardia), the circuit uses the normal AV conduction pathway to activate the ventricles, returning to the atrium via the accessory AV connection. The resultant QRS complex is thus narrow (unless bundle branch block coexists) and without a delta wave. Orthodromic reciprocating tachycardia is typically a short RP tachycardia with the retrograde P wave in the ST segment.

The reentrant circuit rarely revolves in the opposite direction from the atrium to the ventricle via the accessory AV connection, and returns from the ventricle in the retrograde direction up the normal AV conduction system (called antidromic reciprocating tachycardia). The QRS complex is wide because the ventricles are activated abnormally. In patients with 2 accessory AV connections (not uncommon), a reciprocating tachycardia using one accessory connection in the antegrade direction and the other in the retrograde direction may occur. Tachycardias in WPW syndrome may begin as or degenerate into atrial fibrillation (AF), which can be very dangerous. Enlarged atria due to hypertrophic and other forms of cardiomyopathy makes patients with WPW syndrome more prone to AF.

Symptoms and Signs. Most patients are in young adulthood or middle age. They typically have episodes of sudden-onset, sudden-offset, rapid, regular palpitations often associated with symptoms of hemodynamic compromise (e.g, dyspnea, chest discomfort, light-headedness). Attacks may last only a few seconds or persist for several hours. Infants present with episodic breathlessness, lethargy, feeding problems, or rapid precordial pulsations. If the episode of tachycardia is protracted, they may present with heart failure. Examination is usually unremarkable except for a heart rate of 160 to 240 beats/min.

Diagnosis is by ECG showing rapid, regular tachycardia. Previous tracings, if available, are reviewed for signs of manifest WPW syndrome. In most cases of AV node reentry, retrograde P waves are in the terminal portion of the QRS complex (often producing a pseudo-R′ deflection in lead V_1); about one third occur just after the QRS complex, and very few occur before. P waves always follow the QRS complex in orthodromic reciprocating tachycardia of WPW syndrome.

QRS complex is narrow except with coexisting bundle branch block, antidromic tachycardia, or dual accessory connection reciprocating tachycardia. Wide-complex tachycardia must be distinguished from ventricular tachycardia.

Atrial Fibrillation and Wolff-Parkinson-White Syndrome (WPW)

Atrial fibrillation (AF) is a medical emergency when rapid antegrade conduction over an accessory pathway occurs in Wolff-Parkinson-White (WPW) syndrome.

In manifest WPW syndrome, antegrade conduction occurs over the accessory pathway. If AF develops, the normal rate-limiting effects of the atrioventricular (AV) node are bypassed, and the resultant excessive ventricular rates (sometimes 200 to 240 beats/min) may lead to ventricular fibrillation and sudden death. Patients with concealed WPW syndrome are not at risk because in them, antegrade conduction does not occur over the accessory connection.

Atrial Fibrillation. Atrial fibrillation is characterized by chaotic impulses propagating in different directions and causing disorganized atrial depolarizations without effective atrial contraction. In most cases, multiple, small reentrant circuits are constantly arising in the atria, colliding, being extinguished, and arising again. Fibrillation occurs when the atrial cells cannot repolarize in time for the next incoming stimulus. Atrial fibrillation is characterized on the ECG by a grossly disorganized pattern of atrial electrical activity that is irregular with respect to rate and rhythm and the absence of discernible P waves. Atrial activity is depicted by fibrillatory (f) waves of varying amplitude, duration, and morphology. These f waves appear as random oscillation of the baseline. Because of the random conduction through the AV node, QRS complexes appear in an irregular pattern. Atrial fibrillation is the only common arrhythmia in which the ventricular rate is rapid and the rhythm irregular. The atrial rate typically ranges from 400 to

600 beats per minute, with many impulses blocked at the AV node. The ventricular response is completely irregular, ranging from 80 to 180 beats per minute in the untreated state. Because of changes in stroke volumes resulting from varying periods of diastolic filling, not all ventricular beats produce a palpable pulse. The difference between the apical rate and the palpable peripheral pulses is called the pulse deficit. The pulse deficit may increase when the ventricular rate is high. Atrial fibrillation may appear paroxysmally or as a chronic phenomenon. It can be seen in persons without any apparent disease, or it may occur in individuals with coronary artery disease, mitral valve disease, ischemic heart disease, hypertension, myocardial infarction, pericarditis, congestive heart failure, digitalis toxicity, and hyperthyroidism. Spontaneous conversion to sinus rhythm within 24 hours of atrial fibrillation is common, occurring in up to two thirds of persons with the disorder. Once the duration exceeds 24 hours, the likelihood of conversion decreases, and after 1 week of persistent arrhythmia, spontaneous conversion is rare.

The symptoms of chronic atrial fibrillation vary. Some people have minimal symptoms, and others have severe symptoms, particularly at the onset of the arrhythmia. he symptoms may range from palpitations to acute pulmonary edema. Fatigue and other nonspecific symptoms are common in the elderly. The condition predisposes individuals to thrombus formation in the atria, with subsequent risk for embolic stroke.

Diagnostic methods. Disorders of cardiac rhythm and conduction are usually diagnosed based on the surface ECG. Further clarification of conduction defects and cardiac arrhythmias can be obtained using electrophysiologic studies. A resting surface ECG records the impulses originating in the heart as they are recorded at the body surface. These impulses are recorded for a limited time and during periods of inactivity. Although there are no complications related to the procedure, errors related to misdiagnosis may result in iatrogenic heart disease.

Holter Monitoring. Holter monitoring is one form of a long-term monitoring during which a person wears a device that digitally records two or three ECG leads for up to 48 hours. During this time, the person keeps a diary of his or her activities or symptoms, which later are correlated with the ECG recording. Most recording devices also have an event marker button that can be pressed when the individual experiences symptoms, which assists the technician or physician in correlating the diary, symptoms, and ECG changes during analysis. Holter monitoring is useful for documenting arrhythmias, conduction abnormalities, and ST-segment changes. The interpretative accuracy of long-term Holter recordings varies with the system used and clinician expertise. Most computer soft ware packages used to scan Holter recordings are sufficiently accurate to meet clinical demand

Date	Grade	Teacher’s signature

CORONAROGENIC MYOCARDIAL DAMAGE. CORONARY INSUFFICIENCY. ISCHEMIC HEART DISEASE. MYOCARDIAL INFARCTION. CARDIOGENIC SHOCK

Relevance. Heart failure is one of the frequent causes of incapacitation, disability and death of patients suffering from the diseases of the cardiovascular system. The study of the etiology and pathogenesis of these menacing disease forms is necessary for a practice doctor, as heart failure arises from different causes and mechanisms. This knowledge of the causes and mechanisms of pathology facilitates development of clinical thinking, rational choice approaches to treatment of each patient. Studying heart failure in the experiment on the animal can reveal the mechanisms of its development.

Overall Objective is be able to characterize heart failure, to explain main causes and mechanisms of development.

The student should be able to (specific objectives):

1. Disclose the essence of the notion «heart failure».
2. To classify the causes and mechanisms of heart failure.

3. Allocate the main manifestations of heart failure, to explain the mechanisms of their appearance and development.

4. Model acute heart failure on a rat, to explain the mechanisms of compensation and decom-pensation during the experiment.

The student should be able to (required knowledge and skills):

1. Explain the mechanism of heart rate (Depart. of normal physiology).
2. Explain the role of cardiac and extracardiac mechanisms in the regulation of the heart function (Depart. of normal physiology).
3. Interpret the main indicators of the heart function (Depart. of normal physiology).
4. Explain the effect of a changing heart rate and stroke volume values of the efficiency of the heart function (Depart. of normal physiology).

QUESTIONS TO THE LESSON

1. Coronarogenic heart damage.
2. Ischemic heart disease, myocardial infarction. The pathogenesis of ECG changes.
3. Coronary insufficiency. Definition of the notions. Causes. Myocardial reperfusion.
4. Reversible and irreversible damage of coronary blood flow.
5. Cardiogenic shock. Pathogenesis.
6. The experimental model of myocardial necrosis.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

CORONARY ARTERY DISEASE

Coronary artery disease (CAD) involves impairment of blood flow through the coronary arteries, most commonly by atheromas. Clinical presentations include silent ischemia, angina pectoris, acute coronary syndromes (unstable angina, MI), and sudden cardiac death. Diagnosis is by symptoms, ECG, stress testing, and sometimes coronary angiography. Prevention consists of modifying reversible risk factors (eg, hypercholesterolemia, hypertension, physical inactivity, obesity, and smoking).

In the developed countries, CAD is the leading cause of death in both sexes, accounting for about one third of all deaths. Mortality rate among white men is about 1/10,000 at ages 25 to 34 and nearly 1/100 at ages 55 to 64. Mortality rate among white men aged 35 to 44 is 6.1 times that among age-matched white women. For unknown reasons, the sex difference is less marked in nonwhites. Mortality rate among women increases after menopause and, by age 75, equals or even exceeds that of men.

Etiology. CAD is usually due to subintimal deposition of atheromas in large and medium-sized coronary arteries. Less often, CAD is due to coronary spasm. Rare causes include coronary artery embolism, dissection, aneurysm (e.g, in Kawasaki disease), and vasculitis (e.g, in SLE, syphilis).

Pathophysiology. Coronary atherosclerosis is often irregularly distributed in different vessels but typically occurs at points of turbulence (e.g, vessel bifurcations). As the atheromatous plaque grows, the arterial lumen progressively narrows, resulting in ischemia (often causing angina pectoris). The degree of stenosis required to produce ischemia varies with O_2 demand.

Occasionally, an atheromatous plaque ruptures or splits. Reasons are unclear but probably relate to plaque morphology, plaque Ca content, and plaque softening due to an inflammatory process. Rupture exposes collagen and other thrombogenic material, which activates platelets and the coagulation cascade, resulting in an acute thrombus, which interrupts coronary blood flow and causes some degree of myocardial ischemia. The consequences of acute ischemia, collectively referred to as acute coronary syndromes (ACS), depend on the location and degree of obstruction and range from unstable angina to transmural infarction (*Fig. 6).*

Coronary artery spasm is a transient, focal increase in vascular tone, markedly narrowing the lumen and reducing blood flow; symptomatic ischemia may result. Marked narrowing can trigger thrombus formation, causing infarction or life-threatening arrhythmia. Spasm can occur in arteries with or without atheroma. In arteries without atheroma, basal coronary artery tone is probably increased, and response to vasoconstricting stimuli is probably exaggerated. The

exact mechanism is unclear but may involve abnormalities of nitric oxide production or an imbalance between endothelium-derived contracting and relaxing factors. In arteries with atheroma, the atheroma may cause local hypercontractility; proposed mechanisms include loss of sensitivity to intrinsic vasodilators (e.g, acetylcholine) and increased production of vasoconstrictors (eg, angiotensin II, endothelin, leukotrienes, serotonin, thromboxane) in the area of the atheroma. Recurrent spasm may damage the intima, leading to atheroma formation. Use of vasoconstricting drugs (eg, cocaine, nicotine) and emotional stress also can trigger coronary spasm.

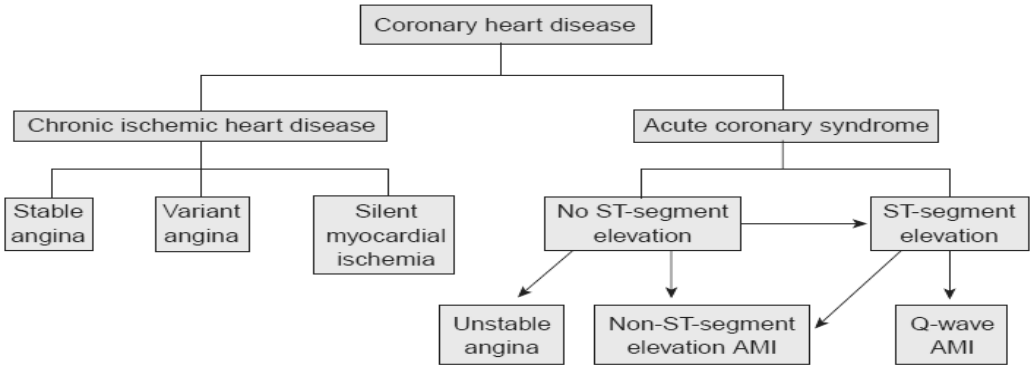


Fig. 6. Coronary heart disease

Risk Factors for CAD are the same as those for atherosclerosis: high blood levels of low-density lipoprotein (LDL) cholesterol and lipoprotein a, low blood levels of high-density lipoprotein (HDL) cholesterol, diabetes mellitus (particularly type 2), smoking, obesity, and physical inactivity. Smoking may be a stronger predictor of MI in women (especially those < 45). Genetic factors play a role, and several systemic disorders (eg, hypertension, hypothyroidism) and metabolic disorders (eg, hyperhomocysteinemia) contribute to risk. A high level of apoprotein B (apo B) is an important risk factor; it may identify increased risk when total cholesterol or LDL level is normal. High blood levels of C-reactive protein indicate plaque instability and inflammation and may be a stronger predictor of risk of ischemic events than high levels of LDL. High blood levels of triglycerides and insulin (reflecting insulin resistance) may be risk factors, but data are less clear. CAD risk is increased by smoking; a diet high in fat and calories and low in phytochemicals (found in fruits and vegetables), fiber, and vitamins C and E; a diet relatively low in ω-3 (n-3) polyunsaturated fatty acids (PUFAs), at least in some people; and poor stress management.

Angina Pectoris

Angina pectoris is a clinical syndrome of precordial discomfort or pressure due to transient myocardial ischemia without infarction. It is typically precipitated by exertion or psychologic stress and relieved by rest or sublingual nitroglycerin. Diagnosis is by symptoms, ECG, and myocardial imaging. Treatment may include nitrates, β-blockers, Ca channel blockers, and coronary angioplasty or coronary artery bypass graft surgery.

Etiology. Angina pectoris occurs when cardiac workload and resultant myocardial O_2 demand exceed the ability of coronary arteries to supply an adequate amount of oxygenated blood, as can occur when the arteries are narrowed. Narrowing usually results from atherosclerosis but may result from coronary artery spasm or, rarely, coronary artery embolism. Acute coronary thrombosis can cause angina if obstruction is partial or transient, but it usually causes MI. Because myocardial O_2 demand is determined mainly by heart rate, systolic wall tension, and contractility, narrowing of a coronary artery typically results in angina that occurs during exertion and is relieved by rest. In addition to exertion, cardiac workload can be increased by disorders such as hypertension, aortic stenosis, aortic regurgitation, or hypertrophic cardiomyopathy. In such cases, angina can result whether atherosclerosis is present or not. These disorders can also decrease relative myocardial perfusion because myocardial mass is increased (causing decreased diastolic flow). A decreased O_2 supply, as in severe anemia or hypoxia, can precipitate or aggravate angina.

Pathophysiology. Unstable angina, the relationship between workload or demand and ischemia is usually relatively predictable. However, atherosclerotic arterial narrowing is not entirely fixed; it varies with the normal fluctuations in arterial tone that occur in all people. Thus, more people have angina in the morning, when arterial tone is relatively high. Abnormal endothelial function may contribute to variations in arterial tone; e.g, in endothelium damaged by atheromas, stress of a catecholamine surge causes vasoconstriction rather than dilation (normal response). As the myocardium becomes ischemic, coronary sinus blood pH falls, cellular K is lost, lactate accumulates, ECG abnormalities appear, and ventricular function deteriorates. Left ventricular (LV) diastolic pressure usually increases during angina, sometimes inducing pulmonary congestion and dyspnea. The exact mechanism by which ischemia causes discomfort is unclear but may involve nerve stimulation by hypoxic metabolites.

Acute Coronary Syndromes (ACS) (Unstable Angina; Acute MI)

Acute coronary syndromes (ACS) result from acute obstruction of a coronary artery. Consequences depend on degree and location of obstruction and range from unstable angina to non–ST-segment elevation MI (NSTEMI), ST-segment elevation MI (STEMI), and sudden cardiac death. Symptoms are similar in each of these syndromes (except sudden death) and include chest discomfort with or without dyspnea, nausea, and diaphoresis. Diagnosis is by ECG and the presence or absence of serologic markers.

In the US, about 1.5 million MIs occur annually. MI results in death for 400,000 to 500,000 people, with about half dying before they reach the hospital).

Etiology. These syndromes usually occur when an acute thrombus forms in an atherosclerotic coronary artery. Atheromatous plaque sometimes becomes unstable or inflamed, causing it to rupture or split, exposing thrombogenic material, which activates platelets and the coagulation cascade and produces an acute thrombus. Platelet activation involves a conformational change in membrane glycoprotein (GP) IIb/IIIa receptors, allowing cross-linking (and thus aggregation) of platelets. Even atheromas causing minimal obstruction can rupture and result in thrombosis; in > 50 % of cases, stenosis is < 40 %. The resultant thrombus abruptly interferes with blood flow to parts of the myocardium. Spontaneous thrombolysis occurs in about two thirds of patients; 24 h later, thrombotic obstruction is found in only about 30 %. However, in virtually all cases, obstruction lasts long enough to cause tissue necrosis. Rarely, these syndromes are caused by arterial embolism (e.g, in mitral or aortic stenosis, infective endocarditis, or marantic endocarditis). Cocaine use and other causes of coronary spasm can sometimes result in MI. Spasm-induced MI may occur in normal or atherosclerotic coronary arteries.

Pathophysiology. Initial consequences vary with size, location, and duration of obstruction and range from transient ischemia to infarction. Measurement of newer, more sensitive markers indicates that some cell necrosis probably occurs even in mild forms; thus, ischemic events occur on a continuum, and classification into subgroups, although useful, is somewhat arbitrary. Sequelae of the acute event depend primarily on the mass and type of cardiac tissue infarcted.

Myocardial dysfunction. Ischemic (but not infarcted) tissue has impaired contractility, resulting in hypokinetic or akinetic segments; these segments may expand or bulge during systole (called paradoxical motion). The size of the affected area determines effects, which range from minimal to mild heart failure to cardiogenic shock. Some degree of heart failure occurs in about two thirds of hospitalized patients with acute MI. It is termed ischemic cardiomyopathy if low cardiac output and heart failure persist. Ischemia involving the papillary muscle may lead to mitral valve regurgitation.

MI. MI is myocardial necrosis resulting from abrupt reduction in coronary blood flow to part of the myocardium. Infarcted tissue is permanently dysfunctional; however, there is a zone of potentially reversible ischemia adjacent to infarcted tissue.

MI affects predominantly the left ventricle (LV), but damage may extend into the right ventricle (RV) or the atria. RV infarction usually results from obstruction of the right coronary or a dominant left circumflex artery; it is characterized by high RV filling pressure, often with

severe tricuspid regurgitation and reduced cardiac output. An inferoposterior infarction causes some degree of RV dysfunction in about half of patients and causes hemodynamic abnormality in 10 to 15 %. RV dysfunction should be considered in any patient who has inferoposterior infarction and elevated jugular venous pressure with hypotension or shock. RV infarction complicating LV infarction may significantly increase mortality risk. Anterior infarcts tend to be larger and result in a worse prognosis than inferoposterior infarcts. They are usually due to left coronary artery obstruction, especially in the anterior descending artery; inferoposterior infarcts reflect right coronary or dominant left circumflex artery obstruction.

Transmural infarcts involve the whole thickness of myocardium from epicardium to endocardium and are usually characterized by abnormal Q waves on ECG. Nontransmural or subendocardial infarcts do not extend through the ventricular wall and cause only ST-segment and T-wave (ST-T) abnormalities. Subendocardial infarcts usually involve the inner one third of myocardium, where wall tension is highest and myocardial blood flow is most vulnerable to circulatory changes. These infarcts may follow prolonged hypotension. Because the transmural depth of necrosis cannot be precisely determined clinically, infarcts are usually classified by the presence or absence of ST-segment elevation or Q waves on the ECG. Volume of myocardium destroyed can be roughly estimated by the extent and duration of CK elevation.

Electrical dysfunction. Ischemic and necrotic cells are incapable of normal electrical activity, resulting in various ECG changes (predominantly ST-T abnormalities), arrhythmias, and conduction disturbances. ST-T abnormalities of ischemia include ST-segment depression (often downsloping from the J point), T-wave inversion, ST-segment elevation (often referred to as injury current), and peaked T waves in the hyperacute phase of infarction. Conduction disturbances can reflect damage to the sinus node, the atrioventricular (AV) node, or specialized conduction tissues. Most changes are transient; some are permanent.

Classification is based on ECG changes and presence or absence of cardiac markers in blood. Distinguishing NSTEMI and STEMI is useful because prognosis and treatment are different.

Unstable angina (acute coronary insufficiency, preinfarction angina, intermediate syndrome) is defined as:

1) Rest angina that is prolonged (usually > 20 min)

2) New-onset angina of at least class III severity in the Canadian Cardiovascular Society (CCS) classification Increasing angina, i.e, previously diagnosed angina that has become distinctly more frequent, more severe, longer in duration, or lower in threshold (e.g, increased by ≥ 1 CCS class or to at least CCS class III)

Also, ECG changes such as ST-segment depression, ST-segment elevation, or T-wave inversion may occur during unstable angina but are transient. Of cardiac markers, CK is not elevated but troponin I or T may be slightly increased. Unstable angina is clinically unstable and often a prelude to MI or arrhythmias or, less commonly, to sudden death.

Non-ST-segment elevation MI (NSTEMI, subendocardial MI) is myocardial necrosis (evidenced by cardiac markers in blood; troponin I or T and CK will be elevated) without acute ST-segment elevation or Q waves. ECG changes such as ST-segment depression, T-wave inversion, or both may be present.

ST-segment elevation MI (STEMI, transmural MI) is myocardial necrosis with ECG changes showing ST-segment elevation that is not quickly reversed by nitroglycerin or showing new left bundle branch block. Q waves may be present. Both troponin and CK are elevated.

Symptoms and Signs

Symptoms of ACS depend somewhat on the extent and location of obstruction and are quite variable. Except when infarction is massive, recognizing the amount of ischemia by symptoms alone is difficult. After the acute event, many complications can occur. They usually involve electrical dysfunction (e.g, conduction defects, arrhythmias), myocardial dysfunction (e.g, heart failure, interventricular septum or free wall rupture, ventricular aneurysm, pseudoaneurysm, mural thrombus formation, cardiogenic shock), or valvular dysfunction (typically

mitral regurgitation). Electrical dysfunction can be significant in any form of ACS, but usually, large parts of myocardium must be ischemic to cause significant myocardial dysfunction. Other complications of ACS include recurrent ischemia and pericarditis. Pericarditis that occurs 2 to 10 wk after an MI is known as post-MI syndrome or Dressler's syndrome.

Unstable angina. Symptoms are those of angina pectoris, except that the pain or discomfort of unstable angina usually is more intense, lasts longer, is precipitated by less exertion, occurs spontaneously at rest (as angina decubitus), is progressive (crescendo) in nature, or involves any combination of these features.

NSTEMI and STEMI. Symptoms of NSTEMI and STEMI are the same. Days to weeks before the event, about two thirds of patients experience prodromal symptoms, including unstable or crescendo angina, shortness of breath, and fatigue. Usually, the first symptom of infarction is deep, substernal, visceral pain described as aching or pressure, often radiating to the back, jaw, left arm, right arm, shoulders, or all of these areas. The pain is similar to angina pectoris but is usually more severe and long-lasting; more often accompanied by dyspnea, diaphoresis, nausea, and vomiting; and relieved little or only temporarily by rest or nitroglycerin. However, discomfort may be mild; about 20 % of acute MIs are silent (ie, asymptomatic or causing vague symptoms not recognized as illness by the patient), more commonly in diabetics. Some patients present with syncope. Patients often interpret their discomfort as indigestion, particularly because spontaneous relief may be falsely attributed to belching or antacid consumption. Women are more likely to present with atypical chest discomfort. Elderly patients may report dyspnea more than ischemic-type chest pain. In severe ischemic episodes, the patient often has significant pain and feels restless and apprehensive. Nausea and vomiting may occur, especially with inferior MI. Dyspnea and weakness due to LV failure, pulmonary edema, shock, or significant arrhythmia may dominate.

Skin may be pale, cool, and diaphoretic. Peripheral or central cyanosis may be present. Pulse may be thready, and BP is variable, although many patients initially have some degree of hypertension during pain. Heart sounds are usually somewhat distant; a 4th heart sound is almost universally present. A soft systolic blowing apical murmur (reflecting papillary muscle dysfunction) may occur. During initial examination, a friction rub or more striking murmurs suggest a preexisting heart disorder or another diagnosis. Detection of a friction rub within a few hours after onset of MI symptoms suggests acute pericarditis rather than MI. However, friction rubs, usually evanescent, are common on days 2 and 3 post-STEMI. The chest wall is tender when palpated in about 15 % of patients. In RV infarction, signs include elevated RV filling pressure, distended jugular veins, clear lung fields, and hypotension.

Diagnosis

1. Serial ECGs.

2. Serial cardiac markers.

3. Immediate coronary angiography for patients with STEMI or complications (eg, persistent chest pain, markedly elevated cardiac markers, unstable arrhythmias).

4. Delayed angiography (24 to 48 h) for patients with NSTEMI or unstable angina.

ACS should be considered in men > 30 yr and women > 40 yr (younger in patients with diabetes) whose main symptom is chest pain or discomfort. Pain must be differentiated from the pain of pneumonia, pulmonary embolism, pericarditis, rib fracture, costochondral separation, esophageal spasm, acute aortic dissection, renal calculus, splenic infarction, or various abdominal disorders. In patients with previously diagnosed hiatus hernia, peptic ulcer, or a gallbladder disorder, the clinician must be wary of attributing new symptoms to these disorders.

Date	Grade	Teacher’s signature

PATHOPHYSIOLOGY OF BLOOD VESSELS. ARTERIAL HYPER- AND HYPOTENSION. ATHEROSCLEROSIS

Relevance. Studying the causes and mechanisms of vessels tone regulation is actual for theoretic and clinic medicine because these disorders are basis of hypertonic disease and symptomatic hypertension, observed in different diseases. To know the causes and mechanisms of disorders is important for understanding of hypotension, especially of acute vascular insufficiency.

Making adequate models is important for identification of causes and mechanisms of those disorders in human, improving the prophylactic measures and treatment of hyper- and hypotension. This pathology leads (avg. 60 %) between all causes of death in different countries. Analyzing the causes of origins of cardio-vascular diseases, we can state that atherosclerosis is the basis almost of 90 % of them.

So studying pathogenesis and outcomes of atherosclerosis is an actual problem for modern medicine.

Overall Objective is:

1) to study common laws and features of different disorders of vascular tone, particularly various etiological types of hypertension;

2) to study the common laws of beginning, development and results of atherosclerosis.

The student should be able to (specific objectives):

1. Determine blood pressure in rabbits.
2. Explain the mechanisms of centrogenic, reflexogenic and renal hypertension.
3. Differ the hyper- and hypotension states, and acute vascular insufficiency.
4. Form the knowledge about atherosclerosis.
5. Explain the mechanisms of atherosclerosis development.
6. Know the morphological characteristic, results and value atherosclerosis in pathology.

The student should be able to (required knowledge and skills):

1. Classify the division of vessels by function (dep. of normal physiology).
2. Explain the neurohumoral regulation of vascular tone (dep. of normal physiology).
3. Classify the division of vessels by function (dep. of normal physiology).
4. Explain the neurohumoral regulation of vascular tone (dep. of normal physiology).

QUESTIONS TO THE LESSON

1. Definition of “vascular tone”. Components of vascular tone.
2. Types of vascular distonia.
3. Factors determining the height of arterial pressure.
4. Changes of system arterial pressure. Definition of “arterial hyper- and hypotension” and “hyper- and hypotensive reaction”.
5. Definition of “arterial hypertension”. Risk factors of arterial hypertension.
6. Classification of arterial hypertension by the level of arterial pressure.
7. Stratification of patients by the risk level of heart and vascular damage in arterial hypertension. Groups of risk.
8. Aim organs and risk groups in arterial hypertension.
9. The most common and dangerous complications of arterial hypertension.
10. Types of arterial hypertension.
11. Hypertensive crisis. Defining the last one. Causes. Risk factors. Manifestations.
12. Symptomatic arterial hypertension. Etiology. Manifestations.
13. Hypertension disease. Etiology.
14. Classification (WHO). Forms of essential arterial hypertension.
15. Pathogenesis of hypertension disease.
16. Stages of hypertension disease, main chains of the pathogenesis.
17. Principles of hypertension disease and arterial hypertension treatment.
18. Arterial hypertension. Types. Causes. Manifestations.
19. Vascular insufficiency. Etiology and pathogenesis.

20. Atherosclerosis, definition. Experimental models.

21. Theories of pathogenesis of atherosclerosis: lipid infiltration, thrombogenic, superoxidic, monoclonal, immunocomplex, etc.

22. Risk factors of atherosclerosis pathogenesis: hereditary dislipoproteinemia, obesity, smoking, arterial hypertension, stress etc.

23. Pathogenesis of atherosclerosis. Morphogenesis of atherosclerosis.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

PRESSURE, FLOW, AND RESISTANCE

The most important factors governing the function of the circulatory system are volume, pressure, resistance, and flow. Optimal function requires a volume that is sufficient to fill the vascular compartment and a pressure that is sufficient to ensure blood flow to all body tissues. Blood flow is determined by two factors: a pressure difference between the two ends of a vessel or group of vessels and the resistance that blood must overcome as it moves through the vessel or vessels.

Relation between pressure, resistance, and flow is expressed by the equation F = P/R, in which F is the blood flow, P is the difference in pressure between the two ends of the system, and R is the resistance to flow through the system. The total resistance that the blood encounters as it flows through the systemic circulation is referred to as the peripheral vascular resistance (PVR) or, sometimes, as the systemic vascular resistance. In the systemic circulation, blood flow is determined by the **cardiac output** (CO) and PVR. The PVR cannot be measured directly. Instead, it is estimated by rearranging the variables in the previous equation (PVR = P/CO), in which P represents the pressure difference between the aortic or mean arterial pressure (approximately 100 mm Hg) and right atrial pressure (approximately 0 mm Hg). The flow (F) or cardiac output is approximately 100 mL/second at rest. The PVR is therefore 100/100 or 1 peripheral resistance unit (PRU). The total resistance in the pulmonary circulation is only approximately 0.12 PRU. In this case, the blood flow is the same as in the systemic circulation, but the pressure difference between the pulmonary artery and left atrium (16 mm Hg versus 4 mm Hg) is much less. A helpful equation ($F = \Delta P \times \pi r^4 / 8n \times L \times \text{viscosity}$) for understanding factors that affect blood flow was derived by the French physician Poiseuille more than a century ago. According to this equation, the two most important determinants of flow in the circulatory system are a difference in pressure (ΔP) and the vessel radius to the fourth power (r4). The length (L) of vessels does not usually change, and 8n is a constant that does not change. Because flow is directly related to the fourth power of the radius, small changes in vessel radius can produce large changes in flow to an organ or tissue. For example, if the pressure difference remains constant, the rate of flow is 16 times greater in a vessel with a radius of 2 mm than in a vessel with a radius of 1 mm. According to Poiseuille's equation, blood flow is also affected by the viscosity of blood. Viscosity is the resistance to flow caused by the friction of molecules in a fluid. The viscosity of a fluid is largely related to its thickness. The more particles that are present in a solution, the greater the frictional forces that develop between the molecules. Unlike water that flows through plumbing pipes, blood is a nonhomogeneous liquid. It contains blood cells, platelets, fat globules, and plasma proteins that increase its viscosity. The red blood cells, which constitute 40 to 45 % of the formed elements of the blood, largely determine the viscosity of the blood. When measured in relation to water, the relative viscosity of plasma is 1.5, and at a normal hematocrit of 42 % to 45 %, that of whole blood is 3.0. Under special conditions, temperature may affect viscosity. There is a 2 % rise in viscosity for each 1°C decrease in body temperature, a fact that helps explain the sluggish blood flow seen in persons with hypothermia.

CROSS-SECTIONAL AREA AND VELOCITY OF FLOW

Velocityis a distance measurement; it refers to the speed or linear movement with time (centimeters per second) with which blood flows through a vessel. Flow is a volume measurement (milliliters per second); it is determined by the cross-sectional area of a vessel and the velocity of flow. When the flow through a given segment of the circulatory system is constantas it must

be for continuous flow-the velocity is inversely proportional to the cross-sectional area of the vessel (i.e., the smaller the cross-sectional area, the greater the velocity of flow). This phenomenon can be compared with cars moving from a two-lane to a single-lane section of a highway. To keep traffic moving at its original pace, cars would have to dou double their speed in the single-lane section of the highway. So it is with flow in the circulatory system. The linear velocity of blood flow in the circulatory system varies widely from 30 to 35 cm/second in the aorta to 0.2 to 0.3 mm/second in the capillaries. This is because even though each individual capillary is very small, the total cross-sectional area of all the systemic capillaries greatly exceeds the cross-sectional area of other parts of the circulation. As a result of this large surface area, the slower movement of blood allows ample time for exchange of nutrients, gases, and metabolites between the tissues and the blood.

LAMINAR AND TURBULENT FLOW

Blood flow normally is **laminar,**with the blood components arranged in layers so that the plasma is adjacent to the smooth, slippery endothelial surface of the blood vessel, and the blood cells, including the platelets, are in the center or axis of the bloodstream. This arrangement reduces friction by allowing the blood layers to slide smoothly over one another, with the axial layer having the most rapid rate of flow. Under certain conditions, blood flow switches from laminar to turbulent flow. **Turbulent** flow is flow in which blood moves crosswise and lengthwise along a vessel in a manner similar to the eddy currents seen in a rapidly flowing river at a point of obstruction. Turbulent flow is influenced by a number of conditions, including high velocity of flow, change in vessel diameter, and low blood viscosity. The tendency for turbulence to occur increases in direct proportion to the velocity of flow. Imagine the chaos as cars from a two- or three-lane highway converge on a single-lane section of the highway. The same type of thing happens in blood vessels that have been narrowed by disease processes, such as atherosclerosis. Low blood viscosity allows the blood to move faster and accounts for the transient occurrence of heart murmurs in some persons who are severely anemic. Turbulent flow predisposes to clot formation as platelets and other coagulation factors come in contact with the endothelial lining of the vessel. Turbulent flow often can be heard through a stethoscope. An audible murmur in a blood vessel experiencing turbulent flow is referred to as a bruit.

WALL TENSION, RADIUS, AND PRESSURE

In a blood vessel, wall tension is the force in the vessel wall that opposes the distending pressure inside the vessel. The French astronomer and mathematician Pierre de Laplace described the relationship among wall tension, pressure, and the radius of a vessel or sphere more than 200 years ago. This relationship, which has come to be known as Laplace's law, can be expressed by the equation, $T = P \times r$, in which T represents wall tension, P the intraluminal pressure, and r the vessel radius. Accordingly, the internal pressure expands the vessel until it is exactly balanced by the tension in the vessel wall. This correlation can be compared with a partially inflated long balloon. Because the pressure is equal throughout, the tension in the part of the balloon with the smaller radius is less than the tension in the section with the larger radius. The same holds true for an arterial aneurysm in which the tension and risk for rupture increase as the aneurysm grows in size.

Laplace's law was later expanded to include wall thickness, with wall tension being inversely related to wall thickness ($T = P \times r/\text{wall thickness}$). Thus, the thicker the vessel wall, the lower the tension, and vice versa. In hypertension, arterial vessel walls hypertrophy and become thicker, thereby reducing the tension and minimizing wall stress. Laplace's law can also be applied to the pressure required to maintain the patency of small blood vessels. Provided that the thickness of a vessel wall remains constant, it takes more pressure to overcome wall tension and to keep a vessel open as its radius decreases in size ($P = T/r$). The critical closing pressure refers to the point at which vessels collapse so that blood can no longer flow through them. In circulatory shock, for example, there is a decrease in blood volume and vessel radii, along with a drop in blood pressure.

DISTENTION AND COMPLIANCE

Complian cerefers to the total quantity of blood that can be stored in a given portion of the circulation for each millimeter rise in pressure. Compliance (C) is defined by the equation, C = V/P, in which V is the change in volume and P is the change in distending pressure. The distending pressure is the difference between the pressure inside the vessel and the pressure outside the vessel. This is called the transmural pressure. As compliance increases, there is less change in transmural pressure with any given change in volume. Compliance reflects the distensibility of the blood vessel (i.e., increase in volume/increase in pressure Ч original volume). The distensibility of the arteries allows them to accommodate the pulsatile output of the heart. The most distensible of all vessels are the veins, which can increase their volume with only slight changes in pressure, allowing them to function as a reservoir for storing large quantities of blood that can be returned to the circulation when it is needed.

BLOOD VESSELS

All blood vessels, except the capillaries, have walls composed of three layers, or coats, called tunicae. The tunica externa, or tunica adventitia, is the outermost covering of the vessel. This layer is composed of fibrous and connective tissues that support the vessel. The tunica media, or middle layer, is largely a smooth muscle layer that constricts to regulate and control the diameter of the vessel. The tunica intima, or inner layer, has an elastic layer that joins the media and a thin layer of endothelial cells that lie adjacent to the blood. The endothelial layer provides a smooth and slippery inner surface for the vessel. This smooth inner lining, as long as it remains intact, prevents platelet adherence and blood clotting. The layers of the different types of blood vessels vary with vessel function. The walls of the arterioles, which control blood pressure, have large amounts of smooth muscle. Veins are thin-walled, distensible, and collapsible vessels. Capillaries are singlecell– thick vessels designed for the exchange of gases, nutrients, and waste materials.

VASCULAR SMOOTH MUSCLE

Smooth muscle contracts slowly and generates high forces for long periods with low energy requirements; it uses only 1/10 to 1/300 the energy of skeletal muscle. These characteristics are important in structures, such as blood vessels, that must maintain their tone day in and day out. Compared with skeletal and cardiac muscle, smooth muscle has less well-developed sarcoplasmic reticulum for storing intracellular calcium, and it has very few fast sodium channels. Depolarization of smooth muscle instead relies largely on extracellular calcium, which enters through calcium channels in the muscle membrane. Sympathetic nervous system control of vascular smooth muscle tone occurs by way of receptor-activated opening and closing of the calcium channels. In general, б-adrenergic receptors are excitatory in that they cause the channels to open and produce vasoconstriction; and в-adrenergic receptors are inhibitory in that they cause the channels to close and produce vasodilation.

Calcium channel blocking drugs cause vasodilation by blocking calcium entry through the calcium channels. Smooth muscle contraction and relaxation also occur in response to local tissue factors such as lack of oxygen, increased hydrogen ion concentrations, and excess carbon dioxide. Nitric oxide, formerly known as the endothelial relaxing factor, acts locally to produce smooth muscle relaxation and regulate blood flow. These factors are discussed more fully in the section on local control of blood flow.

ARTERIAL SYSTEM consists of the large and medium-sized arteries and the arterioles. Arteries are thick-walled vessels with large amounts of elastic fibers. The elasticity of these vessels allows them to stretch during cardiac systole, when the heart contracts and blood enters the circulation, and to recoil during diastole, when the heart relaxes. The arterioles, which are predominantly smooth muscle, serve as resistance vessels for the circulatory system. They act as control valves through which blood is released as it moves into the capillaries. Changes in the activity of sympathetic fibers that innervate these vessels cause them to constrict or to relax as needed to maintain blood BP

ARTERIAL PRESSURE PULSE. The arterial blood pressure, often referred to simply as the blood pressure, results from the intermittent ejection of blood from the left ventricle into the aorta at the onset of systole. It rises during systole as the left ventricle contracts and falls as the heart relaxes during diastole. This creates an impulse or pressure wave that is transmitted from molecule to molecule along the length of the vessel. In the aorta, this pressure wave is transmitted at a velocity of 4 to 6 m/second, which is approximately 20 times faster than the flow of blood. These pressure waves are similar to those created by splashing water in a basin or tub. When taking a pulse, it is the pressure pulses that are felt, and it is the pressure pulses that produce the Korotkoff sounds heard during blood pressure measurement. The tip or maximum deflection of the pressure pulse coincides with the systolic blood pressure, and the minimum point of deflection coincides with the diastolic pressure. As the pressure wave moves out through the aorta into the arteries, it changes as it collides with reflected waves from the periphery. Just as the waves created by splashing water in a tub increase in amplitude as they hit the edge of the tub and reverse their direction of movement, the pressure pulse increases as it moves to the peripheral arteries. This is why the systolic pressure is higher in the medium sized arteries than in the aorta even though the diastoli pressure is lower. With peripheral arterial disease, there is a delay in the transmission of the reflected wave so that the pulse decreases rather than increases in amplitude. After its initial amplification, the pressure pulse becomes smaller and smaller as it moves through the smaller arteries and arterioles, until it disappears almost entirely in the capillaries. This damping of the pressure pulse is caused by the resistance and distensibility characteristics of these vessels. The increased resistance of these small vessels impedes the transmission of the pressure waves; however, their distensibility is great enough so that any small change in flow does not cause a pressure change. Although the pressure pulses usually are not transmitted to the capillaries, there are situations in which this does occur. For example, injury to a finger or other area of the body often results in a throbbing sensation. In this case, extreme dilatation of the small vessels in the injured area produces a reduction in the dampening of the pressure pulse. Capillary pulsations also occur in conditions that cause exaggeration of aortic pressure pulses, such as aortic regurgitation or patent ductus arteriosus.

VENOUS SYSTEM. The veins and venules are thin-walled, distensible, and collapsible vessels. The venules collect blood from the capillaries, and the veins transport blood back to the heart. The veins are capable of enlarging and storing large quantities of blood, which can be made available to the circulation as needed. Even though the veins are thin walled, they are muscular. This allows them to contract or expand to accommodate varying amounts of blood. Veins are innervated by the sympathetic nervous system. When blood is lost from the circulation, the veins constrict as a means of maintaining intravascular volume. The venous system is a low-pressure system, and when a person is in the upright position, blood flow in the venous system must oppose the effects of gravity. Valves in the veins of extremities prevent retrograde flow, and with the help of skeletal muscles that surround and intermittently compress the veins in a milking manner, blood is moved forward to the heart. Their pressure ranges from approximately 10 mm Hg at the end of the venules to approximately 0 mm Hg at the entrance of the vena cava into the heart. There are no valves in the abdominal or thoracic veins, and blood flow in these veins is heavily influenced by the pressure in the abdominal and thoracic cavities, respectively.

CAPILLARIES. Capillaries are microscopic, single-cell–thick vessels that connect the arterial and venous segments of the circulation. In each person, there are approximately 10 billion capillaries, with a total surface area of 500 to 700 m^2. The capillary wall is composed of a single layer of endothelial cells surrounded by a basement membrane. Intracellular junctions join the capillary endothelial cells; these are called the capillary pores. Lipid-soluble materials diffuse directly through the capillary cell membrane. Water and water-soluble materials leave and enter the capillary through the capillary pores.

The size of the capillary pores varies with capillary function. In the brain, the endothelial cells are joined by tight junctions that form the blood–brain barrier. This prevents substances

that would alter neural excitability from leaving the capillary. In organs that process blood contents, such as the liver, capillaries have large pores so that substances can pass easily through the capillary wall. In the kidneys, the glomerular capillaries have small openings called fenestrations that pass directly through the middle of the endothelial cells. Fenestrated capillary walls are consistent with the filtration function of the glomerulus.

Local control of blood flow. Tissue blood flow is regulated on a minute-to-minute basis in relation to tissue needs and on a longer-term basis through the development of collateral circulation. Neural mechanisms regulate the cardiac output and blood pressure needed to support these local mechanisms.

Short-Term Autoregulation. Local control of blood flow is governed largely by the nutritional needs of the tissue. For example, blood flow to organs such as the heart, brain, and kidneys remains relatively constant, although blood pressure may vary over a range of 60 to 180 mm Hg. The ability of the tissues to regulate their own blood flow over a wide range of pressures is called autoregulation that is mediated by changes in blood vessel tone due to changes in flow through the vessel or by local tissue factors, such as lack of oxygen or accumulation of tissue metabolites (i.e., potassium, lactic acid, or adenosine, which is a breakdown product of ATP). Local control is particularly important in tissues such as skeletal muscle, which has blood flow requirements that vary according to the level of activity. An increase in local blood flow is called hyperemia. The ability of tissues to increase blood flow in situations of increased activity, such as exercise, is called functional hyperemia. When the blood supply to an area has been occluded and then restored, local blood flow through the tissues increases within seconds to restore the metabolic equilibrium of the tissues. This increased flow is called reactive hyperemia. The transient redness seen on an arm after leaning on a hard surface is an example of reactive hyperemia. Local control mechanisms rely on a continuous flow from the main arteries; therefore, hyperemia cannot occur when the arteries that supply the capillary beds are narrowed. For example, if a major coronary artery becomes occluded, the opening of channels supplied by that vessel cannot restore blood flow.

Tissue Factors Contributing to Local Control of Blood

Flow. Vasodilator substances, formed in tissues in response to a need for increased blood flow, also aid in the local control of blood flow. The most important of these are histamine, serotonin (i.e., 5-hydroxytryptamine), kinins, and prostaglandins. **Histamine** increases blood flow. Most blood vessels contain histamine in mast cells and non–mast cell stores; when these tissues are injured, histamine is released. In certain tissues, such as skeletal muscle, the activity of the mast cells is mediated by the sympathetic nervous system; when sympathetic control is withdrawn, the mast cells release histamine. Vasodilation then results from increased histamine and the with drawal of vasoconstrictor activity. **Serotonin** is liberated from aggregating platelets during the clotting process; it causes vasoconstriction and plays a major role in control of bleeding. Serotonin is found in brain and lung tissues, and there is some speculation that it may be involved in the vascular spasm associated with some allergic pulmonary reactions and migraine headaches. The **kinins** (i.e., kallidins and bradykinin) are liberated from the globulin kininogen, which is present in body fluids. The kinins cause relaxation of arteriolar smooth muscle, increase capillary permeability, and constrict the venules. In exocrine glands, the formation of kinins contributes to the vasodilation needed for glandular secretion. **Prostaglandin s**are synthesized from constituents of the cell membrane (i.e., the long-chain fatty acid arachidonic acid). Tissue injury incites the release of arachidonic acid from the cell membrane, which initiates prostaglandin synthesis. There are several prostaglandins (e.g., E2, F2, I2), which are subgrouped according to their chemical characteristics; some produce vasoconstriction, and some produce vasodilation.

Endothelial Control of Vasodilation and Vasoconstriction.

The **endothelium**, which lies between the blood and the vascular smooth muscle, serves as a physical barrier for vasoactive substances that circulate in the blood. Once thought to be

nothing more than a single layer of cells that line blood vessels, it is now known that the endothelium plays an active role in controlling vascular function. In capillaries, which are composed of a single layer of endothelial cells, the endothelium is active in transporting cell nutrients and wastes. In addition to its function in capillary transport, the endothelium removes vasoactive agents such as norepinephrine from the blood, and it produces enzymes that convert precursor molecules to active products (e.g., angiotensin I to angiotensin II in lung vessels). One of the important functions of the normal endothelium is to synthesize and release factors that control vessel dilation. The discovery, first reported in the early 1980s, was of particular importance that the intact endothelium was able to produce a factor that caused relaxation of vascular smooth muscle. This factor was originally named **endothelium-derived relaxing factor** and is now known to be **nitric oxide**. Many other cell types produce nitric oxide. In these tissues, nitric oxide has other functions, including modulation of nerve activity in the nervous system. The normal endothelium maintains a continuous release of nitric oxide, which is formed from L-arginine through the action of an enzyme called nitric oxide synthase. The production of nitric oxide can be stimulated by a variety of endothelial agonists, including acetylcholine, bradykinin, histamine, and thrombin. Shear stress on the endothelium resulting from an increase in blood flow or blood pressure also stimulates nitric oxide production and vessel relaxation. Nitric oxide also inhibits platelet aggregation and secretion of platelet contents, many of which cause vasoconstriction. The fact that nitric oxide is released into the vessel lumen (to inactivate platelets) and away from the lumen (to relax smooth muscle) suggests that it protects against both thrombosis and vasoconstriction. It has been suggested that the tendency toward vasoconstriction that characterizes atherosclerotic vessels may be related to impaired vasodilator function due to disruption of the vessel endothelial layer. In addition to nitric oxide, the endothelium also produces other vasodilating substances such as the prostaglandin prostacyclin, which produces vasodilation and inhibits platelet aggregation. The endothelium also produces a number of vasoconstrictor substances, including angiotensin II, vasoconstrictor prostaglandins, and a family of peptides called endothelins. There are at least three endothelins. Endothelin-1, made by human endothelial cells, is the most potent endogenous vasoconstrictor known. Receptors for endothelins also have been identified.

Long-Term Regulation. Collateral circulation is a mechanism for the long-term regulation of local blood flow. In the heart and other vital structures, anastomotic channels exist between some of the smaller arteries. These channels permit perfusion of an area by more than one artery. When one artery becomes occluded, these anastomotic channels increase in size, allowing blood from a patent artery to perfuse the area supplied by the occluded vessel. For example, persons with extensive obstruction of a coronary blood vessel may rely on collateral circulation to meet the oxygen needs of the myocardial tissue normally supplied by that vessel. As with other long-term compensatory mechanisms, the recruitment of collateral circulation is most efficient when obstruction to flow is gradual rather than sudden.

Neural Control of Circulatory Function. The neural control centers for the integration and modulation of cardiac function and blood pressure are located bilaterally in the medulla oblongata. The medullary cardiovascular neurons are grouped into three distinct pools that lead to sympathetic innervation of the heart and blood vessels and parasympathetic innervation of the heart. The first two, which control sympathetic-mediated acceleration of heart rate and blood vessel tone, are called the vasomotor center. The third, which controls parasympathetic-mediated slowing of heart rate, is called the cardioinhibitory center. These brain stem centers receive information from many areas of the nervous system, including the hypothalamus. The arterial baroreceptors and chemoreceptors provide the medullary cardiovascular center with continuous information regarding changes in blood pressure.

Autonomic nervous system regulation. The neural control of the circulatory system occurs primarily through the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS). The ANS contributes to the control of cardiovascular function through

modulation of cardiac (i.e., heart rate and cardiac contractility) and vascular (i.e., peripheral vascular resistance) function.

Autonomic Regulation of Cardiac Function. The heart is innervated by the parasympathetic and sympathetic nervous systems. Parasympathetic innervation of the heart is achieved by means of the vagus nerve. The parasympathetic outflow to the heart originates from the vagal nucleus in the medulla. The axons of these neurons pass to the heart in the cardiac branches of the vagus nerve. The effect of vagal stimulation on heart function is largely limited to heart rate, with increased vagal activity producing a slowing of the pulse. Sympathetic outflow to the heart and blood vessels arises from neurons located in the reticular formation of the brain stem. The axons of these neurons exit the thoracic segments of the spinal cord to synapse with the postganglionic neurons that innervate the heart. Cardiac sympathetic fibers are widely distributed to the sinoatrial and AV nodes and the myocardium. Increased sympathetic activity produces an increase in the heart rate and the velocity and force of cardiac contraction.

Autonomic Regulation of Vascular Function. The sympathetic nervous system serves as the final common pathway for controlling the smooth muscle tone of the blood vessels. Most of the sympathetic preganglionic fibers that control vessel function originate in the vasomotor center of the brain stem, travel down the spinal cord, and exit in the thoracic and lumbar (T1 to L2) segments. The sympathetic neurons that supply the blood vessels maintain them in a state of tonic activity, so that even under resting conditions, the blood vessels are partially constricted. Vessel constriction and relaxation are accomplished by altering this basal input. Increasing sympathetic activity causes constriction of some vessels, such as those of the skin, the gastrointestinal tract, and the kidneys. Blood vessels in skeletal muscle are supplied by both vasoconstrictor and vasodilator fibers. Activation of sympathetic vasodilator fibers causes vessel relaxation and provides the muscles with increased blood flow during exercise. Although the parasympathetic nervous system contributes to the regulation of heart function, it has little or no control over blood vessels.

Autonomic Neurotransmitters. The actions of the ANS are mediated by chemical neurotransmitters. Acetylcholine is the postganglionic neurotransmitter for parasympathetic neurons, and norepinephrine is the main neurotransmitter for postganglionic sympathetic neurons. Sympathetic neurons also respond to epinephrine, released into the bloodstream by the adrenal medulla. The neurotransmitter dopamine can also act as a neurotransmitter for some sympathetic neurons.

Central nervous system responses. It is not surprising that the central nervous system (CNS), which plays an essential role in regulating vasomotor tone and blood pressure, would have a mechanism for controlling the blood flow to the cardiovascular centers that control circulatory function. When the blood flow to the brain has been sufficiently interrupted to cause ischemia of the vasomotor center, these vasomotor neurons become strongly excited, causing massive vasoconstriction as a means of raising the blood pressure to levels as high as the heart can pump against. This response is called the CNS ischemic response, and it can raise the blood pressure to levels as high as 270 mm Hg for as long as 10 minutes. The CNS ischemic response is a last-ditch stand to preserve the blood flow to vital brain centers; it does not become activated until blood pressure has fallen to at least 60 mm Hg, and it is most effective in the range of 15 to 20 mm Hg. If the cerebral circulation is not reestablished within 3 to 10 minutes, the neurons of the vasomotor center cease to function, so that the tonic impulses to the blood vessels stop, and the blood pressure falls precipitously. The Cushing reflex is a special type of CNS reflex resulting from an increase in intracranial pressure. When the intracranial pressure rises to levels that equal intraarterial pressure, blood vessels to the vasomotor center become compressed, initiating the CNS ischemic response. The purpose of this reflex is to produce a rise in arterial pressure to levels above intracranial pressure so that the blood flow to the vasomotor center can be reestablished. Should the intracranial pressure rise to the point that the blood supply to the vasomotor center becomes inadequate, vasoconstrictor

tone is lost, and the blood pressure begins to fall. The elevation in blood pressure associated with the Cushing reflex is usually of short duration and should be considered a protective homeostatic mechanism. The brain and other cerebral structures are located within the rigid confines of the skull, with no room for expansion, and any increase in intracranial pressure tends to compress the blood vessels that supply the brain.

Disorders of Blood Flow in the Systemic Circulation. Blood flow in the arterial and venous systems depends on a system of patent blood vessels and adequate perfusion pressure. Unlike disorders of the respiratory system or central circulation that cause hypoxia and impair oxygenation of tissues throughout the body, the effects of blood vessel disease usually are limited to local tissues supplied by a particular vessel or group of vessels. With arterial disorders, there is decreased blood flow to the tissues along with impaired delivery of oxygen and nutrients. Venous disorders interfere with the outflow of blood from the capillaries, removal of tissue wastes, and return of blood to the heart. Disturbances in blood flow can result from pathologic changes in the vessel wall (i.e., atherosclerosis and vasculitis), acute vessel obstruction due to thrombus or embolus, vasospasm (i.e., Raynaud's phenomenon), abnormal vessel dilation or compression of blood vessels by extravascular forces (i.e., tumors, edema).

Disorders of the Arterial Circulation. The arterial system distributes blood to all the tissues in the body. There are three types of arteries: large elastic arteries, including the aorta and its distal branches; mediumsized arteries, such as the coronary and renal arteries; and small arteries and arterioles that pass through the tissues. Each of these different types of arteries tends to be affected by different disease processes. Pathology of the arterial system affects body function by impairing blood flow. The effect of impaired blood flow on the body depends on the structures involved and the extent of altered flow. The term ischemia (i.e., holding back of blood) denotes a reduction in arterial flow to a level that is insufficient to meet the oxygen demands of the tissues. Infarction refers to an area of ischemic necrosis in an organ produced by occlusion of its arterial blood supply or its venous drainage. The discussion in this section focuses on blood lipids and hypercholesterolemia, atherosclerosis, vasculitis, arterial disease of the extremities, and arterial aneurysms.

HYPERTENSION

Hypertension is sustained elevation of resting systolic BP (≥ 140 mm Hg), diastolic BP (≥ 90 mm Hg), or both. Hypertension with no known cause (primary; formerly, essential hypertension) is most common. Hypertension with an identified cause (secondary hypertension) is usually due to chronic kidney disease or primary aldosteronism. Usually, no symptoms develop unless hypertension is severe or long-standing. Diagnosis is by sphygmomanometry. Tests may be done to determine cause, assess damage, and identify other cardiovascular risk factors.

Table 28 shows BP classification for adults 18 and 18+ years.

In adults, hypertension occurs more often in blacks (41 %) than in whites (28 %) or Mexican Americans (28 %), and morbidity and mortality are greater in blacks. BP increases with age. About two thirds of people > 65 have hypertension, and people with a normal BP at the age of 55 have a 90 % lifetime risk of developing hypertension. Because hypertension becomes so common with age, the age-related increase in BP may seem innocuous, but higher BP increases morbidity and mortality risk. Hypertension may develop during pregnancy.

Table 28

JNC 7 Classification of Blood Pressure in Adults

Classification	BP
Normal	< 120/80 mm Hg
Prehypertension	120–139/80–89 mm Hg
Stage 1	140–159 mm Hg (systolic) or 90–99 mm Hg (diastolic)
Stage 2	≥ 160 mm Hg (systolic) or ≥ 100 mm Hg (diastolic)
JNC = Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure	

Primary hypertension. Hemodynamics and physiologic components (e.g, plasma volume, activity of the renin-angiotensin system) vary, indicating that primary hypertension is unlikely to have a single cause. Even if one factor is initially responsible, multiple factors are probably involved in sustaining elevated BP (the mosaic theory). In afferent systemic arterioles, malfunction of ion pumps on sarcolemmal membranes of smooth muscle cells may lead to chronically increased vascular tone. Heredity is a predisposing factor, but the exact mechanism is unclear. Environmental factors (e.g, dietary Na, obesity, stress) seem to affect only genetically susceptible people at younger ages; however, in patients > 65, high Na intake is more likely to precipitate hypertension.

Secondary hypertension. Causes include primary aldosteronism, renal parenchymal disease (e.g, chronic glomerulonephritis or pyelonephritis, polycystic renal disease, connective tissue disorders, obstructive uropathy), renovascular disease (see Hypertension: Renovascular Hypertension), pheochromocytoma, Cushing syndrome, congenital adrenal hyperplasia, hyperthyroidism, myxedema, and coarctation of the aorta. Excessive alcohol intake and use of oral contraceptives are common causes of curable hypertension. Use of sympathomimetics, NSAIDs, corticosteroids, cocaine, or licorice commonly contributes to worsening of BP control.

Risk Factors Although the cause or causes of essential hypertension are largely unknown, several risk factors have been implicated as contributing to its development. These risk factors include family history of hypertension, race, and age-related increases in blood pressure. Another factor that is thought to contribute to hypertension is the insulin resistance and resultant hyperinsulinemia that occurs in persons with metabolic abnormalities such as those that occur with obesity and type 2 diabetes.

Family History. The inclusion of heredity as a contributing factor in the development of hypertension is supported by the fact that hypertension is seen most frequently among persons with a family history of hypertension. The strength of the prediction depends on the definition of positive family history and the age of the person at risk. Persons with two or more first-degree relatives with hypertension before age 55 years have a 3.8 times greater risk for development of hypertension before age 50 years than persons without a family history. At the same time, older persons in families with a strong family history of developing hypertension at a later age have a risk similar to that of the general population, suggesting they do not share the genetic predisposition associated with early onset hypertension. The inherited predisposition does not seem to rely on other risk factors, but when they are present, the risk apparently is additive. The pattern of heredity is unclear; it is unknown whether a single gene or multiple genes are involved. Whatever the explanation, the higher incidence of hypertension among close family members seems significant enough to be presented as a case for recommending that persons from these high-risk families be encouraged to participate in hypertensive screening programs on a regular basis.

Age-Related Changes in Blood Pressure. Maturation and growth are known to cause predictable increases in blood pressure. For example, in the newborn, arterial blood pressure normally is only approximately 50 mm Hg systolic and 40 mm Hg diastolic. Sequentially, blood pressure increases with physical growth from a value of 78 mm Hg systolic at 10 days of age to 120 mm Hg at the end of adolescence. Systolic blood pressure continues to undergo a slow rate of increase throughout adult life, whereas diastolic pressure increases until 50 years of age and then declines from the sixth decade onward.

Race. The Third National Health and Nutrition Survey (NHANES) III 1988 to 1991, reported that diastolic blood pressures were significantly greater for African Americans than for white men and women 35 years of age and older, and that systolic pressures of African-American women at every age were greater than those of white women. Hypertension tends to occur earlier in African Americans than in whites, and it often is not treated early enough or aggressively enough. Blacks also tend to experience greater cardiovascular and renal damage at any level of pressure. Studies have shown that many African-American persons with

hypertension have lower renin levels than white persons with hypertension. They also do not respond to increased salt intake by increasing their renal excretion of sodium at normal levels of arterial blood pressure. Instead, sodium elimination requires a higher level of blood pressure. These changes in sodium excretion have been linked to what has been called a salt-thrifty gene. It has been suggested that the genetic trait may have developed as an evolutionary adaptation to the severe demands for sodium conservation in the western African environment and the slavery environment of the Western Hemisphere. In both environments, survival under conditions of heavy exertion in a warm climate along with salt and water deprivation depended on the body's ability to conserve sodium. Evidence suggests that blacks, when provided equal access to diagnosis and treatment, can achieve overall reductions in blood pressure and experience fewer cardiovascular complications similar to whites. Barriers that limit access to the health care system include inadequate financial support, inconveniently located health care facilities, long waiting times, and inaccessibility to culturally relevant health education about hypertension. With the high prevalence of salt sensitivity, obesity, and smoking among blacks, health education and lifestyle modifications are particularly important.

Insulin Resistance and Metabolic Abnormalities. Insulin resistance and an accompanying compensatory hyperinsulinemia have been suggested as possible etiologic links to the development of hypertension and associated metabolic disturbances such as impaired glucose tolerance, type 2 diabetes, hyperlipidemias, and obesity. This clustering of cardiovascular risk factors has been named the insulin resistance syndrome, cardiovascular dysmetabolic syndrome, or metabolic syndrome X.

In persons with obesity and type 2 diabetes, the defect appears to be in the ability of insulin to stimulate the uptake and disposal of glucose by skeletal muscle. It has been suggested that the insulin-mediated increase in sympathetic activity is directed at increasing the metabolic rate as a means of burning the calories that cannot be stored because of insulin resistance. Unfortunately, the increase in sympathetic activity also contributes to the development of hypertension by stimulating the heart, blood vessels, and kidney. Insulin resistance may be a genetic or acquired trait. For example, it has been shown that insulin-mediated glucose disposal declines by 30 to 40 % in persons who are 40 % over ideal weight. Nonpharmacologic interventions, such as caloric restriction, weight loss, and exercise, tend to decrease insulin resistance, sympathetic nervous system activity, and blood pressure.

Circadian Variations (Dippers Versus Nondippers). The term dippers is used to refer to persons with a normal circadian blood pressure profile in which blood pressure falls during the night, and nondippers for persons whose 24-hour blood pressure profile is flattened. Changes in the normal circadian blood pressure profile may occur in a number of conditions, including malignant hypertension, Cushing syndrome, preeclampsia, orthostatic hypotension, congestive heart failure. There is increasing evidence that alterations in the normal nocturnal decline in blood pressure may contribute to the development of target-organ damage in persons with hypertension.

Lifestyle Factors can contribute to the development of hypertension by interacting with the risk factors. These lifestyle factors include high sodium intake, excessive calorie intake and obesity, physical inactivity, excessive alcohol consumption, and low intake of potassium. Oral contraceptive drugs also may increase blood pressure in predisposed women. Although stress can raise blood pressure acutely, there is less evidence linking it to chronic elevations in blood pressure. Smoking and a diet high in saturated fats and cholesterol, although not identified as primary risk factors for hypertension, are independent risk factors for coronary heart disease and should be avoided.

High Salt Intake. Increased salt intake has long been suspected as an etiologic factor in the development of hypertension. 24 Just how increased salt intake contributes to the development of hypertension is still unclear. It may be that salt causes an elevation in blood volume, increases the sensitivity of cardiovascular or renal mechanisms to adrenergic influences, or

exerts its effects through some other mechanism such as the renin-angiotensin-aldosterone mechanism. Regardless of the mechanism, numerous studies have shown that a reduction in salt intake can lower blood pressure.

Obesity. Excessive weight commonly is associated with hypertension. Weight reduction of as little as 4.5 kg (10 lb) can produce a decrease in blood pressure in a large proportion of overweight people with hypertension. It has been suggested that fat distribution might be a more critical indicator of hypertension risk than actual overweight. The waist-to-hip ratio commonly is used to differentiate central or upper body obesity (i.e., fat cell deposits in the abdomen) from peripheral or lower body obesity with fat cell deposits in the buttocks and legs. Studies have found an association between hypertension and increased waist-to-hip ratio (i.e., central obesity), even when body mass index and skinfold thickness are taken into account. Abdominal or visceral fat seems to be more insulin resistant than fat deposited over the buttocks and legs.

Excess Alcohol Consumption. Regular alcohol drinking plays a role in the development of hypertension. The effect is seen with different types of alcoholic drinks, in men and women, and in a variety of ethnic groups. One of the first reports of a link between alcohol consumption and hypertension came from the Oakland–San Francisco Kaiser Permanente Medical Care Program study that correlated known drinking patterns and blood pressure levels of 84,000 persons. This study revealed that the regular consumption of three or more drinks per day increases the risk for hypertension. Systolic pressures were more markedly affected than diastolic pressures. Blood pressure may improve or return to normal when alcohol consumption is decreased or eliminated. The mechanism whereby alcohol exerts its effect on blood pressure is unclear. It has been suggested that lifestyle factors such as obesity and lack of exercise may be accompanying factors.

Dietary Intake of Potassium, Calcium, and Magnesium. Low levels of dietary potassium have also been linked to increased blood pressure. Various mechanisms have been proposed to explain the influence of potassium on blood pressure. These include a purported change in the ratio of sodium to potassium in the diet, a direct natriuretic effect, and suppression of the renin-angiotensin system. In terms of food intake, a diet high in potassium usually is low in sodium. One of the major benefits of increased potassium intake is increased elimination of sodium (natriuretic effect) through the renin-angiotensin-aldosterone mechanism. The associations between high blood pressure and calcium and magnesium levels also have been investigated.

Oral Contraceptive Drugs. Oral contraceptives cause a mild increase in blood pressure in many women and overt hypertension in approximately 5 %. Why this occurs is largely unknown, although it has been suggested that estrogen and progesterone are responsible for the effect. Various contraceptive drugs contain different amounts and combinations of estrogen and progestational agents, and these differences may contribute to the occurrence of hypertension in some women but not others.

Stress. Physical and emotional stresses undoubtedly contribute to transient alterations in blood pressure. Studies in which arterial blood pressure was continually monitored on a 24-hour basis as persons performed their normal activities showed marked fluctuations in pressure associated with normal life stresses – increasing during periods of physical discomfort and family crisis and declining during rest and sleep.

Systolic Hypertension. Essential hypertension may be classified as systolic/diastolic hypertension in which both the systolic and diastolic pressures are elevated; as diastolic hypertension in which the diastolic pressure is selectively elevated; or as systolic hypertension in which the systolic pressure is selectively elevated. The JNC-7 report defined systolic hypertension as a systolic pressure of 140 mm Hg or greater and a diastolic pressure of less than 90 mm Hg, indicating a need for increased recognition and control of isolated systolic hypertension. Historically, diastolic hypertension was thought to confer a greater risk for cardiovascular events than systolic hypertension. However, there is mounting evidence that

elevated systolic blood pressure is at least as important, if not more so, than diastolic hypertension. In a recent study that used data from the Framingham Offspring cohort to arrive at a hypertension classification based on the JNC-6 stages, it was found that systolic pressure alone correctly classified 95 % of persons 60 years of age or younger and 99 % of those older than 60 years of age. There are two aspects of systolic hypertension that confer increased risk for cardiovascular events-one is the actual elevation in systolic pressure and the other is the disproportionate rise in pulse pressure. Elevated pressures during systole favor the development of left ventricular hypertrophy, increased myocardial oxygen demands, and eventual left heart failure. At the same time, the absolute or relative lowering of diastolic pressure is a limiting factor in coronary perfusion because coronary perfusion is greatest during diastole. Elevated levels of pulse pressure produce greater stretch of arteries, causing damage to the elastic elements of the vessel and thus predisposing to aneurysms and development of the intimal damage that leads to atherosclerosis and thrombosis.

Pathophysiology. Because BP equals cardiac output (CO) Ч total peripheral vascular resistance (TPR), pathogenic mechanisms must be involved. In most patients, CO is normal or slightly increased, and TPR is increased. This pattern is typical of primary hypertension and hypertension due to primary aldosteronism, pheochromocytoma, renovascular disease, and renal parenchymal disease. In other patients, CO is increased (possibly because of venoconstriction in large veins), and TPR is inappropriately normal for the level of CO. Later in the disorder, TPR increases and CO returns to normal, probably because of autoregulation. Some disorders that increase CO (thyrotoxicosis, arteriovenous fistula, aortic regurgitation), particularly when stroke volume is increased, cause isolated systolic hypertension. Some elderly patients have isolated systolic hypertension with normal or low CO, probably due to inelasticity of the aorta and its major branches. Patients with high, fixed diastolic pressures often have decreased CO. Plasma volume tends to decrease as BP increases; rarely, plasma volume remains normal or increases. Plasma volume tends to be high in hypertension due to primary aldosteronism or renal parenchymal disease and may be quite low in hypertension due to pheochromocytoma. Renal blood flow gradually decreases as diastolic BP increases and arteriolar sclerosis begins. GFR remains normal until late in the disorder; as a result, the filtration fraction is increased. Coronary, cerebral, and muscle blood flow is maintained unless severe atherosclerosis coexists in these vascular beds.

Abnormal Na transport. In many cases of hypertension, Na transport across the cell wall is abnormal, because the Na-K pump (Na^+, K^+-ATPase) is defective or inhibited or because permeability to Na^+ is increased. The result is increased intracellular Na, which makes the cell more sensitive to sympathetic stimulation. Ca follows Na, so accumulation of intracellular Ca may be responsible for the increased sensitivity. Because Na^+, K^+-ATPase may pump norepinephrine back into sympathetic neurons (thus inactivating this neurotransmitter), inhibition of this mechanism could also enhance the effect of norepinephrine, increasing BP. Defects in Na transport may occur in normotensive children of hypertensive parents.

Sympathetic nervous system. Sympathetic stimulation increases BP, usually more in patients with prehypertension (systolic BP 120 to 139 mm Hg, diastolic BP 80 to 89 mm Hg) or hypertension (systolic $BP \geq 140$ mm Hg, diastolic $BP \geq 90$ mm Hg, or both) than in normotensive patients. Whether this hyperresponsiveness resides in the sympathetic nervous system or in the myocardium and vascular smooth muscle is unknown. A high resting pulse rate, which may result from increased sympathetic nervous activity, is a well-known predictor of hypertension. In some hypertensive patients, circulating plasma catecholamine levels during rest are higher than normal.

Renin-angiotensin-aldosterone system. This system helps regulate blood volume and therefore BP. Renin, an enzyme formed in the juxtaglomerular apparatus, catalyzes conversion of angiotensinogen to angiotensin I. This inactive product is cleaved by ACE, mainly in the lungs but also in the kidneys and brain, to angiotensin II, a potent vasoconstrictor that also

stimulates autonomic centers in the brain to increase sympathetic discharge and stimulates release of aldosterone and ADH. Aldosterone and ADH cause Na and water retention, elevating BP. Aldosterone also enhances K excretion; low plasma K (< 3.5 mEq/L) increases vasoconstriction through closure of K channels. Angiotensin III, present in the circulation, stimulates aldosterone release as actively as angiotensin II but has much less pressor activity. Because chymase enzymes also convert angiotensin I to angiotensin II, drugs that inhibit ACE do not fully suppress angiotensin II production *(Fig. 7).*

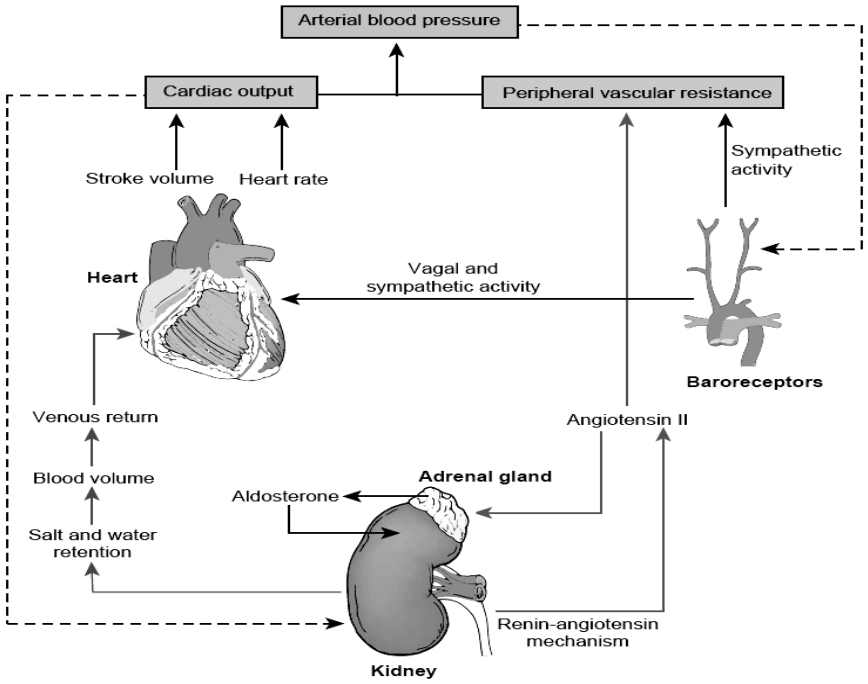


Fig. 7. Renin-angiotensin-aldosterone mechanism

Renin secretion is controlled by at least 4 mechanisms, which are not mutually exclusive: (1) A renal vascular receptor responds to changes in tension in the afferent arteriolar wall; (2) a macula densa receptor detects changes in the delivery rate or concentration of NaCl in the distal tubule; (3) circulating angiotensin has a negative feedback effect on renin secretion; and (4) via the renal nerve, the sympathetic nervous system stimulates renin secretion mediated by в-receptors. Angiotensin is generally acknowledged to be responsible for renovascular hypertension, at least in the early phase, but the role of the renin-angiotensin-aldosterone system in primary hypertension is not established. However, in black and elderly patients with hypertension, renin levels tend to be low. The elderly also tend to have low angiotensin II levels.

Hypertension due to chronic renal parenchymal disease (renoprival hypertension) results from the combination of a renin-dependent mechanism and a volume-dependent mechanism. In most cases, increased renin activity is not evident in peripheral blood. Hypertension is typically moderate and sensitive to Na and water balance.

Vasodilator deficiency: Deficiency of a vasodilator (e.g, bradykinin, nitric oxide) rather than excess of a vasoconstrictor (e.g, angiotensin, norepinephrine) may cause hypertension. If the kidneys do not produce adequate amounts of vasodilators (because of renal parenchymal disease or bilateral nephrectomy), BP can increase. Vasodilators and vasoconstrictors (mainly endothelin) are also produced in endothelial cells. Therefore, endothelial dysfunction greatly affects BP.

Pathology and complications: Severe or prolonged hypertension damages target organs (primarily the cardiovascular system, brain, and kidneys), increasing risk of coronary artery disease (CAD), MI, stroke (particularly hemorrhagic), and renal failure. The mechanism involves development of generalized arteriolosclerosis and acceleration of atherogenesis. Arteriolosclerosis is characterized by medial hypertrophy, hyperplasia, and hyalinization; it is particularly apparent in small arterioles, notably in the eyes and the kidneys. In the kidneys, the changes

narrow the arteriolar lumen, thus, hypertension leads to more hypertension. Furthermore, once arteries are narrowed, any slight additional shortening of already hypertrophied smooth muscle reduces the lumen to a greater extent than in normal-diameter arteries. These effects may explain why the longer hypertension has existed, the less likely specific treatment (eg, renovascular surgery) for secondary causes is to restore BP to normal.

Renovascular Hypertension

Renovascular hypertension is BP elevation due to partial or complete occlusion of one or more renal arteries or their branches. It is usually asymptomatic unless long-standing. A bruit can be heard over one or both renal arteries in < 50 % of patients. Diagnosis is by physical examination and renal imaging with duplex ultrasonography, radionuclide imaging, or magnetic resonance angiography. Angiography is done before definitive treatment with surgery or angioplasty.

Stenosis or occlusion of one or both main renal arteries, an accessory renal artery, or any of their branches can cause hypertension by stimulating release of renin from juxtaglomerular cells of the affected kidney. The area of the arterial lumen must be decreased by ≥ 70 % and a significant poststenotic gradient must also be present before stenosis is likely to contribute to BP elevation. For unknown reasons, renovascular hypertension is much less common among blacks than among whites. Overall, about 80 % of cases are caused by atherosclerosis and 20 % by fibromuscular dysplasia. Atherosclerosis is more common among men > 50 and affects mainly the proximal one third of the renal artery. Fibromuscular dysplasia is more common among younger patients (usually women) and usually affects the distal two third of the main renal artery and the branches of the renal arteries. Rarer causes include emboli, trauma, inadvertent ligation during surgery, and extrinsic compression of the renal pedicle by tumors. Renovascular hypertension is characterized by high cardiac output and high peripheral resistance.

Pheochromocytoma

A pheochromocytoma is a tumor of chromaffin tissue, which contains sympathetic nerve cells stained with chromium salts. The tumor is most commonly located in the adrenal medulla but can occur in other sites, such as sympathetic ganglia, where there is chromaffin tissue. Although only 0.1 to 0.5 % of persons with hypertension have an underlying pheochromocytoma, the disorder can cause serious hypertensive crises. The tumors are malignant 8 to 10 % of the time. Like adrenal medullary cells, the tumor cells of a pheochromocytoma produce and secrete the catecholamines epinephrine and norepinephrine. The developed hypertension is a result of the massive release of these catecholamines. Their release may be paroxysmal rather than continuous, causing periodic episodes of headache, excessive sweating, and palpitations. Headache is the most common symptom and can be quite severe. Nervousness, tremor, facial pallor, weakness, fatigue, and weight loss occur less frequently. Marked variability in blood pressure between episodes is typical. Approximately 50 % of persons with pheochromocytoma have paroxysmal episodes of hypertension, sometimes at dangerously high levels. The other 50 % have sustained hypertension, and some even may be normotensive. Several tests are available to differentiate hypertension due to pheochromocytoma from other forms of hypertension. The most commonly used diagnostic measure is determination of urinary catecholamines and their metabolites. Although measurement of plasma catecholamines also may be used, other conditions can cause elevated catecholamines. After we found pheochromocytoma, the tumor needs to be located. Computed tomographic (CT) scans or MRI may be used for this purpose. Surgical removal of operable tumors is usually curative.

Coarctation of the Aorta

Coarctation represents a narrowing of the aorta. In the adult form of coarctation, the narrowing most commonly occurs just distal to the origin of the subclavian arteries. Because of the narrowing, blood flow to the lower parts of the body and kidneys is reduced. In the infantile form of coarctation, the narrowing occurs proximal to the ductus arteriosus, in which case heart failure and other problems may occur. Many affected children die within their first year of life. In the adult form of coarctation, an increase in cardiac output may result from

renal compensatory mechanisms. The ejection of a large stroke volume into a narrowed aorta with limited ability to accept the runoff results in an increase in systolic blood pressure and blood flow to the upper part of the body. Blood pressure in the lower extremities may be normal, although it frequently is low. It has been suggested that the increase in cardiac output and maintenance of the pressure to the lower part of the body is achieved through the renin-angiotensin-aldosterone mechanism in response to a decrease in renal blood flow. Pulse pressure in the legs almost always is narrowed, and the femoral pulses are weak. Because the aortic capacity is diminished, there usually is a marked increase in pressure (measured in the arms) during exercise, when the stroke volume and heart rate are exaggerated. For this reason, blood pressures in both arms and one leg should be determined; a pressure that is 20 mm Hg more in the arms than in the legs suggests coarctation of the aorta. Involvement of the left subclavian artery or an anomalous origin of the right subclavian may produce decreased or absent left or right brachial pulses, respectively. Palpation of both brachial pulses and measurement of blood pressure in both arms are important. Treatment consists of surgical repair or balloon angioplasty. Although balloon angioplasty is a relatively recent form of treatment, it has been used in children and adults with good results. However, there are few data on long-term follow-up.

Malignant hypertension. A small number of persons with secondary hypertension develop an accelerated and potentially fatal form of the disease: malignant hypertension. This usually is a disease of younger persons, particularly young African-American men, women with toxemia of pregnancy, and persons with renal and collagen diseases. Malignant hypertension is characterized by sudden marked elevations in blood pressure, with diastolic values above 120 mm Hg complicated by evidence of acute or rapidly progressive life-threatening organ dysfunction. There may be intense arterial spasm of the cerebral arteries with hypertensive encephalopathy. Cerebral vasoconstriction probably is an exaggerated homeostatic response designed to protect the brain from excesses of blood pressure and flow. The regulatory mechanisms often are insufficient to protect the capillaries, and cerebral edema frequently develops. As it advances, papilledema (i.e., swelling of the optic nerve at its point of entrance into the eye) ensues, giving evidence of the effects of pressure on the optic nerve and retinal vessels. The patient may have headache, restlessness, confusion, stupor, motor and sensory deficits, and visual disturbances. In severe cases, convulsions and coma follow. Prolonged and severe exposure to exaggerated levels of blood pressure in malignant hypertension injures the walls of the arterioles, and intravascular coagulation and fragmentation of red blood cells may occur. The renal blood vessels are particularly vulnerable to hypertensive damage. Renal damage due to vascular changes probably is the most important prognostic determinant in malignant hypertension. Elevated levels of blood urea nitrogen and serum creatinine, metabolic acidosis, hypocalcemia, and proteinuria provide evidence of renal impairment.

The complications associated with a hypertensive crisis demand immediate and rigorous medical treatment in an intensive care unit with continuous monitoring of arterial blood pressure. With proper therapy, the death rate from this cause can be markedly reduced, as can additional episodes. Because chronic hypertension is associated with autoregulatory changes in coronary artery, cerebral artery, and kidney blood flow, care should be taken to avoid excessively rapid decreases in blood pressure, which can lead to hypoperfusion and ischemic injury. Therefore, the goal of initial treatment measures should be to obtain a partial reduction in blood pressure to a safer, noncritical level, rather than to normotensive levels.

High blood pressure in pregnancy. Hypertensive disorders complicate 6 to 8 % of pregnancies. They are the second leading cause, after embolism, of maternal mortality in the United States, accounting for almost 15 % of such deaths. Hypertensive disorders also contribute to stillbirths and neonatal morbidity and mortality. Premature separation of the placenta (abruptio placentae) is reported to complicate up to 10 % of hypertensive pregnancies. The incidence of hypertensive disorders of pregnancy increases with maternal age and is more common in African-American women.

Classification. In 2008, the National Institutes of Health Working Group on High Blood Pressure in Pregnancy published a revised classification system for high blood pressure in pregnancy that included chronic hypertension, preeclampsia eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension.

Chronic Hypertension. Chronic hypertension is considered as hypertension unrelated to the pregnancy. It is defined as a history of high blood pressure before pregnancy, identification of hypertension before 20 weeks of pregnancy, and hypertension that persists after pregnancy. Hypertension is defined as a systolic pressure of 140 mm Hg or higher or a diastolic pressure of 90 mm Hg or higher. Hypertension that is diagnosed for the first time during pregnancy and does not resolve after pregnancy also is classified as chronic hypertension. In women with chronic hypertension, blood pressure often decreases in early pregnancy and increases during the last trimester (3 months) of pregnancy, resembling preeclampsia. Women with chronic hypertension are at increased risk for the development of preeclampsia.

Preeclampsia-Eclampsia. Preeclampsia-eclampsia is a pregnancy-specific syndrome usually occurring after 20 weeks of gestation. It is defined as an elevation in blood pressure (systolic > 140 mm Hg or diastolic > 90 mm Hg) and proteinuria ($\geq$ 300 g in 24 hours) developing after 20 weeks of gestation. Edema, which previously was included in definitions of preeclampsia, was excluded from this most recent definition. The presence of a systolic blood pressure of 160 mm Hg or higher or a diastolic pressure of 110 mm Hg or higher; hyperproteinuria greater than 2 g in 24 hours; serum creatinine greater than 1.2 mg/dL; platelet counts less than 100,000 cells/mm^3; elevated liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]); persistent headache or cerebral or visual disturbances; and persistent epigastric pain serve to reinforce the diagnosis. Eclampsia occurs in a woman with preeclampsia, of seizures that cannot be attributed to other causes. Preeclampsia occurs primarily during first pregnancies in women with multiple fetuses, diabetes mellitus, or coexisting renal disease. Women with chronic hypertension who become pregnant have an increased risk for preeclampsia and adverse neonatal outcomes, particularly when associated with proteinuria early in pregnancy Pregnancy-induced hypertension is thought to involve a decrease in placental blood flow leading to the release of toxic mediators that alter the function of endothelial cells in blood vessels throughout the body, including those of the kidney, brain, liver, and heart. The endothelial changes result in signs and symptoms of preeclampsia and, in more severe cases, of intravascular clotting and hypoperfusion of vital organs. There is a risk of development of disseminated intravascular coagulation, cerebral hemorrhage, hepatic failure, and acute renal failure. Thrombocytopenia is the most common hematologic complication of preeclampsia. Platelet counts of less than 100,000/mm signal serious disease. The cause of thrombocytopenia has been ascribed to platelet deposition at the site of endothelial injury. The renal changes that occur with preeclampsia include a decrease in glomerular filtration rate and renal blood flow. Sodium excretion may be impaired, although this is variable. Edema may or may not be present. Some of the severest forms of preeclampsia occur in the absence of edema. Even when there is extensive edema, the plasma volume usually is lower than that of normal pregnancy. Liver damage, when it occurs, may range from mild hepatocellular necrosis with elevation of liver enzymes to the more ominous hemolysis, elevated liver function tests, and low platelet count (HELLP) syndrome that is associated with significant maternal mortality. Eclampsia, the convulsive stage of preeclampsia, is a significant cause of maternal mortality. The pathogenesis of eclampsia remains unclear and has been attributed to both increased coagulability and fibrin deposition in the cerebral vessels. Defining the causes of pregnancy-induced hypertension is difficult because of the normal circulatory changes that occur during pregnancy. Blood pressure normally decreases during the first trimester, reaches its lowest point during the second trimester, and gradually rises during the third trimester. The fact that there is a 40 to 60 % increase in cardiac output during early pregnancy suggests the decrease in blood pressure that occurs during the first part of pregnancy results from a decrease in peripheral vascular resistance. Because the cardiac output remains high throughout pregnancy,

the gradual rise in blood pressure that begins during the second trimester probably represents a return of the peripheral vascular resistance to normal. Pregnancy normally is accompanied by increased levels of renin, angiotensin I and II, estrogen, progesterone, prolactin, and aldosterone, all of which may alter vascular reactivity. Women who develop preeclampsia are thought to be particularly sensitive to the vasoconstrictor responses of the renin-angiotensin-aldosterone system. They also are particularly responsive to other vasoconstrictors, including the catecholamines and vasopressin. It has been proposed that some of the sensitivity may be caused by a prostacyclin-thromboxane imbalance. Thromboxane is a prostaglandin with vasoconstrictor properties, and prostacyclin is a prostaglandin with vasodilator properties. Emerging evidence suggests that insulin resistance, including gestational diabetes, polycystic ovary syndrome, and obesity, may predispose to hypertensive disorders in pregnancy.

Hypertensive Emergencies is severe hypertension with signs of damage to target organs (primarily the brain, cardiovascular system, and kidneys). Diagnosis is by BP measurement, ECG, urinalysis, and serum BUN and creatinine measurements.

Target-organ damage includes hypertensive encephalopathy, preeclampsia and eclampsia, acute left ventricular failure with pulmonary edema, myocardial ischemia, acute aortic dissection, and renal failure. Damage is rapidly progressive and often fatal.

Hypertensive encephalopathy may involve a failure of cerebral autoregulation of blood flow. Normally, as BP increases, cerebral vessels constrict to maintain constant cerebral perfusion. Above a mean arterial pressure (MAP) of about 160 mm Hg (lower for normotensive people whose BP suddenly increases), the cerebral vessels begin to dilate rather than remain constricted. As a result, the very high BP is transmitted directly to the capillary bed with transudation and exudation of plasma into the brain, causing cerebral edema, including papilledema. Although many patients with stroke and intracranial hemorrhage present with elevated BP, it is often a consequence rather than a cause of the condition. Whether rapidly lowering BP is beneficial in these conditions is unclear; it may even be harmful.

Orthostatic Hypotension or postural hypotension is an abnormal drop in blood pressure on assumption of the standing position. In the absence of normal circulatory reflexes or blood volume, blood pools in the lower part of the body when the standing position is assumed, cardiac output and blood pressure fall, and blood flow to the brain is inadequate. Dizziness, syncope (i.e., fainting), or both may occur. Some authorities differentiate between orthostatic hypotension, characterized by a rapid decrease in blood pressure and the inability to stand for more than 1 to 2 minutes, and orthostatic intolerance, which generally occurs in younger persons and is characterized by a delayed decrease in blood pressure. Rather than inability to stand, persons with orthostatic intolerance complain of dizziness, visual changes, head and neck discomfort, poor concentration while standing, palpitations, tremor, anxiety, presyncope, and in some cases syncope. This text uses orthostatic hypotension to indicate both types of postural hypotension. After the assumption of the upright posture from the supine position, approximately 500 to 700 mL of blood is momentarily shifted to the lower part of the body, with an accompanying decrease in central blood volume and arterial pressure. Normally, this decrease in blood pressure is transient, lasting through several cardiac cycles, because the baroreceptors located in the thorax and carotid sinus area sense the decreased pressure and initiate reflex constriction of the veins and arterioles and an increase in heart rate, which brings blood pressure back to normal. The initial adjustment to orthostatic stress is mediated exclusively by the ANS. Within a few minutes of standing, blood levels of antidiuretic hormone and sympathetic neuromediators increase as a secondary means of ensuring maintenance of normal blood pressure in the standing position Under normal conditions, the renin-angiotensin-aldosterone system is also activated when the standing position is assumed, and even more so in situations of hypotensive orthostatic stress. Muscle movement in the lower extremities also aids venous return to the heart by pumping blood out of the legs. The unconscious slight body and leg movement during standing (postural sway) is recognized as an important factor in moving venous blood back to the heart. Crossing the legs, which involves

contraction of the agonist and antagonist muscles, has been shown to be a simple and effective way of increasing cardiac output and, therefore, blood pressure. When leg crossing is practiced routinely by persons with autonomic failure, standing systolic and diastolic pressures can be increased by approximately 20/10 mm Hg. The strategic location of the arterial baroreceptors between the heart and brain is designed to ensure that the arterial pressure is maintained within a range sufficient to prevent a reduction in cerebral blood flow.

Causes. A wide variety of conditions, acute and chronic, are associated with orthostatic hypotension. These include reduced blood volume, drug-induced hypotension, altered vascular responses associated with aging, bed rest, and ANS dysfunction.

Reduced Blood Volume. Orthostatic hypotension often is an early sign of reduced blood volume or fluid deficit. When blood volume is decreased, the vascular compartment is only partially filled; although cardiac output may be adequate when a person is in the recumbent position, it often decreases to the point of causing weakness and fainting when the person assumes the standing position. Common causes of orthostatic hypotension related to hypovolemia are excessive use of diuretics, excessive diaphoresis, loss of gastrointestinal fluids through vomiting and diarrhea, and loss of fluid volume associated with prolonged bed rest.

Induced Hypotension. Antihypertensive drugs and psychotropic drugs are the most common cause of chronic orthostatic hypotension. In most cases, the orthostatic hypotension is well tolerated. However, if the hypotension causes lightheadedness or syncope, the dosage of the drug is usually reduced or a different drug substituted.

Aging. Weakness and dizziness on standing are common complaints of elderly persons. The Cardiovascular Health Study reports a 16.2 % prevalence of asymptomatic orthostatic hypotension among persons 65 years of age and older. Orthostatic hypotension was associated with systolic hypertension, major electrocardiographic abnormalities, and carotid artery stenosis. Because cerebral blood flow primarily depends on systolic pressure, patients with impaired cerebral circulation may experience symptoms of weakness, ataxia, dizziness, and syncope when their arterial pressure falls even slightly. This may happen in older persons who are immobilized for brief periods or whose blood volume is decreased owing to inadequate fluid intake or overzealous use of diuretics. Postprandial blood pressure often decreases in elderly persons. The greatest postprandial changes occur after a high-carbohydrate meal. Although the mechanism responsible for these changes is not fully understood, it is thought to result from glucose-mediated impairment of baroreflex sensitivity and increased splanchnic blood flow mediated by insulin and vasoactive gastrointestinal hormones.

Bed Rest. Prolonged bed rest promotes a reduction in plasma volume, a decrease in venous tone, failure of peripheral vasoconstriction, and weakness of the skeletal muscles that support the veins and assist in returning blood to the heart. Physical deconditioning follows even short periods of bed rest. After 3 to 4 days, the blood volume is decreased. Loss of vascular and skeletal muscle tone is less predictable but probably becomes maximal after approximately 2 weeks of bed rest. Orthostatic intolerance is a recognized problem of space flight—a potential risk after reentry into the earth's gravitational field.

Disorders of Autonomic Nervous System Function. The sympathetic nervous system plays an essential role in adjustment to the upright position. Sympathetic stimulation increases heart rate and cardiac contractility and causes constriction of peripheral veins and arterioles. Orthostatic hypotension caused by altered autonomic function is common in peripheral neuropathies associated with diabetes mellitus, after injury or disease of the spinal cord, or as the result of a cerebral vascular accident in which sympathetic outflow from the brain stem is disrupted. The American Autonomic Society of Neurology have distinguished three forms of primary ANS dysfunction:

(1) pure autonomic failure, which is defined as a sporadic, idiopathic cause of persistent orthostatic hypotension and other manifestations of autonomic failure such as urinary retention, impotence, or decreased sweating;

(2) Parkinson disease with autonomic failure;

(3) multiple-system atrophy (Shy-Drager syndrome)- usually develops in middle to late life as orthostatic hypotension associated with uncoordinated movements, urinary incontinence, constipation, and other signs of neurologic deficits referable to the corticospinal, extrapyramidal, corticobulbar, and cerebellar systems.

HYPERLIPIDEMIA. Triglycerides, phospholipids, and cholesterol, which are classified as lipids, are chemical substances composed of long-chain hydrocarbon fatty acids. Triglycerides, which are used in energy metabolism, are combinations of three fatty acids condensed with a single glycerol molecule. Phospholipids, which contain a phosphate group, are important structural constituents of lipoproteins, blood clotting components, the myelin sheath, and cell membranes.

Although cholesterol is not composed of fatty acids, its steroid nucleus is synthesized from fatty acids; thus, its chemical activity is similar to that of other lipid substances. Elevated levels of blood cholesterol (hypercholesterolemia) are implicated in the development of atherosclerosis with its attendant risk for heart attack and stroke. This is a major public health issue that is underscored by striking statistics released by the American Heart Association. An estimated 41.3 million Americans have high serum cholesterol levels that could contribute to a heart attack, stroke, or other cardiovascular event associated with atherosclerosis.

Lipoproteins. Because cholesterol and triglyceride are insoluble in plasma, they are encapsulated by special fat-carrying proteins called lipoproteins for transport in the blood. There are five types of lipoproteins, classified by their densities as measured by ultracentrifugation: chylomicrons, very–low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). VLDL carries large amounts of triglycerides that have a lower density than cholesterol. LDL is the main carrier of cholesterol, whereas HDL actually is 50 % protein. Each type of lipoprotein consists of a large molecular complex of lipids combined with proteins called apoproteins.

The major lipid constituents are cholesterol esters, triglycerides, nonesterified cholesterol, and phospholipids. The insoluble cholesterol esters and triglycerides are located in the hydrophobic core of the lipoprotein macromolecule, surrounded by the soluble phospholipids, nonesterified cholesterol, and apoproteins. Nonesterified cholesterol and phospholipids provide a negative charge that allows the lipoprotein to be soluble in plasma.

There are four major classes of apoproteins: A (i.e., A-I, A-II, and A-IV), B (e.g., B-48, B-100), C (i.e., C-I, C-II, and C-III), and E. The apoproteins control the interactions and ultimate metabolic fate of the lipoproteins. Some of the apoproteins activate the lipolytic enzymes that facilitate the removal of lipids from the lipoproteins; others serve as a reactive site that cellular receptors can recognize and use in the endocytosis and metabolism of the lipoproteins. The major apoprotein in LDL is B-100. HDL is associated with A-I and A-II. Research findings suggest that genetic defects in apoproteins may be involved in hyperlipidemia and accelerated atherosclerosis.

There are two sites of lipoprotein synthesis: the small intestine and the liver. The chylomicrons, which are the largest of the lipoprotein molecules, are synthesized in the wall of the small intestine. They are involved in the transport of dietary (exogenous pathway) triglycerides and cholesterol that have been absorbed from the gastrointestinal tract. Chylomicrons transfer their triglycerides to the cells of adipose and skeletal muscle tissue. The remnant chylomicron particles, which contain cholesterol, are then taken up by the liver, and the cholesterol is used in the synthesis of VLDL or is excreted in the bile.

The liver synthesizes and releases VLDL and HDL. The VLDLs contain large amounts of triglycerides and lesser amounts of cholesterol esters. They provide the primary pathway for transport of the endogenous triglycerides produced in the liver, as opposed to those obtained from the diet. Like chylomicrons, VLDLs carry their triglycerides to fat and muscle cells, where the triglycerides are removed. The resulting IDL fragments are reduced in triglyceride

content and enriched in cholesterol. They are taken to the liver and recycled to form VLDL, or converted to LDL in the vascular compartment. IDLs are the main source of LDL. LDL, sometimes called bad cholesterol, is the main carrier of cholesterol. The LDL is removed from the circulation by either LDL receptors or by nonreceptor mechanisms involving scavenger cells such as monocytes or macrophages. Approximately 70 % of LDL is removed by way of the LDL receptor-dependent pathway. Approximately 75 % are located on hepatocytes; thus, the liver plays an extremely important role in LDL metabolism. Receptor-mediated removal involves binding of LDL to cell surface receptors, followed by endocytosis, a phagocytic process in which LDL is engulfed and moved into the cell in the form of a membrane-covered endocytic vesicle. Within the cell, the endocytic vesicles fuse with lysosomes, and the LDL molecule is enzymatically degraded, causing free cholesterol to be released into the cytoplasm. Other, nonhepatic tissues (i.e., adrenal glands, smooth muscle cells, endothelial cells, and lymphoid cells) also use the receptor-dependent pathway to obtain cholesterol needed for membrane and hormone synthesis. These tissues can control their cholesterol intake by adding or removing LDL receptors. The remaining LDL is removed by non–receptor-dependent mechanisms, including ingestion by phagocytic monocytes and macrophages. These scavenger cells have receptors that bind LDL that has been oxidized or chemically modified. The amount of LDL that is removed by the scavenger pathway is directly related to the plasma cholesterol level. When there is a decrease in LDL receptors or when LDL levels exceed receptor availability, the amount of LDL that is removed by scavenger cells is greatly increased. The uptake of LDL by macrophages in the arterial wall can result in the accumulation of insoluble cholesterol esters, the formation of foam cells, and the development of atherosclerosis. HDL is synthesized in the liver and often is referred to as the good cholesterol. HDL participates in the reverse transport of cholesterol, that is, carrying cholesterol from the peripheral tissues back to the liver. Epidemiologic studies show an inverse relation between HDL levels and the development of atherosclerosis. It is thought that HDL, which is low in cholesterol and rich in surface phospholipids, facilitates the clearance of cholesterol from atheromatous plaques and transports it to the liver, where it may be excreted rather than reused in the formation of VLDL. The mechanism whereby HDL takes up cholesterol from peripheral cells has recently been elucidated. A lipid transporter (adenosine triphosphate [ATP]-binding cassette transporter A class 1, or ABCA1) promotes the movement of cholesterol from peripheral cells to lipid-poor HDL. Defects in this system (resulting from mutations in the ABCA1 transporter) are responsible for Tangier disease, which is characterized by accelerated atherosclerosis and little or no HDL. HDL also is believed to inhibit cellular uptake of LDL. It has been observed that regular exercise and moderate alcohol consumption increase HDL levels. Smoking and the metabolic syndrome, which are in themselves risk factors for atherosclerosis, are associated with decreased levels of HDL. Hypercholesterolemia The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults includes a classification system for hyperlipidemia that describes optimal to very high levels of LDL cholesterol, desirable to high levels of total cholesterol, and low and high levels of HDL cholesterol. The NCEP recommends that all adults 20 years of age and older should have a fasting lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) measured once every 5 years. If testing is done in the nonfasting state, only the total cholesterol and HDL are considered useful. A follow-up lipoprotein profile should be done on persons with nonfasting total cholesterol levels of 200 mg/dL or greater, or HDL levels of less than 40 mg/dL. Lipoprotein measurements are particularly important in persons at high risk for development of coronary heart disease (CHD). Serum cholesterol levels may be elevated as a result of an increase in any of the lipoproteins—the chylomicrons, VLDL, IDL, LDL, or HDL. The commonly used classification system for hyperlipidemia is based on the type of lipoprotein involved. Three factors—nutrition, genetics, and metabolic diseases—can raise blood lipid levels. Most cases of

elevated levels of cholesterol are probably multifactorial. Some persons may have increased sensitivity to dietary cholesterol, others have a lack of LDL receptors, and still others have an altered synthesis of the apoproteins, including oversynthesis of apoprotein B-100, the major apoprotein in LDL. Hypercholesterolemia can be classified as primary or secondary hypercholesterolemia. Primary hypercholesterolemia describes elevated cholesterol levels that develop independent of other health problems or lifestyle behaviors. Secondary hypercholesterolemia is associated with other health problems and behaviors. Many types of primary hypercholesterolemia have a genetic basis. There may be a defective synthesis of the apoproteins, a lack of receptors, defective receptors, or defects in the handling of cholesterol in the cell that are genetically determined. For example, the LDL receptor is deficient or defective in the genetic disorder known as familial hypercholesterolemia (type 2A). This autosomal dominant type of hyperlipoproteinemia results from a mutation in the gene specifying the receptor for LDL. More than 600 different mutations in the LDL receptor have been described. Because most of the circulating cholesterol is removed by receptor-dependent mechanisms, blood cholesterol levels are markedly elevated in persons with this disorder. The disorder is probably one of the most common of all mendelian disorders; the frequency of heterozygotes is 1 in 500 persons in the general population. Plasma LDL levels in heterozygotes range between 250 and 500 mg/dL, whereas in homozygotes, LDL cholesterol levels may rise to 1000 mg/dL. Although heterozygotes commonly have an elevated cholesterol level from birth, they do not develop symptoms until adult life, when they develop xanthomas (i.e., cholesterol deposits) along the tendons, and atherosclerosis appears. Myocardial infarction before 40 years of age is common. Homozygotes are much more severely affected; they have cutaneous xanthomas in childhood and may experience myocardial infarction by as early as 1 to 2 years of age. Causes of secondary hyperlipoproteinemia include obesity with high-calorie intake and diabetes mellitus. High-calorie diets increase the production of VLDL, with triglyceride elevation and high conversion of VLDL to LDL. Excess ingestion of cholesterol may reduce the formation of LDL receptors and thereby decrease LDL removal. Diets that are high in triglycerides and saturated fats increase cholesterol synthesis and suppress LDL receptor activity. In diabetes mellitus and the metabolic syndrome, typical dyslipidemia is seen with elevation of triglycerides, low HDL, and minimal or modest elevation of LDL.

Table 29

Tipes of lipoprotein abnormality

Type	Familiar Name	Lipoprotein Abnormality	Known Underlying Genetic Defects
1	Exogenous dietary hypertriglyceridemia	Elevated chylomicrons and triglycerides	Mutation in lipoprotein lipase gene
2a	Familial hypercholesterolemia	Elevated LDL cholesterol	Mutation in LDL receptor gene or in apoprotein B gene
2b	Combined hyperlipidemia	Elevated LDL, VLDL, and triglycerides	Mutation in LDL receptor gene or apoprotein B gene
3	Remnant hyperlipidemia	Increased remnants (chylomicrons), IDL triglycerides, and cholesterol	Mutation in apolipoprotein E gene
4	Endogenous hypertriglyceridemia	Elevated VLDL and triglycerides	Unknown
5	Mixed hypertriglyceridemia	Elevated VLDL, chylomicrons, and cholesterol; triglycerides greatly elevated	Mutation in apolipoprotein C-II gene

Management of Hyperlipidemia. The NCEP continues to identify reduction in LDL cholesterol as the primary target for cholesterol-lowering therapy, particularly in people at risk for CHD. The major risk factors for CHD, exclusive of LDL cholesterol levels, that modify LDL cholesterol goals include cigarette smoking, hypertension, family history of premature CHD in a first-degree relative, age (men, 45 years and older; women, 55 years and older), and HDL cholesterol levels of less than 40 mg/dL. Accordingly, the NCEP recommends that persons with CHD or CHD equivalents (other forms of atherosclerotic disease or diabetes)

should have an LDL cholesterol goal of less than 100 mg/dL; those with two or more of the major risk factors should have an LDL cholesterol goal of 130 mg/dL; and those with zero or no major risk factors should have an LDL cholesterol goal of 160 mg/dL or lower.

Three dietary elements affect cholesterol and its lipoprotein fractions: (1) excess calorie intake, (2) saturated fats, and (3) cholesterol. Excess calories consistently lower HDL and less consistently elevate LDL. Saturated fats in the diet can strongly influence cholesterol levels. Each 1 % of saturated fat relative to caloric intake increases the cholesterol level an average of 2.8 mg/dL. Depending on individual differences, it raises the VLDL and the LDL. Dietary cholesterol tends to increase LDL cholesterol. On average, each 100 mg/dL of ingested cholesterol raises the serum cholesterol 8 to 10 mg/dL. The aims of dietary therapy are to reduce total and LDL cholesterol levels, to increase HDL cholesterol by reduction in total calories, and to reduce the percentage of total calories from saturated fat and cholesterol. For persons who already have an elevated LDL, the AHA recommends that the upper limit of saturated fat intake be less than 7 % of the total daily intake. However, even with strict adherence to the diet, drug therapy is usually necessary.

Lipid-lowering drugs ultimately work by affecting cholesterol production, decreasing cholesterol absorption from the intestine, increasing intravascular breakdown, or removing cholesterol from the bloodstream.

ATHEROSCLEROSIS

Atherosclerosis is a type of arteriosclerosis or hardening of the arteries. The term atherosclerosis, which comes from the Greek words atheros (meaning “gruel” or “paste”) and sclerosis (meaning “hardness”), denotes the formation of fibro fatty lesions in the intimal lining of the large and medium-sized arteries, such as the aorta and its branches, the coronary arteries, and the large vessels that supply the brain. Although there has been a gradual decline in deaths from atherosclerosis over the past several decades, CHD remains the leading cause of death among men and women in the United States. The reported decline in death rate probably reflects new and improved methods of medical treatment and improved health care practices resulting from an increased public awareness of the factors that predispose to the development of this disorder. The major complications of atherosclerosis, including ischemic heart disease, stroke, and peripheral vascular disease, account for more than 40 % of the deaths in the United States. Atherosclerosis begins as an insidious process, and clinical manifestations of the disease typically do not become.

Risk Factors

The cause or causes of atherosclerosis have not been determined with certainty. Epidemiologic studies have, however, identified predisposing risk factors. In terms of health care behaviors, some of these risk factors can be affected by a change in behavior, and others cannot. The major risk factor for atherosclerosis is hypercholesterolemia. Nonlipid risk factors, such as increasing age, family history of premature CHD, and male sex, cannot be changed. The tendency to the development of atherosclerosis appears to run in families. Persons who come from families with a strong history of heart disease or stroke due to atherosclerosis are at greater risk for developing atherosclerosis than those with a negative family history. Several genetically determined alterations in lipoprotein and cholesterol metabolism have been identified, and it seems likely that others will be identified in the future. The incidence of atherosclerosis increases with age. Other factors being equal, men are at greater risk for developing CHD than are premenopausal women, probably because of the protective effects of natural estrogens. After menopause, the incidence of atherosclerotic-related diseases in women increases, and by the seventh to eighth decade of life, the frequency of myocardial infarction in the two sexes tends to equalize. The major risk factors that can be affected by a change in health care behaviors include cigarette smoking, obesity, hypertension, high blood cholesterol levels, and diabetes mellitus (traditional cardiovascular risk factors). Cigarette smoking is closely linked with CHD and sudden death. One hypothesis is that components of cigarette smoke may be toxic, causing oxidative insult and damage to the endothelial lining of blood vessels.

Endothelial dysfunction may be worsened by cigarette smoke, which is why cessation of smoking by high-risk individuals often is followed within a few years by reduced risk for ischemic heart disease. Obesity, type 2 diabetes, high blood pressure, and high blood cholesterol levels often can be controlled with a change in health care behaviors and medications. There is evidence that elevated serum cholesterol not only contributes to development of atherosclerotic lesions that block arteries but also interferes with vessel relaxation. Observational research indicates that a linear relation exists between serum cholesterol levels and coronary heart disease; a 10 % decrease in serum cholesterol is associated with a 20 % decrease in coronary heart disease. However, not all atherothrombotic vascular disease can be explained by the established genetic and environmental risk factors. Other, so-called nontraditional, cardiovascular risk factors can be associated with an increased risk for developing atherosclerosis, including C-reactive protein (CRP), serum homocysteine, serum lipoprotein (a), infectious agents, and endothelial dysfunction. Considerable interest in the role of inflammation in the etiology of atherosclerosis has emerged during the past few years. In particular, CRP is now considered a major risk factor marker. CRP is a serum marker for systemic inflammation. Several prospective studies have indicated that elevated CRP levels are associated with vascular disease. The pathophysiologic role of CRP in atherosclerosis has not yet been defined. Measurement of high-sensitivity CRP (hs-CRP) may be a better predictor of cardiovascular risk than lipid measurement alone. Indeed, approximately 50 % of myocardial infarction patients have a normal LDL. In the Heart Protection study, statin therapy decreased cardiovascular complications even in patients with normal LDL. This was thought to be due to the anti-inflammatory effects of these agents. Inflammation (as assessed by a decrease in hs-CRP) can be reduced by using certain lifestyle changes and by drugs (including statins, fibrates, and thiazolidinediones [glitazones]). Because CRP is an acute-phase reactant, major infections, trauma, or acute hospitalization can elevate CRP levels (usually 100-fold or more). CRP levels to determine cardiovascular risk should be performed when the patient is clinically stable. If the level remains markedly elevated, an alternative source of systemic inflammation should be considered. Homocysteine is derived from the metabolism of dietary methionine, an amino acid that is abundant in animal protein. The normal metabolism of homocysteine requires adequate levels of folate, vitamin B_6, vitamin B_{12}, and riboflavin. Evidence is growing that an increased plasma level of homocysteine (> 15 мmol/L) is an independent and dose-related risk factor for development of atherosclerosis. Homocysteine inhibits elements of the anticoagulant cascade and is associated with endothelial damage, which is thought to be an important first step in the development of atherosclerosis. Factors tending to increase plasma levels of homocysteine include lower serum levels of folate and vitamins B_6 and B_{12}, genetic defects in homocysteine metabolism, renal impairment, malignancies, increasing age, male sex, and menopause. Supplementation with folic acid, vitamin B6, and vitamin B_{12} to decrease plasma homocysteine levels can be used, especially in persons with premature cardiovascular disease. Lipoprotein (a) is similar to LDL in composition and is an independent risk factor for the development of premature CHD in men. Lipoprotein (a) can cause atherosclerosis by binding to macrophages through a high-affinity receptor that promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques. Lipoprotein (a) levels should be determined in persons who have premature coronary artery disease or a positive family history. There also has been increased interest in the possible connection between infectious agents (Chlamydia pneumoniae, herpesvirus hominis, cytomegalovirus) and the development of vascular disease. The presence of these organisms in atheromatous lesions has been demonstrated by immunocytochemistry, but no cause-and-effect relationship has been established. The organisms may play a role in atherosclerotic development by initiating and enhancing the inflammatory response. Of recent interest is the role of endothelial dysfunction as a key variable in the pathogenesis of atherosclerosis and its complications. Endothelial function reflects a balance between factors such as nitric oxide (NO), which promotes vasodilatation and inhibits inflammation and

vascular smooth muscle proliferation, and endothelial-derived contracting factors, which increase shear stress and promote the development of atherosclerosis.

Mechanisms of Development. The lesions associated with atherosclerosis are of three types: the fatty streak, the fibrous atheromatous plaque, and the complicated lesion. The latter two are responsible for the clinically significant manifestations of the disease. Fatty streaks are thin, flat, yellow intimal discolorations that progressively enlarge by becoming thicker and slightly elevated as they grow in length. Histologically, they consist of macrophages and smooth muscle cells that have become distended with lipid to form foam cells. Fatty streaks are present in children, often in the first year of life. This occurs regardless of geographic setting, sex, or race. They increase in number until about 20 years of age and then remain static or regress. There is controversy about whether fatty streaks, in and of themselves, are precursors of atherosclerotic lesions. The fibrous atheromatous plaque is the basic lesion of clinical atherosclerosis. It is characterized by the accumulation of intracellular and extracellular lipids, proliferation of vascular smooth muscle cells, and formation of scar tissue. The lesions begin as a gray to pearly white elevated thickening of the vessel intima with a core of extracellular lipid (mainly cholesterol, which usually is complexed to proteins) covered by a fibrous cap of connective tissue and smooth muscle. As the lesions increase in size, they encroach on the lumen of the artery and eventually may occlude the vessel or predispose to thrombus formation, causing a reduction of blood flow. The more advanced and complicated lesions contain hemorrhage, ulceration, and scar tissue deposits. Thrombosis is the most important complication of atherosclerosis. It is caused by slowing and turbulence of blood flow in the region of the plaque and ulceration of the plaque. The thrombus may cause occlusion of small vessels in the heart and brain. Aneurysms may develop in arteries weakened by extensive plaque formation. Although the risk factors associated with atherosclerosis have been identified through epidemiologic studies, many unanswered questions remain regarding the mechanisms by which these risk factors contribute to the development of atherosclerosis. The vascular endothelial layer, which consists of a single layer of cells with cell-to-cell attachments, normally serves as a selective barrier that protects the subendothelial layers by interacting with blood cells and other blood components. One hypothesis of plaque formation suggests that injury to the endothelial vessel layer is the initiating factor in the development of atherosclerosis. A number of factors are regarded as possible injurious agents, including products associated with smoking, immune mechanisms, and mechanical stress such as that associated with hypertension. The fact that atherosclerotic lesions tend to form where vessels branch or where there is turbulent flow suggests that hemodynamic factors also play a role. Hyperlipidemia, particularly LDL with its high cholesterol content, is also believed to play an active role in the pathogenesis of the atherosclerotic lesion. Interactions between the endothelial layer of the vessel wall and white blood cells, particularly the monocytes (blood macrophages), normally occur throughout life; these interactions increase when blood cholesterol levels are elevated. One of the earliest responses to elevated cholesterol levels is the attachment of monocytes to the endothelium. The monocytes have been observed to emigrate through the cell-to-cell attachments of the endothelial layer into the subendothelial spaces, where they are transformed into macrophages. Activated macrophages release free radicals that oxidize LDL. Oxidized LDL is toxic to the endothelium, cause causing endothelial loss and exposure of the subendothelial tissue to blood components. This leads to platelet adhesion and aggregation and fibrin deposition. Platelets and activated macrophages release various factors that are thought to promote growth factors that modulate the proliferation of smooth muscle cells and deposition of extracellular matrix in the lesions. Activated macrophages also ingest oxidized LDL to become foam cells, which are present in all stages of atherosclerotic plaque formation. Lipids released from necrotic foam cells accumulate to form the lipid core of unstable plaques. Unstable plaques typically have features of endothelial erosion (plaque erosion) or fissuring (plaque fissuring), or the presence of fresh thrombosis. Thus, “active” atherosclerosis is associated with evidence of inflammation both systemically and at the level of the arterial wall.

Clinical Manifestations. Clinical manifestations of atherosclerosis depend on the vessels involved and the extent of vessel obstruction. Atherosclerotic lesions produce their effects through narrowing of the vessel and production of ischemia; sudden vessel obstruction due to plaque hemorrhage or rupture; thrombosis and formation of emboli resulting from damage to the vessel endothelium; and aneurysm formation due to weakening of the vessel wall. In larger vessels, such as the aorta, the important complications are those of thrombus formation and weakening of the vessel wall. In medium-sized arteries, such as the coronary and cerebral arteries, ischemia and infarction due to vessel occlusion are more common.

Nonatheromatous Arteriosclerosis is age-related fibrosis in the aorta and its major branches. Nonatheromatous arteriosclerosis causes intimal thickening and weakens and disrupts the elastic lamellae. The smooth muscle (media) layer atrophies, and the lumen of the affected artery widens (becomes ectatic), predisposing to aneurysm or dissection. Hypertension is a major factor in development of aortic arteriosclerosis and aneurysm. Intimal injury, ectasia, and ulceration may lead to thrombosis, embolism, or complete arterial occlusion.

Date	Grade	Teacher's signature

PATHOPHYSIOLOGY OF EXTERNAL RESPIRATION. BREATHING INSUFFICIENCY

Relevance. Expiratory system is one of the main life supporting systems of the body. The main aim is to supply the tissues by oxygen and withdraw carbon acid from the body. Study of the etiology and pathogenesis of expiration disorders is required for doctor practice, because breathing insufficiency appears in different diseases of breathing system, and it can be the result of disorders of different functions of other organs and systems. So knowing the causes and mechanisms of expiration disorders will lead to the development of clinical thinking and choice of the rational treatment of this pathology. Studying the expiration disorders in experiment on animals allows us to understand the mechanisms of these developments and manifestations, especially dyspnea.

Overall Objective is to be able to characterize the dyspnea as a manifestation of expiration, explain the common causes and mechanisms of its development.

The student should be able to (specific objectives):

1. Define the "pathological breathing", "dyspnea".
2. Classify the pathological types of breathing, types of dyspnea.
3. Model different types of dyspnea on rabbits. Show the role of reflect influences and disorders of functions of upper respiratory trance in forming dyspnea.
4. Distinguish the main signs and manifestations of dyspnea, explain the main mechanisms of its formation and development.

The student should be able to (required knowledge and skills):

1. Explain the role of mechanoreceptors (Hering-Beuer reflex) in expiration regulation (dep. of normal physiology).
2. Interpret chemoreceptor regulation of expiration (dep. of normal physiology).
3. Explain influence of frequency and depth of expiration changes (dep. of normal physiology).

QUESTIONS TO THE LESSON

1. Definition of "breathing", "expiration", "cell (tissue) breathing". Factors defining the effectiveness of expiration system function.
2. Indicators of functional state of expiration system (lung volumes and capacities), changes in pathology of expiration.
3. Breathing insufficiency. Types. Causes. Typical disorders of expiration.
4. Alveolar hypoventilation. Definition. Common causes. Pathogenesis. Forms. Signs.
5. Alveolar hyperventilation. Causes. Forms. Signs.

6. Lungs perfusion disorders. Lung hypertension: forms, common causes, pathogenesis. Lung hypotension: forms, common causes, pathogenesis.
7. Disorders of respiratory-perfusion correlation. Causes, types.
8. Disorders of diffusive ability if lungs. Causes. Mechanisms.
9. Signs of expiratory insufficiency. Dyspnea: types, mechanisms. Periodical breathing: types, mechanisms. Asphyxia: causes, mechanisms, types.
10. Features of expiration pathology in children.
11. Respiratory distress syndrome of adult. Causes. Pathogenesis. Signs.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

PATHOPHYSIOLOGY OF EXTERNAL RESPIRATION. RESPIRATORY INSUFFICIENCY

Respiration is a set of processes ensuring supply of oxygen into the organism, its use in biological oxidation of the organic substances and elimination of carbon dioxide from the body. As a result of biological oxidation in cells the energy used for realization of physiologic functions, is released.

We distinguish external and internal respiration. External respiration is an exchange of gases (absorbtion of oxygen and elimination of carbon dioxide) between the blood and external environment. As a result, the normal gaseous composition of the blood is provided. Internal respiration is an exchange of the same gases between cells and blood. It is also called cellular or tissue respiration. It is directed to provide normal gaseous composition of cells and tissues. Pathophysiology of internal respiration is manifested in phenomenon of hypoxia (see above). Besides, the concept of respiration includes transport of gases by blood.

ALVEOLAR VENTILATION

Normally, Alveolar Ventilation is unconsciously regulated to maintain constant arterial blood gas tensions (particularly CO_2), despite variable levels of oxygen consumption and CO_2 production.

NORMAL PHYSIOLOGY

Basic Principles

Venous blood always has a lower PaO_2 (40 mmHg or 75 % saturated or 15 ml O_2/100ml blood) and higher $PaCO_2$ (46 mmHg) than inspired gas (PiO_2 150 mmHg, $PiCO_2$ usually 0). Hence there is a partial pressure gradient driving Oxygen in and CO_2 out of the pulmonary capillary blood.

Ventilation of the lungs is the process that mixes fresh inspired gas with alveolar gas. If there is no ventilation at all, there will be no replenishment of oxygen and no removal of CO_2. PAO_2 will fall and $PACO_2$ will rise towards the venous O_2 and CO_2 tensions.

After the onset of apnoea, CO_2 rises rapidly and within about 30s it is about 50mmHg. This causes nearly all of the air hunger experienced while holding your breath. The subsequent rate of rise of CO_2 tension is much slower, taking 15 minutes or so to reach 80mmHg, because it is very soluble. The rapid response of arterial CO_2 to apnoea explains why it is such a good gas for our body to use as the primary control mechanism for ventilation.

In contrast a reservoir of oxygen exists within the alveoli that can maintain acceptable oxygen tensions for about a minute. If the lung volume is adequate, after a deep breath, and in particular if the lung is filled with a higher than usual oxygen partial pressure, acceptable alveolar oxygen tensions can be maintained for much longer.

If the ventilation is greater than is needed, then the alveolar gas tensions will be shift closer to inspired gas, i.e, the CO_2 level will be lower, and the oxygen level a little higher.

Non- ventilated but perfused (very low V/Q) lung units shunt venous blood to the arterial circulation, causing hypoxaemia that cannot be corrected by increasing FiO_2.

Matching of ventilation to perfusion across the majority of alveoli, even in the presence of lung disease, is the key to optimizing ventilation.

Definitions. Ventilation is the process by which oxygen and CO_2 are transported to and from the lungs.

Tidal Volume (Vt) is the amount of gas expired per breath – typically 500 ml at rest.

Deadspace Volume (VD) is the sum of the Anatomic Deadspace, due to the volume of the airways (typically 150 ml), and Physiologic Deadspace, due to alveoli which are ventilated but not perfused (usually insignificant).

Minute Volume (VE) is the amount of gas expired per minute.

Alveolar Ventilation (VA) is the amount of gas which reaches functional respiratory units (i.e, alveoli) per minute. VA = (Tidal Volume – Deadspace) × Respiratory rate

Lung Volumes

1. FRC (Functional Residual Capacity) 2.2l. (supine)
2. TLC (Total Lung Capacity) 6.2l.
3. Maximum Inspiratory Volume 4.0l. above FRC.
4. ERV (Expiratory Reserve Volume) 1.0l. below FRC.
5. RV (Residual Volume) 1.2l.
6. MVV (Maximal Voluntary Ventilation) 150 l/m.

Lung Mechanics – Inspiration. An active process requiring muscular effort; 75 % diaphragmatic at rest; intercostals used on exertion.

Inspiratory effort causes:

1. Fall in intrapleural pressure
2. Fall in Alveolar pressure
3. Pressure gradient from mouth to alveoli
4. Gas flow down pressure gradient

Maximum inspiratory force is sometimes used as an index of resp. effort; if < 20 cm H_2O most patients have difficulty of expiration.

Usually a passive process due to lung recoil:

1. Relaxation of inspiratory muscles causes:
2. Intrapleural pressure becomes less negative
3. Alveolar pressure rises
4. Pressure gradient from alveoli to mouth
5. Gas flow down pressure gradient

Respiratory Rate and I:E ratio

Normal respiratory rate is about 15 breaths per minute, increasing markedly with exertion.

Normal I:E ratio at rest and while asleep is 1:2 or less. On exertion the I:E ratio is 1:1. Inspiration is normally an active process (requiring work). Expiration is passive, and usually longer than the time required for exhalation, resulting an a no-flow period. When breathing spontaneously, the work of breathing is minimised by keeping inspiratory times short and tidal volumes low – just enough to get rid of the produced CO_2. To minimise collapse, sighs are taken from time to time.

Airway Resistance

1. Limits gas flow down airways.
2. Due mostly to airway/ETT diameter (fourth power of radius).
3. Normal response to increased resistance is increased effort.
4. GA's increase resistance and decrease response, causing hypoventilation
5. Asthmatics have increased resistance due to spans (Rx Beta Agonists etc) and oedema (Rx steroids) and mucus.
6. Optimal airway resistance occurs at normal FRC
7. Under conditions of increased airway resistance, slower respiratory rates are better.

a. Intrapleural Pressure

8. Normally -7.5 cm H_2O at mid-chest level, due to elastic recoil of lung opposed by chest wall.

9. Becomes more negative on inspiration.
10. Less negative at the dependent regions of the lung, reducing alveolar size.

DISORDERS OF VENTILATION

Definition and Etiology. Alveolar hypoventilation exists by definition when arterial P_{CO2} ($PaCO_2$) increases above the normal range of 37 to 43 mm Hg, but in clinically important hypoventilation syndromes $PaCO_2$ is generally in the range of 50 to 80 mm Hg. Hypoventilation disorders can be acute or chronic.

Chronic hypoventilation can be a result from numerous disease entities (*Table 30*), but in all cases the underlying mechanism involves a defect in either the metabolic respiratory control system, the respiratory neuromuscular system, or the ventilatory apparatus. Disorders associated with impaired respiratory drive, defects in the respiratory neuromuscular system, some chest wall disorders such as obesity, and upper airway obstruction produce an increase in $PaCO_2$, despite normal lungs, because of a reduction in overall minute volume of ventilation and hence in alveolar ventilation. In contrast, most disorders of the chest wall and disorders of the lower airways and lungs may produce an increase in $PaCO_2$, despite a normal or even increased minute volume of ventilation, because of severe ventilation-perfusion mismatching that results in net alveolar hypoventilation.

Table 30

Chronic Hypoventilation Syndromes

Mechanism	Site of Defect	Disorder
Impaired respiratory drive	Peripheral and central chemoreceptors	Carotid body dysfunction, trauma Prolonged hypoxia, Metabolic alkalosis
	Brainstem respiratory neurons	Bulbar poliomyelitis, encephalitis. Brainstem infarction, hemorrhage, trauma. Brainstem demyelination, Chronic drug administration, Primary alveolar hypoventilation
Defective respiratory neuromuscular system	Spinal cord and peripheral nerves	High cervical trauma, Poliomyelitis, Motor neuron disease, Peripheral neuropathy
	Respiratory muscles	Myasthenia gravis, Muscular dystrophy. Chronic myopathy
Impaired ventilatory apparatus	Chest wall	Kyphoscoliosis, Fibrothorax, Thoracoplasty, Ankylosing spondylitis, Obesity hypoventilation
	Airways and lungs	Laryngeal and tracheal stenosis, Obstructive sleep apnea, Cystic fibrosis, Chronic obstructive pulmonary disease

Physiologic and Clinical Features

Regardless of the cause, the hallmark of all alveolar hypoventilation syndromes is an increase in alveolar PCO_2 ($PACO_2$) and therefore in $PaCO_2$. The resulting respiratory acidosis eventually leads to a compensatory increase in plasma HCO_3^- concentration and a decrease in Cl^- concentration. The increase in PA_{CO2} produces an obligatory decrease in PA_{O2}, resulting in hypoxemia. If severe, the hypoxemia manifests clinically as cyanosis and can stimulate erythropoiesis and induce secondary polycythemia.

Several hypoventilation syndromes involve combined disturbances in two elements of the respiratory system. For example, patients with a chronic obstructive pulmonary disease may hypoventilate not simply because of impaired ventilatory mechanics but also because of a reduced central respiratory drive, which can be inherent or secondary to a coexisting metabolic alkalosis (related to diuretic and steroid therapy).

The combination of chronic hypoxemia and hypercapnia may also induce pulmonary vasoconstriction, leading eventually to pulmonary hypertension, right ventricular hypertrophy, and congestive heart failure. The disturbances in arterial blood gases typically intensify during sleep because of a further reduction in central respiratory drive. The resulting increased nocturnal hypercapnia may cause cerebral vasodilation, leading to morning headache; sleep quality may also be severely impaired, resulting in morning fatigue, daytime somnolence, mental confusion, and intellectual impairment. Other clinical features associated with hypoventilation syndromes are related to the specific underlying disease (*Table 30*).

HYPOVENTILATION SYNDROMES

Primary Alveolar Hypoventilation (PAH) is a disorder of unknown cause characterized by chronic hypercapnia and hypoxemia in the absence of identifiable neuromuscular disease or mechanical ventilatory impairment. The disorder is thought to arise from a defect in the metabolic respiratory control system, but few neuropathologic studies have been reported in such patients. Recent studies in animals suggest an important role for genetic factors in the pathogenesis of hypoventilation. Isolated PAH is relatively rare, and although it occurs in all age groups, the majority of reported cases have been in males aged 20 to 50 years. As the degree of hypoventilation increases, patients typically develop lethargy, fatigue, daytime somnolence, disturbed sleep, and morning headaches; eventually cyanosis, polycythemia, pulmonary hypertension, and congestive heart failure occur. Despite severe arterial blood gas derangements, dyspnea is uncommon, presumably because of impaired chemoreception and ventilatory drive. If left untreated, PAH is usually progressive over a period of months to years and ultimately fatal.

The key diagnostic finding in PAH is a chronic respiratory acidosis in the absence of respiratory muscle weakness or impaired ventilatory mechanics. Because patients can hyperventilate voluntarily and reduce $PaCO_2$ to normal or even hypocapnic levels, hypercapnia may not be demonstrable in a single arterial blood sample, but the presence of an elevated plasma HCO_3^- level should draw attention to the underlying chronic disturbance. Despite normal ventilatory mechanics and respiratory muscle strength, ventilatory responses to chemical stimuli are reduced or absent, and breath-holding time may be markedly prolonged without any sensation of dyspnea. Patients with PAH maintain rhythmic respiration when awake, although the level of ventilation is below normal. However, during sleep, when breathing is critically dependent on the metabolic control system, there is typically a further deterioration in ventilation with frequent episodes of central hypopnea or apnea.

PAH must be distinguished from other central hypoventilation syndromes that are secondary to underlying neurologic disease of the brainstem or chemoreceptors (*Table 30*). This distinction requires a careful neurologic investigation for evidence of brainstem or autonomic disturbances. Unrecognized respiratory neuromuscular disorders, particularly those that produce diaphragmatic weakness, are often misdiagnosed as PAH. Some patients with PAH respond favorably to respiratory stimulant medications and to supplemental oxygen. However, the majority eventually require mechanical ventilatory assistance. Excellent long-term benefits can be achieved with diaphragmatic pacing by electrophrenic stimulation or with negative- or positive-pressure mechanical ventilation. The administration of such treatment only during sleep is sufficient in most patients.

Respiratory Neuromuscular Disorders

Several primary disorders of the spinal cord, peripheral respiratory nerves, and respiratory muscles produce a chronic hypoventilation syndrome. Hypoventilation usually develops gradually over a period of months to years and often first comes to attention when a relatively trivial increase in mechanical ventilatory load (such as mild airways obstruction) produces severe respiratory failure. In some of the disorders (such as motor neuron disease, myasthenia gravis, and muscular dystrophy), involvement of the respiratory nerves or muscles is usually a later feature of a more widespread disease. In other disorders, respiratory involvement can be an early or even isolated feature, and hence the underlying problem is often not suspected. Included in this category are the postpolio syndrome, the myopathy associated with adult acid maltase deficiency, diaphragmatic paralysis.

Generally, respiratory neuromuscular disorders do not result in chronic hypoventilation unless there is significant weakness of the diaphragm. Distinguishing features of bilateral diaphragmatic weakness include orthopnea, paradoxical movement of the abdomen in the supine posture, and paradoxical diaphragmatic movement under fluoroscopy. However, absence of these features does not exclude diaphragmatic weakness.

Obesity-Hypoventilation Syndrome. Massive obesity represents a mechanical load to the respiratory system because the added weight on the rib cage and abdomen serves to reduce

the compliance of the chest wall. As a result, the functional residual capacity (i.e., end-expiratory lung volume) is reduced, particularly in the recumbent posture. An important consequence of breathing at a low lung volume is that some airways, particularly those in the lung bases, may be closed throughout part or even all of each tidal breath, resulting in under ventilation of the lung bases and widening of the (A-a)PO_2. Nevertheless, in the majority of obese individuals, central respiratory drive is increased sufficiently to maintain a normal Pa_{CO2}. However, a small proportion of obese patients develop chronic hypercapnia, hypoxemia, and eventually polycythemia, pulmonary hypertension, and right-sided heart failure. Recent studies in mice demonstrate that genetically obese mice lacking circulating leptin also develop chronic hypoventilation that can be reversed by leptin infusions. Those patients who also develop daytime somnolence have been designated as having the **Pickwickian syndrome**. In many such patients, obstructive sleep apnea is a prominent feature, and even in the patients without sleep apnea, sleep-induced hypoventilation is an important element of the disorder and contributes to its progression. Most patients demonstrate a decrease in central respiratory drive, which may be inherent or acquired, and many have mild to moderate degrees of airflow obstruction, usually related to smoking.

HYPERVENTILATION AND ITS SYNDROMES

Definition and Etiology. Alveolar hyperventilation exists when $PaCO_2$ decreases below the normal range of 37 to 43 mmHg. Hyperventilation is not synonymous with hyperpnea, which refers to an increased minute volume of ventilation without reference to $PaCO_2$. Although hyperventilation is frequently associated with dyspnea, patients who are hyperventilating do not necessarily complain of shortness of breath; and conversely, patients with dyspnea need not be hyperventilating.

Numerous disease entities can be associated with alveolar hyperventilation, but in all cases the underlying mechanism involves an increase in respiratory drive that is mediated through either the behavioral or the metabolic respiratory control systems. Thus hypoxemia drives ventilation by stimulating the peripheral chemoreceptors, and several pulmonary disorders and congestive heart failure drive ventilation by stimulating afferent vagal receptors in the lungs and airways. Low cardiac output and hypotension stimulate the peripheral chemoreceptors and inhibit the baroreceptors, both of which increase ventilation. Metabolic acidosis, a potent respiratory stimulant, excites both the peripheral and central chemoreceptors and increases the sensitivity of the peripheral chemoreceptors to coexistent hypoxemia. Hepatic failure can also produce hyperventilation, presumably as a result of metabolic stimuli acting on the peripheral and central chemoreceptors.

Hypoxemia

A. High altitude, pulmonary disease, cardiac shunts

Pulmonary disorders

A. Pneumonia

B. Interstitial pneumonitis, fibrosis, edema

C. Pulmonary emboli, vascular disease

D. Bronchial asthma, pneumothorax, chest wall disorders

Cardiovascular disorders

A. Congestive heart failure

B. Hypotension

Metabolic disorders

A. Acidosis (diabetic, renal, lactic), hepatic failure

Neurologic and psychogenic disorders

A. Psychogenic or anxiety hyperventilation

B. Central nervous system infection, tumors

Drug-induced

A. Salicylates

B. Methylxanthine derivatives
C. Adrenergic agonists
D. Progesterone

Miscellaneous

A. Fever, sepsis, pain, pregnancy

Several neurologic and psychological disorders are thought to drive ventilation through the behavioral respiratory control system. Included in this category are psychogenic or anxiety hyperventilation and severe cerebrovascular insufficiency, which may interfere with the inhibitory influence normally exerted by cortical structures on the brainstem respiratory neurons. Rarely, disorders of the midbrain and hypothalamus induce hyperventilation, and it is conceivable that fever and sepsis also cause hyperventilation through effects on these structures. Several drugs cause hyperventilation by stimulating the central or peripheral chemoreceptors or by direct action on the brainstem respiratory neurons. Chronic hyperventilation is a normal feature of pregnancy and results from the effects of progesterone and other hormones acting on the respiratory neurons.

Physiologic and Clinical Features

Because hyperventilation is associated with increased respiratory drive, muscle effort, and minute volume of ventilation, the most frequent symptom associated with hyperventilation is dyspnea. However, there is considerable discrepancy between the degree of hyperventilation, as measured by $PaCO_2$, and the degree of associated dyspnea. From a physiologic standpoint, hyperventilation is beneficial in patients who are hypoxemic, because the alveolar hypocapnia is associated with an increase in alveolar and arterial P_{O2}. Conversely, hyperventilation can also be detrimental. In particular, the alkalemia associated with hypocapnia may produce neurologic symptoms, including dizziness, visual impairment, syncope, and seizure activity (secondary to cerebral vasoconstriction); parasthesia, carpopedal spasm, and tetany (secondary to decreased free serum calcium); and muscle weakness (secondary to hypophosphatemia). Severe alkalemia can also induce cardiac arrhythmias and evidence of myocardial ischemia. Patients with a primary respiratory alkalosis are also prone to periodic breathing and central sleep apnea.

SLEEP APNEA is defined as an intermittent cessation of airflow at the nose and mouth during sleep. By convention, apneas of at least 10s duration have been considered important, but in most patients the apneas are 20 to 30s in duration and may be as long as 2 to 3 min. Sleep apnea syndrome refers to a clinical disorder that arises from recurrent apneas during sleep. The clinical importance of sleep apnea arises from the fact that it is one of the leading causes of excessive daytime sleepiness. Indeed, epidemiologic studies have established a prevalence of clinically important sleep apnea of at least 2 % in middle-aged women and 4 % in middle-aged men.

Sleep apneas can be central or obstructive in type. In central sleep apnea (CSA) the neural drive to all the respiratory muscles is transiently abolished. In contrast, in obstructive sleep apnea (OSA) airflow ceases despite continuing respiratory drive because of occlusion of the oropharyngeal airway.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is characterized by increased permeability of the alveolar-capillary membrane, diffuse alveolar damage, and accumulation of proteinaceous pulmonary edema. This clinical syndrome was first described in the archival literature by military physicians when respiratory failure occurred in battlefield casualties during World Wars I and II.

The diagnostic criteria used to define ARDS have evolved over the past three decades. Originally, most definitions required three general criteria: severe hypoxemia, decreased pulmonary compliance, and diffuse pulmonary infiltrates on chest radiograph. With the increasing utilization of pulmonary arterial catheters in the intensive care unit, ARDS was noted to be a "noncardiogenic" form of pulmonary edema. Subsequently, some proposed definitions of ARDS required documentation of a normal pulmonary arterial occlusion pressure (*Table 31*).

Table 31

Recommended Criteria for Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

	Timing	Oxygenation	Chest Radiograph	Pulmonary Arterial Occlusion Pressure
ALI Criteria	Acute onset	Pa_{O2} / FiO_2 < 300 mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	< 18mm Hg when measured or no clinical evidence of left atrial hypertension
ARDS Criteria	Acute onset	PaO_2 / FiO_2 < 200 mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	< 18 mm Hg when measured or no clinical evidence of left atrial hypertension
NOTE: PaO_2, arterial oxygen tension; FiO_2, inspiratory O_2 fraction; PEEP, positive end-expiratory pressure				

Clinical Characteristics

Many predisposing factors are associated with the development of ARDS, including conditions that affect the lung directly and those producing damage through indirect mechanisms via the hematogenous delivery of inflammatory mediators (*Table* 32). The most common of these at-risk conditions are severe sepsis, major trauma, and aspiration of gastric contents. In general, 30 to 40 % of individuals with at least one of these diagnoses will eventually develop ARDS. This incidence increases in patients with more than one at-risk condition. A history of chronic alcohol abuse is also associated with an increased risk of developing ARDS in critically ill patients with an at-risk diagnosis.

Table 32

Conditions That May Lead to the Acute Respiratory Distress Syndrome

Direct injury to alveolar epithelium	Indirect lung injury
Aspiration of gastric contents	Sepsis syndrome
Diffuse pulmonary infection	Severe nonthoracic trauma
Near drowning	Hypertransfusion
Pulmonary contusion	Pancreatitis
Toxic inhalation	Cardiopulmonary bypass

ARDS occurs within 5 days of the initial at-risk diagnosis in the majority of patients, and over 50 % will develop ARDS in the first 24 h. The earliest clinical sign is often an increase in the respiratory frequency, followed by dyspnea. There are no characteristic laboratory abnormalities for ARDS patients except those related to a specific underlying condition, such as leukocytosis in sepsis or an elevated serum amylase level in pancreatitis. Radiographically, the lung fields may be clear initially; diffuse bilateral interstitial or alveolar infiltrates occur as ARDS develops. Though these radiographic changes appear homogeneous on chest radiograph, computed tomography demonstrates a heterogeneous pattern with a predominance of infiltrates in the dependent regions of the lung.

Pathophysiology. ARDS may be the pulmonary manifestation of a systemic process and is the consequence of an overexpression of the normal inflammatory response. This inflammatory cascade has been divided into three overlapping phases-initiation, amplification, and injury. During **initiation**, a precipitating event, such as sepsis, causes both immune and nonimmune cells to produce and release a variety of mediators and cytokines, such as tumor necrosis factor and interleukin 1. Subsequently, during **amplification**, effector cells, such as neutrophils, are activated, recruited, and retained in specific target organs including the lung. Interleukin 8, which is produced by monocytes and other cell types, appears to play an important role in neutrophil activation. Once the effector cells have been sequestered in the lung, they then release reactive oxygen metabolites and proteases, causing cellular damage during the **injury phase**. This inflammatory cascade can occur systemically and therefore may alter the function of many organ systems-a clinical entity called **multiple organ dysfunction syndrome**.

The pathophysiologic feature of ARDS is increased vascular permeability to proteins, so that even mild elevations of pulmonary capillary pressures (due to increased intravenous liquid administration and/or myocardial depression, which may occur in sepsis) greatly increase interstitial and alveolar edema. Alveolar damage is further exaggerated by the quantitative reduction is surfactant synthesis due to injury to type II pneumocytes as well as to

further qualitative abnormalities in the size, composition, and metabolism of the remaining surfactant pool, leading to alveolar collapse. Although these atelectatic and liquid-filled regions of the lung contribute to a reduction in the compliance of the lung as a whole, significant regions of nondependent lung have relatively normal mechanical and gas-exchanging properties. However, the decreased overall pulmonary compliance requires large inspiratory pressures to be generated by the respiratory muscles, resulting in an increase in the work of breathing.

Though ARDS is not routinely considered a disease of the airways, airway resistance may be increased due to bronchial wall edema and cytokine-mediated bronchospasm. Pulmonary vascular resistance and pulmonary arterial pressures may also be elevated as a result of increased pulmonary vascular smooth-muscle tone, perivascular edema, microvascular thrombosis, and the production of humoral factors such as leukotrienes and thromboxane A_2, which can directly cause vasoconstriction.

ASPHYXIA

Asphyxia or **asphyxiation** (from Greekα- "without" and sphyxis, "heartbeat") is a condition of severely deficient supply of oxygen to the body that arises from being unable to breathe normally. An example of asphyxia is choking. Asphyxia causes generalized hypoxia, which primarily affects the tissues and organs. There are many circumstances that can induce asphyxia, all of which are characterized by inability of an individual to acquire sufficient oxygen through breathing for an extended period of time. These circumstances can include, but are not limited to: constriction or obstruction of airways,such as from asthma,laryngospasm, or simple blockage from the presence of foreign materials;from being in environments where oxygen is not readily accessible: such as underwater, in a low oxygen atmosphere, or in a vacuum; environments where sufficiently oxygenated air is present, but cannot be adequately breathed because of air contamination such as excessive smoke. Asphyxia can cause coma or death.

Oxygen deficiency. The body creates the need to breathe from the excess carbon dioxide in the blood. The body has chemosensors to detect oxygen levels in the blood, but these don't typically control respiratory rate. Many gases, though non-toxic, are classified as simple asphyxiants in their pure or inpure form or in high concentrations for this very reason.

One form of asphyxiation is from entering a low oxygen atmosphere or an inert atmosphere, such as in a food oil tank that has a covering blanket of nitrogen or argon to shield the oil from atmospheric oxygen. Without sufficient oxygen to sustain life, people will act normally at first but will then abruptly feel dizzy and black out in a matter of seconds as the remaining oxygen in the blood stream is consumed. Oxygen deficient atmospheres are the basis for many occurrences of single and multiple deaths; the deceased will be found lying prone on the bottom of a tank, and then the observer will rush in to rescue them, and succumb to the same effect, hence the need to vent or purge the inert gases from all tanks before entry.

Other causes of oxygen deficiency include:

1. Carbon monoxide inhalation, such as from a car exhaust: carbon monoxide has a higher affinity than oxygen to the hemoglobin in the blood's red blood corpuscles, bonding with it tenaciously, and, in the process, displacing oxygen and preventing the blood from transporting oxygen around the body
2. Contact with certain chemicals, including pulmonary agents (such as phosgene) and blood agents (such as hydrogen cyanide)
3. Self-induced hypocapnia by hyperventilation, as in shallow water or deep water blackout and the choking game
4. A seizure which stops breathing activity.
5. Sleep apnea.
6. Drug overdose.

Ondine's curse, central alveolar hypoventilation syndrome, or primary alveolar hypoventilation, a disorder of the autonomic nervous system in which a patient must consciously breathe; although it is often said that persons with this disease will die if they fall asleep, this is not usually the case.

1. Acute respiratory distress syndrome.
2. Exposure to extreme low pressure or vacuum to the pattern
3. Hanging, respiratory diseases, drowning

Smothering is the mechanical obstruction of the air flow from the environment into the mouth and/or nostrils, for instance, by covering the mouth and nose with a hand, pillow, or a plastic bag. Smothering can be either partial or complete, where partial indicates that the person being smothered is able to inhale some air, although less than required. In a normal situation, smothering requires at least partial obstruction of both the nasal cavities and the mouth to lead to asphyxia. Smothering with the hands or chest is used in some combat sports to distract the opponent, and create openings for transitions, as the opponent is forced to react to the smothering. In some cases, when performing certain routines, smothering is combined with simultaneous compressive asphyxia. One example is **overlay**, in which an adult accidentally rolls over an infant during co-sleeping, an accident that often goes unnoticed and is mistakenly thought to be sudden infant death syndrome. Other accidents involving a similar mechanism are cave-ins or when an individual is buried in sand or grain.

Compressive asphyxia (also called **chest compression**) is mechanically limiting expansion of the lungs by compressing the torso, hence interfering with breathing. Compressive asphyxia occurs when the chest or abdomen is compressed posteriorly. In accidents, the term traumatic asphyxia or **crush asphyxia** usually refers to compressive asphyxia resulting from being crushed or pinned under a large weight or force. An example of traumatic asphyxia includes cases where an individual has been using a car-jack to repair a car from below, and is crushed under the weight of the vehicle. Pythons, anacondas, and other constrictor snakes kill through compressive asphyxia. In cases of co-sleeping ("overlay"), the weight of an adult or large child may compress an infant's chest, preventing proper expansion of the chest. Risk factors include large or obese adults, parental fatigue or impairment (sedation by drugs) of the co-sleeping adult and a small shared sleeping space.

Restraint asphyxia is death or lost consciousness (to die later in a coma from anoxic brain damage), while being restrained in positions that cause asphyxia by facial compression, neck compression, or chest compression. This mostly occurs during law enforcement or psychiatric restraint situations. It may be that the positional asphyxia deaths of prisoners are actually active chest compression deaths caused by the weight of restrainers holding uncooperative prisoners down in a prone position during the process of being handcuffed and otherwise secured.

Perinatal asphyxia is the medical condition resulting from deprivation of oxygen (hypoxia) to a newborn infant long enough to cause apparent harm. It results most commonly from a drop in maternal blood pressure or interference during delivery with blood flow to the infant's brain. This can also be caused by inadequate circulation or perfusion, impaired respiratory effort, or inadequate ventilation.

Nitrogen asphyxiation is an occasional cause of accidental death and a theoretical method of capital punishment. After just two or three breaths of pure nitrogen, the oxygen concentration in the lungs would be low enough for some oxygen already in the bloodstream to exchange back to the lungs and be eliminated by exhalation.

Pulmonary Hypertension: Causes, Symptoms, Diagnosis, Treatment

Pulmonary hypertension is a rare lung disorder in which the arteries that carry blood from the heart to the lungs become narrowed, making it difficult for blood to flow through the vessels. As a result, the blood pressure in these arteries - called pulmonary arteries - rises far above normal levels. This abnormally high pressure strains the right ventricle of the heart, causing it to expand in size. Overworked and enlarged, the right ventricle gradually becomes weaker and loses its ability to pump enough blood to the lungs. This could lead to the development of right heart failure.

Pulmonary hypertension occurs in individuals of all ages, races, and ethnic backgrounds although it is much more common in young adults and is approximately twice as

common in women as in men. Scientists believe that the process starts with injury to the layer of cells that line the small blood vessels of the lungs. This injury, which occurs for unknown reasons, may cause changes in the way these cells interact with the smooth muscle cells in the vessel wall. As a result, the smooth muscle contracts more than normal and narrows the vessel.

Symptoms of pulmonary hypertension do not usually occur until the condition has progressed. The first symptom of pulmonary hypertension is usually shortness of breath with everyday activities, such as climbing stairs. Fatigue, dizziness, and fainting spells also can be symptoms. Swelling in the ankles, abdomen or legs; bluish lips and skin, and chest pain may occur as strain on the heart increases. Symptoms range in severity and a given patient may not have all of the symptoms. In more advanced stages of the disease, even minimal activity will produce some of the symptoms. Additional symptoms include irregular heart beat (palpitations or strong, throbbing sensation), racing pulse, passing out or dizziness, progressive shortness of breath during exercise or activity, and difficulty breathing at rest. Eventually, it may become difficult to carry out any activities as the disease worsens.

What causes pulmonary hypertension?

The following are some known causes of pulmonary hypertension:

1. **The diet drug "fen-phen. "**Although the appetite suppressant "fen-phen" (dexfenfluramine and phentermine) has been taken off the market, former fen-phen users have a 23-fold increase risk of developing pulmonary hypertension, possibly years later.

2. **Liver diseases, rheumatic disorders, lung conditions.** Pulmonary hypertension also can occur as a result of other medical conditions, such as chronic liver disease and liver cirrhosis; rheumatic disorders such as scleroderma or systemic lupus erythematosus (lupus); and lung conditions including tumors, emphysema, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis.

3. **Certain heart diseases.** Heart diseases including aortic valve disease, left heart failure, mitral valve disease, and congenital heart disease can also cause pulmonary hypertension.

4. **Thromboembolic disease.** A blood clot in a large pulmonary artery can result in the development of pulmonary hypertension.

5. **Low-oxygen conditions.** High altitude living, obesity, and sleep apnea can also lead to the development of pulmonary hypertension.

6. **Genetic predisposition.** Pulmonary hypertension is inherited in a small number of cases. Knowing that someone in the family had or has pulmonary hypertension should prompt you to seek early evaluation should symptoms occur.

Pulmonary hypertension may also be caused by other conditions, and in some cases, the cause is unknown.

Abnormal Breathing Patterns. Breathing isn't just a matter of inhaling good air and exhaling bad used air. The entire respiratory pattern is important. Rate, depth, timing, and consistency of breaths are all important to the delicate balance of respiration and metabolism.

Certain illnesses or injuries can cause changes in the breathing pattern. Changes other than the typical fast or slow breathing that is most common with many conditions. Below are some of the less common breathing patterns that make many healthcare professionals ask themselves… "Hey, what is that pattern anyway?"

Cheyen-Stokes:

1. This breathing pattern is characterized by periods of respirations during which the spontaneous tidal volume starts shallow and progressively gets deeper with each breathe, then gets progressively more shallow with each breathe. This is followed by a period of apnea that can last anywhere from 15 seconds to 120 seconds. This cycle is repeated over and over.

2. Causes: Cheyen-Stokes breathing is often caused by strokes, traumatic brain injuries, brain tumors, carbon dioxide poisoning, and metabolic encephalopathy. This pattern can also be seen in healthy patients experiencing first-time high altitude sickness, and can also be a normal side effect of IV morphine administration.

Biot's Breathing (aka "Cluster" breathing):

1. Biot's breathing is characterized by periods, or "clusters", of fairly rapid respirations of close to equal depth followed by reular periods of apnea that can last between 15 seconds to 120 seconds. Biot's breathing is very imilar to Cheyen-Stokes except the spontaneous tidal volume is equal throughout the period of respiration.

2. **Causes:** Biot's breathing is usually caused by damage to the medulla oblongata by stroke (CVA) or trauma, or pressure on the medulla due to uncal or tenorial herniation. Biot's breathing can also be caused by prolonged opioid abuse.

Kussmaul's Breathing:

1. Labored hyperventilation characterized by a deep and rapid respiratory pattern.

2. **Causes:** This type of labored hyperventilation is usually seen in the late stages of a severe metabolic acidosis. An example would be an acute diabetic ketoacidosis (DKA).

3. The patient becomes "air hungry" and the desperate gasping characteristic of Kussmaul's breathing almost appears involuntary. Most of the time a respiratory pattern secondary to a metabolic acidosis is rapid and shallow, and the true Kussmaul breathing pattern is rarely seen because the acidosis is often corrected before the patient reaches that stage of the condition.

Apneustic Breathing:

1. An apneustic breathing pattern has prolonged inspiratory phases with each breathe, followed by a prolonged expiratory phase that is often mistaken for an apneic period.

2. **Causes:** Apneustic breathing is usually caused by damage to the upper part of the pons, which is the uppermost section of the brain stem. The pons contains, among other things, the "respiratory center" of the brain.

Ataxic Breathing:

1. A completely irregular breathing pattern with irregular pauses and unpredictable periods of apnea. As breathing continues to deteriorate, ataxic breathing begins to merge with agonal respirations.

2. Ataxic breathing is usually caused by damage to the medulla oblongata secondary to trauma or stroke. This respiratory pattern indicates a very poor prognosis.

DYSPNEA: DEFINITION, CAUSES, AND PROVEN TREATMENT

Dyspnea (pronounced as "disp-ne´ah") is characterized as being unable to take a satisfying deep inspiration. This weird definition was likely invented by proponents of breathing more air (as if breathing more than the medical norm provides health benefits). Now large official websites promote this implication related to goodness of breathing more air at rest.

Dyspnea is caused by overbreathing (deep breathing), mouth breathing and chest breathing. All these activities reduce brain and body oxygenation and create the sensation of air hunger. Let us start with evidence related to chronic deep breathing in people with dyspnea.

Chronic hyperventilation leads to alveolar hypocapnia (CO_2 deficiency) which is normal in people with heart disease, asthma, COPD, cancer, cystic fibrosis, diabetes, pregnancy. Low brain oxygenation is the known effect of overbreathing. Hyperventilation leads to greatly increased work of breathing due to large minute ventilation rates. But there are other effects as well. For example, alveolar hyperventilation always leads to cell hypoxia (regardless of ventilation-perfusion ratio).

The main physiological factors (causes of dyspnea) that increase the work of breathing (often several-fold) are:

1) constriction of airways due to alveolar hypocapnia;

2) reduced oxygen tension in the diaphragm and chest muscles due to worsened oxygen transport;

3) tense states of the diaphragm and chest muscles due to arterial hypocapnia.

Exacerbating causes in the pathophysiology of dyspnea are:

1. Mouth breathing (due to reduction in nitric oxide absorption and alveolar CO_2).

2. Chest breathing (due to reduction in the arterial oxygenation).

3. Presence of inflammation and mucus in airways causing further narrowing or obstruction of air flow.

Exertion, exercise (with mouth breathing), meals (or eating, and especially overeating), overheating, stress, anxiety, attempts to breathe deeply, deep breathing exercises, night sleep and being in the horizontal position (especially supine sleep), poor posture, pregnancy and many other factors are all known causes of hyperventilation. Therefore, these lifestyle factors exacerbate the problem with breathlessness. For example, physical exertion, due to anaerobic cell respiration at rest and elevated-resting-blood lactate, worsens gas exchange and causes overbreathing. This leads to acute exertional dyspnea.

DISORDERS OF PULMONARY BLOODSTREAM

There are two blood streams in the lungs: lesser circulation and a system of bronchial vessels of greater circulation. Lesser circulation has some features, connected with physiology of expiratory apparatus.

Pressure in the pulmonary vessels is low. In the pulmonary artery it is 15 mm Hg. Pressure in the left atrium is 5 mm Hg. Perfusion is provided by pressure of 10 mm Hg. This is enough to provide perfusion against gravitation in the upper parts of lungs. But the gravitation is the important part of irregular perfusion in lungs. In the horizontal position the bloodstream in the upper parts is increased, but is less than in the lower. The vertical gradient of bloodstream appears – it decreases from dorsal parts to the ventral. During changes of the body position the weight gradient doesn't change.

In pathologic states gravity influences the functional lung parameters. The example is critical picture of orthopnea with the acute insufficiency of left part of heart. In the clinostatic position the blood stream to the left atrium becomes harder; in the orthostatic – becomes easier.

The feature of lesser circulation is that the big and medium arteria are the vessels of elastic type. Vasomotor reactions are realized in the arteries of muscular type. In normal conditions the minute rate of right ventricle is less than left, due to escape of blood from greater circulation through anastomosis of bronchial vessel. In valuable increasing of pressupe of lesser circulation the blood escape can be reversed; the minute rate of right ventricle is higher that left.

The changes of perfusion are promoted by:

1. Decrease in contractive function of right ventricle.
2. Insufficiency of left part of heart.
3. Some inheriting or acquired heart diseases.
4. Vascular insufficiency.
5. Thrombosis or embolism in the system of lung arteries. In these pathologic states there isn't hypoxemia, because the ventilation of lungs prevails on the bloodstream.

Bronchial vessels are the branched bronchial arteries of greater circulation. The volume of blood in them is 1–2 % of minute heart rate. Most part of blood goes to left atrium through precapillary, capillary and venous shunts. The ruptures of bronchial arteries are the most common cause of hemorrhages of lung pathologies.

DISORDERS OF COMMON AND REGIONAL VENTILATION-PERFUSION CORRELATIONS

There are two variants of disorders of ventilation-perfusion correlation.

First is – ventilation of non-perfusion parts of lung tissue. This happens after the irregular perfusion. This can be caused by decreasing of blood steam in some branches of lung arteries, local reduction of capillary etc. Causes of those events are embolism in the lung artery, pressing of its branches etc. The basis of disorders of ventilation-perfusion correlation can be the excessive anatomic intrapulmonary shunt. This is in emphysema, heart disease etc. Ventilated but non-perfusing alveolus and their groups are useless. Ventilation begins to prevail over the perfusion. Normal alveolar ventilation is 4–5 liters per minute. The blood stream is also 4–5 liters per minute. So the correlation is 0,8–1,0, This provides the normal gaseous content of blood. In prevail of ventilation over the perfusion this correlation grows. In those cases the CO_2 from the blood is removed more quickly; the hypocapnia is developed. Lung space, which isn't perfusive is involved into dead space.

Second type of disorders is the perfusion of non-ventilated space. This happens in irregular ventilation of lungs (irregular tension of different parts of lungs); irregular disorders of bronchial pass ability (tumors, abscess etc.); the disorders of expiration and inspiration (paralysis of diaphragm etc.). The correlation is less than 0,8. Blood becomes more venous. This leads to hypoxemia. For the oxygen passage the hyperventilated parts aren't effective, because the oxygen capacity of blood is limited

Date	Grade	Teacher's signature

PATHOPHYSIOLOGY OF DIGESTION. INSUFFICIENCY OF DIGESTION. PATHOPHYSIOLOGY OF LIVER. LIVER INSUFFICIENCY

Relevance. The number of patients with different stomach diseases and digestion disorders constantly grows, leading to a decrease in working capacity and invalidation. Quite often, these diseases cause death. One of important and earliest violations of stomach functions is disorder of gastric secretion, which can develop owing to violation of neuroendocrine regulation, in pathological processes in a stomach, in other organs and systems, under various external impacts on an organism. Stomach disorders of secretion are characterized by both quantitative changes, and qualitative. Knowledge of the main regularities of gastric secretion disorders, quantitative and high-quality changes of gastric juice thus gives the chance to correctly carry out prevention and rational therapy the secretion stomach disorders.

Violation of bile production and secretion function of a liver followed by developing of jaundice is a pathological syndrome which can be observed in diseases of a liver and the bile excreting ways of a therapeutic, infectious and surgical profile, a number of haemolytic situations of hereditary, immune and toxic character. The knowledge of questions of an etiology and pathogenesis of different types of jaundices, bases of their clinical and laboratory differential diagnostics is necessary in general-theoretical training of the general practitioner. Besides, at the heart of many clinical manifestations of liver diseases and the bile excreting ways of a different etiology lies kholemia development.

Overall Objective is to be able to determine and characterize acidity of gastric juice in different disorders of gastric secretion, essence of jaundices as the pathological syndromes, which are a consequence of violation of a bile production and a bile excreting to interpret the main laboratory indicators used for differential diagnostics of different types of jaundices. To interpret a kholemic syndrome as set the functional changes in an organism at diseases of a liver and the bile excreting ways which are followed by mechanical or parenchymatous jaundice.

The student should be able to (specific objectives):

1. Explain normal and pathological types of gastric secretion.
2. Analyze the mechanism of hypo- and hypersecretion, hypo- and hyperacidity.
3. Explain the influence of secretion disorders on the mechanism of gastric motor function violation.
4. Use the knowledge of the mechanisms for correct understanding of their role in pathogenesis of diseases of digestive tract.
5. Define the concept of jaundice as pathological syndrome.
6. Classify jaundices, taking into account their etiology and pathogenesis.
7. Prove application of the used laboratory indicators as required for the research of differential diagnosis of jaundices.
8. Carry out high-quality definition of direct and indirect bilirubin of serum of blood.
9. Carry out differential diagnostics of different types of jaundices, using knowledge on mechanisms of biochemical violations emergence.
10. List the main symptoms of a kholemic syndrome.
11. Explain the mechanism of emergence and development of the main manifestations of a kholemic syndrome.

The student should be able to (required knowledge and skills):

1. Characterize the content and acidity of gastric juice (dep. of normal physiology).
2. Interpret and explain the regulation mechanisms of gastric secretion (dep. of normal physiology).
3. Represent an anatomic and histological structure of a liver and the bile excreting ways (dep. normal anatomy and histology).
4. Know the main stages of an exchange of bilious pigments in a human body (dep. biochemistry).
5. Explain the main physiological mechanisms of bile excreting function of a liver (dep. normal physiology).
6. Characterize processes of bile production and bile excreting and a chemical composition of bile (dep. normal physiology).
7. Explain the value of bile in the course of digestion (dep. normal physiology).

QUESTIONS TO THE LESSON

1. Definition of the terms "digestion", "digestive insufficiency", "syndrome of digestion insufficiency "dyspepsia". Main reasons for digestioninsufficiency.
2. Disorders of taste, appetite, feeling of thirst. Types. Reasons. Consequences.
3. Digestion disorders in oral cavities and swallowing. Types. Reasons. Consequences.
4. Gullet dysfunction. Types. Reasons. Consequences.
5. Digestion disorders in stomach. Disorders of secret, motor, absorptive, barrier and protective function of stomach.
6. Digestion disorders in intestines. Disorders of the digesting, motor, barrier and protective function of intestines.
7. Stomach ulcer and duodenum. Etiology. Pathogenesis. Manifestations. Complications.
8. Malabsorption syndrome. Main reasons and manifestations. Coeliacs disease. Nonspecific ulcer colitis. Reasons. Manifestations.
9. Main pathological syndromes of liver damage, their biochemical markers.
10. Functional insufficiency of liver. Disorders of metabolic and protective function. Reasons. Pathogenesis. Manifestations. Syndrome of hepatocerebral insufficiency.
11. Disorders of liver excretory function. Frustration of bile production and bile excretion. Reasons. Manifestations.
12. Jaundice. Definition of a concept. Types of jaundice. Haemolytic jaundice. Reasons. Pathogenesis. Manifestations.
13. Parenchymatous (hepatic) jaundice. Reasons. Pathogenesis. Manifestations.
14. Mechanical (subhepatic) jaundice. Reasons. Holemic syndrome. Pathogenesis. Manifestations.
15. Violation of haemodynamic function of a liver. Syndrome of portal hypertensia. Etiology. Pathogenesis. Manifestations.
16. Hepatic coma. Etiology. Pathogenesis.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

PATHOPHYSIOLOGY OF DIGESTIVE SYSTEM

The digestive system is a group of organs, working together to convert food into energy and basic nutrients to feed the entire body. Food passes through a long tube inside the body known as the alimentary canal or the gastrointestinal tract (GI tract). The alimentary canal is made up of the oral cavity, pharynx, esophagus, stomach, small intestines, and large intestines. In addition to the alimentary canal, there are several important accessory organs that help your body to digest food, but do not have food pass through them. Accessory organs of the digestive system include the teeth, tongue, salivary glands, liver, gallbladder, and pancreas. To achieve the goal of providing energy and nutrients to the body, six major functions take place in the digestive system:

1. Ingestion
2. Secretion

3. Mixing and movement
4. Digestion
5. Absorption
6. Excretion

Digestive System Physiology

The digestive system is responsible for taking whole foods and turning them into energy and nutrients to allow the body to function, grow, and repair itself. The six primary processes of the digestive system include:

1. Ingestion of food
2. Secretion of fluids and digestive enzymes
3. Mixing and movement of food and wastes through the body
4. Digestion of food into smaller pieces
5. Absorption of nutrients
6. Excretion of wastes

Ingestion

The first function of the digestive system is ingestion, or the intake of food. The mouth is responsible for this function, as it is the orifice through which all food enters the body. The mouth and stomach are also responsible for storage of food as it is waiting to be digested. This storage capacity allows the body to eat only a few times each day and to ingest more food than it can process at one time.

Secretion

In the course of a day, the digestive system secretes around 7 liters of fluids. These fluids include saliva, mucus, hydrochloric acid, enzymes, and bile. Saliva moistens dry food and contains salivary amylase, a digestive enzyme that begins the digestion of carbohydrates. Mucus serves as a protective barrier and lubricant inside of the GI tract. Hydrochloric acid helps to digest food chemically and protects the body by killing bacteria present in our food. Enzymes are like tiny biochemical machines that disassemble large macromolecules like proteins, carbohydrates, and lipids into their smaller components. Finally, bile is used to emulsify large masses of lipids into tiny globules for easy digestion.

Mixing and Movement. The digestive system uses 3 main processes to move and mix food:

Swallowing. Swallowing is the process of using smooth and skeletal muscles in the mouth, tongue, and pharynx to push food out of the mouth, through the pharynx, and into the esophagus.

Peristalsis. Peristalsis is a muscular wave that travels the length of the GI tract, moving partially digested food a short distance down the tract. It takes many waves of peristalsis for food to travel from the esophagus, through the stomach and **intestines**, and reach the end of the GI tract.

Segmentation. Segmentation occurs only in the small intestine as short segments of intestine contract like hands squeezing a toothpaste tube. Segmentation helps to increase the absorption of nutrients by mixing food and increasing its contact with the walls of the intestine.

Digestion is the process of turning large pieces of food into its component chemicals. Mechanical digestion is physical breakdown of large pieces of food into smaller pieces. This mode of digestion begins with chewing of food with teeth and continues through muscular mixing of food by the stomach and intestines. Bile produced by the liver is also used to mechanically break fats into smaller globules. While food is being mechanically digested it is also being chemically digested as larger and more complex molecules are being broken down into smaller molecules that are easier to absorb. Chemical digestion begins in the mouth with salivary amylase in saliva splitting complex carbohydrates into simple carbohydrates.

The enzymes and acid in the stomach continue chemical digestion, but the bulk of chemical digestion takes place in the small intestine thanks to the action of the pancreas. The pancreas secretes an incredibly strong digestive cocktail known as pancreatic juice, which is capable of digesting lipids, carbohydrates, proteins and nucleic acids. By the time food has left the **duodenum**, it has been reduced to its chemical building blocks—fatty acids, amino acids, monosaccharides, and nucleotides.

Absorption. Once food has been reduced to its building blocks, it is ready to be absorbed by the body. Absorption begins in the stomach with simple molecules like water and alcohol being absorbed directly into the bloodstream. Most absorption takes place in the walls of the small intestine, which are densely folded to maximize the surface area in contact with digested food. Small blood and lymphatic vessels in the intestinal wall pick up.

Dyspepsia

Dyspepsia is a sensation of pain or discomfort in the upper abdomen; it often is recurrent. It may be described as indigestion, gassiness, early satiety, postprandial fullness, gnawing, or burning.

Etiology. There are several common causes of dyspepsia (*see Table 33*).

Table 33

Some Causes of Dyspepsia

Cause	Suggestive Findings	Diagnostic Approach
Achalasia	Slowly progressive dysphagia. Early satiety, nausea, vomiting, bloating, and symptoms that are worsened by food. Sometimes nocturnal regurgitation of undigested food. Chest discomfort	Barium swallow. Esophageal manometry. Endoscopy
Cancer (eg, esophageal, gastric)	Chronic, vague discomfort. Later, dysphagia (esophageal) or early satiety (gastric). Weight loss	Upper endoscopy
Coronary ischemia	Symptoms described as gas or indigestion rather than chest pain by some patients. May have exertional component. Cardiac risk factors	ECG. Serum cardiac markers. Sometimes stress testing
Delayed gastric emptying (caused by diabetes, viral illness, or drugs)	Nausea, bloating, fullness	Scintigraphic test of gastric emptying
Drugs (eg, bisphosphonates, erythromycin and other macrolide antibiotics, estrogens, iron, NSAIDs,)	Use apparent on history. Symptoms coincident with use	Clinical evaluation
Esophageal spasm	Substernal chest pain with or without dysphagia for liquids and solids	Barium swallow. Esophageal manometry
Gastroesophageal reflux disease	Heartburn. Sometimes reflux of acid or stomach contents into mouth. Symptoms sometimes triggered by lying down. Relief with antacids	Clinical evaluation. Sometimes endoscopy. Sometimes 24-h pH testing
Peptic ulcer disease	Burning or gnawing pain relieved by food or antacids	Upper endoscopy

Many patients have findings on testing (e.g, duodenitis, pyloric dysfunction, motility disturbance,Helicobacter pylorigastritis, lactose deficiency, cholelithiasis) that correlate poorly with symptoms (i.e, correction of the condition does not alleviate dyspepsia).

Excretion. The final function of the digestive system is the excretion of waste in a process known as defecation. Defecation removes indigestible substances from the body so that they do not accumulate inside the gut. The timing of defecation is controlled voluntarily by the conscious part of the brain, but must be accomplished on a regular basis to prevent a backup of indigestible materials.

Nonulcer (functional) dyspepsia is defined as dyspeptic symptoms in a patient who has no abnormalities on physical examination and upper GI endoscopy.

Physical examination: Review of vital signs should note presence of tachycardia or irregular pulse.

General examination should note the presence of pallor or diaphoresis, cachexia, or jaundice. Abdomen is palpated for tenderness, masses, and organomegaly. Rectal examination is done to detect gross or occult blood.

The following findings are of particular concern:

1. Acute episode with dyspnea, diaphoresis, or tachycardia
2. Anorexia

3. Nausea or vomiting
4. Weight loss
5. Blood in the stool
6. Dysphagia or odynophagia
7. Failure to respond to therapy with H_2 blockers or proton pump inhibitors (PPIs).

DISORDERS IN SENSATIONS OF HUNGER AND THIRST

Hunger and Eating Disorders

They are manifested in decreased sensation of hunger (a lack of appetite, **anorexia**), increased sensation of hunger (insatiable hunger, **hyperorexia**, or bulimia, which leads to a sharp increase in food consumption – **polyphagia**), and consumption of nonalimentary substances, for example, vinegar, chalk (perverted appetite – **parorexia**).

The Biology of Hunger

We usually first become aware of the fact that we are hungry when we feel "hunger pangs," which are just our **stomach contractions**. For many people, this is a strong incentive to eat, but it is not, physiologically, the most significant indication of hunger.

More important is the level of **glucose** (blood sugar) in the blood. Most of the food you eat gets converted to glucose, much of which is converted by the liver into fat for later use. When the levels of glucose are low, the liver sends signals to the hypothalamus - specifically, the **lateral hypothalamus** – that levels are low. The hypothalamus in turn triggers whatever habits you have accumulated relating to food seeking and consumption.

Another portion of the hypothalamus (the**paraventricular hypothalamus**) actually tells you more specifically which foods you need, and seems to be responsible for many of our "cravings".

The feeling that it is time to stop eating is called**satiety**. Again, the first indicators may be the distension of the stomach and the intestines - that full or even bloated feeling we all know from Thanksgiving dinner.

There is also a certain hormone called **CCK** (Cholecystokinin) that is released when food begins to move from the stomach to the intestines and that signals the hypothalamus that it's time to stop eating. And there is a hormone released by the fat cells themselves called **leptin** that decreases appetite via the hypothalamus.

I'm sure you've all talked about one person having a better **metabolism** than another. Some people just seem to burn calories as quick as they eat them, while others gain weight just by looking at food. This is called the **set point** hypothesis. It suggests that everyone has a certain metabolic set point, a certain weight that your body is geared towards, which is determined by your metabolism, or the rate at which you burn calories. Different people have different set points, and it is believed that these set points can change depending on a number of factors, including eating patterns and exercise.

The Psychology of Hunger

Hunger is not, of course, entirely a physical process. For one thing, the cultural and even individually learned preferences and eating habits can make a difference. For example, some of us eat regular meals and rarely snack, while others just nibble throughout the day. Every culture has its collection of foods that are preferred and those that are avoided. Many people like the burned flesh of large herbivores (i.e. a steak); others prefer raw squid; others still prefer to graze on a variety of vegetation.

Eating Disorders

As is the case with anything as important as eating, human beings have developed a number of eating disorders. One is called **bulimia nervosa**, and consists of a pattern of "binging" and "purging" - periods of sometimes extreme overeating followed by periods of vomiting or the use of laxatives.

Bulimics are usually obsessed with maintaining or reducing their weight. They tend to suffer from depression, anxiety, poor self-esteem, and poor impulse control. They tend to come from families with a history of emotional problems such as depression, as well as families with obesity problems.

Anorexia nervosa is another eating disorder which involves dieting to the point of starvation. They have an intense fear of being fat and are obsessed with being thin. They often have a distorted body image, meaning that when they look in the mirror, they tend to see someone overweight, when others see them as walking skeletons. Anorexics often come from very competitive, demanding families, and are often perfectionists with a strong need to control all aspects of their lives.

Physiologically, anorexia has been linked to abnormal levels of the neurotransmitter serotonin, which is involved in eating regulation. Twin research suggests that there may be a genetic aspect to anorexia as well.

Most anorexics and bulimics are young women, including from 1 to 4 % of high school and college girls. But a sig-nificant root of these disorders is likely social. In our society at this point in history, the standards of beauty tend to emphasize thinness, and women in particular tend to be judged on the basis of beauty, sometimes to the exclusion of all else. It is interesting that cultures with standards of beauty that have more respect for a woman's personality or other traits, and cultures that appreciate heavier women, have little or no trouble with bulimia or anorexia.

Disorders in the Sensation of Thirst

Thirst is a conscious sensation that results in a desire to drink. Three factors are typically recognized as components of thirst: a body water deficit, brain integration of central and peripheral nerve mes-sages relating to the need for water, and an urge to drink. In laboratory experiments, thirst is meas-ured empirically with subjective perceptual scales (for example, ranging from "not thirsty at all" to "very, very thirsty") and drinking behavior is quantified by observing the timing and volume of fluid consumed.

Psychologists classify thirst as a drive, a basic compelling urge that motivates action. Other human drives involve a lack of nutrients (for example, glucose, sodium), oxygen, or sleep; these are satiated by eating, breathing, and sleeping. Numerous investigations have verified that thirst and drinking behavior are complex entities. For example, drinking behavior (that is, the timing and the amount of fluid consumed) is not linearly related to the intensity of perceived thirst. Nor should we infer that individuals experience thirst simply because they drink. These facts indicate that thirst and drinking behavior are distinct entities that influence each other and are influenced by numerous internal and external factors.

Physiological Components of Thirst

Thirst is often viewed by physiologists and physicians as a central nervous system mechanism that regulates the body's water and minerals. No single mechanism can account for all drinking behavior and that multiple mechanisms, sometimes with identical functions, act concurrently. Because water is essential to life, the existence of redundant mechanisms has great survival value. Among these, thirst appears to be regulated primarily by evaluation of changes in the concentration of extracellular fluid, measured as the osmolality of blood plasma.

Below a certain threshold level of plasma osmolality, thirst is absent. Above this threshold, a strong desire to drink appears in response to an increase of 2 to 3 percent in the level of dissolved substances in blood. The brain's thirst center lies deep within the brain, in an area known as the hypothalamus. When the thirst center is stimulated by an increased concentration of blood (that is, dehydration), thirst and fluid consumption increase.

As the brain senses the concentration of blood, it allows a minor loss of body water before stimulating the drive to drink. This phenomenon has been named voluntary dehydration.

Reduced extracellular fluid volume, including blood volume, also increases thirst (for example, reducing blood volume without altering blood concentration). Thus, thirst is extinguished when body fluid concentration decreases and fluid volume increases. Osmolality-sensitive nerves in the mouth, throat, and stomach also play a role in abating thirst. As fluid passes through the

mouth and upper gastrointestinal tract, the sense of dryness decreases. When this fluid fills the stomach, stretch receptors sense an increase in gastric fullness and the thirst drive diminishes.

As dehydration causes the body's extracellular fluid to become more concentrated, the fluid inside cells moves outward, resulting in intracellular dehydration and cell shrinkage, and the hormone arginine vasopressin (AVP, also known as the antidiuretic hormone) is released from the brain. AVP serves two purposes: to reduce urine output at the kidneys and to enhance thirst; both serve to restore normal fluid balance. Other hormones influence fluid-mineral balance directly and thirst indirectly. Renin, angiotensin II, and aldosterone are noteworthy examples. As dehydration reduces circulating blood volume, blood pressure decreases and renin is secreted from blood vessels inside the kidneys. Renin activates the hormone angiotensin II, which subsequently stimulates the release of aldosterone from the adrenal glands. Both angiotensin II and aldosterone increase blood pressure and enhance the retention of sodium and water; these effects indirectly reduce the intensity of thirst. Angiotensin II also affects thirst directly.

Host Factors

Repeated training sessions in cool or hot environments alter fluid consumption in four ways.

First, physical training increases secretion of the hormone AVP, which stimulates drinking and body water retention.

Second, exercise-heat acclimation (that is, adaptations due to exercise in a hot environment over eight days) increases the volume of fluid consumed and the number of times that adults drink during exercise.

Third, frequent rest periods, in the midst of labor or exercise, will increase fluid replacement time and enhance fluid consumption. Humans tend to drink less when they are preoccupied or are performing physical or mental tasks.

Fourth, learned behaviors can enhance fluid consumption when thirst is absent. This phenomenon is widely appreciated among military personnel and athletes who are trained to consume water at regular intervals, whether they are thirsty or not.

DIGESTION DISORDERS IN THE ORAL CAVITY

They include:

1) disorders of mastication;
2) disorders in salivary secretion;
3) disorders of the tonsils.

DISORDERS IN MASTICATION

They arise as a result of:

1) affections of teeth (absence of a large number of teeth, caries, pulpitis, periodontitis, parodontosis);
2) stomatitides and gingivitides;
3) disorders of the masticative muscles (traumas, inflammation);
4) disorders of the masticative nerves;
5) lesions of the temporal-mandibular joint;
6) lesions of masticative apparatus as a whole;
7) bulbar paralyses.

Results of mastication disorders: traumatisation of the mucosa of the mouth, gums, esophagus and stomach, infecting, inflammation, affection of the gastric and pancreatic secretion (normally mastication of food reflexly causes secretion of gastric and pancreatic juices) and, thus, of functions of the lower parts of the digestive tract.

DISORDERS OF SALIVARY SECRETION

They are manifested as hypersalivation and hyposalivation (the normal secretion is 1–2 litres a day).

1. Hypersalivation may be:

1.1) reflex one (pregnancy, vomiting, nausea, stomatitis, gingivitis, pulpitis, periodontitis, and lesions in abdominal organs);

1.2) central one – after lesions of the CNS (epidemic encephalitis), bulbar paralyses (in association with disturbed swallowing of saliva) and under the action of parasympathomimetics (physostigmine, muscarine, pilocarpine, etc.).

Results of hypersalivation:

1) hypersalivation can have the protective significance (excretion of salts of hydrargium, plumbum, cooper, poisons, products of disturbed metabolism, etc.);

2) overlubrication of the alimentary bolus and disturbance in deglutition;

3) neutralisation of the gastric juice with the result that digestion in the stomach diminishes and processes of fermentation and putrefaction develop;

4) maceration of the skin;

5) entering into the respiratory tract with development of pneumonia or asphyxia;

6) loss of large amounts of saliva (sometimes up to 12–14 litres a day) may lead to exhausting of the organism.

2. Hyposalivation also may be reflex (pain), central (fear, excitement, suppression of parasympathetic innervation of salivary glands, for example, under the action of atropine or scopolamine); also it can be a result of disorders in water metabolism, as in cases of infectious and febrile processes, excessive sweating, massive hemorrhages, or protracted diarrheas. It may be also due to direct lesions of salivary glands in sialoadenitis, parotitis, submaxillitis, formation of calculi and scars in the salivary ducts), systemic lesions of salivary and lachrymal glands (xerostomia – dryness of the mucous membranes, or Sjogren's syndrome).

Results of hyposalivation:

1) digestion disorders in the oral cavity;

2) disorders of mastication and swallowing;

3) traumatisation of the mucous membranes by the food which lead to inflammatory processes;

4) fermentation and putrefaction in the oral cavity;

5) development of caries;

6) inflammation of the salivary glands;

7) disorders of secretion in the stomach;

8) insufficiency of the endocrine function of salivary glands.

Alongside with hyper- and hyposalivation a changed reaction of saliva is possible. It is observed in disturbed digestion and metabolism (diabetes, fiver) and promotes destruction of teeth.

Disorders of the Tonsils. They are observed in tonsillitis and abscesses and hinder mastication, swallowing and affect secretion of saliva.

DISORDERS OF DEGLUTITION (DYSPHAGIA)

They include disorders of the voluntary and involuntary (reflex) phases of deglutition.

The causes of voluntary phase disorders:

1) inherent and acquired defects of the hard and soft palate;

2) bulbar paralysis (diphtheria, botulism);

3) paralysis of the tongue (mainly of bulbar origin);

4) paralysis of the deglutitive nerves or muscles;

5) spasm of the pharyngeal muscles (tetanus, rabies, hysteria);

6) poisoning with narcotics, diabetic coma, uremia;

7) disturbances of the receptors of the oral cavity;

8) tonsillitis and abscesses.

Disorders of the reflex phase of deglutition are connected with disorders of the esophagus – constriction, dilatation and formation of diverticula. A constriction of the esophagus may be due to anatomic changes in its wall (tumours and scars), its mechanical compression (tumours and abscesses of the mediastinum, aneurysm of the aorta), spasm (stimulation of the sympathetic nerve, acid reaction of gastric juice, hysteria).

Dilatation of the esophagus is observed in its paralysis owing to affection of its nerves.

Diverticula of the esophagus are its local dilatations in which the part of the wall protruding like a hernia consists of the mucosa and submucous tissue with a thinned muscular layer; the latter may even be totally absent. Diverticula are formed as a result of stretching of the esophageal wall by a foreign body or trauma.

Hiccups

Hiccups (hiccough, singultus) are repeated involuntary spasms of the diaphragm followed by sudden closure of the glottis, which checks the inflow of air and causes the characteristic sound. Transient episodes are very common. Persistent (> 2 days) and intractable (> 1 mo) hiccups are uncommon but quite distressing.

Etiology. Hiccups follow irritation of afferent or efferent diaphragmatic nerves or of medullary centers that control the respiratory muscles, particularly the diaphragm. Hiccups are more common among men. Their cause is generally unknown but transient hiccups are often caused by the following:

Gastric distention, alcohol consumption, swallowing hot or irritating substances.

Persistent and intractable hiccups have myriad causes (*see Table 34*).

Rumination

Rumination is the (usually involuntary) regurgitation of small amounts of food from the stomach (most often 15 to 30 min after eating) that are rechewed and, in most cases, again swallowed. Patients do not complain of nausea or abdominal pain. Rumination is commonly observed in infants. The incidence in adults is unknown.

Etiology. Patients with achalasia or a Zenker's diverticulum may regurgitate undigested food without nausea. In the majority of patients who do not have these obstructive esophageal conditions, the pathophysiology is poorly understood. The reverse peristalsis in ruminants has not been reported in humans. The disorder is probably a learned, maladaptive habit and may be part of an eating disorder. The person learns to open the lower esophageal sphincter and propel gastric contents into the esophagus and throat by increasing gastric pressure via rhythmic contraction and relaxation of the diaphragm.

Table 34

Some Causes of Intractable Hiccups

Category	Examples
Esophageal	Gastroesophageal reflux disease, Other esophageal disorders
Abdominal	Abdominal surgery, Bowel diseases, Gallbladder disease, Hepatic metastases Hepatitis, Pancreatitis, Pregnancy
Thoracic	Diaphragmatic pleurisy, Pericarditis, Pneumonia, Thoracic surgery
Other	Alcoholism, Posterior fossa tumors or infarcts, Uremia

Symptoms and Signs. Nausea, pain, and dysphagia do not occur. During periods of stress, the patient may be less careful about concealing rumination. Seeing the act for the first time, others may refer the patient to a physician. Rarely, patients regurgitate and expel enough food to lose weight.

Nausea and Vomiting

Nausea, the unpleasant feeling of needing to vomit, represents awareness of afferent stimuli (including increased parasympathetic tone) to the medullary vomiting center. Vomiting is the forceful expulsion of gastric contents caused by involuntary contraction of the abdominal musculature when the gastric fundus and lower esophageal sphincter are relaxed.

Vomiting should be distinguished from regurgitation, the spitting up of gastric contents without associated nausea or forceful abdominal muscular contractions. Patients with achalasia or a Zenker's diverticulum may regurgitate undigested food without nausea.

Complications. Severe vomiting can lead to symptomatic dehydration and electrolyte abnormalities (typically a metabolic alkalosis with hypokalemia) or rarely to an esophageal tear, either partial (Mallory-Weiss) or complete (Boerhaave's syndrome). Chronic vomiting can result in undernutrition, weight loss, and metabolic abnormalities.

Etiology. Nausea and vomiting occur in response to conditions that affect the vomiting center. Causes may originate in the GI tract or CNS or may result from a number of systemic conditions (*see Table 35*).

Table 35

Some Causes of Nausea and Vomiting

Cause	Suggestive Findings*	Diagnostic Approach
GI disorders		
Bowel obstruction	Obstipation, distention, tympany. Often bilious vomiting, abdominal surgical scars, or hernia	Flat and upright abdominal x-rays
Gastroenteritis	Vomiting, diarrhea. Benign abdominal examination	Clinical evaluation
Gastroparesis or ileus	Vomiting of partially digested food a few hours after ingestion. Often in diabetics or after abdominal surgery	Flat and upright abdominal x-rays
Hepatitis	Mild to moderate nausea for many days, sometimes vomiting. Jaundice, anorexia, malaise. Sometimes slight tenderness over the liver	Serum aminotransferases, bilirubin, viral hepatitis titers
Perforated viscus or other acute abdomen (eg, appendicitis, cholecystitis, pancreatitis)	Significant abdominal pain Usually peritoneal signs	See Acute Abdomen and Surgical Gastroenterology: Acute Abdominal Pain
Toxic ingestion (numerous)	Usually apparent based on history	Varies with substance
CNS disorders		
Closed head injury	Apparent based on history	Head CT
CNS hemorrhage	Sudden-onset headache, mental status change. Often meningeal signs	Head CT, Lumbar puncture if CT is normal
CNS infection	Gradual-onset headache. Often meningeal signs, mental status change. Sometimes petechial rash*due to meningococcemia	Head CT. Lumbar puncture
Increased intracranial pressure (eg, caused by hematoma or tumor)	Headache, mental status change. Sometimes focal neurologic deficits	Head CT
Labyrinthitis	Vertigo, nystagmus, symptoms worsened by motion. Sometimes tinnitus	
Migraine	Headache sometimes preceded or accompanied by a neurologic aura or photophobia. Often a history of recurrent similar attacks. In patients with known migraine, possible development of other CNS disorders	Clinical evaluation Head CT and lumbar puncture considered if evaluation is unclear
Motion sickness	Apparent based on history	Clinical evaluation
Psychogenic disorders	Occurring with stress. Eating food considered repulsive	Clinical evaluation
Systemic conditions		
Advanced cancer (independent of chemotherapy or bowel obstruction)	Apparent, based on history	Clinical evaluation
Diabetic ketoacidosis	Polyuria, polydipsia. Often significant dehydration. With or without history of diabetes	Serum glucose, electrolytes, ketones
Drug adverse effect or toxicity	Apparent, based on history	Varies with substance
Liver failure or renal failure	Often is apparent based on history. Often jaundice in advanced liver disease, uremic odor in renal failure	Laboratory tests of liver and renal function
Pregnancy	Often occurring in the morning or is triggered by food. Benign examination (possibly dehydration)	Pregnancy test
Radiation exposure	Apparent, based on history	Clinical evaluation
Severe pain (e.g, due to a kidney stone)	Varies with cause	Clinical evaluation

The most common causes are the following:

1. Gastroenteritis
2. Drugs
3. Toxins

Cyclic vomiting syndrome (CVS) is an uncommon disorder characterized by severe, discrete attacks of vomiting or sometimes only nausea that occur at varying intervals, with normal health between episodes and no demonstrable structural abnormalities. It is most common in childhood (mean age of onset 5 yr) and tends to remit with adulthood. CVS in adults is often due to chronic marijuana (cannabis) use.

Physical examination: Vital signs should particularly note fever and signs of hypovolemia (e.g, tachycardia, hypotension, or both).

General examination should seek presence of jaundice and skin rash.

On abdominal examination, the clinician should look for distention and surgical scars; listen for presence and quality of bowel sounds (e.g, normal, high-pitched); percuss for tympany; and palpate for tenderness, peritoneal findings (e.g, guarding, rigidity, rebound), and any masses, organomegaly, or hernias. Rectal examination and (in women) pelvic examination to locate tenderness, masses, and blood are essential.

Neurologic examination should particularly note mental status, nystagmus, meningismus (e.g, stiff neck, Kernig's or Brudzinski's signs), and ocular signs of increased intracranial pressure (e.g, papilledema, absence of venous pulsations, 3rd cranial nerve palsy) or subarachnoid hemorrhage (retinal hemorrhage).

Red flags: The following findings are of particular concern:

Signs of hypovolemia

Headache, stiff neck, or mental status change

Peritoneal signs

Distended, tympanitic abdomen

DISORDERS IN GASTRIC DIGESTION

They include the disorders of reservoir, secretory, motor and excretory (evacuatory) functions.

DISORDERS IN THE RESERVOIR FUNCTION

Stomach is the specific part of the digestive tract which combines functions of the digestive organ and food depot. In dependence on kind of animal, quantity and composition of food the latter is detained in the stomach up to 4–10 hours, in human – 3.5–4 hours.

The causes of disturbed reservoir function of the stomach: resection of the stomach, atrophy of the gastric wall, gastrointestinal anastomosis, reflex inhibition of the gastric tone (operations on the abdominal organs, contusion of the stomach, overeating, and acute infections).

Results of the disturbed reservoir function of the stomach: dilatation of the stomach, thinning of its wall, weakened peristalsis, reduced secretion, eructation, vomiting, delay of food and gases, fermentation and putrefaction, delay of water and chlorides which leads to alkalosis, dehydration, convulsions, collapse.

DISORDERS OF THE SECRETORY FUNCTION

We distinguish gastric hypersecretion and hyposecretion (in norm the quantity of gastric juice is 2–2.5 litres a day). Achlorhydria has been defined by multiple separate systems in reference to gastric acid secretion.

First, achlorhydria has been defined by a peak acid output in response to a maximally effective stimulus that results in an intragastric pH of greater than 5.09 in men and greater than 6.81 in women.

Second, achlorhydria has been defined by a maximal acid output of less than 6.9 m/mole/h in men and less than 5.0 m/mole/h in women.

Third, achlorhydria has been defined as a ratio of serum pepsinogen I/pepsinogen II of less than 2.9.

Pathophysiology. Acid secretion by gastric epithelial cells is related to the physiologic function of oxyntic cells, called parietal cells. Parietal cells are mainly present in the gastric corpus and fundus, although complete mapping in the human stomach is not fully known. Parietal cells are responsible for secretion of hydrochloric acid and also produce intrinsic factor. Parietal cells have large mitochondria with short microvilli and a cytoplasmic canaliculi system in contact with the lumen. The H^+/K^+ -ATPase responsible for acid secretion resides in the apical microvillus membrane. The relationship between parietal cell function and achlorhydria is illustrated using genetic knockout mice models, as follows: absence of the H^+/K^+ -ATPase is chronically associated with achlorhydria and mucosal hyperplasia but with no histological evidence for neoplasia. In a gastrin knockout model, achlorhydria is present because of the inactivation of enterochromaffinlike (ECL) cells and parietal cells. This model leads to intestinal metaplasia, bacterial overgrowth, and, in some instances, gastric tumors.

In the Kcne2 potassium channel ancillary subunit knockout model, disruption of this gene induces achlorhydria and is related to reduced parietal cell protein secretion and abnormal parietal cell morphology. Disruption of this channel is a possible risk factor for gastric neoplasia.

Genetic ablation of a Na^+/H^+ exchanger (NHE2), expressed in the stomach at high levels, leads to a decrease in gastric acid secretion, along with decreased viability of parietal cells, severe metaplasia, and hyperplasia of gastric mucosa.

Chronic inflammatory changes related to gastric Helicobacter pylori infection can also induce parietal cell changes.

Among the origins of achlorhydria related to medical care, medications that block H+/K+ -ATPase activity can induce achlorhydria.

Motor Dysfunctions of the Stomach

Disorders of the motor activity of the stomach may manifest themselves as changes in muscular tone and changes in peristalsis.

The **changed muscular tone** is manifested in gastric hypertonia and hypotonia (atonia).

Gastric hypertonia is observed in ulcer disease, in the beginning of acute gastritis, under reflex influences (renal or hepatic colics, etc.), neurosis. Hypotonia, or relaxation of the stomach, may arise in splanchnoptosis, gastroptosis, paresis of the muscular layer, reflexly – when obstruction to the movement of the chyme toward the pyloric end of the stomach appear locally (neoplasm, scars), infectious diseases of the gastrointestinal tract (typhus, dysentery, etc.), action of psychic factors (various emotions).

Gastric hypertonia and hypotonia are usually manifested in increased or diminished ability of the stomach to claps and compress the food masses (peristola) and in disturbances of digestion.

Changes in gastric peristalsis are manifested in hyperkinesis and hypokinesis.

Hyperkinesis, or so-called **peristaltic rush**, is mainly due to neurosis, irritation of the vagus nerve, tabetic crises (in tabes dorsalis), irritant food, reception of alcohol, action of lactic acid, histamine, insulin, choline substances, pylorospasm, pylorostenosis, hyperacidity, ulcer disease. As far as hyperkinesis is combined with increased gastric secretion and acidity it leads to pylorospasm and slowing in evacuation of the stomach contents.

Hypokinesis is observed in gastric atonia, disorders in the nervus vagus, gastritis and perigastritis, calloused ulcer, cachexia, gastroenteroanastomosis and leads to slowing in evacuations.

Disorders of Evacuation

Evacuation (movement of the chyme towards the duodenum) mainly depends on the motor activity of the pylorus.

Accelerated evacuation of the stomach contents is in most cases due to decreased acidity of gastric juice (as the pylorus is opened owing to rapid neutralisation of the gastric contents inbeginning of the duodenum), tumours and inflammatory processes in the pylorus which disturb its contractility, rapid emptying of the duodenum. As a result, food digestion is disturbed.

Slowing evacuation is observed more commonly. Here the most important part is played by mechanical obstructions to movement of food (stenosis, tumours, scars, and compression), pylorospasm due to increased acidity, spasm of the stomach or pylorus (reflex, in ulcer of the pylorus, disturbed vegetative regulation).

Stagnation of food in the stomach leads to fermentation and putrefaction in the stomach, dehydration and alkalosis.

ACUTE GASTRITIS

Acute gastritis is a term covering a broad spectrum of entities that induce inflammatory changes in the gastric mucosa. Different etiologies share the same general clinical presentation. However, they differ in their unique histologic characteristics. Inflammation may involve the entire stomach (e.g, pangastritis) or an area of the stomach (e.g, antral gastritis). Acute gastritis can be broken down into 2 categories: erosive (e.g, superficial erosions, deep erosions, hemorrhagic erosions) and nonerosive (generally caused by Helicobacter pylori).

No correlation exists between microscopic inflammation (histologic gastritis) and the presence of gastric symptoms (e.g, abdominal pain, nausea, vomiting). In fact, most patients with histologic evidence of acute gastritis (inflammation) are asymptomatic. The diagnosis is usually obtained during endoscopy performed for other reasons. Acute gastritis may present with an array of symptoms, the most common being nondescript epigastric discomfort. Other symptoms include nausea, vomiting, loss of appetite, belching, and bloating. Occasionally, acute abdominal pain can be a presenting symptom. This is the case in phlegmonous gastritis (gangrene of the stomach) where severe abdominal pain accompanied by nausea and vomiting of potentially purulent gastric contents can be the presenting symptoms. Fever, chills, and hiccups also may be present.

Pathophysiology. Acute gastritis has a number of causes, including certain drugs; alcohol; bile; ischemia; bacterial, viral, and fungal infections; acute stress (shock); radiation; allergy and food poisoning; and direct trauma. The common mechanism of injury is an imbalance between the aggressive and the defensive factors that maintain the integrity of the gastric lining (mucosa). Acute erosive gastritis can result from the exposure to a variety of agents or factors. This is referred to as reactive gastritis. These agents/factors include nonsteroidal anti-inflammatory medications (NSAIDs), alcohol, cocaine, stress, radiation, bile reflux, and ischemia. The gastric mucosa exhibits hemorrhages, erosions, and ulcers. NSAIDs, such as aspirin, ibuprofen, and naproxen, are the most common agents associated with acute erosive gastritis. This results from oral or systemic administration of these agents either in therapeutic doses or in supratherapeutic doses. Because of gravity, the inciting agents lie on the greater curvature of the stomach. This partly explains the development of acute gastritis distally on or near the greater curvature of the stomach in the case of orally administered NSAIDs. However, the major mechanism of injury is the reduction in prostaglandin synthesis. Prostaglandins are chemicals responsible for maintaining mechanisms that result in the protection of the mucosa from the injurious effects of the gastric acid. Long-term effects of such ingestions can include fibrosis and stricture.

Bacterial infection is another cause of acute gastritis. The corkscrew-shaped bacterium calledH pylori is the most common cause of gastritis. Complications result from a chronic infection rather than from an acute infection. Prevalence of **H. pylori** in otherwise healthy individuals varies depending on age, socioeconomic class, and country of origin. The infection is usually acquired in childhood. In the Western world, the number of people infected with **H. pylori** increases with age. Evidence of **H. pylori** infection can be found in 20 % of individuals younger than 40 years and in 50 % of individuals older than 60 years. H pylori gastritis typically starts as an acute gastritis in the antrum, causing intense inflammation, and over time, it may extend to involve the entire gastric mucosa resulting in chronic gastritis.

Acute gastritis encountered with **H. pylori**is usually asymptomatic. The bacterium imbeds itself in the mucous layer, a protective layer that coats the gastric mucosa. It protects itself from the acidity of the stomach through the production of large amounts of urease, an enzyme that catalyzes

the breakdown of urea to the alkaline ammonia and carbon dioxide. The alkaline ammonia neutralizes the gastric acid in the immediate vicinity of the bacterium conferring protection.

H. pylori also has flagella that enable it to move and help it to penetrate the mucous layer so that it comes into contact with gastric epithelial cells. It also has several adhesions that help it to adhere to these cells. It produces inflammation by activating a number of toxins and enzymes that activate IL-8, which eventually attracts polymorphs and monocytes that cause acute gastritis.

Antigen-presenting cells activate lymphocytes and other mononuclear cells that lead to chronic superficial gastritis. The infection is established within a few weeks after the primary exposure to **H. pylori**. It produces inflammation via the production of a number of toxins and enzymes. The intense inflammation can result in the loss of gastric glands responsible for the production of acid. This is referred to asatrophic gastritis. Consequently, gastric acid production drops. The virulence genotype of the microbe is an important determinant for the severity of the gastritis and the formation of intestinal metaplasia, the transformation of gastric epithelium. This transformation can lead to gastric cancer. Reactive gastropathy is the second most common diagnosis made on gastric biopsy specimens after **H. pylori** gastritis. This entity is believed to be secondary to bile reflux and was originally reported after partial gastrectomy (Billroth I or II). It is now considered to represent a nonspecific response to a variety of other gastric irritants.

Helicobacter heilmanii is a gram-negative, tightly spiraled, helical-shaped organism with 5–7 turns. The prevalence of **H. heilmanii** is extremely low (0.25–1.5 %). The source of H heilmanii infection is unclear, but animal contact is thought to be the means of transmission. Tuberculosis is a rare cause of gastritis, but an increasing number of cases have developed because of patients who are immunocompromised. Gastritis caused by tuberculosis is generally associated with pulmonary or disseminated disease.

Secondary syphilis of the stomach is a rare cause of gastritis.

Viral infections can cause gastritis. Cytomegalovirus (CMV) is a common viral cause of gastritis. It is usually encountered in individuals who are immunocompromised, including those with cancer, immunosuppression, transplants, and AIDS. Gastric involvement can be localized or diffuse.

Fungal infections that cause gastritis include **Candida albicans** and histoplasmosis. Gastric phycomycosis is another rare lethal fungal infection. The common predisposing factor is immunosuppression. **C. albicans** rarely involves the gastric mucosa. When isolated in the stomach, the most common locations tend to be within a gastric ulcer or an erosion bed. It is generally of little consequence. Disseminated histoplasmosis can involve the stomach. The usual presenting clinical feature is bleeding from gastric ulcers or erosions on giant gastric folds.

Parasitic infections are rare causes of gastritis. Anisakidosis is caused by a nematode that embeds itself in the gastric mucosa along the greater curvature. Anisakidosis is acquired by eating contaminated sushi and other types of contaminated raw fish. It often causes severe abdominal pain that subsides within a few days. Microscopic evidence of acute gastritis can be seen in patients with Crohn disease, though clinical manifestations are rare (occurring in only about 2–7 % of patients with Crohn disease). Focally enhancing gastritis is now recognized as a condition seen in both Crohn desease and ulcerative colitis.

Eosinophilic gastritis is often found in conjunction with eosinophilic gastroenteritisbut can be associated with various disorders, including food allergies (e.g, cow milk, soy protein), collagen vascular diseases, parasitic infections, gastric cancer, lymphoma, Crohn disease, vasculitis, drug allergies, and **H. pylori** infections. An eosinophilic infiltrate is seen involving the gastric wall or epithelium.

CHRONIC GASTRITIS

Chronic gastritis is a histopathologic entity characterized by chronic inflammation of the stomach mucosa. Gastritides can be classified on the basis of the underlying cause (e.g, Helicobacter pylori,bile reflux, nonsteroidal anti-inflammatory drugs [NSAIDs], autoimmunity, or allergic response) and the histopathologic pattern, which may suggest the cause and the likely clinical course (e.g, H pylori – associated multifocal atrophic gastritis).

Other classifications are based on the endoscopic appearance of the gastric mucosa (e.g, varioliform gastritis). Although some gastropathies, such as those associated with NSAID intake, exhibit minimal inflammation, these entities are discussed in this article because they are frequently included in the differential diagnosis of chronic gastritis.

Chemical or reactive gastritis is caused by injury to the gastric mucosa resulting from reflux of bile and pancreatic secretions into the stomach, but it can also be caused by exogenous substances, including NSAIDs, acetylsalicylic acid, chemotherapeutic agents, and alcohol. These chemicals cause epithelial damage, erosions, and ulcers that are followed by regenerative hyperplasia detectable as foveolar hyperplasia, and damage to capillaries, with mucosal edema, hemorrhage, and increased smooth muscle in the lamina propria.

H. pylori gastritis is a primary infection of the stomach and is the most frequent cause of chronic gastritis. Cases of histologically documented chronic gastritis are diagnosed as chronic gastritis of undetermined etiology or gastritis of undetermined type when none of the findings reflect any of the described patterns of gastritis and a specific cause cannot be identified.

Etiology. Chronic gastritis may be caused by either infectious or noninfectious conditions. Infectious forms of gastritis include the following:

1. Chronic gastritis caused by **H. pylori** infection – This is the most common cause of gastritis.
2. Gastritis caused by Helicobacter heilmannii infection.
3. Granulomatous gastritis associated with gastric infections in mycobacteriosis, syphilis, histoplasmosis, mucormycosis, South American blastomycosis, anisakiasis, or anisakidosis.
4. Chronic gastritis associated with parasitic infections –Strongyloidesspecies, schistosomiasis, orDiphyllobothrium latum.
5. Gastritis caused by viral (e.g, CMV or herpesvirus) infection.

Non-infectious forms of gastritis include the following:

1. Autoimmune gastritis.
2. Chemical gastropathy, usually related to chronic bile reflux or NSAID and aspirin intake.
4. Uremic gastropathy.
5. Chronic non-infectious granulomatous gastritis – This may be associated with Crohn disease, sarcoidosis,Wegener granulomatosis, foreign bodies, cocaine use, isolated granulomatous gastritis, chronic granulomatous disease of childhood, eosinophilic granuloma, allergic granulomatosis and vasculitis, plasma cell granulomas, rheumatoid nodules, tumoral amyloidosis and granulomas associated with gastric carcinoma, gastric lymphoma, or Langerhans cell histiocytosis:

1) Lymphocytic gastritis, including gastritis associated with celiac disease (also called collagenous gastritis);
2) eosinophilic gastritis;
3) radiation injury to the stomach;
4) graft-versus-host disease (GVHD);
5) ischemic gastritis;
6) gastritis secondary to drug therapy;
7) some patients have chronic gastritis of undetermined etiology or gastritis of undetermined type (e.g, autistic gastritis).

Pathophysiology. The pathophysiology of chronic gastritis complicating a systemic disease, such as hepatic cirrhosis, uremia, or another infection, is described in the articles specifically dealing with these diseases. The pathogenesis of the most common forms of gastritis is described below.

H pylori –**associated chronic gastritis**

H pylori is a gram-negative rod that has the ability to colonize and infect the stomach. The bacteria survive within the mucous layer that covers the gastric surface epithelium and the upper portions of the gastric foveolae. The infection is usually acquired during childhood. Once the bacteria get into the body, passes through the mucous layer, and becomes established at the luminal surface of the stomach, an intense inflammatory response of the underlying tissue develops.

Interaction of *H pylori* with the surface mucosa results in the release of interleukin (IL)-8, which leads to recruitment of PMNs and may start the entire inflammatory process. Gastric epithelial cells express class II molecules, which may increase the inflammatory response by presenting *H pylori* antigens, leading to further cytokine release and more inflammation. High levels of cytokines, particularly tumor necrosis factor-α (TNF-α) and multiple interleukins (e.g, IL-6, IL-8, IL-10), are detected in the gastric mucosa of patients with *H pylori* gastritis.

Leukotriene levels are also quite elevated, especially the level of leukotriene B4, which is synthesized by host neutrophils and is cytotoxic to gastric epithelium. This inflammatory response leads to functional changes in the stomach, depending on the areas of the stomach involved. When inflammation affects the gastric corpus, parietal cells are inhibited, leading to reduced acid secretion. Continued inflammation results in loss of parietal cells, and the reduction in acid secretion becomes permanent.

Antral inflammation alters the interplay between gastrin and somatostatin secretion, affecting G cells (gastrin-secreting cells) and D cells (somatostatin-secreting cells), respectively. Specifically, gastrin secretion is abnormal in individuals who are infected with *H pylori*,with an exaggerated meal-stimulated release of gastrin being the most prominent abnormality.

When the infection is cured, neutrophil infiltration of the tissue quickly resolves, with slower resolution of the chronic inflammatory cells. Paralleling the slow resolution of the monocytic infiltrates, meal-stimulated gastrin secretion returns to normal.

Various strains of *H pylori* exhibit differences in virulence factors, and these differences influence the clinical outcome of H. pylori infection. People infected with *H pylori* strains that secrete the vacuolating toxin A (vac A) are more likely to develop peptic ulcers than people infected with strains that do not secrete this toxin.

H pylori - associated chronic gastritis progresses according to the following 2 main topog-raphic patterns, which have different clinical consequences:

Antral predominant gastritis – This is characterized by inflammation and is mostly limited to the antrum; individuals with peptic ulcers usually demonstrate this pattern

Multifocal atrophic gastritis – This is characterized by involvement of the corpus and gastric antrum with progressive development of gastric atrophy (loss of the gastric glands) and partial replacement of gastric glands by an intestinal-type epithelium (intestinal metaplasia); individuals who develop gastric carcinoma and gastric ulcers usually demonstrate this pattern

Some individuals who carry additional risk factors may develop peptic ulcers, gastric mucosa–associated lymphoid tissue (MALT) lymphomas, or gastric adenocarcinomas.

An increased duodenal acid load may precipitate and wash out bile salts, which normally inhibit the growth of *H pylori*. Progressive damage to the duodenum promotes gastric foveolar metaplasia, resulting in sites for *H pylori* growth and more inflammation. This cycle renders the duodenal bulb increasingly unable to neutralize acid entering from the stomach until changes in bulb structure and function are sufficient for an ulcer to develop. *H pylori* can survive in areas of gastric metaplasia in the duodenum, contributing to the development of peptic ulcers.

Another complication of *H pylori* gastritis is the development of gastric carcinomas, especially in individuals who develop extensive atrophy and intestinal metaplasia of the gastric mucosa. Although the relationship between *H pylori* and gastritis is constant, only a small proportion of individuals infected with *H pylori* develop gastric cancer. The incidence of gastric cancer usually parallels the incidence of *H pylori* infection in countries with a high incidence of gastric cancer and is consistent with *H pylori* being the cause of the precursor lesion, chronic atrophic gastritis.

Persistence of the organisms and associated inflammation during long-standing infection is likely to permit the accumulation of mutations in the gastric epithelial cells' genome, leading to an increased risk of malignant transformation and progression to adenocarcinoma. Studies have provided evidence of the accumulation of mutations in the gastric epithelium secondary to oxidative DNA damage associated with chronic inflammatory byproducts and secondary to deficiency of DNA repair induced by chronic bacterial infection.

Although the role of *H pylori* in peptic ulcer disease is well-established, the clinical role of the infection in nonulcer dyspepsia remains highly controversial. *H pylori* eradication may be beneficial for symptom relief in a small proportion of patients, but routine H. pylori testing and treatment in nonulcer dyspepsia are not currently widely accepted. Therefore, *H pylori* eradication strategies in patients with nonulcer dyspepsia must be considered on a patient-by-patient basis.

GASTRITIS IN PATIENTS WHO ARE IMMUNOSUPPRESSED

Cytomegalovirus (CMV) infection of the stomach is observed in patients with underlying immunosuppression. Histologically, typical intranuclear eosinophilic inclusions and, occasionally, smaller intracytoplasmic inclusions are found. A patchy, mild inflammatory infiltrate is observed in the lamina propria. Viral inclusions are present in gastric epithelial cells and in endothelial or mesenchymal cells in the lamina propria. Severe necrosis may result in ulceration. Herpes simplex causes basophilic intranuclear inclusions in epithelial cells. Mycobacterial infections involvingMycobacterium avium-intracellulareare characterized by diffuse infiltration of the lamina propria by histiocytes, which rarely form granulomas.

Autoimmune gastritis. Autoimmune gastritis is associated with serum antiparietal and anti–intrinsic factor (IF) antibodies. The gastric corpus undergoes progressive atrophy, IF deficiency occurs, and patients may developanemia.

The development of chronic gastritislimited to corpus-fundus mucosa and marked diffuse atrophy of parietal and chief cells characterize autoimmune atrophic gastritis. Autoimmune gastritis is associated with serum antiparietal and anti-IF antibodies that cause IF deficiency, which, in turn, causes decreased cobalamin and, eventually, pernicious anemia in some patients. Autoantibodies are directed against at least 3 antigens, including IF, cytoplasmic (microsomal-canalicular), and plasma membrane antigens. Two types of IF antibodies are detected (types I and II). Type I IF antibodies block the IF-cobalamin binding site, thus preventing the uptake of vitamin B_{12}. Cell-mediated immunity also contributes to the disease. T lymphocytes infiltrate the gastric mucosa and contribute to epithelial cell destruction and resulting gastric atrophy.

Chronic reactive chemical gastropathy. Chronic reactive chemical gastritis is associated with long-term intake of aspirin or NSAIDs. It also develops when bile-containing intestinal contents reflux into the stomach. Although bile reflux may occur in the intact stomach, most of the features associated with bile reflux are typically found in patients with partial gastrectomy, in whom the lesions develop near the surgical stoma. The mechanisms through which bile alters the gastric epithelium involve the effects of several bile constituents. Both lysolecithin and bile acids can disrupt the gastric mucous barrier, allowing the back diffusion of positive hydrogen ions and resulting in cellular injury. Pancreatic juice enhances epithelial injury in addition to bile acids. In contrast to other chronic gastropathies, minimal inflammation of the gastric mucosa typically occurs in chemical gastropathy.

Chronic noninfectious granulomatous gastritis. Noninfectious diseases are the usual cause of gastric granulomas; they include Crohn disease and isolated granulomatous gastritis. Crohn disease demonstrates gastric involvement in approximately 33 % of the cases. Granulomas have also been described in association with gastric malignancies, including carcinoma and malignant lymphoma. Sarcoidlike granulomas may be observed in people who use cocaine, and foreign material is occasionally observed in the granuloma.

Lymphocytic gastritis. Lymphocytic gastritis is a type of chronic gastritis characterized by dense infiltration of the surface and foveolar epithelium by T lymphocytes and associated chronic infiltrates in the lamina propria. Because its histopathology is similar to that of celiacia, lymphocytic gastritis has been proposed to result from intraluminal antigens. High anti– *H pylori* antibody titers have been found in patients with lymphocytic gastritis, and in limited studies, the inflammation disappeared after *H pylori* was eradicated. However, many patients with lymphocytic gastritis are serologically negative for *H pylori.* A number of cases may develop secondary to intolerance to gluten and drugs such as ticlopidine.

Eosinophilic gastritis Large numbers of eosinophils may be observed with parasitic infections such as those caused by *Eustoma rotundatum* and *Anisakis marina*. Eosinophilic gastritis can be part of the spectrum of gastroenteritis Although the gastric antrum is commonly affected and can cause gastric outlet obstruction, this condition can affect any segment of the GI tract and can be segmental. Patients frequently have peripheral blood eosinophilia. In some cases, especially in children, eosinophilic gastroenteritis can result from food allergy, usually to milk or soy protein. Eosinophilic gastroenteritis can also be found in some patients with connective tissue disorders, including scleroderma, polymyositis, and dermatomyositis.

Radiation gastritis Small doses of radiation (up to 15 Gy) cause reversible mucosal damage, whereas higher doses cause irreversible damage with atrophy and ischemic-related ulceration. Reversible changes consist of degenerative changes in epithelial cells and nonspecific chronic inflammatory infiltrate in the lamina propria. Higher amounts of radiation cause permanent mucosal damage, with atrophy of fundic glands, mucosal erosions, and capillary hemorrhage. Associated submucosal endarteritis results in mucosal ischemia and secondary ulcer development.

Ischemic gastritis Ischemic gastritis is believed to result from atherosclerotic thrombi arising from the celiac and superior mesenteric arteries.

PEPTIC ULCER DISEASE

Gastric and duodenal ulcers usually cannot be differentiated based on history alone, although some findings may be suggestive. Epigastric pain is the most common symptom of both gastric and duodenal ulcers. It is characterized by a gnawing or burning sensation and occurs after meals—classically, shortly after meals with gastric ulcer and 2–3 hours afterward with duodenal ulcer. In uncomplicated peptic ulcer disease (PUD), the clinical findings are few and nonspecific. “Alarm features" that warrant prompt gastroenterology referral include bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia or odynophagia, recurrent vomiting, and family history of GI cancer. Patients with perforated PUD usually present with a sudden onset of severe, sharp abdominal pain. In most patients with uncomplicated PUD, routine laboratory tests usually are not helpful; instead, documentation of PUD depends on radiographic and endoscopic confirmation. Testing for *H pylori* infection is essential in all patients with peptic ulcers. Rapid urease tests are considered the endoscopic diagnostic test of choice. Of noninvasive tests, fecal antigen testing is more accurate than antibody testing and is less expensive than urea breath tests. A fasting serum gastrin level should be obtained in certain cases to screen for Zollinger-Ellison syndrome.

Upper GI endoscopy is preferred diagnostic test in the evaluation of patients with suspected PUD. Endoscopy gives an opportunity to visualize the ulcer, to determine the presence and degree of active bleeding, and to attempt hemostasis by direct measures, if required. Endoscopy should be performed early in patients older than 45–50 years and in patients with associated so-called alarm features. Most patients with PUD are treated successfully with cure of *H pylori* infection and/or avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs), along with the appropriate use of antisecretory therapy. In the United States, the recommended primary therapy for *H pylori* infection is proton pump inhibitor (PPI)–based triple therapy. These regimens result in a cure of infection and ulcer healing in approximately 85–90 % of cases. Ulcers can recur in the absence of successful *H pylori* eradication.

Etiology. Peptic ulcer disease (PUD) may be due to any of the following:

1. H pyloriinfection
2. Drugs
3. Lifestyle factors
4. Severe physiologic stress
5. Hypersecretory states (uncommon)
6. Genetic factors

Drugs. NSAID use is a common cause of PUD. These drugs disrupt the mucosal permeability barrier, rendering the mucosa vulnerable to injury. As many as 30 % of adults taking NSAIDs have GI adverse effects. Factors associated with an increased risk of duodenal ulcers in the setting of NSAID use include history of previous peptic ulcer disease, advanced age, female sex, high doses or combinations of NSAIDs, long-term NSAID use, concomitant use of anticoagulants, and severe comorbid illnesses.

Hypersecretory states (uncommon)

The following are among hypersecretory states that may, uncommonly, cause PUD:

1. Gastrinoma (Zollinger-Ellison syndrome) or multiple endocrine neoplasia type I (MEN-I).
2. Antral G cell hyperplasia.
3. Systemic mastocytosis.
4. Basophilic leukemias.
5. Cystic fibrosis.
6. Short bowel syndrome.
7. Hyperparathyroidism.

Physiologic factors. In up to one third of patients with duodenal ulcers, basal acid output (BAO) and maximal acid output (MAO) are increased. In one study, increased BAO was associated with an odds ratio [OR] of up to 3.5, and increased MAO was associated with an OR of up to 7 for the development of duodenal ulcers. Individuals at especially high risk are those with a BAO greater than 15 mEq/h. The increased BAO may reflect the fact that in a significant proportion of patients with duodenal ulcers, the parietal cell mass is increased to nearly twice that of the reference range. In addition to the increased gastric and duodenal acidity observed in some patients with duodenal ulcers, accelerated gastric emptying is often present. This acceleration leads to a high acid load delivered to the first part of the duodenum, where 95 % of all duodenal ulcers are located. Acidification of the duodenum leads to gastric metaplasia, which indicates replacement of duodenal villous cells with cells that share morphologic and secretory characteristics of gastric epithelium. Gastric metaplasia may create an environment that is well suited to colonization by *H pylori*.

Genetics. More than 20 % of patients have a family history of duodenal ulcers, compared with only 5-10 % in the control groups. In addition, weak associations have been observed between duodenal ulcers and blood type O. Furthermore, patients who do not secrete ABO antigens in their saliva and gastric juices are known to be at higher risk. The reason for these apparent genetic associations is unclear. A rare genetic association exists between familial hyperpepsinogenemia type I (a genetic phenotype leading to enhanced secretion of pepsin) and duodenal ulcers. However, *H pylori* can increase pepsin secretion, and a retrospective analysis of the sera of one family studied before the discovery of *H pylori* revealed that their high pepsin levels were more likely related to *H pylori* infection.

Additional etiologic factors

Any of the following may be associated with PUD:

1. Hepatic cirrhosis
2. Chronic obstructive pulmonary disease
3. Allergic gastritis and eosinophilic gastritis
4. Uremic gastropathy
5. Henoch-Schönlein gastritis
6. Corrosive gastropathy
7. Bile gastropathy
8. Autoimmune disease
9. Crohn disease
10. Other granulomatous gastritides
11. Phlegmonous gastritis and emphysematous gastritis

12. Other infections, including Epstein-Barr virus, HIV, Helicobacter heilmannii, herpes simplex. Chemotherapeutic agents, such as 5-fluorouracil (5-FU), methotrexate (MTX), and cyclophosphamide

Pathophysiology. Peptic ulcers are defects in the gastric or duodenal mucosa that extend through the muscularis mucosa. The epithelial cells of the stomach and duodenum secrete mucus in response to irritation of the epithelial lining and as a result of cholinergic stimulation. The superficial portion of the gastric and duodenal mucosa exists in the form of a gel layer, which is impermeable to acid and pepsin. Other gastric and duodenal cells secrete bicarbonate, which aids in buffering acid that lies near the mucosa. Prostaglandins of the E type (PGE) have an important protective role, because PGE increases the production of both bicarbonate and the mucous layer. In the event of acid and pepsin entering the epithelial cells, additional mechanisms are in place to reduce injury. Within the epithelial cells, ion pumps in the basolateral cell membrane help to regulate intracellular pH by removing excess hydrogen ions. Through the process of restitution, healthy cells migrate to the site of injury. Mucosal blood flow removes acid that diffuses through the injured mucosa and provides bicarbonate to the surface epithelial cells.

Under normal conditions, a physiologic balance exists between gastric acid secretion and gastroduodenal mucosal defense. Mucosal injury and, thus, peptic ulcer occur when the balance between the aggressive factors and the defensive mechanisms is disrupted. Aggressive factors, such as NSAIDs, *H pylori* infection, alcohol, bile salts, acid, and pepsin, can alter the mucosal defense by allowing back diffusion of hydrogen ions and subsequent epithelial cell injury. The defensive mechanisms include tight intercellular junctions, mucus, mucosal blood flow, cellular restitution, and epithelial renewal.

The gram-negative spirochete *H pylori* was first linked to gastritis in 1983. Since then, further study of *H pylori* has revealed that it is a major part of the triad, which includes acid and pepsin, that contributes to primary peptic ulcer disease. The unique microbiologic characteristics of this organism, such as urease production, allows it to alkalinize its microenvironment and survive for years in the hostile acidic environment of the stomach, where it causes mucosal inflammation and, in some individuals, worsens the severity of peptic ulcer disease.

When *H pylori* colonizes the gastric mucosa, inflammation usually results. The causal association between *H pylori* gastritis and duodenal ulceration is now well established in the adult and pediatric literature. In patients infected with *H pylori*, high levels of gastrin and pepsinogen and reduced levels of somatostatin have been measured. In infected patients, exposure of the duodenum to acid is increased. Virulence factors produced by *H pylori*, including urease, catalase, vacuolating cytotoxin, and lipopolysaccharide, are well described.

Most patients with duodenal ulcers have impaired duodenal bicarbonate secretion, which has also proven to be caused by *H pylori* because its eradication reverses the defect. The combination of increased gastric acid secretion and reduced duodenal bicarbonate secretion lowers the pH in the duodenum, which promotes the development of gastric metaplasia (i.e., the presence of gastric epithelium in the first portion of the duodenum). *H pylori* infection in areas of gastric metaplasia induces duodenitis and enhances the susceptibility to acid injury, thereby predisposing to duodenal ulcers.

DISORDERS OF INTESTINAL DIGESTION

The disorders of intestinal digestion include those of secretion, motorium, excretion, absorption and intestinal fermentation and putrefaction (changes in the microbial flora).

Secretory Dysfunction of the Intestines

Secretory disorders in the intestinum depend on disturbed secretion of bile, pancreatic and intestinal juices. Causes of absence or insufficient delivery of bile to the duodenum and appropriate disturbances of intestinal digestion will be considered in the next chapter.

Digestive disorders associated with an absence or deficiency of pancreatic juice may be observed in calculi, tumours, inflammation, atrophy, disturbed innervation, etc.

Disorders in the secretion of bile and pancreatic juice **are manifested** by disturbed cavital and membrane intestinal digestion and absorption of fats (steatorrhea), proteins, carbohydrates, nucleic acids, vitamins.

Disorders in membrane digestion may be also connected with disturbed secretion **of intestinal juice**. Its causes are:

1) reduced number of piles and micropiles of enterocytes per unit of surface which is observed in cholera, enteritis, intensive neomycin or tetracycline therapy, etc;

2) hereditary and acquired insufficiency of the key enzymes of the membrane digestion (for example, failure of lactase to be delivered to the intestine prevents assimilation of milk sugar);

3) decreased absorptive ability of cellular membranes of the intestinum to pancreatic enzymes (for example, to pancreatic amylase in children after gastric resection);

4) disturbances of intestinal peristalsis.

Motor Dysfunction of the Intestines

It consists in excessive or diminished peristalsis.

Excessive peristalsis arises as a result of inflammatory processes in the intestinal mucosa (enteritis, colitis), mechanical or chemical irritations by coarse and barely digestible parts of food, accumulated decomposition products, acids and toxic substances, dysfunction of the nervous system (for example, in strong emotions – fear – and in hypersensitivity of the receptor apparatus. It results in diarrhea – increased frequency of the stool. **Frequent diarrheas lead** to deep disturbances of intestinal secretion, digestion, absorption, insufficiency of digestion, dehydration, hypovolemia, collapse, starvation, general nutritional disturbances.

Diminished peristalsis causes constipation which may be atonic and spastic. Its causes are: inherent spasms of intestines in Hirschsprung's disease, acquired spasms in plumbum poisoning, psychic influences, atonia of the intestinum in quantitative and qualitative food insufficiency – deficit of cellulose, potassium, calcium, vitamin B_1, etc., stimulation of the nervus vagus, action of glucagon, etc. Constipation leads to putrefaction, accumulation of gases, intoxication, meteorism, ileus (intestinal obstruction).

Disorders in Defecation

Defecation is essentially a reflex act.

Delay of defecation is observed in contraction of the sphincters, levator ani muscles and a number of voluntary muscles of the perineum due to excitation of corresponding centres (in sacral segments of the spinal cord); in weakening of the sensory nerves in the rectum, the nerves perceiving the stimulation by fecal matter, with the result that the defecation reflex is inhibited; in diminished intestinal peristalsis or flabbiness of the abdominal muscles, as in women after child birth or in old people.

Rectal incontinence is observed in paralysis of the sphincters resulting from dysfunction of the centres, for example, in advanced age, tumours, epilepsy, fear; in trauma of the spinal chord, severe encephalomyelitis, increased sensitivity of the mucous membrane to pressure of fecal matter (as in inflammation of the mucosa in the region of the sphincters), as a result the urge to defecate increases.

Disorders in the Absorptive and Excretory Functions of the Intestines

Disorders in absorption are observed in disorders of secretory and motor activity of various departments of digestive system, especially in insufficiency of bile and pancreatic juices, cavitive digestion in the stomach and intestines; in action of the same factors which disturb membrane digestion; in diarrheas, disorders of intestinal hemo- and lymphocirculation, inflammation and atrophy of the mucosa. They result in death and sensitisation by proteins.

Disturbances in excretion are observed in organic and functional changes of the intestinal wall and result in intoxication. Expressed excretion of water results in diarrhea.

Diarrhea

Diarrhea is the frequent passage of loose, watery, soft stools with or without abdominal bloating, pressure, and cramps commonly referred to as gas. Diarrhea can come on suddenly, run its course, and be helped with home care to prevent complications such as dehydration.

Diarrhea is one of the most common illnesses in all age groups and ranks along with the common cold as a main cause of lost days of work or school. People of all ages can suffer from diarrhea, and the average adult has one episode of acute diarrhea per year, and young children average two acute episodes per year. Diarrhea and related complications can cause severe illness. The most significant cause of severe illness is loss of water and electrolytes. In diarrhea, fluid passes out of the body before it can be absorbed by the intestines. When the ability to drink fluids fast enough to compensate for the water loss because of diarrhea is impaired, dehydration can result. Most deaths from diarrhea occur in the very young and the elderly whose health may be put at risk from a moderate amount of dehydration.

Diarrhea can be further defined in the following ways:

1) chronic diarrhea is the presence of loose or liquid stools for over two weeks;

2) acute enteritis is inflammation of the intestine;

3) gastroenteritis (stomach flu) is diarrhea associated with nausea and vomiting; or

4) dysentery is diarrhea that contains blood, pus, or mucus.

Causes of Viral infections. Most cases of diarrhea are typically associated with mild-to-moderate symptoms with frequent, watery bowel movements, abdominal cramps, and a low-grade fever. Viral diarrhea generally lasts approximately 3 to 7 days.

The following are the common causes of diarrhea caused by viral infections:

1) rotavirus is a common cause of diarrhea in infants;

2) norovirus is the most common cause of epidemics of diarrhea among adults and schoolage children (for example, cruise ship infection, schools, nursing home);

3) adenovirus infections are common in all age groups.

Bacterial infections cause the more serious cases of diarrhea. Typically, infection with bacteria occurs from contaminated food or drinks (food poisoning). Bacterial infections also cause severe symptoms, often with vomiting, fever, and severe abdominal cramps orabdominal pain. Bowel movements occur frequently and may be watery.

The following are examples of diarrhea caused by bacterial infections: In more serious cases, the stool may contain mucus, pus, orblood. Most of these infections are associated with local outbreaks of disease. Family members or others eating the same food may have similar illnesses. Foreign travelis a common way for a person to contracttraveler's diarrhea.

Campylobacter salmonellae, and shigella organisms are the most common causes of bacterial diarrhea. Less common causes are Escherichia coli (commonly called E coli) Yersinia, and listeria.

Parasites cause infection of the digestive system by the use of contaminated water. Common parasitic causes of diarrhea include Giardia lamblia, Entamoeba histolytica, and Cryptosporidium.

Intestinal disorders or diseases including inflammatory bowel disease, irritable bowel syndrome(IBS), diverticulitis, microscopic colitis, and celiac disease can cause diarrhea.

Reaction to certain medications can cause diarrhea. Common medications include antibiotics, blood pressure medications, cancer drugs, gout medications, weight loss drugs, and antacids (especially those containing magnesium).

Intolerance to foods such as artificial sweeteners and lactose (sugar in milk) can cause diarrhea.

Symptoms. Watery, liquid stools. The stools may be any color. The passage ofred stools suggests intestinal bleedingand could be a sign of a more severe infection. The passage of thick, tarry black stools suggests significant bleeding in the stomach or upper portions of the intestine and is not usually caused by acute infections.

Abdominal cramps. Occasionally diarrhea is accompanied with mild-to-moderate abdominal pain. Severe abdominal or stomach pain is not common and, if present, may suggest more severe disease.

Fever. A high fever is not common. If present, the affected person may have a more severe illness than acute diarrhea.

Dehydration. If diarrhea leads to dehydration, it is a sign of potentially serious disease.

Signs and symptoms of dehydration include: Adults may be very thirsty and have a dry mouth. The skin of older people may appear to be loose. The elderly may also become very sleepy or have behavioral changes and confusion when dehydrated.

Dehydrated infants and children may have sunken eyes, dry mouths, and urinate less frequently than usual. They may appear very sleepy or may refuse to eat or drink.

Diarrhea Diagnosis. Blood tests are sometimes necessary for patients with other medical problems or with severe disease.

Constipation

Constipation is difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation. Many people incorrectly believe that daily defecation is necessary and complain of constipation if stools occur less frequently. Others are concerned with the appearance (size, shape, color) or consistency of stools. Constipation is blamed for many complaints (abdominal pain, nausea, fatigue, anorexia) that are actually symptoms of an underlying problem (eg, irritable bowel syndrome [IBS], depression). Patients should not expect all symptoms to be relieved by a daily bowel movement, and measures to aid bowel habits should be used judiciously.

Etiology. Acute constipation suggests an organic cause, whereas chronic constipation may be organic or functional (*see Table 36*). In many patients, constipation is associated with sluggish movement of stool through the colon. This delay may be due to drugs, organic conditions, or a disorder of defecatory function (i.e, pelvic floor dysfunction). Patients with disordered defecation do not generate adequate rectal propulsive forces, do not relax the puborectalis and the external anal sphincter during defecation, or both. Excessive straining, perhaps secondary to pelvic floor dysfunction, may contribute to anorectal pathology (e.g, hemorrhoids, anal fissures, and rectal prolapse) and possibly even to syncope. Fecal impaction, which may cause or develop from constipation, is also common among elderly patients, particularly with prolonged bed rest or decreased physical activity.

Table 36

Causes of Constipation

Causes	Examples
Acute constipation*	
Bowel obstruction	Volvulus, hernia, adhesions, fecal impaction
Adynamic ileus	Peritonitis, major acute illness (eg, sepsis), head or spinal trauma, bed rest
Drugs	Anticholinergics (eg, antihistamines, antipsychotics, antiparkinsonian drugs, antispasmodics), cations (iron, aluminum, Ca, barium), opioids, Ca channel blockers, Constipation shortly after start of therapy with the drug
Chronic constipation*	
Colonic tumor	Adenocarcinoma of sigmoid colon
Metabolic disorders	Diabetes mellitus, hypothyroidism, hypocalcemia or hypercalcemia, pregnancy, uremia, porphyria
CNS disorders	Parkinson's disease, multiple sclerosis, stroke, spinal cord lesions
Periphera lNS disorders	Hirschsprung's disease, neurofibromatosis, autonomic neuropathy
Systemic disorders	Systemic sclerosis, amyloidosis, dermatomyositis, myotonic dystrophy
Functional disorders	Slow-transit constipation, irritable bowel syndrome, pelvic floor dysfunction (functional defecatory disorders)
Dietary factors	Low-fiber diet, chronic laxative abuse

Certain findings raise suspicion of a more serious etiology of chronic constipation:

1. Distended, tympanitic abdomen.
2. Vomiting.
3. Blood in stool.
4. Weight loss.
5. Severe constipation of recent onset/worsening in elderly patients.

Interpretation of findings. Certain symptoms (e.g, a sense of anorectal blockage, prolonged or difficult defecation), particularly when associated with abnormal (i.e, increased or reduced) perineal motion during simulated evacuation, suggest a defecatory disorder. A tense, distended, tympanitic abdomen, particularly when there is nausea and vomiting, suggests mechanical obstruction.

Patients with IBS typically have abdominal pain with disordered bowel habits. Chronic constipation with modest abdominal discomfort in a patient who has used laxatives for a long time suggests slow-transit constipation. Acute constipation coincident with the start of a constipating drug in patients without red flag findings suggests the drug is the cause. New-onset constipation that persists for weeks or occurs intermittently with increasing frequency or severity, in the absence of a known cause, suggests colonic tumor or other causes of partial obstruction. Excessive straining or prolonged or unsatisfactory defecation, with or without anal digitation, suggests a defecatory disorder. Patients with fecal impaction may have cramps and may pass watery mucus or fecal material around the impacted mass, mimicking diarrhea (paradoxic diarrhea).

Testing. Testing is guided by clinical presentation.

Constipation with a clear etiology (drugs, trauma, bed rest) may be treated symptomatically without further study. Patients with symptoms of bowel obstruction require flat and upright abdominal x-rays, possibly a water-soluble contrast enema to evaluate for colonic obstruction, and possibly a CT scan or barium x-ray of the small intestine. Most patients without a clear etiology should have sigmoidoscopy or colonoscopy and a laboratory evaluation (CBC, thyroid-stimulating hormone, fasting glucose, electrolytes, and Ca). Further tests are usually reserved for patients with abnormal findings on the previously mentioned tests or who do not respond to symptomatic treatment. If the primary complaint is infrequent defecation, colonic transit times should be measured with radiopaque markers or scintigraphy. If the primary complaint is difficulty with defecation, anorectal manometry and rectal balloon expulsion should be assessed.

Disorders in Fermentation and Putrefaction

Disorders in the intestinal microflora are observed in action of large doses of antibiotics, stagnation in the intestinum (atonia, meteorism, obstruction), colitis and result in development of pathogenic microbes, acceleration of putrefactive processes, formation of the intestinal poisons, autointoxication, especially in diminished barrier function of the liver and excretory ability of the kidneys; in disturbance of immunity, deficiency of vitamins and amino acids which are synthesised by the microflora; in disturbed formation of fecal matter, etc.

Crohn's disease

Crohn's (also spelled Crohn disease) disease is a chronic (slowly developing, long-term) inflammation of the digestive tract. It can affect any part of the digestive tract from the mouth to the anus but usually involves the terminal part of the small intestine, the beginning of the large intestine (cecum), and the area around the anus. The inflammation causes uncomfortable and bothersome symptoms and may produce serious damage to the digestive tract. Crohn's disease is sometimes called regional enteritis or ileitis. It and a similar condition called ulcerative colitis are referred to together as inflammatory bowel diseases. These illnesses are known for their unpredictable flares and remissions.

The inflammation usually starts in one or more areas of the mucosa that lines the inside of the intestines.

The disease may invade deeper tissues of the intestinal wall and spread to involve more areas of the bowel. Ulcers may form at the sites of the most intense inflammation. The ulcers may spread and become very large but are usually separated by areas of relatively healthy tissue with little or no inflammation. The mucosal lining of the intestines in Crohn's disease is often described as looking like a cobblestone street, with areas of ulceration separated by narrow areas of healthy tissue. The damage to the intestinal wall caused by the inflammation results in a wide variety of symptoms and complications.

The inflammation damages the lining of the intestine so that it cannot absorb nutrients, water, and fats from the food you eat. This is called malabsorption, and it can result in malnutrition, dehydration, vitamin and mineral deficiencies, gallstones, and kidney stones.

As the inflammation invades deeper into the intestinal tissues, the intestinal wall becomes thicker, narrowing the bowel lumen (the space through which food passes). The intestinal lumen may become so narrow that it becomes obstructed, so that food cannot pass through at all. This obstruction is usually intermittent, meaning that it comes and goes, and gets better with medical treatment. Eventually, however, the obstruction can become permanent. If the inflammation in one area spreads all the way through the intestinal wall, the inflamed area can stick to other organs and structures in the abdomen.

Crohn's disease can also cause problems around the anus. These may include tiny but painful cracks in the skin known as anal fissures; tunneling sores called fistulas that cause abnormal connections between the bowel and the skin; or an abscess, a pocket of inflamed or dead tissue that is usually very painful.

Sometimes fistulas can develop between the intestine and other organs and structures it is not normally connected to, such as between different parts of the bowel, the bladder, the vagina, or even the skin on the outside of the body. This is serious because the contents of the intestine can enter into these other sites, causing infection and other problems.

Crohn's disease can cause a variety of related inflammatory conditions outside of the digestive tract. The usual sites are skin, joints, mouth, eyes, liver, and bile ducts. Children with Crohn's disease may experience delayed development and stunted growth.

In the United States, the incidence (number of new cases) and prevalence (number of people who have the disease) have increased steadily during the last 50 years.

Crohn's disease is slightly more common among men than women. In general, the prevalence is higher in urban areas than in rural areas. It is also higher in higher socioeconomic classes. Crohn's disease can occur at any age, but most people newly diagnosed with Crohn's disease are aged 15–30 years. It is sometimes newly diagnosed in people aged 60–80 years.

Crohn's disease can be a debilitating illness. However, with medical treatment and other measures used to reduce the discomfort of flares, most people learn to cope with the condition. Almost everyone with Crohn's disease can live a normal life.

Causes. The exact cause of Crohn's disease remains unknown. Current theories suggest that genetics, environment, diet, blood vessel abnormalities, and/or even psychosocial factors cause Crohn's disease. Crohn's disease definitely runs in families. People who have Crohn's disease may have an inherited predisposition to abnormal immunologic response to one or more provoking factors.

Symptoms. Crohn's disease is intermittent. This means that the inflammation occurs (flares) without warning and then goes away (goes intoremission) over time. It is impossible to predict when the condition will flare, how long the flare will last, and when it will flare again. Most people feel pretty well when their disease is not active.

The most common symptoms in Crohn's disease are those related to the inflammatory damage to the digestive tract.

1) Diarrhea – Waxes and wanes; stool may contain mucus, blood, or pus

2) Pain in the abdomen – Crampy or steady; in the right lower part of the abdomen or around the belly button; often relieved temporarily by having a bowel movement

3) Bloating after eating – Less common, usually seen in cases of bowel obstruction

4) Constipation – Usually seen in cases of bowel obstruction

5) Pain or bleeding with bowel movement

6) Infection of the urinary tract or vagina – Suggests a fistula from the intestinal tract

7) General symptoms occur in some but not all cases.

8) Low-grade fevers

9) Weight loss

10) Other symptoms of Crohn's disease may be attributable to related medical conditions affecting the skin, joints, mouth, eyes, liver, and bile ducts.

PANCREAS

Acute Pancreatitis. Pancreatitis is an inflammatory process in which pancreatic enzymes autodigest the gland. The gland sometimes heals without any impairment of function or any morphologic changes; this process is known as acute pancreatitis. Pancreatitis can also recur intermittently, contributing to the functional and morphologic loss of the gland; recurrent attacks are referred to as chronic pancreatitis. Both forms of pancreatitis present in the emergency department (ED) with acute clinical findings. Recognizing patients with severe acute pancreatitis as soon as possible is critical for achieving optimal outcomes.

Once a working diagnosis of acute pancreatitis is reached, laboratory tests are obtained to support the clinical impression, to help define the etiology, and to look for complications. Diagnostic imaging is unnecessary in most cases but may be obtained when the diagnosis is in doubt, when severe pancreatitis is present, or when a given imaging study might provide specific information needed to answer a clinical question. Image-guided aspiration may be useful. Genetic testing may be considered.

Management depends largely on severity. Medical treatment of mild acute pancreatitis is relatively straightforward. Treatment of severe acute pancreatitis involves intensive care; the goals of medical management are to provide aggressive supportive care, to decrease inflammation, to limit infection or superinfection, and to identify and treat complications as appropriate. Surgical intervention (open or minimally invasive) is indicated in selected cases.

Etiology. Long-standing alcohol consumption and biliary stone disease cause most cases of acute pancreatitis, but numerous other etiologies are known. In 10–30 % of cases, the cause is unknown, though studies have suggested that as many as 70 % of cases of idiopathic pancreatitis are secondary to biliary microlithiasis.

Biliary tract disease. One of the most common causes of acute pancreatitis in most developed countries (accounting for approximately 40 % of cases) is gallstones passing into the bile duct and temporarily lodging at the sphincter of Oddi. The risk of a stone causing pancreatitis is inversely proportional to its size.

It is thought that acinar cell injury occurs secondary to increasing pancreatic duct pressures caused by obstructive biliary stones at the ampulla of Vater, although this has not been definitively proven in humans. Occult microlithiasis is probably responsible for most cases of idiopathic acute pancreatitis.

Alcohol. Alcohol use is a major cause of acute pancreatitis (accounting for at least 35 % of cases). On the cellular level, ethanol leads to intracellular accumulation of digestive enzymes and their premature activation and release. On the ductal level, it increases the permeability of ductules, allowing enzymes to reach the parenchyma and cause pancreatic damage. Ethanol increases the protein content of pancreatic juice and decreases bicarbonate levels and trypsin inhibitor concentrations. This leads to the formation of protein plugs that block pancreatic outflow. Currently, there is no universally accepted explanation for why certain alcoholics are more predisposed to developing acute pancreatitis than other alcoholics who ingest similar quantities are.

Endoscopic retrograde cholangiopancreatography

Pancreatitis occurring after endoscopic retrograde cholangiopancreatography (ERCP) is probably the third most common type (accounting for approximately 4 % of cases). Whereas retrospective surveys indicate that the risk is only 1 %, prospective studies have shown the risk to be at least 5 %. The risk of post-ERCP acute pancreatitis increases if the endoscopist is inexperienced, if the patient is thought to have sphincter of Oddi dysfunction, or if manometry is performed on the sphincter of Oddi.

Trauma. Abdominal trauma (approximately 1.5 %) causes an elevation of amylase and lipase levels in 17 % of cases and clinical pancreatitis in 5 % of cases. Pancreatic injury (see the image below) occurs more often in penetrating injuries (e.g, from knives, bullets) than in blunt abdominal trauma (e.g, from steering wheels, horses, bicycles). Blunt injury to the

abdomen or back may crush the gland across the spine, leading to a ductal injury. CT scan of abdomen in child with traumatic pancreatitis. Fluid collection adjacent to pancreas will become pseudocyst. Note that pancreas is lacerated, nearly cut in half, by force of abdominal trauma. Also, note typical location of this injury in relation to vertebral column.

Drugs. Considering the small number of patients who develop pancreatitis compared to the relatively large number who receive potentially toxic drugs, drug-induced pancreatitis is a relatively rare occurrence (accounting for approximately 2 % of cases) that is probably related to an unknown predisposition. Fortunately, drug-induced pancreatitis is usually mild. In addition, there are many drugs that have been reported to cause acute pancreatitis in isolated or sporadic cases.

Less common causes. The following causes each account for less than 1 % of cases of pancreatitis. Several infectious diseases may cause pancreatitis, especially in children. These cases of acute pancreatitis tend to be milder than cases of acute biliary or alcohol-induced pancreatitis.

Viral causes include mumps virus, coxsackievirus, cytomegalovirus (CMV), hepatitis virus, Epstein-Barr virus (EBV), echovirus, varicella-zoster virus (VZV), measles virus, and rubella virus. Bacterial causes include Mycoplasma pneumoniae, Salmonella, Campylobacter, and Mycobacterium tuberculosis. Worldwide, Ascaris is a recognized cause of pancreatitis resulting from the migration of worms in and out of the duodenal papillae. Pancreatitis has been associated with AIDS; however, this may be the result of opportunistic infections, neoplasms, lipodystrophy, or drug therapies.

Hereditary pancreatitis. Hereditary pancreatitis is an autosomal dominant gain-of-function disorder related to mutations of the cationic trypsinogen gene (PRSS1), which has an 80 % penetrance. Mutations in this gene cause premature activation of trypsinogen to trypsin.

In addition, the CFTR mutation plays a role in predisposing patients to acute pancreatitis by causing abnormalities of ductal secretion. At present, however, the phenotypic variability of patients with the CFTR mutation is not well understood. Certainly, patients homozygous for the CFTR mutation are at risk for pancreatic disease, but it is not yet clear which of the more than 800 mutations carries the most significant risk. In addition, the role of CFTR heterozygotes in pancreatic disease is unknown. Mutations in the SPINK1 protein, which blocks the active binding site of trypsin, rendering it inactive, also probably play a role in causing a predisposition toward acute pancreatitis.

Hypercalcemia. Hypercalcemia from any cause can lead to acute pancreatitis. Causes include hyperparathyroidism, excessive doses of vitamin D, familial hypocalciuric hypercalcemia, and total parenteral nutrition (TPN). Routine use of automated serum chemistries has allowed earlier detection and reduced the frequency of hypercalcemia manifesting as pancreatitis. Annular pancreas is an uncommon congenital anomaly in which a band of pancreatic tissue surrounds the second part of the duodenum. Usually, it does not cause symptoms until later in life. This condition is a rare cause of acute pancreatitis, probably through an obstructive mechanism. Sphincter of Oddi dysfunction can lead to acute pancreatitis by causing increased pancreatic ductal pressures. However, the role of pancreatitis induced by such dysfunction in patients without elevated sphincter pressures on manometry remains controversial.

Hypertriglyceridemia. Clinically significant pancreatitis usually does not occur until a person’s serum triglyceride level reaches 1000 mg/dL. It is associated with type I and type V hyperlipidemia. Although this view is somewhat controversial, most authorities believe that the association is caused by the underlying derangement in lipid metabolism rather than by pancreatitis causing hyperlipidemia. This type of pancreatitis tends to be more severe than alcohol- or gallstone-induced disease.

Tumors. Obstruction of the pancreatic ductal system by a pancreatic ductal carcinoma, ampullary carcinoma, islet cell tumor, solid pseudotumor of the pancreas, sarcoma, lymphoma, cholangiocarcinoma, or metastatic tumor can cause acute pancreatitis. The chance of pancreatitis occurring when a tumor is present is approximately 14 %. Pancreatic cystic

neoplasm, such as intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenoma, or serous cystadenoma, can also cause pancreatitis.

Toxins. Exposure to organophosphate insecticide can cause acute pancreatitis. Scorpion and snake bites may also be causative; in Trinidad, the sting of the scorpion *Tityus trinitatis* is the most common cause of acute pancreatitis. Hyperstimulation of pancreas exocrine secretion appears to be the mechanism of action in both instances.

Surgical procedures. Acute pancreatitis may occur in the postoperative period of various surgical procedures (e.g, abdominal or cardiopulmonary bypass surgery, which may insult the gland by causing ischemia). Postoperative acute pancreatitis is often a difficult diagnosis to confirm, and it has a higher complication rate than pancreatitis associated with other etiologies. The mechanism is unclear.

Vascular abnormalities. Vascular factors, such as ischemia or vasculitis, can play a role in causing acute pancreatitis. Vasculitis can predispose patients to pancreatic ischemia, especially in those with polyarteritis nodosa and systemic lupus erythematosus.

Autoimmune pancreatitis. Autoimmune pancreatitis, a relatively newly described entity, is an extremely rare cause of acute pancreatitis (prevalence, 0.82 per 100,000 individuals). When it does cause acute pancreatitis, it is usually in young people (approximately 40 years) who also suffer from inflammatory bowel disease. The pathogenesis is unclear.

Pathogenesis of acute pancreatitis may occur when factors involved in maintaining cellular homeostasis are out of balance. The initiating event may be anything that injures the acinar cell and impairs the secretion of zymogen granules; examples include alcohol use, gallstones, and certain drugs.

At present, it is unclear exactly what pathophysiologic event triggers the onset of acute pancreatitis. It is believed, however, that both extracellular factors (eg, neural and vascular response) and intracellular factors (eg, intracellular digestive enzyme activation, increased calcium signaling, and heat shock protein activation) play a role. In addition, acute pancreatitis can develop when ductal cell injury leads to delayed or absent enzymatic secretion, as with the CFTR gene mutation.

Once a cellular injury pattern has been initiated, cellular membrane trafficking becomes chaotic, with the following deleterious effects: Lysosomal and zymogen granule compartments fuse, enabling activation of trypsinogen to trypsin. Intracellular trypsin triggers the entire zymogen activation cascade. Secretory vesicles are extruded across the basolateral membrane into the interstitium, where molecular fragments act as chemoattractants for inflammatory cells

Activated neutrophils then exacerbate the problem by releasing superoxide (the respiratory burst) or proteolytic enzymes (cathepsins B, D, and G; collagenase; and elastase). Finally, macrophages release cytokines that further mediate local (and, in severe cases, systemic) inflammatory responses. The early mediators defined to date are tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-8.

These mediators of inflammation cause an increased pancreatic vascular permeability, leading to hemorrhage, edema, and eventually pancreatic necrosis. As the mediators are excreted into the circulation, systemic complications can arise, such as bacteremia due to gut flora translocation, acute respiratory distress syndrome (ARDS), pleural effusions, gastrointestinal (GI) hemorrhage, and renal failure. The systemic inflammatory response syndrome (SIRS) can also develop, leading to the development of systemic shock. Eventually, the mediators of inflammation can become so overwhelming to the body that hemodynamic instability and death ensue.

In acute pancreatitis, parenchymal edema and peripancreatic fat necrosis occur first; this is known as acute edematous pancreatitis. When necrosis involves the parenchyma, accompanied by hemorrhage and dysfunction of the gland, the inflammation evolves into hemorrhagic or necrotizing pancreatitis. Pseudocysts and pancreatic abscesses can result from necrotizing pancreatitis because enzymes can be walled off by granulation tissue (pseudocyst formation) or via bacterial seeding of pancreatic or peripancreatic tissue (pancreatic abscess formation).

Chronic Pancreatitis

Chronic pancreatitis usually is envisioned as an atrophic fibrotic gland with dilated ducts and calcifications. However, findings on conventional diagnostic studies may be normal in the early stages of chronic pancreatitis, as the inflammatory changes can be seen only by histologic examination. This endoscopic retrograde cholangiopancreatography (ERCP) shows advanced chronic pancreatitis. The pancreatogram has blunting of the lateral branches, dilation of the main pancreatic duct, and filling defects consistent with pancreatolithiasis. The cholangiogram also shows a stenosis of the distal bile duct and a dilated biliary tree. This patient has recurrent abdominal pain.

By definition, chronic pancreatitis is a completely different process from acute pancreatitis. In acute pancreatitis, the patient presents with acute and severe abdominal pain, nausea, and vomiting. The pancreas is acutely inflamed (neutrophils and edema), and the serum levels of pancreatic enzymes (amylase and lipase) are elevated. Full recovery is observed in most patients with acute pancreatitis, whereas in chronic pancreatitis, the primary process is a chronic, irreversible inflammation (monocyte and lymphocyte) that leads to fibrosis with calcification.

The patient with chronic pancreatitis clinically presents chronic abdominal pain and normal or mildly elevated pancreatic enzyme levels. When the pancreas loses its endocrine and exocrine function, the patient presents diabetes mellitus and steatorrhea.

Etiology of chronic pancreatitis usually is metabolic in nature. The proposed pathologic mechanisms of chronic pancreatitis are as follows:

1. Intraductal plugging and obstruction – E.g, ethanol, stones, tumors.
2. Direct toxins and toxic metabolites – These act on the pancreatic acinar cell to stimulate the release of cytokines, which stimulate the stellate cell to produce collagen and to establish fibrosis; cytokines also act to stimulate inflammation by neutrophils, macrophages, and lymphocytes.
3. Oxidative stress – E.g, idiopathic pancreatitis
4. Necrosis-fibrosis – Recurrent acute pancreatitis that heals with fibrosis
5. Ischemia – From obstruction and fibrosis; important in exacerbating or perpetuating disease rather than in initiating disease
6. Autoimmune disorders – Chronic pancreatitis has been found in association with other autoimmune diseases, such as Sjögren syndrome, primary biliary cirrhosis, and renal tubular acidosis.

Secondary forms of autoimmune chronic pancreatitis are associated with primary biliary cirrhosis, primary sclerosing cholangitis, and Sjögren syndrome.

Autoimmune pancreatitis. Autoimmune pancreatitis is a more recently described entity. Clinical characteristics include symptomatic or asymptomatic, diffuse enlargement of the pancreas, diffuse and irregular narrowing of the main pancreatic duct, increased circulating levels of gamma globulin, the presence of autoantibodies, and a possible association with other autoimmune diseases. Fibrosis with lymphocytic infiltration is seen on pathology. The disorder is associated with elevated immunoglobulin G4 (IgG4) concentrations.

Alcoholic chronic pancreatitis. Excessive alcohol consumption is the most common cause of pancreatitis, accounting for about 60 % of all cases. In the affected gland, alcohol appears to increase protein secretion from acinar cells while decreasing fluid and bicarbonate production from ductal epithelial cells. The resulting viscous fluid results in proteinaceous debris becoming inspissated within the lumen, causing ductular obstruction, upstream acinar atrophy, and fibrosis. GP2, which is secreted from the acinar cell and is homologous to a protein involved in renal tubular casts, is an integral component of these ductal plugs.

Lithostathine (formerly called pancreatic stone protein), which also is produced by acinar cells, accounts for about 5 % of secretory protein and inhibits the growth of calcium carbonate crystals. Abnormal lithostathine S1, whether inherited or acquired through trypsin digestion, appears to play a role in stone formation; it is insoluble at the neutral pH of pancreatic juice and is the major constituent of pancreatic stones.

A competing theory suggests that the persistent demands of metabolizing alcohol (and probably other xenobiotics, such as drugs, tobacco smoke, environmental toxins, and pollution) cause oxidative stress within the pancreas and may lead to cellular injury and organ damage, especially in the setting of malnutrition. Oxidative and nonoxidative pathways metabolize ethanol. Alcohol dehydrogenase oxidatively metabolizes ethanol first to acetaldehyde and then to acetate. When the alcohol concentration increases, cytochrome P-450 2E1 is induced to meet the metabolic demands.

Although these reactions occur principally in the liver, further increases in ethanol concentration induce pancreatic cytochrome P-450 2E1, and the level of acetate within the pancreas begins to approach that observed in the liver. Reactive oxygen species produced by this reaction may overwhelm cellular defenses and damage important cellular processes.

Hereditary pancreatitis. Several inherited disorders also are considered metabolic in origin. Hereditary pancreatitis is an autosomal dominant disorder with an 80 % penetrance, accounting for about 1 % of cases. Research of families with hereditary pancreatitis has led to the identification of several mutations in the cationic trypsinogen gene on chromosome . These mutations apparently render the activated enzyme resistant to second-line proteolytic control mechanisms. Mutations were found in the pancreatic secretory serine protease inhibitor Kazal type 1 (SPINK1) gene in 18 of 96 patients with idiopathic or hereditary chronic pancreatitis.

Idiopathic chronic pancreatitis. This form of chronic pancreatitis accounts for approximately 30 % of cases. It has been arbitrarily divided into early onset and late-onset forms. While the cause of idiopathic chronic pancreatitis is not yet known, some evidence points to atypical genetic mutations in CFTR, cationic trypsinogen, and other proteins.

Congenital abnormalities in chronic pancreatitis

Congenital abnormalities, such as pancreas divisum and annular pancreas divisum, are uncommon (even rare) causes of chronic pancreatitis and usually require an additional factor to induce chronic pancreatitis. For example, while pancreas divisum usually does not cause chronic pancreatitis, patients with divisum and minor papilla stenosis are at risk. In these patients, clear evidence of disease exists in the dorsal pancreas, whereas the ventral pancreas is normal histologically.

Acquired obstructive chronic pancreatitis. Acquired obstructive forms typically result from blunt abdominal trauma or accidents involving motor vehicles, bicycles, horses, or, on occasion, severe falls. In these cases, the pancreas is whiplashed against the spine, causing trauma to the ductal system and resulting in a stricture close to the surgical genu. In rare instances, chronic inflammatory conditions affecting the duodenum, or primarily the duodenal papilla, can induce fibrosis and papillary stenosis in a subset of patients, leading to chronic pancreatitis.

Additional causes

Other causes of chronic pancreatitis include the following:

1. Hyperlipidemia (usually type I and type V) – However, hyperlipidemia usually presents with repeated attacks of acute pancreatitis.

2. Hypercalcemia due to hyperparathyroidism – Now is a rare cause of chronic pancreatitis, probably because automation of serum chemistries reveals hypercalcemia before it results in pancreatitis.

3. Nutritional, or tropical, chronic pancreatitis – Rare in the United States, but an important cause of disease in other parts of the world.

4. Medications – An infrequent, or possibly underrecognized, cause of chronic pancreatitis.

5. Obstruction of the flow of pancreatic juice can cause chronic pancreatitis. Obstructive forms account for less than 10 % of cases and may be congenital or acquired.

Pathophysiology. Whatever the etiology of chronic pancreatitis, pancreatic fibrogenesis appears to be a typical response to injury. This involves a complex interplay of growth factors, cytokines, and chemokines, leading to deposition of extracellular matrix and fibroblast proliferation. In pancreatic injury, local expression and release of transforming growth factor

beta (TGF-beta) stimulates the growth of cells of mesenchymal origin and enhances synthesis of extracellular matrix proteins, such as collagens, fibronectin, and proteoglycans.

Evidence indicates involvement of distinct chemokines in the initiation and perpetuation of chronic pancreatitis.

PATHOPHYSIOLOGY OF LIVER

The main functions of the liver are the digestive and homeostatic which, in turn, are supported by such private functions such as: 1) the formation and secretion of bile, 2) participation in all types of metabolism, and 3) neutralization of the barrier function, and 4) formation and secretion of cholesterol, biliary excretion of metabolites, and toxic drugs, 5) the deposit of blood, the maintenance of vascular tone, 6) participation in the processes of blood (hepatic hematopoiesis in the embryonic period in postnatal erythropoiesis – as forming protein body, stores of iron, vitamin B_{12}, folic acid and etc.), and 7) synthesis of components of coagulation and anticoagulation systems, etc. All the functions of the liver are complex (multicomponent) and interconnected.

Acute Liver Failure. Acute liver failure (ALF) is an uncommon condition in which rapid deterioration of liver function results in coagulopathy and alteration in the mental status of a previously healthy individual. Acute liver failure often affects young people and leads to very high mortality.

The term acute liver failure describes the development of coagulopathy, usually with an international normalized ratio (INR) of greater than 1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of less than 26 weeks' duration.

Acute liver failure is a broad term that encompasses both fulminant hepatic failure (FHF) and subfulminant hepatic failure (or late-onset hepatic failure). Fulminant hepatic failure is generally used to describe development of encephalopathy within 8 weeks of the onset of symptoms in a patient with a previously healthy liver. Subfulminant hepatic failure is reserved for patients with liver disease for up to 26 weeks before the development of hepatic encephalopathy. The outcome of acute liver failure is related to the etiology, the degree of encephalopathy, and related complications. Although mortality from FHF remains significantly high, improved intensive care and use of orthotopic liver transplantation have improved survival from less than 20 % to approximately 60 %.

Pathophysiology. Development of cerebral edema is the major cause of morbidity and mortality in patients with acute liver failure. The etiology of this intracranial hypertension (ICH) is not fully understood, but it is considered to be multifactorial. Briefly, hyperammonemia may be involved in the development of cerebral edema. Brain edema is thought to be both cytotoxic and vasogenic in origin.

Cytokine profiles are also deranged. Elevated serum concentrations of bacterial endotoxin, tumor necrosis factor–alpha (TNF-α), and interleukin (IL)–1 and IL-6 have been found in fulminant hepatic failure.

Cytotoxic edema. Cytotoxic edema is the consequence of impaired cellular osmoregulation in the brain, resulting in astrocyte edema. Cortical astrocyte swelling is the most common observation in neuropathologic studies of brain edema in acute liver failure. In the brain, ammonia is detoxified to glutamine via amidation of glutamate by glutamine synthetase. The accumulation of glutamine in astrocytes results in astrocyte swelling and brain edema. There is clear evidence of increased brain concentration of glutamine in animal models of acute liver failure. Scientists have reported a relationship between high ammonia and glutamine levels and raised ICH in humans.

Vasogenic factors. An increase in intracranial blood volume and cerebral blood flow is a factor in acute liver failure. The increased cerebral blood flow is the result of cerebral autoregulation disruption. The disruption of cerebral autoregulation is thought to be mediated by elevated systemic concentrations of nitric oxide, which acts as a potent vasodilator.

Multisystem organ failure. Another consequence of fulminant hepatic failure is multisystem organ failure, often observed in the context of a hyperdynamic circulatory state that mimics sepsis (low systemic vascular resistance); therefore, circulatory insufficiency and poor organ perfusion possibly either initiate or promote complications of fulminant hepatic failure.

Acetaminophen hepatotoxicity

Development of liver failure represents the final common outcome of a wide variety of potential causes, as the broad differential diagnosis suggests. As with many drugs that undergo hepatic metabolism (in this case, by cytochrome P-450), the oxidative metabolite of acetaminophen is more toxic than the drug. The highly reactive active metabolite N -acetyl-p-benzoquinone-imine (NAPQI) appears to mediate much of the acetaminophen-related damage to liver tissue by forming covalent bonds with cellular proteins.

Ordinarily, NAPQI metabolizes in the presence of glutathione to N-acetyl-p-aminophenol-mercaptopurine. Glutathione quenches this reactive metabolite and acts to prevent nonspecific oxidation of cellular structures, which might result in severe hepatocellular dysfunction. This mechanism fails in 2 different yet equally important settings. The first is an overdose (accidental or intentional) of acetaminophen. Acetaminophen ingestion of more than 10 g simply overwhelms normal hepatic stores of glutathione, allowing reactive metabolites to escape.

Etiology. Numerous causes of fulminant hepatic failure exist, but hepatotoxicity due to acetaminophen and idiosyncratic drug reactions is the most common cause in the United States. For nearly 15 % of patients, the cause remains indeterminate. Viral hepatitis may lead to hepatic failure. Hepatitis A and B account for most of these cases. In the developing world, acute hepatitis B virus (HBV) infection dominates as a cause of fulminant hepatic failure because of the high prevalence of the disease.

Hepatitis C rarely causes acute liver failure. Hepatitis D, as a co-infection or superinfection with hepatitis B virus, can lead to fulminant hepatic failure. Hepatitis E (often observed in pregnant women) in endemic areas is an important cause of fulminant hepatic failure.

.**Atypical causes of viral hepatitis and fulminant hepatic failure include the following:**

1. Cytomegalovirus
2. Hemorrhagic fever viruses
3. Herpes simplex virus
4. Paramyxovirus
5. Epstein-Barr virus

Autoimmune hepatitis may also result in hepatic failure

Hepatic failure in pregnancy

Acute fatty liver of pregnancy (AFLP) frequently culminates in fulminant hepatic failure. AFLP typically occurs in the third trimester; preeclampsia develops in approximately 50 % of these patients. AFLP has been estimated to occur in 0.008 % of pregnancies. The most common cause of acute jaundice in pregnancy is acute viral hepatitis, and most of these patients do not develop fulminant hepatic failure. The one major exception to this is the pregnant patient who develops hepatitis E virus infection, in whom progression to fulminant hepatic failure is unfortunately common and often fatal.

The exposure history in patients with hepatitis E is usually remarkable for travel and/or residence in the Middle East, India and the subcontinent, Mexico, or other endemic areas. In the United States, hepatitis E is relatively uncommon but must be considered in the appropriate setting.

The HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome occurs in 0.1–0.6 % of pregnancies. It is usually associated with preeclampsia and may rarely result in liver failure.

Drug-related hepatotoxicity

Many drugs (both prescription and illicit) are implicated in the development of fulminant hepatic failure. The more common agents are discussed below.

Idiosyncratic drug reactions may occur with virtually any medication. Fortunately, these appear to lead to fulminant hepatic failure only rarely, although they are the most common form of drug reaction to lead to fulminant hepatic failure (with the exception of acetaminophen poisoning).

Acetaminophen (also known as paracetamol and N-acetyl-p-aminophenol [APAP]) may lead to liver failure caused by intentional or accidental overdose. Prescription medications that have been associated with idiosyncratic hypersensitivity reactions include the following:

1. Antibiotics (ampicillin-clavulanate, ciprofloxacin, doxycycline, erythromycin, isoniazid, nitrofurantoin, tetracycline)
2. Antidepressants (amitriptyline, nortriptyline)
3. Antiepileptics (phenytoin, valproate)
4. Anesthetic agents (halothane)
5. Lipid-lowering medications (atorvastatin, lovastatin, simvastatin)
6. Immunosuppressive agents (cyclophosphamide, methotrexate)
7. Nonsteroidal anti-inflammatory agents (NSAIDs)
8. Salicylates (as a result of Reye syndrome)
9. Ecstasy (3,4-methylenedioxymethamphetamine [MDMA])
10. Cocaine (may be the result of hepatic ischemia)
11. Herbal or alternative medicines that have been associated with idiosyncratic hypersensitivity reactions include the following:
12. Pennyroyal oil
13. Chaparral or germander tea

Toxin-related hepatotoxicity. The following toxins are associated with dose-related toxicity:

1. Amanita phalloides mushroom toxin
2. Bacillus cereus toxin
3. Cyanobacteria toxin
4. Organic solvents (eg, carbon tetrachloride)
5. Yellow phosphorus
6. A phalloides mushroom intoxication is much more common in Europe and in California than in the remainder of the United States.

Vascular causes. The following are vascular causes of hepatic failure:

1. Ischemic hepatitis (consider especially in the setting of severe hypotension or recent hepatic tumor chemoembolization)
2. Hepatic vein thrombosis (Budd-Chiari syndrome)
3. Hepatic veno-occlusive disease
4. Portal vein thrombosis
5. Hepatic arterial thrombosis (consider posttransplant)

Metabolic causes. The following metabolic diseases can cause hepatic failure:

1. Alpha1-antitrypsin deficiency
2. Fructose intolerance
3. Galactosemia
4. Lecithin-cholesterol acyltransferase deficiency
5. Reye syndrome
6. Tyrosinemia
7. Wilson disease

Malignancies. Malignancies that can cause hepatic failure include the following:

1. Primary liver tumor (usually hepatocellular carcinoma, rarely cholangiocarcinoma)
2. Secondary tumor (extensive hepatic metastases or infiltration from adenocarcinoma, such as breast, lung, melanoma primaries [common]; lymphoma; leukemia)

Miscellaneous

Miscellaneous causes of hepatic failure include adult-onset Still disease, heatstroke, and primary graft nonfunction in liver transplant recipients.

Basic Pathophysiology of Liver Disease

The basic pathophysiology of all forms of liver disease represents failures of the numerous and complex hepatic metabolic functions. Although there is some variability in basic pathophysiology from one type of liver disease to another, all forms of liver disease can

reasonably be called hepatic failure. The signs and symptoms, the natural history, and the rationale of treatment for all forms of liver disease derives from certain relatively simple basic pathophysiologic concepts. It should be made clear at the outset that jaundice, an obvious physical sign, **sometimes represents problems other than liver disease and is** by no means synonymous with it. There are other, far more important and more complex metabolic problems associated with liver disease so that the problem of jaundice will be dealt with only briefly in this minicourse. The liver plays several complex roles in amino acid metabolism, protein synthesis, carbohydrate metabolism and lipid metabolism. It is also the site of manufacture of a number of blood coagulation proteins.

Basic derangements of hepatic failure will be discussed first. These will then be applied to the most common forms of liver disease, acute hepatitis and cirrhosis.

Defects in Amino Acid Metabolism

The liver is the most important single organ involved in amino acid metabolism. Amino acids are delivered to the liver either from the gut or from the general circulation. In the liver there are two major processes in the metabolism of amino acids: **oxydative deamination** and **transamination**.

Oxydative deaminiation is a process by which the amino radical is removed from the amino acid thus converting it into two products: a keto acid and ammonia.

Since oxydative deamination results in the production of ammonia, **any impairment of the above function results in a diminution of the blood urea nitrogen level** (BUN) and an increase in the amount of circulating ammonia. Elevated serum ammonia levels can become extremely toxic, especially to the brain, often leading to a state called **hepatic coma.**

The ketoacid produced by deamination can follow several metabolic pathways:

1. It can be modified and cycled through the Krebs cycle, producing energy in the form of ATP.
2. It can be converted (depending on the structure of the amino acid from which it was derived) into glycogen or fatty acids, or it can be transaminated.
3. It can be transaminated whereby the amino radical from another amino acid is transferred to it, thus converting it back to its original form and leaving another kind of keto acid which itself can then undergo any of the above three steps.

Amino acid metabolism is controlled primarily by the hepatocyte, one of the three types of cells in the liver. In widespread, advanced hepatic parenchymal disease, or in severe acute hepatic failure, as can happen in severe acute hepatitis of any form, this particular hepatocyte failure results in a severe derangement of amino acid metabolism and thus of ammonia and urea levels.

Defects in Protein Synthesis. Two of the liver's cell types, the hepatocyte and the Kupffer cell, are responsible for synthesizing many kinds of proteins. The hepatocyte synthesizes albumin and some immune globulins. The Kupffer cells, which line the hepatic sinusoids, and which are a part of the so-called reticuloendothelial system, synthesize several kinds of immune globulins. Since the functions of both of these kinds of cells can be impaired in either chronic diffuse liver disease or in severe acute liver disease, a diminution of the levels of circulating albumin and of the immune globulins often appears in liver disease. Since impaired amino acid metabolism may also be found in liver disease, protein synthesis may be doubly impaired because of a decreased availability of amino acids and because of direct impairment of the synthetic processes themselves in the hepatocyte and in the Kupffer cell. Defects in protein synthesis are responsible for some of the more protean manifestations of severe diffuse chronic liver disease and of severe acute liver disease.

Defects in Carbohydrate Metabolism

The hepatocyte actively stores glucose by converting it to the longchain starch, glycogen. Glycogen can then be later broken down to release glucose into the general circulation. The factors that control thisinsulin, epinephrine, growth hormone (STH), glucagon and the thyroid hormonestend to counterbalance each other so that the hepatocytes store glycogen as the blood sugar rises and break it back down into glucose as blood sugar level falls. Again, this is a

critical function, an impairment of which produces some of the more serious manifestations of liver disease hyperglycemia and hypoglycemia. In fact, patients with severe liver disease often have glucose tolerance curves very much like those seen in diabetes mellitus. That is to say, with food ingestion, they tend to become hyperglycemic because the hepatocytes cannot store glycogen while, as dietary intake is decreased or absent, the hepatocytes are not well able to mobilize glucose from what little stored glycogen there is, and so these patients have episodes of hypoglycemia. This phenomenon is sometimes called "hepatic diabetes."

Defects in Lipid Metabolism

The liver has an extremely complex role in lipid metabolism, very little of which will be discussed here. In the diseased liver, there are two prime manifestations of liver failure with regard to lipid metabolism. The first of these is the deposition of triglycerides within the organ itself. This is the basic mechanism of the so-called "fatty liver," which develops most often due to chronic alcoholism. The second prime feature of disordered hepatic lipid metabolism is a diminution in the rate of cholesterol synthesis. In fact, a decrease below the normal level of serum cholesterol is often found in advanced diffuse liver disease or in severe acute liver disease.

Impaired Production of Clotting Factors

Fibrinogen, prothrombin, Factors V, VII, and X are all produced in the liver, and impairment of their production leads to coagulation defects. In fact, production of clotting factors is so exquisitely affected in liver disease that the measurement of prothrombin time is a very sensitive indicator of the progress of acute hepatitis. For example, in the patient profoundly ill with severe acute hepatitis with a circulating bilirubin level 20 times normal, measurement of the bilirubin and observation of jaundice become far less reliable indicators than the prothrombin time.

Impairment of Detoxification Functions

The liver is responsible for detoxifying many substances that enter itby chemical modification. This includes substances drained from the gut, many kinds of drugs, and circulating hormones. Some substances are converted to water soluble salts or esters and are excreted in the bile. Others are chemically modified and released into the general circulation for renal excretion. Sometimes, toxic substances are modified, released into the bile, excreted into the gut, reabsorbed from the gut in their modified form, and later find their way to the kidneys for renal excretion.

Mechanisms of Hepatic Failure in Acute Hepatitis

The basic problem in acute hepatitis is a widespread inflammatory reaction throughout the liver. This results in edema and congestion, and these compromise hepatic function. Kupffer cell functions are impaired. Hepatocyte functions are impaired. Formation and excretion of bile is impaired. In every case, all of the basic pathophysiologic mechanisms already discussed become operative. In other words, every case of acute hepatitis represents acute hepatic failure with all of its attendant interruptions of normal physiologic functions. The pathologic changes (tissue changes) that occur within the liver itself include hepatocyte necrosis, hyperplasia of the Kupffer cells, and some microscopic anatomic changes. As the liver becomes edematous and engorged, bile canaliculi become obstructed, and bile stasis develops. This undoubtedly contributes further to degeneration of liver tissue.

Cirrhosis mechanisms. Over the years, the term "cirrhosis" has been used to label a wide variety of patterns of chronic diffuse parenchymal liver disease. The single common denominator among all forms of "cirrhosis" is the presence of widespread microscopic, hepatic anatomic changes.

There are many causes of cirrhosis. Certainly, the most common kind of chronic diffuse par-enchymal liver disease is that seen in alcoholism. This form of cirrhosis, which is also called alcoholic cirrhosis, portal cirrhosis, fatty cirrhosis and Laennec's cirrhosis, is believed to be primarily the result of ethanol's direct effect on normal hepatocyte lipid metabolism. The presence of ethanol in the hepatocyte impairs the usual lipid metabolic pathways within the

hepatocyte and results in the deposition of fat throughout the organ. There is also scattered fine scarring that follows patchy necrosis; this results in diffuse hepatic fibrosis. Since fibrosis is the result of parenchymal necrosis, there must be the necessary antecedent necrosis and, this, too, is also often found by biopsy.

Alcohol probably accounts for ninety five percent of all cirrhosis. The remaining small percentage of cases develop from various metabolic abnormalities. Socalled "biliary cirrhosis," which occurs almost exclusively in middle-aged women, for example, is believed to be produced by an autoimmune abnormality that results in necrosis of bile ducts. This leads to bile stasis which, in turn, leads to further necrotic changes, further duct damage, further bile stasis, and so on. This same vicious cycle may develop in a person who suffers a severe episode of acute infectious hepatitis that produces widespread scarring and obstructive ductal changes. All forms of cirrhosis tend to be progressive.

Since any kind of cirrhosis involves widespread diffuse parenchymal disease, there is usually some impairment of every kind of hepatic function. Nevertheless, there does tend to be impairment of many kinds of hepatic function, including impaired amino acid metabolism, impaired storage and release of glycogen, im-paired lipid metabolism, some impairment of formation of coagulation factors, and some impairment of the liver's ability to modify and excrete toxic substances (including drugs). One should bear in mind that most patients with acute infectious hepatitis do not slip into this cyclic pattern of hepatic damage, bile stasis, further damage and selfperpetuating, progressive, cirrhotic changes. This pattern is seen most often in patients with noninfectious diffuse liver disease, most often alcoholinduced Laennec's cirrhosis.

Jaundice and Bilirubin

Bilirubin, a yellow pigment, is one of several products of hemoglobin breakdown. Since hemoglobin synthesis and breakdown are continuous processes, small amounts of bilirubin (and other products of hemoglobin breakdown) are released into the general circulation continuously. Many kinds of cells can, given enough time, modify bilirubin chemically so that it can be excreted. The hepatocyte, though, is the prime bilirubin processor, and so hepatocyte impairment results in disordered bilirubin metabolism.

In its original form, bilirubin is fat soluble, not water soluble. A hepatocyte enzyme, **glucuronyl transferase**, modifies bilirubin as it arrives at the liver, and converts it to a water soluble compound. This process is **called bilirubin conjugation** because one of the steps involved is the attachment of bilirubin to another molecule. The conjugated bilirubin is then excreted into the bile and is released into the gut. Impairment of any of these steps results in distribution of bilirubin unconjugated, conjugated, or both throughout the body. The unconjugated bilirubin, which is fat soluble, accumulates in fatty tissues, most notably the skin, where the presence of this yellow pigment produces jaundice. If excretion of water soluble, conjugated bilirubin is impaired, jaundice may also occur. Most bilirubin is produced by RBC breakdown in the spleen. Jaundice indicates one of four problems: (increased RBC breakdown, failure of hepatocyte conjugation, failure of hepatocyte excretion of conjugated bilirubin into the bile canaliculi, extrahepatic obstruction, In liver disease, problems 2 and 3 usually occur together.

Portal Hypertension

As widespread, diffuse parenchymal liver disease progresses, there is loss of the hepatic vascular bed and an increase in fibrotic tissue scattered throughout the organ. If these anatomic changes progress beyond a certain point, there is, eventually, definite impairment of blood flow through the liver. Since the liver receives two thirds of its blood supply from the hepatic portal vein and one third from the hepatic artery, circulatory impairment through the liver results primarily in an increase in venous pressure in the portal drainage system. This direct increase in hydrostatic pressure in the portal system, which drains the entire gastrointestinal (GI). tract, results in an increase in hydrostatic pressure in all of the GI. tract's venous drainage system. This increase in pressure is called portal hypertension. If venous pressure in the gut drainage system is raised high enough, hydrostatic pressure overcomes intravascular osmotic

pressure and fluid begins to seep out of the gut capillary bed and into the peritoneal space (ascites). At the same time, the GI. tract itself, because of impaired venous drainage, becomes somewhat edematous, and this results in impairment of gastrointestinal function. That is the basis for the non-hepatic gastrointestinal signs and symptoms that develop in advanced cirrhosis. The amount of fluid that accumulates in the peritoneal space may be enormous. Because there is impairment of venous drainage in advanced cirrhosis, there is a natural tendency for venous drainage from the GI. tract to flow through alternate channels. The most conspicuous of these in advanced liver disease is the umbilical venous system which connects the portal system with the systemic circulation. An increase in pressure in the umbilical veins results in the dilation of veins on the abdominal wall, producing the so-called "caput medusae" sometimes seen in far advanced cirrhosis.

An increase in portal venous pressure also results in two common problems that are a direct result of portal hypertension. One of these is hemorrhoids, which are actually varices of the hemorrhoidal veins. Hemorrhoids certainly develop often in patients who do not have cirrhosis but they are also a rather common finding in patients who do. Similarly, esophageal varices develop in these patient sand for the same reason. Both of these phenomena are a direct result of increased portal venous pressure. Hemorrhoids tend to be more of a nuisance than a threat, but esophageal varices, which can, and often do hemorrhage massively, can be life threatening.

Liver Disease - Prime Clinical Features

Acute Viral Hepatitis is a systemic infection which affects the liver. Two viruses have been identified (A and B). The third type is referred to as non-A, non-B. It is recognized that a distinction between hepatitis A and B cannot be made solely by clinical features or by epidemiologic features because ways of transmission overlap. The distinction must be made by specific serologic testing.

Hepatitis compromises hepatic function. With hepatic function impaired, hepatocyte formation and excretion of bile are also impaired. Since bile salts are necessary for the degradation of foodstuffs in the gut, particularly of fatty foodstuffs, obvious gastrointestinal signs and symptoms are likely to develop early.

In fact, all signs and symptoms of **hepatitis fall broadly into three categories:**

1**.** gastrointestinal symptoms produced by impairment of bile flow

2. signs and symptoms referable to the liver itself, such as enlargement and tenderness

3. the signs and symptoms that develop from disruption of hepatic functions that affect the whole body, such as jaundice, evidence of coagulation defects, and weight loss.

The clinical course of acute viral hepatitis has three major phases: the pre-icteric stage, the icteric stage, and the recovery stage. The signs and symptoms tend to vary considerably from one stage to the next. The first symptoms that appear in the preicteric phase are vague constitutional symptoms and, usually, symptoms directly referable to the GI. tract. Thus, this infectious disease is heralded by fatigue, malaise, and anorexia. There may be fever, with hepatitis A, there may be upper respiratory symptoms, which are unusual in hepatitis B. During the course of the first week or so, the patient's anorexia is likely to become nausea, possibly with vomiting and diarrhea. During the pre-icteric stage, a mild polyarthritis may develop. In other words, during the pre- icteric stage both hepatitis A and B may resemble a "flu-like" illness.

During the preicteric stage of the disease, there may be no findings on physical examination except slight fever, right upper quadrant tenderness, and splenomegaly (occasionally).

Jaundice develops in hepatitis because the widespread hepatic parenchymal inflammation and edema interfere with bilirubin conjugation and with bile excretion. Most patients who contract infectious hepatitis do develop jaundice. Hepatitis in children is more apt to be anicteric. During the icteric phase, gastrointestinal symptoms tend to subside. A mild to moderate anorexia, though, may persist and may be a fairly substantial management problem. Many patients will observe that their urine has become dark, due to renal excretion of excess conjugated bilirubin.

There is invariably hepatic enlargement and right upper quadrant abdominal tenderness in the icteric phase. Also, during this phase of the illness, splenomegaly and posterior cervical lymphadenopathy appear in about one-fifth of the cases. Fever usually subsides when jaundice appears, and the persistence of fever into the icteric stage of the illness suggests the possibility of problems other than acute infectious viral hepatitis. It is usually at about this point that the famous clay-colored (acholic) stools appear. This color is produced by lack of bile pigments.

Jaundice usually progresses slowly over two to four days, peaks, and then subsides slowly, usually over a span of about two weeks. A three-week subsidence, however, is not unusual. Since the clearing of jaundice represents a return toward normal hepatic function, the patient usually feels generally well by the time jaundice has cleared. Generalized weakness, however, persists for two to six weeks after clearing of jaundice. The liver returns only slowly to a normal size and so hepatic enlargement may still be evident throughout this recovery phase.

Cirrhosis. Many of the physical signs encountered in cirrhosis are difficult to describe and must be seen to be appreciated. Some are poorly understood. With regard to symptoms in cirrhosis, it is fair to say that, except in far-advanced disease, there are no symptoms directly attributable to the hepatic dysfunction present. The reason for this is that very little normal hepatic function is required for successful carrying- on of everyday activities.

Physical evidence of cirrhosis falls broadly into these categories:

1) changes in life;
2) evidence of portal hypertension;
3) evidence of impaired protein synthesis;
4) evidence of nutritional deficiencies, particularly of the fat soluble vitamins;
5) evidence of altered bilirubin metabolism (jaundice);
6) evidence of impaired degradative abilities;
7) other associated phenomena.

As cirrhosis progresses, and as fatty infiltration continues, there is a tendency for the liver to enlarge. This may continue slowly and steadily for many years. Because there is persistent necrosis, there is a steady accumulation of fibrous scar tissue within the organ, and so, as the organ enlarges, it tends to become firmer than normal. Eventually, necrosis and fibrosis supersede fatty enlargement, and the liver begins to shrink under the influence of fibrotic retraction.

During the period of enlargement the lower border may also become palpable, and is usually firmer than normal. As diffuse interstitial fibrosis progresses, the liver edge is often felt to be much firmer than normal and may become quite hard. If fibrotic retraction shrinks the organ to such an extent that the lower border is far above the right costal margin, then the edge is no longer palpable.

There is little correlation between changes in size and consistency, and the degree of physiologic insult that produces the cirrhosis. A young adult alcoholic, for example, can easily double his liver size in the span of a year or less by heavy and persistent drinking. If the alcohol insult carries on long enough and at a great level, that same liver could easily be smaller than normal a year later and the patient could easily be on the verge of death from acute hepatic failure. On the other hand, a moderate brand of alcoholism or a mild degree of chronic biliary obstruction may produce significant cirrhotic changes only after many years, and post-cirrhotic retraction may never occur.

In fact, there are only two safe rules of thumb with regard to liver size and consistency:

1) hepatic enlargement strongly suggests ongoing pathologic processes;
2) a liver size definitely less than normal strongly suggests late pathologic changes.

Portal hypertension, a serious consequence of advanced liver disease, often exists for years before evidence of its presence is observed. The usual evidence of portal hypertension, ascites, the caput medusae and hemorrhoids, are late findings that develop after the gastrointestinal vasculature is no longer able to compensate for the persistent increase in venous pressure.

Pathophysiology of portal hypertension. In a healthy individual, the liver is a very low resistance organ which passively receives whatever blood flow is coming from the mesenteric

bed, a value that changes over the course of the day. The liver is able to accommodate these changes in blood flow without an increase in portal pressures by decreasing the resistance n the liver through the recruitment of additional hepatic sinusoids. Thus, the ΔP does not change despite an increase in Q because the R is reduced. One needs to understand how changes in both the resistance to blood flow in the portal system and volume of blood flow in the portal system in patients with cirrhosis combine to produce portal hypertension.

Patients with cirrhosis have an increasing resistance to blood flow through the liver at the level of sinusoids and hepatic and portal venules. This is predominantly due to fibrosis and regenerative nodules compressing/obliterating these vessels. The increased resistance to blood flow in portal hypertension may be pre-hepatic (such as blockage of the portal vein), intra-hepatic (pre-sinusoidal, sinusoidal, or post-sinusoidal), or post-hepatic (such as blockage of the IVC).

There is also an increased rate of blood flow to the splanchnic circulation in patients with cirrhosis. Patients with cirrhosis have a hyperdynamic circulation marked by low peripheral vascular resistance and high cardiac output. Studies have shown that there is a 50 % increase in flow to the GI tract, pancreas, and spleen in patients with cirrhosis. This hyperdynamic circulation is due to an elevated level of vasodilators is due to an elevated level of vasodilators (such as glucagon) in the blood and a decreased vascular sensitivity to vasoconstriction. The elevated levels of vasodilators are due to decreased hepatic metabolism due to shunting around the liver from the presence of collaterals and due to an increase in the production of local vasodilators (such as nitric oxide) by endothelial cells.

Classification (based on the location of the increased resistance). While attempts to categorize portal hypertension in this fashion have proven somewhat useful, these classifications may be idealized in many cases as most liver conditions have more than one site of increased resistance. In general, patients with involvement of the sinusoids with fibrosis will have elevated HVPGs.

Pre-hepatic:

1. Portal or splenic vein thrombosis.
2. Arteriovenous fistulas in the splanchnic bed or spleen.

Intrahepatic:

Pre-sinusoidal:

Schistosomiasis (Inflammatory rxn to eggs in the portal venules:

1. Sarcoidosis

Sinusoidal:

2. Cirrhosis of any etiology

Post-sinusoidal:

3. Hepatic vein thrombosis (Budd-Chiari syndrome). These patients are diagnosed not by the presence of changes in the HVPG, but rather by the fact their hepatic veins cannot be cannulated due to the presence of clot.

Post-hepatic (these patients have a normal HVPG because both the WHVP and the FHVP are elevated):

1. Webs (congenital or acquired) in the inferior vena cava
2. Cardiac disease – e.g., constrictive pericarditis, mitral stenosis

Complications of Portal Hypertension. Portosystemic Collaterals

Collateral vessels can develop wherever there is a communication between the portal and systemic circulations. Sites include the umbilical vein (resulting in caput medusae), dilated abdominal wall veins, retroperitoneal veins and the clinically most important collateral, esophageal and gastric varices. In patients with portal hypertension, bleeding from varices rarely occurs if the HVPG is below 12 mm Hg. While the varices form as a consequence of increased portal pressures, actual rupture of the varices is more related to variceal wall pressure That is, at equal portal pressures, patients with large varices tend to bleed more often than those with smaller ones.

Pathophysiology. There is considerable evidence which suggests that ascites is related to an increase in hepatic sinusoidal pressure rather than an increase in splanchnic capillary pressure. Patients with pre-sinusoidal portal hypertension rarely develop ascites while those with post-hepatic portal hypertension have ascites as a prominent feature of their illness. An increase in the hepatic sinusoidal pressure in combination with a decreased oncotic pressure results in the increased production of hepatic lymph. When the production of lymph exceeds the ability of the lymphatics and the thoracic duct to return the lymph of the general circulation, ascites results.

Because ascitic fluid is derived from the vascular space, for it to continue to be produced, the intravascular space must be continuously replenished. This mainly occurs by the cirrhotic patient inappropriately holding on to urinary sodium (and therefore free water).

The first step in the process appears to be production of the hyperdynamic circulation. The hyperdynamic sate is marked by low peripheral vascular resistance induced by the presence of elevated level of vasodilators (such as glucagon and nitric oxide) in the blood and a decreased vascular sensitivity to vasoconstrictive agents. The body attempts to compensate for apparent decrease in the circulating blood volume by increasing cardiac output and by activation of the rennin-angiotensin system which results in increased renal sodium and free fluid retention. Because of this, the intravascular space continues to be inappropriately replenished and excessive hepatic lymph production/ascites production continues.

Diagnosis. The presence of ascites does not always mean cirrhosis/portal hypertension. Work-up of newly identified ascites should include: Serum-ascites albumin gradient: calculated by subtracting the ascitic fluid albumin from the serum albumin. An albumin of greater than 1.1 gm/dl indicates portal hypertension as the cause in almost all of the cases. Causes of a "low albumin gradient" ascites include infection, malignancy, and pancreatitis among others. Cell count and ascitic fluid cultures.

If hepatic production of plasma proteins is impaired, the level of circulating plasma proteins drops, their osmotic effect is lost, and intravascular water begins to escape into interstitial spaces. This tends to be most marked in the dependent portions of the body, as one would expect, and in the abdomen, where portal hypertension exaggerates the process. The resultant edema is usually slight to moderate but can be profound.

Patients with advanced cirrhosis tend to have evidence of multiple vitamin deficiencies. The vast majority of these patients are alcoholics, many of whom have grossly inadequate diets, with a large percentage of caloric needs supplied by alcohol rather than by other foodstuffs. Folic acid and B_{12} deficiencies produce peripheral neuropathies and anemia and these can be easily demonstrated in most patients with advanced liver disease. Vitamin A deficiency produces visual impairment, vitamin D deficiency produces abnormal calcium metabolism, and vitamin K deficiency produces the expected impairment of blood coagulation. Since the vitamin K deficiency is likely to be superimposed on an impaired ability to synthesize coagulation proteins, the tendency toward bleeding disorders is strong, and some of these patients may have physical evidences of this, including petechiae, ecchymoses and pallor.

Jaundice in a patient with advanced, diffuse, parenchymal disease is an ominous sign. In these patients, the development of jaundice frequently heralds the arrival of terminal hepatic failure.

Evidence of impairment of degradation abilities is manifested primarily by the signs of inability to degrade certain circulating hormones. In the male, the inability to degrade circulating estrogens results in some degree of feminization with the development of gynecomastia, testicular atrophy and alteration of hair distribution. In the female, inability to degrade circulating androgens produces some degree of masculinization and may also produce amenorrhea.

The Problem of Jaundice. As an indicator of liver disease, jaundice is overrated. Jaundice (French-yellowness) indicates the deposition of bilirubin in skin and mucous membranes. Normally, all bilirubin is conjugated in the liver and excreted in the bile. There are four basic mechanisms by which jaundice develops:

1) overproduction of bilirubin, as in acute hemolysis of RBCs;
2) impaired hepatocyte conjugation of bilirubin;
3) impaired excretion of conjugated bilirubin, as in ductal disease;
4) extra-hepatic obstruction.

In acute viral hepatitis, direct and indirect (that is, conjugated and unconjugated) bilirubin levels tend to rise together, then to fall back toward normal together. In severe cases, where serum bilirubin concentrations may rise to 20–30 times normal, large amounts of bilirubin are deposited in the skin and mucous membranes, and their presence in the skin may produce fairly severe itching. The itching tends to resolve only slowly, usually more slowly than does the apparent jaundice. Jaundice is not a common feature of cirrhosis.

Symptoms in Cirrhosis. Patients with various kinds of cirrhosis tend to have many kinds of symptoms simultaneously. Most of them are not directly referable to the liver and suggest extensive multisystem disease. The alcoholic, for example, with advanced portal cirrhosis is very likely to have the symptoms of a peripheral neuropathy, such as numbness and tingling (paraesthesia) as well as impairment of the sense of touch and of the vibratory sense, usually in all four extremities but more often in the feet and hands. Patients with biliary cirrhosis are most likely to present with generalized, intractable pruritus. Although there are not many definitive signs and symptoms, pale-colored stools, dark urine, Uterus and melanosis of exposed skin frequently accompany pruritus of biliary cirrhosis. Signs of early liver failure are few. Although pruritus may be the only symptom, xanthalasmas, xanthomas, hepatomegaly, splenomegaly and clubbing of the finger may be noted.

Signs and Symptoms in Severe Hepatic Failure. Severe, acute, life-threatening hepatic failure produces many complex and bizarre alterations of metabolic functions. Patients may develop an elevated serum ammonia level because of a disordered amino acid and urea metabolism, and the elevated serum ammonia level may produce, by the way of cerebral toxicity, profound alterations in the state of consciousness. By way of a poorly understood hepato-renal physiologic link, renal failure may be superimposed and, consequently, there may be severe disorders of fluid and electrolyte balance. This is known as the "hepato-renal syndrome," (alcoholic hepititis and infectious hepititis).

Hyperglycemia and Hypoglycemia in Cirrhosis. Patients who have widespread parenchymal disease and impairment of glycogen storage and release, often have episodes of hyperglycemia and of hypoglycemia. Transitory episodes of hyperglycemia tend not to produce symptoms but, rather, episodes of hypoglycemia. These episodes are most likely to happen during the early morning hours after overnight fasting, when blood sugar level may drop to about 50 mg. They produce drowsiness and shaking chills accompanied by frank hunger.

Hepatorenal Syndrome Definition. Azotemia and oliguria (less than 500 cc of urine/day) in association with a low urine sodium concentration (less than 10 meq/L) in a patient with advanced liver disease. The condition is marked by severe renal vasoconstriction, the etiology of which is unknown. This occurs without any intrinsic renal disease. In fact, if kidneys from patients with hepatorenal syndrome were removed and put into a patient without cirrhosis they would work perfectly well.

Diagnosis. A low urine sodium and high urine osmolarity with a bland urinary sediment. This syndrome may be precipitated by infection (especially SBP [spontaneous bacterial peritonitis]), volume depletion from an overly aggressive diuresis or blood loss, or drugs such as aminoglycosides (antibiotics which are nephrotoxic) or NSAIDs (blocks the renal production of vasodilatory prostaglandins).

Pathophysiology is incompletely understood, but there are some humoral agents not cleared by the liver, which results in persistent vasoconstriction in the kidney.

Table 37

Symptoms and mechanisms associated with hepato-renal syndrome

Precipitant	Possible mechanism	Associated coprecipitant
GI bleeding	Nitrogen load, hepatic hypoperfusion, arterial hypoxemia	Infection, Banked blood transfusion,
Sepsis	Protein catabolism	Azotemia, hypotension, anemia
Hypokalemia (diarrhea, diuretics)	Ammonia generation	GI bleeding, Alikalosis
Dehydration (diuretics, paracentesis)	Hepatic hypoperfusion	Hypokalemia, Azotemia
Azotemia	Increased ammonia production (urealysis)	GI bleeding, Hypotension
Acute hepatitis	Hepatocellular dysfunction, Impaired detoxification	Sepsis

Hepatic Encephalopathy. A metabolic abnormality of CNS function which can occur in either fulminant or chronic liver disease. When it occurs in fulminant liver failure, it carries a poor prognosis.

Clinical features. It is often graded on a scale of I (personality changes, reversal of day-night cycle) to IV (frank coma). The diagnosis is made by the presence of asterixis (a flapping tremor of hands elicited by dorsiflexion at the wrists), constructional apraxia, and an abnormal EEG showing a general slowing.

Pathophysiology. Much debate exists, but it is clear that there is some neurotoxic substance escaping decontamination in the liver because of shunting around the liver and a decrease in hepatic function due to the loss of hepatocytes. GABA (gamma amino butyric acid). GABA is the principle inhibitory neurotransmitter in the brain. A study suggested that patients with hepatic encephalopathy had excessive amounts of circulating GABA. However, this study could not be reproduced.

Date	Grade	Teacher's signature

PATHOPHYSIOLOGY OF KIDNEY. KIDNEY INSUFFICIENCY

Relevance. Kidneys are the main effector organ of the systems providing water and electrolytic and acid-alkaline organism homeostasis. Functions of kidneys: support of constant volume of the circulating blood, ensuring constancy of blood osmotic pressure, support of constant ions concentration in blood, in particular hydrogen ions (acid and secretory function). Besides, kidneys take part in extrectionof final products of a metabolism from the body (excretory function), in a metabolism of vitamin D, carbohydrates and low-molecular proteins. Kidneys form renin, prostaglandins, kinin, erythropoietin and inhibitor of an erythropoiesis influences on kidneys regulation of arterial pressure and erythropoiesis.

A limited number of kidney processes provide the functions: filtration, reabsorption, secretion and incretion. Disorder of any of them inevitably leads to disorder of others. As kidneys are very sensitive to disorders of blood circulation and action of toxic substances, diseases of kidneys, various on an etiology, cause similar pathological processes in them and identical clinical manifestations (syndromes) which disrupts the body functioning. Thus, there is a need to study the main regularities of kidney processes disorders and the mechanisms of kidneys insufficiency connected with it.

Overall Objective is to be able to characterize the main reasons and mechanisms of urine production and urinary functions of kidneys disorders, pathogenesis of changes of diuresis and composition of urine.

The student should be able to (specific objectives):

1. Characterize the main reasons and pathogenetic mechanisms of filtration, reabsorption and secretion disorders, their manifestations.
2. Explain the mechanism of emerging changes in qualitative composition of urine.
3. Explain pathological components of urine by means of biochemical methods of research: protein, glucose, acetone, bilirubin to interpret their diagnostic value.

The student should be able to (required knowledge and skills):

1) explain the mechanism of urine formation (dep. normal physiology);

2) estimate the main indicators characterizing urine production and urinary functions of kidneys (dep. normal physiology);

3) define an order of carrying out high-quality reactions to the content in urine of protein, sugar, bilious pigments, acetone, and also to be able to determine the specific weight of urine (dep. normal physiology).

QUESTIONS TO THE LESSON

1. Main functions of kidneys. Causes of kidneys pathology (by the nature, an origin, level of primary realization of action).
2. Disorders of a glomerular filtration, reabsorption, secretion. Causes.
3. Frustration of a urine production and urination. Manifestations.
4. Changes of relative density and composition of urine. The causes and pathology of kidneys in which they are observed.
5. Extrarenal manifestations of disorders of kidneys function.
6. Types of pathology of kidneys by origin. Standard forms of pathology of kidneys.
7. Acute glomerulonephritis. Etiology. Pathogenesis. Classification. Manifestations.
8. Chronic glomerulonephritis. Etiology. Pathogenesis. Classification. Manifestations.
9. Pyelonephritis. Etiology. Risk factors. Pathogenesis. Manifestations.
10. Nephrotic syndrome. Definition of concept. Causes. Pathogenesis. Manifestations.
11. Renal failure. Definition of concept. Acute renal failure. Causes. Pathogenesis. Manifestations. Criteria of diagnostics.
12. Chronic renal failure. Etiology. Pathogenesis. Manifestations.
13. Chronic Illness of Kidneys (CIK). Definition of concept. Modern criteria of CIK. Classification. Markers of injury of kidneys (laboratory, visual). Assessment of kidneys function.
14. Uraemia. Definition of concept. Causes. Major factors of tissues and bodies damage in uraemia and kidney coma.
15. Nephrolithiasis, urolithiasis. Definition of concepts. Causes, conditions and mechanisms of development. Consequences.
16. Principles of treatment of disorders of functions of kidneys.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

Control of Renal Function

Kidneys are remarkable organs. Each of them is smaller than a person's fist, but in a single day, the two organs process approximately 1700 L of blood and combine its waste products into approximately 1.5 L of urine. As part of their function, the kidneys filter physiologically essential substances, such as sodium and potassium ions, from the blood and selectively reabsorb those substances that are needed to maintain the normal composition of internal body fluids. Substances that are not needed for this purpose or are in excess pass into the urine. In regulating the volume and composition of body fluids, kidneys perform excretory and endocrine functions. The renin-angiotensin mechanism participates in the regulation of blood pressure and the maintenance of circulating blood volume, and erythropoietin stimulates red blood cell production. The discussion in this chapter focuses on the structure and function of the kidneys, tests of renal function, and the physiologic action of diuretics.

GROSS STRUCTURE AND LOCATION

Kidneys are paired, bean-shaped organs that lie outside the peritoneal cavity in the back of the upper abdomen, one on each side of the vertebral column at the level of the 12th thoracic to 3rd lumbar vertebrae.

The right kidney normally is situated lower than the left, presumably because of the position of the liver. In the adult, each kidney is approximately 10 to 12 cm long, 5 to 6 cm wide, and 2.5 cm deep and weighs approximately 113 to 170 g. The medial border of the kidney is indented by a deep fissure called the hilus. It is here that blood vessels and nerves

enter and leave the kidney. The ureters, which connect the kidneys to the bladder, also enter the kidney at the hilus. The kidney is a multilobular structure, composed of up to 18 lobes. Each lobule is composed of nephrons, which are the functional units of the kidney. Each nephron has a glomerulus that filters the blood and a system of tubular structures that selectively reabsorb material from the filtrate back into the blood and secrete materials from the blood into the filtrate as urine is being formed. On longitudinal section, a kidney can be divided into an outer cortex and an inner medulla. The cortex, which is reddish brown, contains the glomeruli and convoluted tubules of the nephron and blood vessels. The medulla consists of light-colored, cone-shaped masses—the renal pyramids—that are divided by the columns of the cortex (i.e., columns of Bertin) that extend into the medulla. Each pyramid, topped by a region of cortex, forms a lobe of the kidney. The apices of the pyramids form thepapillae (i.e., 8 to 18 per kidney, corresponding to the number of lobes), which are perforated by the openings of the collecting ducts. The renal pelvis is a wide, funnelshaped structure at the upper end of the ureter. It is made up of the calyces or cuplike structures that drain the upper and lower halves of the kidney.

The kidney is ensheathed in a fibrous external capsule and surrounded by a mass of fatty connective tissue, especially at its ends and borders. The adipose tissue protects the kidney from mechanical blows, and it assists, together with the attached blood vessels and fascia, in holding the kidney in place. Although the kidneys are relatively well protected, they may be bruised by blows to the loin or by compression between the lower ribs and the ilium. Because the kidneys are outside the peritoneal cavity, injury and rupture do not produce the same threat of peritoneal involvement as the rupture of organs such as the liver or spleen

RENAL BLOOD SUPPLY

Each kidney is supplied by a single renal artery that arises on either side of the aorta. As the renal artery approaches the kidney, it divides into five segmental arteries that enter the hilus of the kidney. In the kidney, each segmental artery branches into several lobular arteries that supply the upper, middle, and lower parts of the kidney. The lobar arteries further subdivide to form the interlobular arteries at the level of the cortical medullary junction. These arteries give off branches, called the arcuate arteries, that arch across the top of the pyramids. The nephron is supplied by two capillary systems: the glomerulus and the peritubular capillary network. The glomerulus is a unique, high-pressure capillary filtration system located between two arterioles-the afferent and the efferent arterioles-that selectively dilate or constrict to regulate glomerular capillary pressure. The peritubular capillary network is a low-pressure reabsorptive system that originates from the efferent arteriole. These capillaries surround all portions of the tubules, an arrangement that permits rapid movement of solutes and water between the fluid in the tubular lumen and the blood in the capillaries. The medullary nephrons are supplied with two types of capillaries: the peritubular capillaries, which are similar to those in the cortex, and the vasa recta, which are long, straight capillaries. The vasa recta accompany the long loops of Henle in the medullary portion of the kidney to assist in exchange of substances flowing in and out of that portion of the kidney. The peritubular capillaries rejoin to form the venous channels by which blood leaves the kidneys and empties into the inferior vena cava. Under conditions of decreased perfusion or increased sympathetic nervous system stimulation, blood flow is redistributed away from the cortex toward the medulla. This redistribution of blood flow decreases glomerular filtration while maintaining the urine concentrating ability of the kidneys, a factor that is important during conditions such as shock.

NEPHRON. Each kidney is composed of more than 1 million of tiny, closely packed functional units called nephrons. Each nephron consists of a glomerulus, where blood is filtered, and a tubular component. Here, water, electrolytes, and other substances needed to maintain the constancy of the internal environment are reabsorbed into the bloodstream while other unneeded materials are secreted into the tubular filtrate for elimination.

Glomerulus consists of a compact tuft of capillaries encased in a thin, double-walled capsule, called Bowman's capsule. Blood flows into the glomerular capillaries from the afferent arteriole and flows out of the glomerular capillaries into the efferent arteriole, which leads into the peritubular capillaries. Fluid and particles from the blood are filtered through the capillary membrane into a fluid-filled space in Bowman's capsule, called Bowman's space. The portion of the blood that is filtered into the capsule space is called the filtrate. The mass of capillaries and its surrounding epithelial capsule are collectively referred to as the renal corpuscle.

The glomerular capillary membrane is composed of three layers: the capillary endothelial layer, the basement membrane, and the single-celled capsular epithelial layer. The endothelial layer lines the glomerulus and interfaces with blood as it moves through the capillary. This layer contains many small perforations, called fenestrations. The epithelial layer that covers the glomerulus is continuous with the epithelium that lines Bowman's capsule. The cells of the epithelial layer have unusual octopus-like structures that possess a large number of extensions, or foot processes (i.e., podocytes), which are embedded in the basement membrane. These foot processes form slit pores through which the glomerular filtrate passes. The basement membrane consists of a homogeneous acellular meshwork of collagen fibers, glycoproteins, and mucopolysaccharides.

Spaces between the fibers that make up the basement membrane represent pores of a filter and determine the size-dependent permeability barrier of the glomerulus. The size of the pores in the basement membrane normally prevents red blood cells and plasma proteins from passing through the glomerular membrane into the filtrate. There is evidence that the epithelium plays the major role in producing the basement membrane components, and it is probable that the epithelial cells are active in forming new basement membrane material throughout life.

Another important component of the glomerulus is the mesangium. In some areas, the capillary endothelium and the basement membrane do not completely surround each capillary. Instead, the mesangial cells, which lie between the capillary tufts, provide support for the glomerulus in these areas.

The mesangial cells produce an intercellular substance similar to that of the basement membrane. This substance covers the endothelial cells where they are not covered by basement membrane. Mesangial cells also exhibit contractile properties in response to neurohumoral substances and are thought to contribute to the regulation of blood flow through the glomerulus. In normal glomeruli, the mesangial area is narrow and contains only a small number of cells.

Tubular Components of the Nephron. The nephron tubule is divided into four segments: a highly coiled segment called the proximal convoluted tubule, which drains Bowman's capsule; a thin, looped structure called the loop of Henle; a distal coiled portion called the distal convoluted tubule; and the final segment called the collecting tubule, which joins with several tubules to collect the filtrate. The filtrate passes through each of these segments before reaching the pelvis of the kidney. Nephrons can be roughly grouped into two categories. Approximately 85 % of the nephrons originate in the superficial part of the cortex and are called cortical nephrons. They have short, thick loops of Henle that penetrate only a short distance into the medulla. The remaining 15 % are called juxtamedullary nephrons. They originate deeper in the cortex and have longer and thinner loops of Henle that penetrate the entire length of the medulla. The juxtamedullary nephrons are largely concerned with urine concentration. The proximal tubule is a highly coiled structure that dips toward the renal pelvis to become the descending limb of the loop of Henle. The ascending loop of Henle returns to the region of the renal corpuscle, where it becomes the distal tubule. The distal convoluted tubule, which begins at the juxtaglomerular complex, is divided into two segments: the diluting segment and the late distal tubule. The late distal tubule fuses with the collecting tubule. Like the distal tubule, the collecting duct is divided into two segments: the cortical collecting tubule and the inner medullary collecting tubule. Throughout its course, the tubule is composed of a single layer of epithelial cells resting on a basement membrane. The structure of the epithelial cells varies with tubular function. The

cells of the proximal tubule have a fine villous structure that increases the surface area for reabsorption; they also are rich in mitochondria, which support active transport processes.

Tubular Reabsorption and Secretion. From Bowman's capsule, the glomerular filtrate moves into the tubular segments of the nephron. In its movement through the lumen of the tubular segments, the glomerular filtrate is changed considerably by the tubular transport of water and solutes. Tubular transport can result in reabsorption of substances from the tubular fluid into the blood or secretion of substances into the tubular fluid from the blood. The basic mechanisms of transport across the tubular epithelial cell membrane are similar to those of other cell membranes in the body and include active and passive transport mechanisms. Water and urea are passively absorbed along concentration gradients. Sodium, potassium, chloride, calcium, and phosphate ions, as well as urate, glucose, and amino acids, are reabsorbed using primary or secondary active transport mechanisms to move across the tubular membrane. This means that the average output of urine is approximately 60 mL/hour. Renal tubular cells have two membrane surfaces through which substances must pass as they are reabsorbed from the tubular fluid. The side of the cell that is in contact with the tubular lumen and tubular filtrate is called the luminal membrane. The outside membrane that lies adjacent to the interstitial fluid is called the basolateral membrane. In most cases, substances move from the tubular filtrate into the tubular cell along a concentration gradient, but they require facilitated transport or carrier systems to move across the basolateral membrane into the interstitial fluid, where they are absorbed into the peritubular capillaries. The bulk of energy used by the kidney is for active sodium transport mechanisms that facilitate sodium reabsorption and cotransport of other electrolytes and substances such as glucose and amino acids. This is called secondary active transport or cotransport.

Secondary active transport depends on the energy-dependent sodium-potassium adenosine triphosphatase (ATPase) pump on the basolateral side of renal tubular cells. Cotransport uses a carrier system in which the downhill movement of one substance such as sodium is coupled to the uphill movement (i.e., from a lower to higher concentration) of another substance such as glucose or an amino acid.

Proximal Tubule. Approximately 65 % of all reabsorptive and secretory processes that occur in the tubular system take place in the proximal tubule. There is almost complete reabsorption of nutritionally important substances, such as glucose, amino acids, lactate, and water-soluble vitamins. Electrolytes, such as sodium, potassium, chloride, and bicarbonate, are 65 to 80 % reabsorbed. As these solutes move into the tubular cells, their concentration in the tubular lumen decreases, providing a concentration gradient for the osmotic reabsorption of water and urea. The proximal tubule is highly permeable to water, and the osmotic movement of water occurs so rapidly that the concentration difference of solutes on either side of the membrane seldom is more than a few milliosmoles. Many substances, such as glucose, are freely filtered in the glomerulus and reabsorbed by energy-dependent cotransport carrier mechanisms.

The maximum amount of substance that these transport systems can reabsorb per unit of time is called the transport maximum. The transport maximum is related to the number of carrier proteins that are available for transport and usually is sufficient to ensure that all of a filtered substance such as glucose can be reabsorbed rather than being eliminated in the urine. The plasma level at which the substance appears in the urine is called the renal threshold. Under some circumstances, the amount of substance filtered in the glomerulus exceeds the transport maximum. For example, when the blood glucose level is elevated in uncontrolled diabetes mellitus, the amount that is filtered in the glomerulus often exceeds the transport maximum (approximately 320 mg/ minute), and glucose spills into the urine.

The Loop of Henle. The loop of Henle is divided into three segments: a thin descending segment, athin ascending segment, and a thick ascending segment. Each of these segments has special structural and functional properties. Fluid that enters the loop of Henle is iso-osmotic to plasma, but it becomes hypo-osmotic as it moves through the loop. The thin descending limb is highly permeable to water and moderately permeable to urea, sodium, and other ions. The

ascending limb, in contrast to the descending limb, is impermeable to water. As fluid moves down the descending limb, water is reabsorbed until the osmolality of the tubular fluid reaches an equilibrium with the interstitial fluid, which is more hypertonic. In the ascendingм limb, which is impermeable to water, solutes are reabsorbed, but water cannot follow; as a result, the tubular fluid becomes more and more dilute, often reaching an osmolality of 100 mOsm/kg of H_2O as it enters the distal convoluted tubule, compared with the 285 mOsm/kg of H_2O in plasma.

The thick segment of the loop of Henle begins in the ascending limb where the epithelial cells become thickened. As with the thin ascending limb, this segment is impermeable to water. The thick segment contains a Na+/K+–2Cl− cotransport system. This system involves the cotransport of a positively charged sodium and a positively charged potassium ion accompanied by two negatively charged chloride ions. The gradient for the operation of this cotransport system is provided by the basolateral sodium–potassium pump, which maintains a low intracellular sodium concentration. The repetitive reabsorption of sodium chloride from the thick ascending limb of Henle and the continued inflow of new sodium chloride from the proximal tubule into the loop of Henle serve to trap solutes in the medullary interstitium, contributing to the high osmolality in this part of the nephron. Approximately 20 to 25 % of the filtered load of sodium, potassium, and chloride is reabsorbed in the thick loop of Henle.

Movement of these ions out of the tubule leads to the development of a transmembrane po-tential that favors the passive reabsorption of small divalent cations such as calcium and magnesium. Sodium reabsorption occurs in the proximal tubule, the thick ascending loop of Henle, and the distal tubule, where aldosterone regulates sodium and potassium exchange. A countercurrent mechanism controls water and solute movement so that water is kept out of the peritubular area and sodium and urea are retained. The term countercurrent refers to a flow of fluids in opposite directions in adjacent structures. Because of these exchange processes, a high concentration of osmotically active particles (approximately 1200 mOsm/kg of H_2O) collects in the interstitium of the kidney medulla. The presence of these osmoti-cally active particles in the interstitium surrounding the medullary collecting tubules facilitates the antidiuretic hormone (ADH)–mediated reabsorption of water (see following discussion). Distal Convoluted Tubule. Like the thick ascending loop of Henle, the distal convoluted tubule is relatively impermeable to water, and reabsorption of sodium chloride from this segment further dilutes the tubular fluid.

Sodium reabsorption occurs through a sodium and chloride cotransport mechanism. Approximately 10 % of filtered sodium chloride is reabsorbed in this section of the tubule. Unlike the thick ascending loop of Henle, neither calcium nor magnesium is passively absorbed in this segment of the tubule. Instead, calcium ions are actively reabsorbed in a process that is largely regulated by parathyroid hormone and possibly by vitamin D.

The thick ascending loop of Henle, the distal tubule, and the cortical collecting tubule are often referred to as the diluting segment of the tubule. As solutes are reabsorbed from these segments, the urine becomes more and more dilute, often reaching an osmolar concentration that is equal to or less than that of plasma. This allows excretion of free water from the body.

Late Distal Tubule and Cortical Collecting Tubule. The late distal tubule and the cortical collecting tubule constitute the site where aldosterone exerts its action on sodium and potassium reabsorption. Although responsible for only 2 to 5 % of sodium chloride reabsorption, this site is largely responsible for determining the final sodium concentration of the urine. Late distal tubule with the cortical collecting tubule also is the major site for regulation of potassium excretion by the kidney. When the body confronts with potassium excess, as occurs with a diet high in potassium content, the amount of potassium secreted at this site may exceed the amount filtered in the glomerulus.

The mechanism for sodium reabsorption and potassium secretion by this section of the kidney is distinct from other tubular segments. This tubular segment is composed of two types of cells: the principal cells and the intercalated cells. The principal cells reabsorb sodium and

water from the tubular filtrate and secrete potassium into the tubular filtrate. The intercalated cells reabsorb potassium and secrete hydrogen ions into the tubular filtrate. The principal cells use separate channels for transport of sodium and potassium rather than cotransport mechanisms. Aldosterone is thought to exert its effect on sodium and potassium excretion by increasing the number of ion channels and the function of the basolateral sodium–potassium pump. Medullary Collecting Duct. The epithelium of the inner medullary collecting duct is well designed to resist extreme changes in the osmotic or pH characteristics of tubular fluid, and it is here that the urine becomes highly concentrated, highly diluted, highly alkaline, or highly acidic. During periods of water excess or dehydration, the kidneys play a major role in maintaining water balance. ADH exerts its effect in the medullary collecting duct. ADH maintains extracellular volume by returning water to the vascular compartment and leads to the production of a concentrated urine by removing water from the tubular filtrate. Osmoreceptors in the hypothalamus sense the increase in osmolality of extracellular fluids and stimulate the release of ADH from the posterior pituitary gland. The permeability of the collecting ducts to water is determined mainly by the concentration of ADH. In exerting its effect, ADH, also known as vasopressin, binds to vasopressin receptors on the basolateral side of the tubular cells. Binding of ADH to the vasopressin receptors causes water channels, known as aquaporin-2 channels, to move into the luminal side of the tubular cell membrane, producing a marked increase in water permeability. At the basolateral side of the membrane, water exits the tubular cell through aquaporin-3 and aquaporin-4 cells into the hyperosmotic interstitium of the medullary area, where it enters the peritubular capillaries for return to the vascular system. In the absence of ADH, the inserted aquaporin channels are removed, the tubular cells lose their water permeability, and dilute urine is formed.

Regulation of renal blood flow

In adults, kidneys are perfused with 1000 to 1300 mL of blood per minute this large blood flow is mainly needed to ensure a sufficient GFR for the removal of waste products from the blood, rather than for the metabolic needs of the kidney. Feedback mechanisms, both intrinsic (e.g., autoregulation, local hormones) and extrinsic (e.g., sympathetic nervous system, blood-borne hormones), normally keep blood flow and GFR constant despite changes in arterial blood pressure. Neural and Humoral Control Mechanisms. The kidney is richly innervated by the sympathetic nervous system. Increased sympathetic activity causes constriction of the afferent and efferent arterioles and thus a decrease in renal blood flow. Intense sym-pathetic stimulation such as occurs in shock and trauma can produce marked decreases in renal blood flow and GFR, even to the extent of causing blood flow to cease altogether. Several humoral substances, including angiotensin II, ADH, and endothelins, cause vasoconstriction of renal vessels. The endothelins are a group of peptides released from damaged endothelial cells in the kidney and other tissues.

Other substances such as dopamine, nitric oxide, and prostaglandins (i.e., E2 and I2) produce vasodilation. Nitric oxide, a vasodilator produced by the vascular endothelium, appears to be important in preventing excessive vasoconstriction of renal blood vessels and allowing normal excretion of sodium and water. Prostaglandins are a group of mediators of cell function that are produced locally and exert their effects locally. Although prostaglandins do not appear to be of major importance in regulating renal blood flow and GFR under normal conditions, they may protect the kidneys against the vasoconstricting effects of sympathetic stimulation and angiotensin II. Aspirin and nonsteroidal antiinflammatory drugs that inhibit prostaglandin synthesis may cause reduction in renal blood flow and GFR under certain conditions. Autoregulation. Constancy of renal blood flow is maintained by a process called autoregulation. Normally, autoregulation of blood flow is designed to maintain blood flow at a level consistent with the metabolic needs of the tissues. In the kidney, autoregulation of blood flow also must allow for precise regulation of renal excretion of water and solutes. For autoregulation to occur, the resistance to blood flow through the kidneys must be varied in

direct proportion to the arterial pressure. The exact mechanisms responsible for the intrarenal regulation of blood flow are unclear. One of the proposed mechanisms is a direct effect on vascular smooth muscle that causes the blood vessels to relax when there is an increase in blood pressure and to constrict when there is a decrease in pressure. A second proposed mechanism is the juxtaglomerular complex.

The Juxtaglomerular Complex. The juxtaglomerular complex is thought to represent a feedback control system that links changes in the GFR with renal blood flow. The juxtaglomerular complex is located at the site where the distal tubule extends back to the glomerulus and then passes between the afferent and efferent arteriole. The distal tubular site that is nearest the glomerulus is characterized by densely nucleated cells called the macula densa. In the adjacent afferent arteriole, the smooth muscle cells of the media are modified as special secretory cells called juxtaglomerular cells. These cells contain granules of inactive renin, an enzyme that functions in the conversion of angiotensinogen to angiotensin. Renin functions by means of angiotensin II to produce vasoconstriction of the efferent arteriole as a means of preventing serious decreases in GFR. Angiotensin II also increases sodium reabsorption indirectly by stimulating aldosterone secretion from the adrenal gland and directly by increasing sodium reabsorption by the proximal tubule cells.

Because of its location between the afferent and efferent arteriole, the juxtaglomerular complex is thought to play an essential feedback role in linking the level of arterial blood pressure and renal blood flow to the GFR and the composition of the distal tubular fluid. The juxtaglomerular complex monitors the systemic blood pressure by sensing the stretch of the afferent arteriole, and it monitors the concentration of sodium chloride in the tubular filtrate as it passes through the macula densa. This information is then used in determining how much renin should be released to keep the arterial blood pressure within its normal range and maintain a relatively constant GFR.

Effect of Increased Protein and Glucose Load. Although renal blood flow and glomerular filtration are relatively stable under most conditions, two conditions can increase renal blood flow and glomerular filtration. These are an increased amount of protein in the diet and an increase in blood glucose. With ingestion of a high-protein diet, renal blood flow increases 20 % to 30 % within 1 to 2 hours. Although the exact mechanism for this increase is uncertain, it is thought to be related to the fact that amino acids and sodium are absorbed together in the proximal tubule (secondary active transport). As a result, delivery of sodium to the macula densa is decreased, which elicits an increase in renal blood flow through the juxtaglomerular complex feedback mechanism. The resultant increase in blood flow and GFR allows sodium excretion to be maintained at a near-normal level while increasing the excretion of the waste products of protein metabolism, such as urea.

ELIMINATION FUNCTIONS OF THE KIDNEY

Renal Clearance is the volume of plasma completely cleared each minute of any substance that finds its way into the urine. It is determined by the ability of the substance to be filtered in the glomeruli and the capacity of the renal tubules to reabsorb or secrete the substance. Every substance has its own clearance rate, the units of which are always in volume of plasma cleared per unit of time. It can be determined by measuring the amount of a substance that is excreted in the urine (i.e., urine concentration urine flow rate in milliliters per minute) and dividing by its plasma concentration. Inulin, a large polysaccharide, is freely filtered in the glomeruli and neither reabsorbed nor secreted by the tubular cells. After intravenous injection, the amount that appears in the urine is equal to the amount that is filtered in the glomeruli (i.e., the clearance rate is equal to the GFR). Because of these properties, inulin can be used as a laboratory measure of the GFR. Some substances, such as urea, are freely filtered in the glomeruli, but the volume that is cleared from the plasma is less than the GFR, indicating that at least some of the substance is being reabsorbed. At normal plasma levels, glucose has a clearance of zero because it is reabsorbed in the tubules and none appears in the urine.

Regulation of Sodium and Potassium Elimination. Elimination of sodium and potassium is regulated by the GFR and by humoral agents that control their reabsorption. Aldosterone functions in the regulation of sodium and potassium elimination. Atrial natriuretic peptide (ANP) contributes to the regulation of sodium elimination.

Aldosterone. Sodium reabsorption in the distal tubule and collecting duct is highly variable and depends on the presence of aldosterone, a hormone secreted by the adrenal gland. In the presence of aldosterone, almost all the sodium in the distal tubular fluid is reabsorbed, and the urine essentially becomes sodium free. In the absence of aldosterone, virtually no sodium is reabsorbed from the distal tubule. The remarkable ability of the distal tubular and collecting duct cells to alter sodium reabsorption in relation to changes in aldosterone allows the kidneys to excrete urine with sodium levels that range from a few tenths of a gram to 40 g/day. Like sodium, potassium is freely filtered in the glomerulus, but unlike sodium, potassium is reabsorbed from and secreted into the tubular fluid. Secretion of potassium into the tubular fluid occurs in the distal tubule and, like that of sodium, is regulated by aldosterone. Only approximately 70 mEq of potassium is delivered to the distal tubule each day, but the average person consumes this much or more potassium in the diet. Excess potassium that is not filtered in the glomerulus and delivered to the collecting tubule therefore must be secreted (i.e., transported from the blood) into the tubular fluid for elimination from the body. In the absence of aldosterone, potassium secretion becomes minimal. In these circumstances, potassium reabsorption exceeds secretion, and blood levels of potassium increase.

Atrial Natriuretic Peptide. Atrial natriuretic peptide is a hormone believed to have an important role in salt and water excretion by the kidney. It is synthesized in muscle cells of the atria of the heart and released when the atria are stretched. The actions of ANP include vasodilation of the afferent and efferent arterioles, which results in an increase in renal blood flow and GFR. ANP inhibits aldosterone secretion by the adrenal gland and sodium reabsorption from the collecting tubules through its action on aldosterone and through direct action on the tubular cells. It also inhibits ADH release from the posterior pituitary gland, thereby increasing excretion of water by the kidneys. ANP also has vasodilator properties. Whether these effects are sufficient to produce longterm changes in blood pressure is uncertain. Regulation of pH The kidneys regulate body pH by conserving base bicarbonate and eliminating hydrogen ions (H+). Neither the blood buffer systems nor the respiratory control mechanisms for carbon dioxide elimination can eliminate hydrogen ions from the body. This is accomplished by the kidneys.

The ability of kidneys to excrete hydrogen ions depends on buffers in the urine that combine with the hydrogen ion. The three major urine buffers are bicarbonate (HCO_3^-), phosphate (HPO_4^-), and ammonia (NH_3). Bicarbonate ions, which are present in the urine filtrate, combine with hydrogen ions that have been secreted into the tubular fluid; this results in the formation of carbon dioxide and water. Carbon dioxide is then absorbed into the tubular cells, and bicarbonate is regenerated. Phosphate ion is a metabolic end product that is filtered into the tubular fluid; it combines with a secreted hydrogen ion and is not reabsorbed. Ammonia is synthesized in tubular cells by deamination of the amino acid glutamine; it diffuses into the tubular fluid and combines with the hydrogen ion. An important aspect of this buffer system is that the deamination process increases whenever the body's hydrogen ion concentration remains elevated for 1 to 2 days.

Uric Acid Elimination. Uric acid is a product of purine metabolism. Excessively high blood levels (i.e., hyperuricemia) can cause gout, and excessive levels in the urine can cause kidney stones. Uric acid is freely filtered in the glomerulus and is reabsorbed and then secreted back into the proximal tubules. Uric acid is one of the anions that use the previously described anion transport system in the proximal tubule. Tubular reabsorption normally exceeds secretion, and the net effect is removal of uric acid from the filtrate. Although the rate of reabsorption exceeds secretion, the secretory process is homeostatically controlled to maintain

a constant plasma level. Many persons with elevated uric acid levels secrete less uric acid than do persons with normal uric acid levels.

Urea Elimination. Urea is an end product of protein metabolism. Normal adult produces 25 to 30 g/day; the quantity rises when a high-protein diet is consumed, when there is excessive tissue breakdown, or in the presence of gastrointestinal bleeding. With gastrointestinal bleeding, the blood proteins are broken down to form ammonia in the intestine; the ammonia is then absorbed into the portal circulation and converted to urea by the liver before being released into the bloodstream. The kidneys, in their role as regulators of blood urea nitrogen (BUN) levels, filter urea in the glomeruli and then reabsorb it in the tubules. This enables maintenance of a normal BUN, which is in the range of 8 to 25 mg/dL (2.9 to 8.9 mmol/L). During periods of dehydration, the blood volume and GFR drop, and BUN levels increase. The renal tubules are permeable to urea, which means that the longer the tubular fluid remains in the kidneys, the greater is the reabsorption of urea into the blood. Only small amounts of urea are reabsorbed into the blood when the GFR is high, but relatively large amounts of urea are returned to the blood when the GFR is reduced.

Endocrine functions of the kidney. In addition to their function in regulating body fluids and electrolytes, kidneys function as an endocrine organ in that they produce chemical mediators that travel through the blood to distant sites where they exert their actions. Kidneys participate in control of blood pressure by way of the renin-angiotensin mechanism, in calcium metabolism by activating vitamin D, and in regulating red blood cell production through the synthesis of erythropoietin.

Erythropoietin is a polypeptide hormone that regulates differentiation of red blood cells in the bone marrow. Between 89 and 95 % of erythropoietin is formed in the kidneys. Synthesis of erythropoietin is stimulated by tissue hypoxia, which may be brought about by anemia, residence at high altitudes, or impaired oxygenation of tissues due to cardiac or pulmonary disease. Persons with end-stage kidney disease often are anemic because of an inability of the kidneys to produce erythropoietin. This anemia usually is managed by the administration of epoetin-alfa, a synthetic form of erythropoietin produced through DNA technology, to stimulate erythropoiesis.

Vitamin D. Activation of vitamin D occurs in kidneys. Vitamin D increases calcium absorption from the gastrointestinal tract and helps to regulate calcium deposition in bone. It also has a weak stimulatory effect on renal calcium absorption. Although vitamin D is not synthesized and released from an endocrine gland, it often is considered as a hormone because of its pathway of molecular activation and mechanism of action. Vitamin D exists in several forms: natural vitamin D (cholecalciferol), which results from ultraviolet irradiation of the skin, and synthetic vitamin D (ergocalciferol), which is derived from irradiation of ergosterol. The active form of vitamin D is 1,25-dihydroxycholecalciferol. Cholecalciferol and ergocalciferol must undergo chemical transformation to become active: first to 25-hydroxycholecalciferol in the liver and then to 1,25-dihydroxycholecalciferol in the kidneys. Persons with end-stage renal disease are unable to transform vitamin D to its active form and must rely on pharmacologic preparations of the active vitamin (calcitriol) for maintaining mineralization of their bones. The function of kidneys is to filter blood, selectively reabsorb those substances that are needed to maintain the constancy of body fluid, and excrete metabolic wastes. Composition of urine and blood provides valuable information about the adequacy of renal function.

The Renin-Angiotensin-Aldosterone Mechanism

The renin-angiotensin-aldosterone mechanism plays an important part in short-term and long-term regulation of blood pressure. Renin is an enzyme that is synthesized and stored in the juxtaglomerular cells of the kidney. This enzyme is thought to be released in response to a decrease in renal blood flow or a change in the composition of the distal tubular fluid, or as the result of sympathetic nervous system stimulation. Renin itself has no direct effect on blood pressure. Rather, it acts to convert a circulating plasma protein called angiotensinogen to angiotensin I.

Angiotensin I, which has few vasoconstrictor properties, leaves kidneys and enters the circulation; as it is circulated through the lungs, angiotensin-converting enzyme catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor, and it acts directly on the kidneys to decrease salt and water excretion. Both mechanisms have relatively short periods of action.

Angiotensin II also stimulates aldosterone secretion by the adrenal gland. Aldosterone acts on the distal tubule to increase sodium reabsorption and exerts a longer-term effect on the maintenance of blood pressure. Renin also functions by means of angiotensin II to produce constriction of the efferent arteriole as a means of preventing a serious decrease in glomerular filtration pressure.

Urinalysis. Urine is a clear, amber-colored fluid approximately 95 % water and 5 % dissolved solids. Kidneys normally produce approximately 1.5 L of urine each day. Normal urine contains metabolic wastes and few or no plasma proteins, blood cells, or glucose molecules. Urine tests can be performed on a single urine specimen or on a 24-hour urine specimen. First-voided morning specimens are useful for qualitative protein and specific gravity testing. A freshly voided specimen is most reliable. Urine specimens that have been left standing may contain lysed red blood cells, disintegrating casts, and rapidly multiplying bacteria. (*Table 38)* describes urinalysis values for normal urine. Casts are molds of the distal nephron lumen. A gellike substance called Tamm-Horsfall mucoprotein, which is formed in the tubular epithelium, is the major protein constituent of urinary casts. Casts composed of this gel but devoid of cells are called hyaline casts. These casts develop when the protein concentration of the urine is high (as in nephrotic syndrome), urine osmolality is high, and urine pH is low. The inclusion of granules or cells in the matrix of the protein gel leads to the formation of various other types of casts. Because of the glomerular capillary filtration barrier, less than 150 mg of protein is excreted in the urine over 24 hours in a healthy person. Qualitative and quantitative tests to determine urinary protein content are important tools to assess the extent of glomerular disease. pH-sensitive reagent strips are used to test for the presence of proteins, whereas immunoassay methods are used to test for microalbuminuria. The specific gravity (or osmolality) of urine varies with its concentration of solutes. Urine specific gravity provides a valuable index of the hydration status and functional ability of the kidneys. Although there are more sophisticated methods for measuring specific gravity, it can be measured easily using an inexpensive piece of equipment called a urinometer. Healthy kidneys can produce a concentrated urine with a specific gravity of 1.030 to 1.040.

During periods of marked hydration, the specific gravity can approach 1.000. With diminished renal function, there is a loss of renal concentrating ability, and the urine specific gravity may fall to levels of 1.006 to 1.010 (usual range is 1.010 to 1.025 with normal fluid intake). These low levels are particularly significant if they occur during periods that follow a decrease in water intake (e.g., during the first urine specimen on arising in the morning).

Table 38

Normal values for routhine urinalysys

General Characteristics and Measurements	Chemical Determinations	Microscopic Examination of Sediment
Color: yellow-amber—indicates a high specific gravity and small output of urine	Glucose: negative	Casts negative: occasional hyaline casts
Turbidity: clear to slightly hazy	Ketones: negative	Red blood cells: negative or rare
Specific gravity: 1.010–1.025 with a normal fluid intake	Blood: negative	Crystals: negative
pH: 4.6–4.8—average person has a pH of about 6 (acid)	Protein: negative	White blood cells; negative or rare
	Bilirubin: negative	Epithelial cells: few
	Urobilinogen: 0.1–1	
	Nitrate for bacteria: negative	
	Leukocyte esterase: negative	

Glomerular filtration rate. The GFR provides a gauge of renal function. It can be measured clinically by collecting timed samples of blood and urine. Creatinine, a byproduct of creatine metabolism by the muscle, is filtered by the kidneys but not reabsorbed in the renal tubule. Creatinine levels in the blood and urine can be used to measure GFR. The clearance rate for creatinine is the amount that is completely cleared by the kidneys in 1 minute.

The formula is expressed as C = UV/P, in which C is the clearance rate (mL/minute), U is the urine concentration (mg/dL), V is the urine volume excreted (mL/minute or 24 hours), and P is plasma concentration (mg/dL). Normal creatinine clearance is 115 to 125 mL/minute. This value is corrected for body surface area, which reflects the muscle mass where creatinine metabolism takes place. The test may be done on a 24-hour basis, with blood being drawn when the urine collection is completed. In another method, two 1-hour urine specimens are collected, and a blood sample is drawn in between.

Blood tests can provide valuable information about the kidneys' ability to remove metabolic wastes from the blood and maintain normal electrolyte and pH composition of the blood. Serum levels of potassium, phosphate, BUN, and creatinine increase in renal failure.

Table 39

Normal blood chemistry levels

Substance	Normal Value*
Blood urea nitrogen	8.0–20.0 mg/dL (2.9–7.1 mmol/L)
Creatinine	0.6–1.2 mg/dL (50–100 mmol/L)
Sodium	135–145 mEq/L (135–148 mmol/L)
Chloride	98–106 mEq/L (98–106 mmol/L)
Potassium	3.5–5 mEq/L (3.5–5 mmol/L)
Carbon dioxide (CO_2 content)	24–29 mEq/L (24–29 mmol/L)
Calcium	8.5–10.5 mg/dL (2.1–2.6 mmol/L)
Phosphate	2.5–4.5 mg/dL (0.77–1.45 mmol/L)
Uric acid	1.4–7.4 mg/dL (0.154–0.42 mmol/L)
pH	7.35–7.45

Serum pH, calcium, and bicarbonate levels decrease in renal failure. Serum Creatinine Serum creatinine levels reflect the glomerular filtration rate. Because these measurements are easily obtained and relatively inexpensive, they often are used as a screening measure of renal function. Creatinine is a product of creatine metabolism in muscles; its formation and release are relatively constant and proportional to the amount of muscle mass present. Creatinine is freely filtered in the glomeruli, is not reabsorbed from the tubules into the blood, and is only minimally secreted into the tubules from the blood; therefore, its blood values depend closely on the GFR.

The normal creatinine value is approximately 0.6 mg/dL of blood for a woman with a small frame, approximately 1.0 mg/dL of blood for a normal adult man, and approximately 1.2 mg/dL of blood (50 to 100 mmol/L) for a muscular man. Because both muscle mass and GFR decline with age, serum creatinine values should be adjusted in the elderly to account for the changes. A normal serum creatinine level usually indicates normal renal function. In addition to its use in calculating the GFR, the serum creatinine level is used in estimating the functional capacity of the kidneys. If the value doubles, the GFR—and renal function—probably has fallen to one half of its normal state. A rise in the serum creatinine level to three times its normal value suggests that there is a 75 % loss of renal function, and with creatinine values of 10 mg/dL or more, it can be assumed that approximately 90 % of renal function has been lost. Recently, it has been proposed that another serum protein, cystatin-C (a cysteine protease inhibitor), could be useful as a marker of GFR because it has a stable production rate, is freely filtered at the glomerulus, and in several studies to date has shown a greater sensitivity in detecting a decreased GFR. Further clinical studies are needed to determine the clinical efficacy of cystatin-C as a marker and to determine whether there is an advantage in its use compared with creatinine.

Blood Urea Nitrogen. Urea is formed in the liver as a byproduct of protein metabolism and is eliminated entirely by the kidneys. BUN therefore is related to the GFR but, unlike creatinine, also is influenced by protein intake, gastrointestinal bleeding, and hydration status.

Increased protein intake and gastrointestinal bleeding increase urea by means of protein metabolism. In gastrointestinal bleeding, the blood is broken down by the intestinal flora, and the nitrogenous waste is absorbed into the portal vein and transported to the liver, where it is converted to urea. During dehydration, elevated BUN levels result from increased concentration. Approximately two thirds of renal function must be lost before a significant rise in the BUN level occurs. The BUN is less specific for renal insufficiency than creatinine, but the BUN–creatinine ratio may provide useful diagnostic information. The ratio normally is approximately 10/1. Ratios greater than 15/1 represent prerenal conditions, such as congestive heart failure and upper gastrointestinal tract bleeding, that produce an increase in BUN but not in creatinine. A ratio of less than 10/1 occurs in persons with liver disease and in those who receive a low-protein diet or chronic dialysis because BUN is more readily dialyzable than creatinine.

RENAL FAILURE

Renal failure is a condition in which the kidneys fail to remove metabolic end products from the blood and regulate the fluid, electrolyte, and pH balance of the extracellular fluids. The underlying cause may be renal disease, systemic disease, or urologic defects of nonrenal origin. Renal failure can occur as an acute or a chronic disorder. Acute renal failure is abrupt in onset and often is reversible if recognized early and treated appropriately. In contrast, chronic renal failure is the end result of irreparable damage to the kidneys. It develops slowly, usually over the course of a number of years.

Acute renal failure

Acute renal failure represents a rapid decline in renal function sufficient to increase blood levels of nitrogenous wastes and impair fluid and electrolyte balance. Unlike chronic renal failure, acute renal failure is potentially reversible if the precipitating factors can be corrected or removed before permanent kidney damage has occurred. Acute renal failure is a common threat to seriously ill persons in intensive care units, with a mortality rate ranging from 40 % to 75 %. Although treatment methods such as dialysis and renal replacement methods are effective in correcting life-threatening fluid and electrolyte disorders, the mortality rate from acute renal failure has not changed substantially since the 1960s. This probably is because acute renal failure is seen more often in older persons than before, and because it frequently is superimposed on other life-threatening conditions, such as trauma, shock, and sepsis. The most common indicator of acute renal failure is azotemia, an accumulation of nitrogenous wastes (urea nitrogen, uric acid, and creatinine) in the blood. In acute renal failure, the glomerular filtration rate (GFR) is decreased. As a result, excretion of nitrogenous wastes reduces, and fluid and electrolyte balance cannot be maintained.

Types of acute renal failure

Acute renal failure can be caused by several types of conditions, including a decrease in blood flow without ischemic injury; ischemic, toxic, or obstructive tubular injury; and obstruction of urinary tract outflow.

The causes of acute renal failure commonly are categorized as **prerenal, intrinsic, and postrenal.**

Prerenal Failure

Prerenal failure, the most common form of acute renal failure, is characterized by a marked decrease in renal blood flow. It is reversible if the cause of the decreased renal blood flow can be identified and corrected before kidney damage occurs.

Causes of prerenal failure include profound depletion of vascular volume (e.g., hemorrhage, loss of extracellular fluid volume), impaired perfusion due to heart failure and cardiogenic shock, and decreased vascular filling because of increased vascular capacity (e.g., anaphylaxis or sepsis). Elderly persons are particularly at risk because of their predisposition to hypovolemia and their high prevalence of renal vascular disorders. Some vasoactive mediators, drugs, and diagnostic agents stimulate intense intrarenal vasoconstriction and induce glomerular hypoperfusion and prerenal failure.

Examples include hypercalcemia, endotoxins, radiocontrast agents such as those used for cardiac catheterization, cyclosporine (an immunosuppressant drug that is used to prevent transplant rejection), amphotericin B (an antifungal agent), epinephrine, and high doses of dopamine. Many of these drugs also cause acute tubular necrosis (discussed later). In addition, several commonly used classes of drugs impair renal adaptive mechanisms and can convert compensated renal hypoperfusion into prerenal failure. Angiotensin-converting enzyme (ACE) inhibitors reduce the effects of renin on renal blood flow; when combined with diuretics, they may cause prerenal failure in persons with decreased blood flow due to large or small vessel renal vascular disease. Prostaglandins have a vasodilatory effect on renal blood vessels. Nonsteroidal anti-inflammatorydrugs (NSAIDs) reduce renal blood flow through inhibition of prostaglandin synthesis. In somepersons with diminished renal perfusion, NSAIDs can precipitate prerenal failure. A new class of NSAIDs that selectively inhibit the cyclooxygenase type 2 (COX-2) isoform of the enzyme have become widely available for clinical use. Although the NSAIDS that selectively inhibit COX-2are less toxic to the gastrointestinal tract, they appear to exert the same effect on the kidney as the conventional nonselective NSAIDS. This large blood supply is required to remove metabolic wastes and regulate body fluids and electrolytes. Fortunately, the normal kidney can tolerate relatively large reductions in blood flow before renal damage occurs. As renal blood flow is reduced, the GFR decreases, the amount of sodium and other substances that is filtered by the glomeruli is reduced, and the need for energy-dependent mechanisms to reabsorb these substance is reduced. As the GFR and urineoutput approach zero, oxygen consumption by the kidney approximates that required to keep renal tubular cells alive. Acute renal failure is manifested by a sharp decrease in urine output and a disproportionate elevation of blood urea nitrogen (BUN) in relation to serum creatinine levels. The kidney normally responds to a decrease in the GFR with a decrease in urine output. Thus, an early sign of prerenal failure is a sharp decrease in urine output. A low fractional excretion of sodium (< 1 %) suggests that oliguria is due to decreased renal perfusion and that the nephrons are responding appropriately by decreasing the excretion of filtered sodium in an attempt to preserve vascular volume. BUN levels also depend on the GFR. A low GFR allows more time for small particles such as urea to be reabsorbed into the blood. Creatinine, which is larger and nondiffusible, remains in the tubular fluid, and the total amount of creatinine that is filtered, although small, is excreted in theurine. Thus, there also is a disproportionate elevation in the ratio of BUN to serum creatinine to greater than 15/1 to 20/1 (normal, approximately 10/1).

Postrenal failureresults from obstruction of urine outflow from the kidneys. The obstruction can occur in the ureter (i.e., calculi and strictures), bladder (i.e., tumors or neurogenic bladder), or urethra (i.e., prostatic hypertrophy). Prostatic hyperplasia is the most common underlying problem. Because both ureters must be occluded to produce renal failure, obstruction of the bladder rarely causes acute renal failure unless one of the kidneys already is damaged or a personhas only one kidney. The treatment of acute postrenal failure consists of treating the underlying cause of obstruction so that urine flow can be reestablished before permanent nephron damage occurs.

Intrinsic renal failureor intrarenal renal failure results from conditions that cause damage to structures within the kidney-glomerular, tubular, or interstitial. The major causes of intrarenal failure are ischemia associated with prerenal failure, toxic insult to the tubular structures of the nephron, and intratubular obstruction. Acute glomerulonephritis and acute pyelonephritis also are intrarenal causes of acute renal failure. Injury to the tubules (acute tubular necrosis) is most common and often is ischemic or toxic in origin.

Acute Tubular Necrosis. Acute tubular necrosis (ATN) is characterized by destruction of tubular epithelial cells with acute suppression of renal function. ATN can be caused by a variety of conditions, including acute tubular damage due to ischemia, the nephrotoxic effects of drugs, tubular obstruction, and toxins from a massive infection. Tubular epithelial cells are

particularly sensitive to ischemia and also are vulnerable to toxins. The tubular injury that occurs in ATN frequently is reversible. The process depends on the recovery of the injured cells, removal of the necrotic cells and intratubular casts, and regeneration of renal cells to restore the normal continuity of the tubular epithelium. If, however, the ischemia is severe enough to cause cortical necrosis, irreversible renal failure occurs. Ischemic ATN occurs most frequently in persons who have major surgery, severe hypovolemia, overwhelming sepsis, trauma, and burns. Sepsis produces ischemia by provoking a combination of systemic vasodilation and intrarenal hypoperfusion. In addition, sepsis results in the generation of toxins that sensitize renal tubular cells to the damaging effects of ischemia. ATN complicating trauma and burns frequently is multifactorial in origin and due to the combined effects of hypovolemia and myoglobinuria or other toxins released from damaged tissue.

Nephrotoxic ATN complicates administration or exposure to many structurally diverse drugs and other toxic agents. Nephrotoxic agents cause renal injury by inducing varying combinations of renal vasoconstriction, direct tubular damage, or intratubular obstruction. The kidney is particularly vulnerable to nephrotic injury because of its rich blood supply and ability to concentrate toxins to high levels in the medullary portion of the kidney. In addition, the kidney is an important site for metabolic processes that transform relatively harmless agents into toxic metabolites. Pharmacologic agents that are directly toxic to the renal tubule include antimicrobials such as the aminoglycosides, chemotherapeutic agents such as cisplatin and ifosfamide, and the radiocontrast agents. Several factors contribute to aminoglycoside nephrotoxicity, including a decrease in the GFR, preexisting renal disease, hypovolemia, and concurrent administration of other drugs that have a nephrotoxic effect. Nonoliguric ATN occursin 10 % to 30 % of courses of aminoglycoside therapy, even when the blood levels of the drug are within therapeutic range. Cisplatin accumulates in proximal tubule cells, inducing mitochondrial injury and inhibition of adenosine triphosphatase (ATP) activity and solute transport. ATN complicates up to 70 % of courses of cisplatin therapy. Radiocontrast media–induced nephrotoxicity is thought to result from direct tubular toxicity and renal ischemia. The risk for renal damage caused by radiocontrast media is greatest in elderly persons, in persons with diabetes mellitus, and in persons who, for various reasons, are susceptible to kidney disease. Heavy metals (e.g., lead, mercury) and organic solvents (e.g., carbon tetrachloride, ethylene glycol) are other nephrotoxic agents.

Presence of myoglobin, hemoglobin, uric acid, myeloma light chains, or excess uric acid in the urine is the most frequent cause of ATN due to intratubular obstruction. Both myeloma cast nephropathy and acute urate nephropathy usually are seen in the setting of widespread malignancy or massive tumor destruction by therapeutic agents. Hemoglobinuria results from blood transfusion reactions and other hemolytic crises. Skeletal and cardiac muscles contain myoglobin, which accounts for their rubiginous color. Myoglobin corresponds to hemoglobin in function, serving as an oxygen reservoir in the muscle fibers. Myoglobin normally is not found in the serum or urine. It has a low molecular weight of 17,000 daltons; if it escapes into the circulation, it is rapidly filtered in the glomerulus. Myoglobinuria most commonly results from muscle trauma but may result from extreme exertion, hyperthermia, sepsis, prolonged seizures, potassium or phosphate depletion, and alcoholism or drug abuse. Both myoglobin and hemoglobin discolor the urine, which may range from the color of tea to red, brown, or black. The course of ATN can be divided into three phases: the onset or initiating phase, the maintenance phase, and the recovery or convalescent phase. The onset or initiating phase, which lasts hours or days, is the time from the onset of the precipitating event (e.g., ischemic phase of prerenal failure or toxin exposure) until tubular injury occurs. The maintenance phase of ATN is characterized by a marked decrease in the GFR, causing sudden retention of endogenous metabolites such as urea, potassium, sulfate, and creatinine that normally are cleared by the kidneys. The urine output usually is lowest at this point. Fluid retention gives rise to edema, water intoxication, and pulmonary congestion. If the period of oliguria is

prolonged, hypertension frequently develops and with it signs of uremia. When untreated, the neurologic manifestations of uremia progress from neuromuscular irritability to seizures, somnolence, coma, and death. Hyperkalemia usually is asymptomatic until serum levels of potassium rise above 6.0 to 6.5 mEq/L, at which point characteristic electrocardiographic changes and symptoms of muscle weakness are seen. Formerly, most patients with ATN were oliguric. During the past several decades, a nonoliguric form of ATN has become increasingly prevalent. Persons with nonoliguric failure have higher levels of glomerular filtration and excrete more nitrogenous waste, water, and electrolytes in their urine than persons with acute oliguric renal failure. Abnormalities in blood chemistry levels usually are milder and cause fewer complications. The decrease in oliguric ATN probably reflects new approaches to the treatment of poor cardiac performance and circulatory failure that focus on vigorous plasma volume expansion and the selective use of dopamine and other drugs to improve renal blood flow. Dopamine has renal vasodilator properties and inhibits sodium reabsorption in the proximal tubule, thereby decreasing the work demands of the nephron. The recovery phase is the period during which repair of renal tissue takes place. Its onset usually is heralded by a gradual increase in urine output and a fall in serum creatinine, indicating that the nephrons have recovered to the point at which urine excretion is possible. Diuresis often occurs before renal function has fully returned to normal.

Diagnosis and treatment

Given the high morbidity and mortality rates associated with acute renal failure, attention should be focused on prevention and early diagnosis. This includes assessment measures to identify persons at risk for development of acute renal failure, including those with preexisting renal insufficiency and diabetes. These persons are particularly at risk for development of acute renal failure due to nephrotoxic drugs such as aminoglycosides and contrast agents, or to drugs such as the NSAIDs that alter intrarenal hemodynamics. Elderly persons are susceptible to all forms of acute renal failure because of the effects of aging on renal reserve. Careful observation of urine output is essential for persons at risk for development of acute renal failure. Urine tests that measure urine osmolality, urinary sodium concentration, and fractional excretion of sodium help differentiate prerenal azotemia, in which the reabsorptive capacity of the tubular cells is maintained, from tubular necrosis, in which these functions are lost. One of the earliest manifestations of tubular damage is the inability to concentrate the urine. Further diagnostic information that can be obtained from the urinalysis includes evidence of proteinuria, hemoglobinuria, and casts or crystals in the urine. Blood tests for BUN and creatinine provide information regarding the ability to remove nitrogenous wastes from the blood. It also is important to exclude urinary obstruction. A major concern in the treatment of acute renal failureis identifying and correcting the cause (e.g., improving renal perfusion, discontinuing nephrotoxic drugs). Fluids are carefully regulated in an effort to maintain normal fluid volume and electrolyte concentrations

Chronic renal failure. Unlike acute renal failure, chronic renal failure is progressive and irreversible destruction of kidney structures. As recently as 1965, many patients with chronic renal failure progressed to the final stages of the disease and then died. High mortality rate was associated with limitations in the treatment of renal disease and with the tremendous cost of ongoing treatment. In 1972, federal support began for dialysis and transplantation through a Medicare entitlement program. Technologic advances in renal replacement therapy (i.e., dialysis therapy and transplantation) have improved the outcomes for persons with renal failure. The number of persons with kidney failure who are treated with dialysis and transplantation is projected to increase from 340,000 in 1999 to 651,000 in 2010.13 Chronic renal failure can result from a number of conditions that cause permanent loss of nephrons, including diabetes, hypertension, glomerulonephritis, and polycystic kidney disease.

Stages of progression. Regardless of the cause, chronic renal failure results in loss of renal cells with progressive deterioration of glomerular filtration, tubular reabsorptive capacity,

and endocrine functions of the kidneys. All forms of renal failure are characterized by reduction in the GFR, reflecting a corresponding reduction in the number of functional nephrons. The rate of nephron destruction differs from case to case, ranging from several months to many years. The progression of chronic renal failure usually occurs in four stages: diminished renal reserve, renal insufficiency, renal failure, and end-stage renal disease. Typically, the signs and symptoms of chronic renal failure occur gradually and do not become evident until the disease is far advanced. This is because of the amazing compensatory ability of the kidneys. As kidney structures are destroyed, the remaining nephrons undergo structural and functional hypertrophy, each increasing its function as a means of compensating for those that have been lost.

Diminished Renal Reserve

The GFR is considered the best measure of overall function of the kidney. The normal level of GFR varies with age, sex, and body size. The normal GFR for young healthy adults is approximately 120 to 130 mL/minute (1.73 mL/minute per mm^2). Diminished renal reserve occurs when the GFR drops to approximately 50 % of normal. At this point, the serum BUN and creatinine levels still are normal, and no symptoms of impaired renal function are evident. This issupported by the fact that many persons survive an entire lifetime with only one kidney. Because of the diminished reserve, the risk for development of azotemia increases with an additional renal insult, such as that due to nephrotoxic drugs.

Renal Insufficiency is a reduction in the GFR to 20 to 50 % of normal. Kidneys initially have tremendous adaptive capabilities. As nephrons are destroyed, the remaining nephrons undergo changes to compensate for those that are lost. In the process, each of the remaining nephrons must filter more solute particles from the blood.

Because the solute particles are osmotically active, they cause additional water to be lost in the urine. One of the earliest symptoms of renal insufficiency is **isosthenuria**, or polyuria with urine that is almost isotonic with plasma. It is during this stage that azotemia, anemia, and hypertension also begin to appear. Conservative treatment during this stage includes measures to retard deterioration of renal function and assist the body in managing the effects of impaired function. Urinary tract infections should be treated promptly, and medication with renal damaging potential should be avoided. Blood pressure control is important, as is control of blood sugar in persons with diabetes. Smoking cessation is recommended, particularly in persons with diabetic nephropathy. Because the kidneys have difficulty eliminating the waste products of protein metabolism, a restricted-protein diet usually produces fewer uremic symptoms and slows progression of renal failure. The few remaining nephrons that constitute the functional reserve of the kidneys can be easily disrupted, after which renal failure progresses rapidly.

Renal Failure and End-Stage Renal Disease

Renal failure develops when the GFR is less than 20 % of normal. At this point, kidneys cannot regulate volume and solute composition, and edema, metabolic acidosis, and hyperkalemia develop. Overt uremia may ensue with neurologic, gastrointestinal, and cardiovascular manifestations. End-stage renal disease (ESRD) occurs when the GFR is less than 5 % of normal. Histologic findings of an endstage kidney include a reduction in renal capillaries and scarring in the glomeruli. Atrophy and fibrosis are evident in the tubules. The mass of the kidneys usually is reduced. At this final phase of renal failure, treatment with dialysis or transplantation is necessary for survival.

Accumulation of nitrogenous wastes is an early sign of renal failure, usually occurring before other symptoms become evident. Urea is one of the first nitrogenous wastes to accumulate in the blood, and the BUN level becomes increasingly elevated as renal failure progresses. The normal concentration of urea in the plasma is usually less than 20 mg/dL. In renal failure, this level may rise to as high as 800 mg/dL. Creatinine, a by-product of muscle metabolism, is freely filtered in the glomerulus and is not reabsorbed in the renal tubules. Creatinine is produced at a relatively constant rate, and any creatinine that is filtered in the glomerulus is lost in the urine rather than being reabsorbed into the blood. Thus, serum

creatinine can be used as an indirect method for assessing the GFR and the extent of renal damage that has occurred in renal failure.

Uremia, which literally means "urine in the blood," is the term used to describe clinical manifestations of renal failure. Few symptoms of uremia appear until at least two thirds of the nephrons have been destroyed. Uremia differs from azotemia, which merely indicates the accumulation of nitrogenous wastes in the blood and can occur without symptoms. The uremic state includes signs and symptoms of altered fluid, electrolyte, and acid-base balance; alterationsin regulatory functions (e.g., hypertension, anemia, osteodystrophy); and the effects of uremia on body function (e.g., uremic encephalopathy, peripheral neuropathy, pruritus). At this stage, virtually every organ and structure in the body is affected. The symptoms at the onset of uremia(e.g., weakness, fatigue, nausea, apathy) often are subtle. More severe symptoms include extreme weakness, frequent vomiting, lethargy, and confusion. Without treatment, coma and death follow.

Disorders of Water, Electrolyte, and Acid-Base Balance

Sodium and Water Balance. The kidneys function in regulation of extracellular fluid volume. They do this by either eliminating or conserving sodium and water. Chronic renal failure can produce dehydration or fluid overload, depending on the pathology of the renal disease. In addition to volume regulation, the ability of kidneys to concentrate the urine diminishes. In renal failure, specific gravity of the urine becomes fixed (1.008 to 1.012) and varies little from voiding to voiding. Polyuria and nocturia are common. As renal function declines further, the ability to regulate sodium excretion is reduced. The kidneys normally tolerate large variations in sodium intake while maintaining normal serum sodium levels. In chronic renal failure, they lose the ability to regulate sodium excretion. There is impaired ability to adjust to a sudden reduction in sodium intake and poor tolerance of an acute sodium overload. Volume depletion with an accompanying decrease in the GFR can occur with a restricted sodium intake or excess sodium loss caused by diarrhea or vomiting. Salt wasting is a common problem in advanced renal failure because of impaired tubular reabsorption of sodium. Increasing sodiumintake in persons with chronic renal failure often improves the GFR and whatever renal function remains. In patients with associated hypertension, the possibility of increasing blood pressure or production of congestive heart failure often excludes supplemental sodium intake.

Potassium Balance. Approximately 90 % of potassium excretion is through the kidneys. In renal failure, potassium excretion by each nephron increases as the kidneys adapt to a decrease in the GFR. As a result, hyperkalemia usually does not develop until renal function is severely compromised. Because of this adaptive mechanism, it usually is not necessary to restrict potassium intake in patients with chronic renal failure until the GFR has dropped below 10 mL/minute. In patients with chronic renal failure, hyperkalemia often results from failure to follow dietary potassium restrictions and ingestion of medications that contain potassium, or from an endogenous release of potassium, as in trauma or infection.

Acid-Base Balance. The kidneys normally regulate blood pH by eliminating hydrogen ions produced in metabolic processes and regenerating bicarbonate. This is achieved through hydrogen ion secretion, sodium and bicarbonate reabsorption, and the production of ammonia, which acts as a buffer for titratable acids. With a decline in renal function, these mechanisms become impaired, and metabolic acidosis results. In chronic renal failure, acidosis seems to stabilize as the disease progresses, probably as a result of the tremendous buffering capacity of bone. However, this buffering action is thought to increase bone resorption and contribute to the skeletal disorders that occur in persons with chronic renal failure.

Mineral and Bone Disorders Abnormalities of calcium, phosphate, and vitamin D metabolism occur early in the course of chronic renal failure. Regulation of serum phosphate levels requires a daily urinary excretion of an amount equal to that ingested in the diet. With deteriorating renal function, phosphate excretion is impaired, and as a result, serum phosphate levels rise. At the same time, serum calcium levels, which are inversely regulated in relation to

serum phosphate levels, fall. In turn, the drop in serum calcium stimulates parathyroid hormone (PTH) release, with a resultantincrease in calcium resorption from bone. Mostpersons with ESRD develop a secondary hyperparathyroidism, the result of chronic stimulation of the parathyroid glands. Although serum calcium levels are maintained through increased PTH function, this adjustment is accomplished at the expense of the skeletal system and other body organs.

Vitamin D synthesis also is impaired in renal failure. The kidneys regulate vitamin D activity by converting the inactive form of vitamin D [25(OH) vitamin D_3] to its active form (1,25-OH_2 vitamin D_3). Decreased levels of active vitamin D lead to a decrease in intestinal absorption of calcium with a resultant increase in PTH levels. Vitamin D also regulates osteoblast differentiation, thereby affecting bone matrix formation and mineralization.

Skeletal Disorders. The term renal osteodystrophy is used to describe the skeletal complications of ESRD. Several factors are thought to contribute to the development of renal osteodystrophy, including elevated serum phosphate levels, decreased serum calcium levels, impaired renal active tion of vitamin D, and hyperparathyroidism. The skeletal changes that occur with renal failure have been divided into two major types of disorders: high-turnover and lowturnover osteodystrophy. Inherent to both of these conditions is abnormal reabsorption and defective remodeling of bone.

High-bone-turnover osteodystrophy, sometimes referred to as osteitis fibrosa, is characterized by increased bone resorption and formation, with bone resorption predominating. The disorder is associated with secondary hyperparathyroidism; altered vitamin D metabolism, along with resistance to the action of vitamin D; and impaired regulation of locally produced growth factors and inhibitors. There is an increase in both osteoblast and osteoclast numbers and activity. Although the osteoblasts produce excessive amounts of bone matrix, mineralization fails to keeppace, and there is a decrease in bone density and formation of porous and coarse-fibered bone. Cortical bone is affected more severely than cancellous bone. Marrow fibrosis is another component of osteitis fibrosa; it occurs in areas of increased bone cell activity. In advanced stages of the disorder, cysts may develop in the bone, a condition called osteitis fibrosa cystica.

The symptoms of renal osteodystrophy, which occur late in the disease, include bone tenderness and muscle weakness. Proximal muscle weakness in the lower extremities is common, making it difficult to get out of a chair or climb stairs. Fractures are more common with lowturnover osteomalacia and adynamic renal bone disease. Early treatment of hyperphosphatemia and hypocalcemia is important to prevent or slow long-term skeletal complications. Milk products and other foods high in phosphorus content are restricted in the diet. Phosphatebinding antacids (aluminum salts, calcium carbonate, or calcium acetate) may be prescribed to decrease absorption of phosphate from the gastrointestinal tract. Calciumcontaining phosphate binders can lead to hypercalcemia, thus worsening soft tissue calcification, especially in persons receiving vitamin D therapy. Activated forms of vitamin D (e.g., calcitriol) and calcium supplements often are used to facilitate intestinal absorption of calcium, increase serum calcium levels, and prevent parathyroid gland overactivity. Although calcitriol is effective in controlling PTH overproduction and improving bone structure, its stimulatory effects on intestinal absorption of both calcium and phosphorus, combined with its suppressive effects on bone turnover, predispose to hypercalcemia and hyperphosphatemia and an increase in the calcium-phosphate (Ca P) product.

Hematologic Disorders

Anemia. Chronic anemia is the most profound hematologic alteration that accompanies renal failure. Anemia first appears when the GFR falls below 40 mL/minute, and is present in most persons with ESRD. Nephrologists have defined clinically significant anemia as a hemoglobin level of less than 10 g/dL and a hematocrit of less than 30 %, in the absence of erythropoietin therapy. An analysis of patients beginning dialysis in the United States found that 67 % had a hematocrit of less than 30 %, and 51 % had a hematocrit of less than 28 %. The kidneys are the primary site for the production of the hormone erythropoietin, which

controls red blood cell production. In renal failure, erythropoietin production usually is insufficient to stimulate adequate red blood cell production by the bone marrow. The accumulation of uremic toxins further suppresses red cell production in the bone marrow, and the cells that are produced have a shortened life span. Iron is essential for erythropoiesis. Many persons on maintenance hemodialysis also are iron deficient because of blood sampling and accidental loss of blood during dialysis. Other causes of iron deficiency include factors such as anorexia and dietary restrictions that limit intake. When untreated, anemia causes or contributes to weakness, fatigue, depression, insomnia, and decreased cognitive function. There also is an increasing concern regarding the physiologic effects of anemia on cardiovascular function. The anemia of renal failure decreases blood viscosity and a compensatory increase in heart rate. The decreased blood viscosity also exacerbates peripheral vasodilatation and contributes to decreased vascular resistance. Cardiac output increases in a compensatory fashion to maintain tissue perfusion.

Thus, anemia, when coupled with hypertension, may be a major contributing factor to the development of left ventricular dysfunction and congestive heart failure in persons with ESRD. A remarkable advance in medical management of ESRD occurred with the availability of recombinant human erythropoietin (rhEPO). Secondary benefits of treating anemia with rhEPO, previously attributed to the correction of uremia, include improvement in appetite, energy level, sexual function, skin color, and hair and nail growth, and reduced cold intolerance. Because worsening of hypertension and seizures have occurred when the hematocrit was raised too suddenly, frequent measurements of hematocrit are necessary. Because iron deficiency is common among persons with chronic renal failure, iron supplementation often is needed.

Coagulopathies. Bleeding disorders are manifested by epistaxis, menorrhagia, gastro-intestinal bleeding, and bruising of the skin and subcutaneous tissues. Although platelet production often is normal in ESRD, platelet function is impaired. Coagulative function improves with dialysis butdoes not completely normalize, suggesting that uremia contributes to the problem. Anemia may accentuate the problem by changing the position of the platelets with respect to the vessel wall. Normally, the red cells occupy the center of the bloodstream, and the platelets are in the skimming layer along the endothelial surface. In anemia, the platelets become dispersed, impairing the platelet– endothelial cell adherence needed to initiate hemostasis.

Cardiovascular disorders. Cardiovascular disease is the major cause of death in patients with ESRD. The overall mortality rate from cardiovascular disease in people with renal failure is 30 times that of the general population. Even after stratification for age, the incidence of cardio-vascular disease remains 10 to 20 times higher in persons with ESRD than in the general population.

Hypertension. Hypertension commonly is an early manifestation of chronic renal failure. The mechanisms that produce hypertension in ESRD are multifactorial; they include an increased vascular volume, elevation of peripheral vascular resistance, decreased levels of renal vasodilator prostaglandins, and increased activity of the renin-angiotensin system. Early identification and aggressive treatment of hypertension has been shown to slow the rate of renal impairment in many types of renal disease. Treatment involves salt and water restriction and the use of antihypertensive medications to control blood pressure. Many persons with renal insufficiency need to take several antihypertensive medications to control blood pressure.

Heart Disease. The spectrum of cardiovascular disease includes left ventricular hypertrophy and ischemic heart disease. Congestive heart failure and pulmonary edema tend to occur in the late stages of renal failure. Coexisting conditions that have been identified as contributing to the burden of cardiovascular disease include hypertension, anemia, diabetes mellitus, dyslipidemia, and coagulopathies. Anemia, in particular, has been correlated with the presence of left ventricular hypertrophy. People with renal failure tend to have an increased prevalence of left ventricular dysfunction, with both depressed left ventricular ejection fraction, as in systolic dysfunction, and impaired ventricular filling, as in diastolic failure. Multiple factors lead to development of left ventricular dysfunction, including extracellular fluid overload, shunting of blood through an arteriovenous fistula for dialysis, and anemia.

Pericarditis. Pericarditis occurs in approximately 20 % of persons receiving chronic dialysis. It can result from metabolic toxins associated with the uremic state or from dialysis. Manifestations of uremic pericarditis resemble those of viral pericarditis, with all its potential complications, including cardiac tamponade. The presenting signs include mild to severe chest pain with respiratory accentuation and a pericardial friction rub. Fever is variable in the absence of infection and is more common in dialysis than uremic pericarditis.

Gastrointestinal Disorders. Anorexia, nausea, and vomiting are common in patients with uremia, along with a metallic taste in the mouth that further depresses the appetite. Early-morning nausea is common. Ulceration and bleeding of the gastrointestinal mucosa may develop, and hiccups are common. A possible cause of nausea and vomiting is the decomposition of urea by intestinal flora, resulting in a high concentration of ammonia. PTH increases gastric acid secretion and contributes to gastrointestinal problems. Nausea and vomiting often improve with restriction of dietary protein and after initiation of dialysis, and disappear after kidney transplantation.

Disorders of Neural Function. Many people with chronic renal failure have alterations in peripheral and central nervous system function. Peripheral neuropathy, or involvement of the peripheral nerves, affects the lower limbs more frequently than the upper limbs. It is symmetric and affects both sensory and motor function. Neuropathy is caused by atrophy and demyelination of nerve fibers, possibly caused by uremic toxins. Restless legs syndrome is a manifestation of peripheral nerve involvement and can be seen in as many as two thirds of patients on dialysis. This syndrome is characterized by creeping, prickling, and itching sensations that typically are more intense at rest. Temporary relief is obtained by moving the legs. A burning sensation of the feet, which may be followed by muscle weakness and atrophy, is a manifestation of uremia. Sometimes referred to as uremic encephalopathy, the condition is poorly understood and may result, at least in part, from an excess of toxic organic acids that alter neural function. The manifestations are more closely related to the progress of the uremic disorder than to the level of the metabolic end products. Reductions in alertness and awareness are the earliest and most significant indications of uremic encephalopathy. These often are followed by an inability to fix attention, loss of recent memory, and perceptual errors in identifying persons and objects. Delirium and coma occur late in the course; seizures are the preterminal event. During the early stages, there often is difficulty in performing fine movements of the extremities; the gait becomes unsteady and clumsy with tremulousness of movement. Asterixis (dorsiflexion movements of the hands) occurs as the disease progresses.

Altered immune function. Infection is a common complication and cause of hospitalization and death of patients with chronic renal failure. Immunologic abnormalities decrease the efficiency of the immune response to infection. All aspects of inflammation and immune function may be affected adversely by the high levels of urea and metabolic wastes, including a decrease in granulocyte count, impaired humoral and cellmediated immunity, and defective phagocyte function. The acute inflammatory response and delayed-type hypersensitivity response are impaired. Skin and mucosal barriers to infection also may be defective. In persons who are maintained on dialysis, vascular access devices are common portals of entry for pathogens.

Disorders of Skin Integrity. Skin manifestations are common in persons with renal failure. The skin often is pale owing to anemia and may have a sallow, yellow-brown hue. The skin and mucous membranes often are dry, and subcutaneous bruising is common. Skin dryness is caused by a reduction in perspirationowing to the decreased size of sweat glands and the diminished activity of oil glands. Pruritus is common; it results from the high serum phosphate levels and the development of phosphate crystals that occur with hyperparathyroidism. Severe scratching and repeated needlesticks, especially with hemodialysis, break the skin integrity and increase the risk for infection. In the advanced stages of untreated renal failure, urea crystals may precipitate on the skin as a result ofthe high urea concentration in body fluids.

The fingernails may become thin and brittle, with a dark band just behind the leading edge of the nail, followed by a white band. This appearance is known as Terry's nails.

Date	Grade	Teacher's signature

PATHOPHYSIOLOGY OF ENDOCRINE SYSTEM

Relevance. The works of H. Selye and other scientists show the significance of the endocrine system especially the hypothalamic-pituitary-adrenal system, protective and adaptive reactions of the body (general adaptation syndrome, or stress). Changes in the activity of this system occurs in response to any physiological or pathological stimuli. The works also show dependence of any vegetative functions of the organism on the functional state of the adrenal and pituitary glands. From here, we see an exceptionally significant role of hormones in the pituitary and adrenal glands pathology. As regulators, they are involved in the pathogenesis of diseases and pathological processes. Numerous pathologies are possible on the part of the glands in hypo- or hyperfunction. All this underlines the relevance of the topic.

Overall Objective is to know basic mechanisms of functional activity disorders of the endocrine glands, the value of the hypothalamic-pituitary-adrenal system in the non-specific resistance of the body and its disorders, manifestations of hypo- or hyperfunction of these glands.

The student should be able to (specific objectives):

1. Describe the etiologic factors of the functional activity disorders of the hypothalamic-pituitary-adrenal system;
2. Describe the pathogenesis of disorders arising in the pathology of the hypothalamic-pituitary-adrenal system;
3. Describe stress and disease adaptation.

The student should be able to (required knowledge and skills):

1. Describe the endocrine system, to determine its place in the system of functional interaction in the whole organism (Depart. of normal physiology);
2. Interpret the principles of the regulation of the functional activity of the endocrine glands (Depart. of normal physiology);
3. Describe the pituitary and parapituitary way of regulation and the principle of feedback (Depart. of normal physiology);
4. Explain the physiological role in the organism of various adrenal hormones (Depart. of normal physiology).

QUESTIONS TO THE LESSON

1. The endocrine system. Definition of the concept. Hormones and their basic function. Variants of hormonal effects on target cells. Causes of endocrine disorders.
2. Pathogenic mechanisms of endocrine disorders (Centrogenic, initially glandular, postglandular).
3. Disorders hypothalamic-pituitary system. Typical forms of pathology adenohypophysis. Classification.
4. Hypo- and hyperpituitarizm. Causes. Pathogenesis. Manifestation.
5. Pathology neurohypophysis. Diabetes insipidus. Pathogenesis. Manifestation.
6. Typical forms of adrenal pathology.
7. Hyper- and hypofunctional state of the adrenal glands. Causes. Pathogenesis. Manifestation.
8. Acute adrenocortical insufficiency. Causes. Manifestation.
9. Typical forms of thyroid gland disease. Assessment of thyroid status.
10. Hyper- and hypothyroidism. Types. Causes. Pathogenesis. Manifestation.
11. Mechanisms of regulation of homeostasis of calcium and phosphorus.
12. Typical forms of pathology of the parathyroid glands. Hyperparathyroidism. Hypoparathyroidism. Causes. Manifestations and their mechanisms.
13. Pathophysiology of gonads. Hypo- and hyperfunction of the gonads. Causes. Manifestation.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

Endocrine disorders

Endocrine disorders can result from dysfunction originating in the peripheral endocrine gland itself (primary disorders) or from understimulation or overstimulation by the pituitary (secondary disorders). The disorders can result in hormone overproduction (hyperfunction) or underproduction (hypofunction). Rarely, endocrine disorders (usually hypofunction) occur because of abnormal tissue responses to hormones. Clinical manifestations of hypofunction disorders are often insidious and nonspecific.

Hyperfunction: Hyperfunction of endocrine glands may result from overstimulation by the pituitary but is most commonly due to hyperplasia or neoplasia of the gland itself. In some cases, cancers from other tissues can produce hormones (ectopic hormone production). Hormone excess also can result from exogenous hormone administration. In some cases, patients take hormones without telling the physician (factitious disease). Tissue hypersensitivity to hormones can occur. Antibodies can stimulate peripheral endocrine glands, as occurs in hyperthyroidism of Graves' disease. Destruction of a peripheral endocrine gland can rapidly release stored hormone (e.g, thyroid hormones in thyroiditis). Enzyme defects in the synthesis of a peripheral endocrine hormone can result in overproduction of hormones proximal to the block. Finally, overproduction of a hormone can occur as an appropriate response to a disease state.

Hypofunction: Hypofunction of an endocrine gland can result from understimulation by the pituitary. Hypofunction originating within the peripheral gland itself can result from congenital or acquired disorders (including autoimmune disorders, tumors, infections, vascular disorders, and toxins). Genetic disorders causing hypofunction can result from deletion of a gene or by production of an abnormal hormone. A decrease in hormone production by the peripheral endocrine gland with a resulting increase in production of pituitary regulating hormone can lead to peripheral endocrine gland hyperplasia. For example, if synthesis of thyroid hormone is defective, thyroid-stimulating hormone (TSH) is produced in excessive amounts, causing goiter.

Several hormones require conversion to an active form after secretion from the peripheral endocrine gland. Certain disorders can block this step (e.g, renal disease can inhibit production of the active form of vitamin D). Antibodies to the circulating hormone or its receptor can block the ability of the hormone to bind to its receptor. Disease or drugs can cause increased rate of clearance of hormones. Circulating substances may also block the function of hormones. Abnormalities of the receptor or elsewhere in the peripheral endocrine tissue can also cause hypofunction.

PITUITARY GLAND
HYPOPITUITARISM (PANHYPOPITUITARISM)

Background

Hypopituitarism is a clinical syndrome of deficiency in pituitary hormone production. This may result from disorders involving the pituitary gland, hypothalamus, or surrounding structures. Panhypopituitarism refers to involvement of all pituitary hormones; however, only one or more pituitary hormones are often involved, resulting in isolated or partial hypopituitarism.

Etiology. Causes of pituitary insufficiency include pituitary adenomas or other intrasellar and parasellar tumors, inflammatory and infectious destruction, surgical removal, radiation-induced destruction of pituitary tissue, traumatic brain injury (TBI), subarachnoid hemorrhage, and postpartum pituitary necrosis (Sheehan syndrome). Similar diseases originating in the hypothalamus or pituitary stalk may also result in pituitary insufficiency. Pituitary tumors, or adenomas, are the most common cause of hypopituitarism in adults, although traumatic brain injury as a cause is more frequently recognized.

Hypopituitarism resulting from pituitary adenomas is due to impaired blood flow to the normal tissue, compression of normal tissue, or interference with the delivery of hypothalamic hormones via the hypothalamus-hypophysial portal system.

In primary pituitary destruction, the anterior pituitary is destroyed, causing a deficiency in some or all pituitary hormones, including prolactin. Disease involving the hypothalamus or pituitary stalk may cause pituitary hormone deficiency with an elevated serum prolactin. Pituitary tumors, or adenomas, can be secretory or nonsecretory. Approximately 30 % of all macroadenomas larger than 10 mm produce at least 1 hormone.

Hypothalamic disease involves destruction of the hypothalamus. This causes a deficiency or loss of hypothalamic regulatory hormone input to the pituitary, which leads to the loss of anterior pituitary hormone secretion, with an elevated serum prolactin level. Loss of antidiuretic hormone (ADH) may have concomitant diabetes insipidus.

Hypersecretion of the secretory pituitary tumor hormone is suggestive of an adenoma. Another indication of a pituitary adenoma is a deficiency in some pituitary hormones with concomitant hyperprolactinemia. Normally, dopamine, produced in the hypothalamus, inhibits prolactin secretion by the anterior pituitary. Compressing the pituitary stalk decreases the inhibitory effect of dopamine and increases prolactin levels.

Longstanding target gland disease may result in hyperplasia of the relevant pituitary cell secreting the tropic hormone, the level of which would be elevated, with an enlarged pituitary gland simulating a mass. Although uncommon, this may appear to be a pituitary adenoma, but the target gland is not hyperfunctioning.

Another common intracranial tumor is craniopharyngioma, a squamous cell tumor that arises from remnants of the Rathke pouch. One third of these tumors extend into the sella, while approximately two thirds remain suprasellar.

Sheehan syndrome occurs with a large volume of postpartum hemorrhage. During pregnancy, the pituitary gland enlarges due to hyperplasia and hypertrophy of the lactotroph cells, which produce prolactin. The hypophyseal vessels, which supply the pituitary, constrict in response to decreasing blood volume, and subsequent vasospasm occurs, causing necrosis of the pituitary gland. The degree of necrosis correlates with the severity of the hemorrhage.

As many as 30 % of women experiencing postpartum hemorrhage with hemodynamic instability may develop some degree of hypopituitarism. These patients can develop adrenal insufficiency, hypothyroidism, amenorrhea, diabetes insipidus, and an inability to breastfeed (an early symptom). Lymphocytic hypophysitis occurs most commonly in the postpartum state and may appear as Sheehan syndrome with postpartum hypopituitarism.

Pituitary apoplexy denotes the sudden destruction of the pituitary tissue resulting from infarction or hemorrhage into the pituitary. The most likely cause of the apoplexy is brain trauma; however, it can occur in patients with diabetes mellitus, pregnancy, sickle cell anemia, blood dyscrasias or anticoagulation, or increased intracranial pressure. Apoplexy usually spares the posterior pituitary and solely affects the anterior pituitary. In patients with such underlying diseases, Sheehan syndrome can occur with lesser degrees of postpartum hemorrhage or hypotension.

Head trauma from a motor vehicle accident, a fall, or a projectile can cause hypopituitarism by direct damage to the pituitary or by injuring the pituitary stalk or the hypothalamus. Hypopituitarism may occur immediately, or it may develop months or years later. Recovery is uncommon. Many studies show an incidence of 15–40 %, but a study by Kokshoorn et al found the incidence of posttraumatic hypopituitarism to be low.

Other causes of hypopituitarism include empty sella syndrome and infiltrative diseases. Empty sella syndrome occurs when the arachnoid herniates into the sella turcica through an incompetent sellar diaphragm and flattens the pituitary against bone, but resulting pituitary insufficiency is uncommon. Infiltrative diseases, such as Wegener granulomatosis and sarcoidosis, can cause destruction of the anterior pituitary. Lymphocytic hypophysitis is an autoimmune destructive disease that may be directed towards the pituitary or its stalk.

Physiologic or psychological states can influence the hypothalamus by impairing synthesis and secretion of regulating hormones. For example, poor nutrition may impair the hypothalamic secretion of gonadotropin-releasing hormone (GnRH), resulting in reversible

pituitary gonadotropin deficiency. Medications may affect measured hormone levels, such as opioids decreasing serum LH and testosterone.

The degree of hormone deficiency varies greatly and depends on the extent of the process and its location. Some functional causes include emotional disorders, changes in body weight, habitual exercise, anorexia, bulimia, congestive heart failure (CHF), renal failure, and certain medications.

Hypopituitarism occurs in adult patients after cranial radiotherapy performed to treat nonpituitary tumors. Thus, patients who undergo cranial radiotherapy should be periodically assessed for pituitary functions.

Additional causes of hypopituitarism include the following:

1. Histiocytosis X
2. Hemochromatosis
3. Tuberculosis
4. Syphilis
5. Meningitis
6. Iatrogenic causes – Radiation, surgery, chronic glucocorticoid replacement
7. Kallmann syndrome
8. Lymphocytic hypophysitis
9. Transsphenoidal adenomectomy
10. Congenital – Usually presents in childhood, but can present later with features such as delayed puberty; heritable pituitary disease usually involves homeodomain transcription factors.

With regard to the last item above, in a study of 435 patients, Fatemi et al found evidence that the likelihood of hypopituitarism development after transsphenoidal adenoma removal was higher when the tumor was larger than 20 mm. In contrast, some with hypopituitarism prior to adenomectomy may have improved pituitary function following surgery, if the cause of the hypopituitarism was increased suprasellar pressure resulting from the mass itself.

Pathophysiology. When pituitary hormone production is impaired, target gland hormone production is reduced because of lack of trophic stimulus. Normally, subphysiologic target hormone levels stimulate the pituitary gland to increase trophic hormone production; however, in hypopituitarism, the pituitary gland response is absent, suboptimal, or inappropriate (with biologically inert hormone production). This results in progressive secondary failure of the target glands. Patients with hypopituitarism typically present with low target hormone levels accompanied by low or inappropriately normal levels of the corresponding trophic hormone. The tropic hormone level may appear to be within the reference range with a corresponding subphysiologic target hormone level. Such a tropic hormone level would be inappropriately low for the subphysiologic target hormone level. Sometimes, the assayed tropic hormone level may be biologically inert.

Thus, pituitary function is assessed by the target gland function, not by measuring the pituitary hormone as an isolated event. This is in contrast to target gland function being assessed by the pituitary hormone. For example, adequate pituitary thyrotropin secretion is best assessed by the serum free thyroxin. Primary thyroid gland hypofunction is best assessed by the serum thyrotropin. A low serum free thyroxin yet normal serum thyrotropin indicates pituitary, not thyroid, disease, and central hypothyroidism would be missed by only measuring serum thyrotropin.

HYPERPITUITARISM

Hyperpituitarism, or primary hypersecretion of pituitary hormones, is rare in children. It typically results from a pituitary microadenoma. The most frequently encountered adenoma in children is the prolactinoma, followed by corticotropinoma and somatotropinoma. Fewer than 20 cases of thyrotropinoma in children have been reported, all with onset after age 11 years. Pediatric gonadotropinoma has not been reported.

Hypersecretion of pituitary hormones secondary to macroadenomas (see the image below) can interfere with other pituitary hormone functions, resulting in target organ hormone deficiencies (hypogonadism, hypoadrenalism ,hypothyroidism). In some cases, long-standing

hormonal hypersecretion is accompanied by sufficient hyperplasia of the pituitary to produce sellar enlargement.

Elevated pituitary hormone levels that result from primary endocrine organ deficiency (eg, high circulating thyroid-stimulating hormone [TSH] levels in primary hypothyroidism due to Hashimoto thyroiditis) quickly suppress to reference range values upon replacement of the active hormone. Most rarely, ectopic tumors can secrete pituitary hormones. This article focuses on the endocrine manifestations of pituitary adenomas in children.

Pathophysiology. Hypothalamic dysfunction clearly may promote tumor growth, but overwhelming evidence indicates intrinsic pituicyte genetic disruption leads to pituitary tumorigenesis. The monoclonal nature of most pituitary adenomas, confirmed by X-inactivation studies, implies their usual origin from a clonal event in a single cell. Most pituitary adenomas are functional and secrete a hormone that produces a characteristic clinical presentation. Nonfunctioning pituitary adenomas are rare in children, accounting for only 3–6 % of all adenomas in 2 large series, whereas they comprise 30 % of adenomas in adults. In children, disruption of growth regulation and/or sexual maturation is common, either because of hormone hypersecretion or because of manifestations caused by local compression by the tumor.

Prolactinoma. Overall, prolactinoma is the most common pituitary adenoma encountered in childhood. Most pediatric cases occur in adolescence, more commonly in females than males. Boys tend to have larger tumors and higher serum prolactin (PRL) levels than girls. Females with these tumors present with amenorrhea, and males present with gynecomastia and hypogonadism. Prolactinomas arise from acidophilic cells that are derived from the same lineage as the somatotropes and thyrotropes. Hence, PRL-secreting adenomas may also stain for and secrete growth hormone (GH) and, occasionally, TSH.

Thyrotropinoma. Very few cases of thyrotropinoma have been reported in children. These adenomas may secrete excess PRL, GH, and alpha subunit in addition to TSH. They are usually large because of their aggressive features and because their diagnosis is often delayed. The clinical presentation consists of signs and symptoms of hyperthyroidism, visual symptoms, and headaches. Biochemical features include the elevation of circulating free thyroxine (T4) and total triiodothyronine (T3) levels but inappropriately unsuppressed TSH.

Corticotropinoma (Cushing disease)

In children, corticotropinomas are the most common adenomas observed before puberty, although they occur in people of all ages. They increase in frequency in pubescent and post pubescent children, with a female preponderance. First described by Harvey Cushing in the early 1900s, Cushing disease specifically refers to an adrenocorticotropic hormone (ACTH)–producing pituitary adenoma that stimulates excess cortisol secretion.

A 16-year-old boy with Cushing disease.

Adenomas that cause Cushing disease are significantly smaller than all other types of adenomas at presentation. Children have clinical courses somewhat different from adults. They most commonly present with weight gain (usually not centripetal) and growth failure. As in adults, most patients display an absence of the physiologic diurnal rhythm of plasma cortisol and ACTH with increased urinary excretion of free cortisol and 17-hydroxycorticosteroids (17-OHCS).

Somatotropinoma

Gigantism and Acromegalyare syndromes of excessive secretion of growth hormone (hypersomatotropism) that are nearly always due to a pituitary adenoma. Before closure of the epiphyses, the result is gigantism. Later, the result is acromegaly, which causes distinctive facial and other features. Diagnosis is clinical and by skull and hand x-rays and measurement of growth hormone levels. Treatment involves removal or destruction of the responsible adenoma.

Many growth hormone (GH)–secreting adenomas contain a mutant form of the G_s protein, which is a stimulatory regulator of adenylate cyclase. Cells with the mutant form of G_s protein secrete GH even in the absence of growth hormone–releasing hormone (GHRH). A few cases of ectopic GHRH-producing tumors, especially of the pancreas and lung, also have been described.

Symptoms and Signs

Pituitary gigantism: This rare condition occurs if GH hypersecretion begins in childhood, before closure of the epiphyses. Skeletal growth velocity and ultimate stature are increased, but little bony deformity occurs. However, soft-tissue swelling occurs, and the peripheral nerves are enlarged. Delayed puberty or hypogonadotropic hypogonadism is also frequently present, resulting in a eunuchoid habitus.

Acromegaly: In acromegaly, GH hypersecretion usually starts between the 20s and 40s. When GH hypersecretion begins after epiphyseal closure, the earliest clinical manifestations are coarsening of the facial features and soft-tissue swelling of the hands and feet. Appearance changes, and larger rings, gloves, and shoes are needed.

In adults with acromegaly, coarse body hair increases and the skin thickens and frequently darkens. The size and function of sebaceous and sweat glands increase, such that patients frequently complain of excessive perspiration and offensive body odor. Overgrowth of the mandible leads to protrusion of the jaw (prognathism) and malocclusion of teeth. Cartilaginous proliferation of the larynx leads to a deep, husky voice. The tongue is frequently enlarged and furrowed. In long-standing acromegaly, costal cartilage growth leads to a barrel chest. Articular cartilaginous proliferation occurs early in response to GH excess, with the articular cartilage possibly undergoing necrosis and erosion. Joint symptoms are common, and crippling degenerative arthritis may occur.

Peripheral neuropathies occur commonly because of compression of nerves by adjacent fibrous tissue and endoneural fibrous proliferation. Headaches are common because of the pituitary tumor. Bitemporal hemianopia may develop if suprasellar extension compresses the optic chiasm. The heart, liver, kidneys, spleen, thyroid, parathyroid glands, and pancreas are larger than normal. Cardiac disease occurs in perhaps one third of patients, with a doubling in the risk of death from cardiac disease. Hypertension occurs in up to one third of patients. The risk of cancer, particularly of the GI tract, increases 2-fold to 3-fold. GH increases tubular reabsorption of phosphate and leads to mild hyperphosphatemia. Impaired glucose tolerance occurs in nearly half the patients with acromegaly and in gigantism, but clinically significant diabetes mellitus occurs in only about 10 % of patients.

Galactorrhea occurs in some women with acromegaly, usually in association with hyperprolactinemia. However, galactorrhea may occur with GH excess alone, because GH itself stimulates lactation. Decreased gonadotropin secretion often occurs with GH-secreting tumors. About one third of men with acromegaly develop erectile dysfunction, and nearly all women develop menstrual irregularities or amenorrhea

THYROID GLAND HYPERTHYROIDISM

Hyperthyroidism is a set of disorders involving excess synthesis and secretion of thyroid hormones by the thyroid gland. The resulting elevation in levels of FT_4, free triiodothyronine (FT_3), or both leads to the hypermetabolic condition of thyrotoxicosis. Thus, although many clinicians (endocrinologists excluded) use the terms hyperthyroidism and thyrotoxicosis interchangeably, the 2 words have distinct meanings. For example, both exogenous thyroid hormone intake and subacute thyroiditis can cause thyrotoxicosis, but neither constitutes hyperthyroidism, because the conditions are not associated with new hormone production.

The most common forms of hyperthyroidism include diffuse toxic goiter (Graves disease), toxic multinodular goiter (Plummer disease), and toxic adenoma (see Etiology). Together with subacute thyroiditis, these conditions constitute 85–90 % of all causes of thyrotoxicosis. The disorder is known as Graves' disease (after Robert J. Graves) in the English-speaking world and as Basedow disease (after Karl A. von Basedow) in Europe. The most reliable screening measure of thyroid function in the healthy ambulatory adult population is the TSH level. The degree of thyrotoxicosis is determined by measurement of thyroid hormone levels. Autoantibody testing and nuclear thyroid scintigraphy in some cases can give useful etiologic information.

Etiology. Genetic factors appear to influence the incidence of thyrotoxicosis. Autoimmune thyroid disease, including Hashimoto hypothyroidism and Graves' disease, often occurs in multiple members of a family.

Several genetic syndromes have been associated with hyperthyroidism, especially autoimmune thyroid disease. McCune-Albright's syndrome is caused by mutations in the GNAS gene. This gene encodes the stimulatory G-protein alpha subunit, which is a key component of many signal transduction pathways. Patients present with the classic triad of polyostotic fibrous dysplasia, irregular café-au-lait spots, and precocious puberty. The syndrome may also include facial asymmetry, Cushing syndrome, hyperthyroidism, and acromegaly.

A number of disorders of thyroid function have been found to be caused by mutations in the TSHR gene, which encodes the TSH receptor protein.

These disorders include the following:

1. Familial gestational hyperthyroidism

2. One type of nonimmune hyperthyroidism

3. Congenital nongoiterous thyrotoxicosis

4. Toxic thyroid adenoma with somatic mutation

Type II autoimmune polyendocrine syndrome is associated with hyperthyroidism and hypothyroidism, as well as type 1 diabetes mellitus and adrenal insufficiency. Patients may also have immune deficiency, as manifested by chronic mucosal candidiasis.

Autoimmune thyroid disease has a higher prevalence in patients with human leukocyte antigen (HLA)-DRw3 and HLA-B89. Graves' disease is felt to be an HLA-related, organ-specific defect in suppressor T-cell function. Similarly, subacute painful or granulomatous thyroiditis occurs more frequently in patients with HLA-Bw35. Like other immune diseases, these thyroid conditions occur more frequently in women than in men.

With the available genome-wide association studies, more than a dozen genes and gene regions have been found to be associated with an increased risk for development of thyrotoxicosis, particularly Graves' disease. Unsurprisingly, these studies have shown associations between these same genes and the development of other endocrine autoimmune disorders, such as type 1 diabetes mellitus.

The loci for which specific function can be deduced appear to involve genes related to HLA, non-HLA immune function, and thyroid function. However, the odds ratios that have been determined generally indicate only a mildly increased risk for Graves' disease. Most of the genome-wide association studies have focused on diffuse toxic goiter (i.e, Graves' disease). One study, however, found an association between development of toxic multinodular goiter (Plummer disease) and a single-nucleotide polymorphism (SNP) in the TSHR gene.

Iodine intake

Iodine intake also appears to influence the occurrence of thyrotoxicosis. Clearly, patients in borderline iodine-deficient areas of the world develop nodular goiter, often with areas of thyroid autonomy. When members of this population move to areas of sufficient iodine intake, thyrotoxicosis occurs. Evidence exists that iodine can act as an immune stimulator, precipitating autoimmune thyroid disease and acting as a substrate for additional thyroid hormone synthesis.

Graves' disease

The most common cause of thyrotoxicosis is Graves' disease (50–60 % of cases). Graves' disease is an organ-specific autoimmune disorder characterized by a variety of circulating antibodies, including common autoimmune antibodies, as well as anti-TPO and anti-TG antibodies.

The most important autoantibody is TSI, directed toward epitopes of the TSH receptor and acts as a TSH-receptor agonist. Like TSH, TSI binds to the TSH receptor on the thyroid follicular cells to activate thyroid hormone synthesis and release and thyroid gland growth (hypertrophy). This results in the characteristic picture of Graves' thyrotoxicosis, with a diffusely enlarged thyroid, very high radioactive iodine uptake, and excessive thyroid hormone levels compared with a healthy thyroid.

Thyroid hormone levels can be highly elevated in Graves' disease. Clinical findings specific to Graves' disease include thyroid ophthalmopathy (periorbital edema, chemosis [conjunctival edema], injection, or proptosis) and, rarely, dermopathy over the lower extremities. This autoimmune condition may be associated with other autoimmune diseases, such as pernicious anemia, myasthenia gravis, vitiligo, adrenal insufficiency, celiac disease, and type 1 diabetes mellitus.

Subacute thyroiditis. The next most common cause of thyrotoxicosis is subacute thyroiditis (approximately 15–20 % of cases), a destructive release of preformed thyroid hormone. A typical nuclear scintigraphy scan shows no radioactive iodine uptake (RAIU) in the thyrotoxic phase of the disease. Thyroid hormone levels can be highly elevated in this condition.

Toxic multinodular goiter. Toxic multinodular goiter (Plummer disease) accounts for 15–20 % of thyrotoxicosis cases (see the image below). It occurs more commonly in elderly individuals, especially those with a long-standing goiter. Thyroid hormone excess develops very slowly over time and often is only mildly elevated at the time of diagnosis.

Symptoms of thyrotoxicosis are mild, often because only a slight elevation of thyroid hormone levels is present, and the signs and symptoms of thyrotoxicosis often are blunted (apathetic hyperthyroidism) in older patients. However, very high thyroid hormone levels may occur in this condition after high iodine intake (e.g, with iodinated radiocontrast or amiodarone exposure).

Toxic adenomais caused by a single hyperfunctioning follicular thyroid adenoma. This disorder accounts for approximately 3–5 % of thyrotoxicosis cases. The excess secretion of thyroid hormone occurs from a benign monoclonal tumor that usually is larger than 2.5 cm in diameter. The excess thyroid hormone suppresses TSH levels. RAIU usually is normal, and the radioactive iodine scan shows only the hot nodule, with the remainder of the normal thyroid gland suppressed because the TSH level is low.

Other causes of thyrotoxicosis. There are **s**everal rare causes of thyrotoxicosis,that deserve mention. Struma ovarii is ectopic thyroid tissue associated with dermoid tumors or ovarian teratomas that can secrete excessive amounts of thyroid hormone and produce thyrotoxicosis. Iodide-induced thyrotoxicosis (Jod-Basedow syndrome) occurs in patients with excessive iodine intake (e.g, from an iodinated radiocontrast study). The antiarrhythmic drug amiodarone, rich in iodine and bears some structural similarity to T_4, may cause thyrotoxicosis. Iodide-induced thyrotoxicosis also occurs in patients with areas of thyroid autonomy, such as a multinodular goiter or autonomous nodule.

Iodide-induced thyrotoxicosis appears to result from loss of the normal adaptation of the thyroid to iodide excess. It is treated with cessation of the excess iodine intake and with administration of antithyroid medication. Usually, after depletion of the excess iodine, thyroid functions return to preexposure levels.

Patients with a molar hydatidiform pregnancy or choriocarcinoma have extremely high levels of beta human chorionic gonadotropin (β-hCG), which can weakly activate the TSH receptor. At very high levels of β-hCG, activation of the TSH receptors is sufficient to cause thyrotoxicosis.

Metastatic follicular thyroid carcinoma may also result in thyrotoxicosis.

Pathophysiology. Normally, the secretion of thyroid hormone is controlled by a complex feedback mechanism involving the interaction of stimulatory and inhibitory factors (see the image below). Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the pituitary to release TSH.

Binding of TSH to receptors on the thyroid gland leads to the release of thyroid hormones—primarily T_4 and to a lesser extent T_3. In turn, elevated levels of these hormones act on the hypothalamus to decrease TRH secretion and thus the synthesis of TSH.

Synthesis of thyroid hormone requires iodine. Dietary inorganic iodide is transported into the gland by an iodide transporter, converted to iodine, and bound to thyroglobulin by the enzyme thyroid peroxidase through a process called organification. This results in the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are coupled to form T_3 and T_4; these are then stored with thyroglobulin in the thyroid's follicular lumen. The thyroid contains

a large supply of its preformed hormones. Thyroid hormones diffuse into the peripheral circulation. More than 99.9 % of T_4 and T_3 in the peripheral circulation is bound to plasma proteins and is inactive. Free T_3 is 20–100 times more biologically active than free T_4. Free T_3 acts by binding to nuclear receptors (DNA-binding proteins in cell nuclei), regulating the transcription of various cellular proteins.

Any process that causes an increase in the peripheral circulation of unbound thyroid hormone can cause thyrotoxicosis. Disturbances of the normal homeostatic mechanism can occur at the level of the pituitary gland, the thyroid gland, or in the periphery. Regardless of etiology, the result is an increase in transcription in cellular proteins, causing an increase in the basal metabolic rate. In many ways, signs and symptoms of hyperthyroidism resemble a state of catecholamine excess, and adrenergic blockade can improve these symptoms.

In Graves' disease, circulating autoantibodies against the thyrotropin receptor provide continuous stimulation of the thyroid gland. These antibodies cause release of thyroid hormones and thyroglobulin, and they also stimulate iodine uptake, protein synthesis, and thyroid gland growth.

Ophthalmopathy. The underlying pathophysiology of Graves' ophthalmopathy (also called thyroid-associated orbitopathy) is not completely characterized. It most likely involves an antibody reaction against the TSH receptor that results in activation of T cells against tissues in the retro-orbital space that share antigenic epitopes with thyroid follicular cells. These immune processes lead to an active phase of inflammation, with lymphocyte infiltration of the orbital tissue and release of cytokines that stimulate orbital fibroblasts to multiply and produce mucopolysaccharides (glycosaminoglycans), which absorb water. In consequence, the extraocular muscles thicken and the adipose and connective tissue of the retro-orbit increase in volume.

HYPOTHYROIDISM

Background. Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. It usually is a primary process in which the thyroid gland is unable to produce sufficient amounts of thyroid hormone.

Hypothyroidism can also be secondary—that is, the thyroid gland itself is normal, but it receives insufficient stimulation because of low secretion of thyrotropin (i.e, thyroid-stimulating hormone [TSH]) from the pituitary gland. In tertiary hypothyroidism, inadequate secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus leads to insufficient release of TSH, which in turn causes inadequate thyroid stimulation. Worldwide, iodine deficiency remains the foremost cause of hypothyroidism. In the United States and other areas of adequate iodine intake, autoimmune thyroid disease (Hashimoto disease) is the most common cause. Hypothyroidism may also be drug-induced or otherwise iatrogenic.

The patient’s presentation may vary from asymptomatic to myxedema coma with multisystem organ failure. Because nearly all metabolically active cells require thyroid hormone, deficiency of the hormone has a wide range of effects. Classic signs and symptoms, such as cold intolerance, puffiness, decreased sweating, and coarse skin, may not be present, especially in younger patients.

Third-generation TSH assays are readily available and are generally the most sensitive screening tool for primary hypothyroidism. The generally accepted reference range for normal serum TSH is 0.40–4.2 mIU/L. If TSH levels are above the reference range, the next step would be to measure free thyroxine (T_4). Subclinical hypothyroidism, also referred to as mild hypothyroidism, is defined as normal serum levels of free T4 and triiodothyronine (T_3) with a slightly high serum TSH concentration. For hypothyroidism, thyroid hormone is administered to supplement or replace endogenous production. In general, hypothyroidism can be adequately treated with a constant daily dose of levothyroxine (LT_4). Congenital hypothyroidism, which affects one in every 4000 newborns, is due to congenital mal development of the thyroid.

Etiology. In the United States adequate iodine intake, autoimmune thyroid disease (Hashimoto disease) is the most common cause of hypothyroidism. Prevalence of antibodies is higher in women and increases with age.

Primary hypothyroidism

Types of primary hypothyroidism include the following:

1) Chronic lymphocytic (autoimmune) thyroiditis
2) Postpartum thyroiditis
3) Subacute (granulomatous) thyroiditis
4) Drug-induced hypothyroidism
5) Iatrogenic hypothyroidism

Chronic lymphocytic (autoimmune) thyroiditis

The most frequent cause of acquired hypothyroidism is chronic lymphocytic (autoimmune) thyroiditis (Hashimoto thyroiditis). The body considers the thyroid antigens as foreign, and a chronic immune reaction ensues, resulting in lymphocytic infiltration of the gland and progressive destruction of functional thyroid tissue. The majority of affected individuals will have circulating antibodies to thyroid tissue. Anti–thyroid peroxidase (anti-TPO) antibodies are the hallmark of this disease. It should be noted that antibody levels can vary over time, may not be present early in the disease process, and usually disappear over time. Given this change in antibody concentration, it should be understood that the absence of antibodies does not exclude the diagnosis of chronic lymphocytic (autoimmune) thyroiditis.

Postpartum thyroiditis. Up to 10 % of postpartum women may develop lymphocytic thyroiditis (postpartum thyroiditis) in the 2–12 months after delivery. The frequency may be as high as 25 % in women with type 1 diabetes mellitus. Although a short course of treatment with levothyroxine (LT_4) may be necessary, the condition is usually transient (2–4 months). However, patients with postpartum thyroiditis (anti-TPO–positive) are at increased risk of permanent hypothyroidism or recurrence of postpartum thyroiditis with future pregnancies.

The hypothyroid state can be preceded by a short thyrotoxic state. High titers of anti-TPO antibodies during pregnancy have been reported to have high sensitive and specificity for postpartum autoimmune thyroid disease.

Subacute granulomatous thyroiditis. Also known as de Quervain disease, subacute granulomatous thyroiditis is a relatively uncommon disease that occurs most frequently in middle-aged women. Disease features include low grade fever, thyroid pain, dysphagia, and elevated erythrocyte sedimentation rate (ESR). The disease is usually self-limited and does not normally result in longstanding thyroid dysfunction. It is important to note that inflammatory conditions or viral syndromes may be associated with transient hyperthyroidism followed by transient hypothyroidism (i.e, de Quervain or painful thyroiditis and subacute thyroiditis).

Iodine deficiency or excess. Worldwide, iodine deficiency is the most common cause of hypothyroidism. Excess iodine, as in radiocontrast dyes, amiodarone, health tonics (herbal and dietary supplements), and seaweed, can transiently inhibit iodide organification and thyroid hormone synthesis (the Wolff-Chiakoff effect). Most healthy individuals have a physiologic escape from this effect. In patients with iodine overload, the sodium-iodide symporter shuts down, and this allows intracellular iodine levels to drop and hormone secretion to resume.

The Wolff-Chiakoff effect is short-lived because the sodium-iodide symporter is capable of rapidly downregulation. However, exposure to excess iodine can produce more profound and sustained hypothyroidism in individuals with abnormal thyroid glands (e.g, from autoimmune thyroiditis, subtotal thyroidectomy, or prior radioiodine therapy).

Central hypothyroidism (secondary or tertiary) results when the hypothalamic-pituitary axis is damaged. The following potential causes should be considered:

1. Pituitary adenoma
2. Tumors impinging on the hypothalamus
3. Lymphocytic hypophysitis
4. Sheehan syndrome
5. Drugs (e.g, dopamine, prednisone, or opioids)
6. Congenital nongoiterous hypothyroidism type 4
7. TRH resistance, TRH deficiency

Tumors in or around the pituitary cause impaired pituitary function by exerting pressure on normal pituitary cells and thereby affect the secretion of TRH, TSH, or both. Radiation, hypophysitis, and Sheehan syndrome cause death of these cells. Drugs such as dopamine and corticosteroids result in decreased TSH secretion.

Congenital nongoiterous hypothyroidism type 4 is caused by a mutation in the TSHB gene and is inherited in an autosomal recessive pattern. Patients have hypothyroidism and a low TSH level that does not rise with administration of TRH. Many patients with this condition were the products of consanguineous unions. TRH resistance is caused by a mutation in the TRHR gene and is inherited in an autosomal recessive manner. Patients with this condition have hypothyroidism and, unsurprisingly, have insensitivity to thyrotropin secretion. That only a handful of cases of TRH resistance have been reported in the literature suggests that this is a rare condition.

TRH deficiency is caused by mutation in the TRH gene and is inherited in an autosomal recessive manner. The index case was a girl evaluated for short stature who was found to have an isolated deficiency of TRH.

Pathophysiology The hypothalamic-pituitary-thyroid axis governs thyroid hormone secretion. Although hypothalamic or pituitary disorders can affect thyroid function, localized disease of the thyroid gland that results in decreased thyroid hormone production is the most common cause of hypothyroidism. Under normal circumstances, the thyroid releases 100–125 nmol of T_4 daily and only small amounts of T_3. The half-life of T_4 is approximately 7–10 days. T_4, a prohormone, is converted to T_3, the active form of thyroid hormone, in the peripheral tissues by 5'-deiodination.

Early in the disease process, compensatory mechanisms maintain T_3 levels. Decreased production of T_4 causes an increase in the secretion of TSH by the pituitary gland. TSH stimulates hypertrophy and hyperplasia of the thyroid gland and 5'-deiodinase activity, thereby increasing T_3 production.

The hypothalamic-pituitary-thyroid axis. Levels of circulating thyroid hormones are regulated by a complex feedback system involving the hypothalamus and pituitary gland.

Deficiency of thyroid hormone has a wide range of effects. Systemic effects are the result of either derangements in metabolic processes or direct effects by myxedematous infiltration (ie, accumulation of glucosaminoglycans in the tissues). The hypothyroid changes in the heart result in decreased contractility, cardiac enlargement, pericardial effusion, decreased pulse, and decreased cardiac output. In the gastrointestinal (GI) tract, achlorhydria and prolonged intestinal transit time with gastric stasis can occur. Delayed puberty, anovulation, menstrual irregularities, and infertility are common. TSH screening should be a routine part of any investigation into menstrual irregularities or infertility.

Decreased thyroid hormone effect can cause increased levels of total cholesterol and low-density lipoprotein (LDL) cholesterol and a possible change in high-density lipoprotein (HDL) cholesterol because of a change in metabolic clearance. In addition, hypothyroidism may result in an increase in insulin resistance

PARATHYROID GLAND HYPERPARATHYROIDISM

Primary Hyperparathyroidism

Definition of the problem. Primary hyperparathyroidism is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis.

Etiology. In approximately 85 % of cases, primary hyperparathyroidism is caused by a single adenoma. In 15 % of cases, multiple glands are involved (i.e, either multiple adenomas or hyperplasia). Rarely, primary hyperparathyroidism is caused by parathyroid carcinoma. The etiology of adenomas or hyperplasia remains unknown in most cases. Familial cases can occur either as part of the multiple endocrine neoplasia syndromes (MEN 1 or MEN 2a), hyperparathyroid-jaw tumor (HPT-JT) syndrome, or familial isolated hyperparathyroidism (FIHPT). Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism also belong to this category.

Pathophysiology. In primary hyperparathyroidism due to adenomas, the normal feedback on parathyroid hormone production by extracellular calcium seems to be lost, resulting in a change in the set point. However, this is not the case in primary hyperparathyroidism from parathyroid hyperplasia. An increase in the cell numbers is probably the cause. Chronic excessive resorption of calcium from bone caused by excessive parathyroid hormone can result in osteopenia. In severe cases, this may result in osteitis fibrosa cystica, which is characterized by subperiosteal resorption of the distal phalanges, tapering of the distal clavicles, salt-and-pepper appearance of the skull, and brown tumors of the long bones. This is not commonly seen now. In addition, the chronically increased excretion of calcium in the urine can predispose to the formation of renal stones. Other symptoms of hyperparathyroidism are due to the hypercalcemia itself and are not specific to hyperparathyroidism. These can include muscle weakness, fatigue, volume depletion, nausea and vomiting, and in severe cases, coma and death. Neuropsychiatric manifestations are particularly common and may include depression, confusion, or subtle deficits that are often characterized poorly and may not be noted by the patient. Increased calcium can increase gastric acid secretion, and persons with hyperparathyroidism may have a higher prevalence of peptic ulcer disease. Rare cases of pancreatitis have been attributed to hypercalcemia.

Secondary Hyperparathyroidism is the overproduction of parathyroid hormone secondary to a chronic abnormal stimulus for its production. Typically, this is due to chronic renal failure. Another common cause is vitamin D deficiency. A study by Bleskestad et al has found that more than 50 % of patients who undergo kidney transplantation have elevated levels of intact PTH more than 1 year after transplantation. If these elevated levels are associated with mortality, it may have a major impact on future guidelines.

Secondary hyperparathyroidism (SHPT) develops early in chronic kidney disease (CKD), before dialysis is required. Consequently, most patients with chronic kidney disease stage 5 or end-stage renal disease (ESRD) have elevated parathyroid hormone and secondary hyperparathyroidism of variable severity. Vitamin D deficiency is common and is underdiagnosed.

Etiology. In chronic kidney disease, overproduction of parathyroid hormone occurs in response to hyperphosphatemia, hypocalcemia, and impaired 1.25-dihydroxyvitamin D production by the diseased kidneys. Hyperphosphatemia appears to be particularly important; it can directly stimulate parathyroid hormone synthesis and parathyroid hyperplasia and indirectly promotes secondary hyperparathyroidism by decreasing free calcium level.

Pathophysiology. Chronic overproduction of parathyroid hormone in patients with renal failure contributes to the spectrum of bone disease observed in patients on dialysis (e.g, osteitis fibrosa cystica and mixed uremic osteodystrophy). Nonskeletal consequences include cardiovascular calcification, soft tissue calcification, endocrine disturbances, compromised immune system, neurobehavioral changes, and altered erythropoiesis.

Tertiary Hyperparathyroidism is a state of excessive secretion of parathyroid hormone after longstanding secondary hyperparathyroidism and resulting in hypercalcemia. Some authorities reserve the term for secondary hyperparathyroidism that persists after successful renal transplantation.

Etiology. Tertiary disease is characterized by the development of autonomous hypersecretion of parathyroid hormone causing hypercalcemia. The etiology is unknown but may be due to monoclonal expansion of parathyroid cells (nodule formation within hyperplastic glands). A change may occur in the set point of the calcium-sensing mechanism to hypercalcemic levels. Four-gland involvement occurs in most patients.

Pathophysiology. We observe tertiary hyperparathyroidism most commonly in patients with chronic secondary hyperparathyroidism and often after renal transplantation. The hypertrophied parathyroid glands fail to return to normal and continue to oversecrete parathyroid hormone, despite serum calcium levels that are within the reference range or even elevated. In these cases, the hypertrophied glands become autonomic and cause hypercalcemia,

even after withdrawal of calcium and calcitriol therapy. They also may become resistant to calcimimetic treatment. This type of tertiary disease is particularly dangerous because the phosphate level is often elevated. If the calcium value multiplied by the phosphate value yields a high product, diffuse calcinosis may occur.

HYPOPARATHYROIDISM is a condition of parathyroid hormone (PTH) deficiency.

Primary hypoparathyroidism is a state of inadequate PTH activity. In absence of adequate PTH activity, the ionized calcium concentration in the extracellular fluid falls below the reference range. Primary hypoparathyroidism, the subject of this article, is a syndrome resulting from iatrogenic causes or one of many rare diseases.

Secondary hypoparathyroidism is a physiologic state in which PTH levels are low in response to a primary process that causes hypercalcemia.

Causes. Most people have 4 parathyroid glands; consequently, primary hypoparathyroidism is uncommon. Hypocalcemia from hypoparathyroidism requires all 4 parathyroid glands to be affected. Primary hypoparathyroidism may be permanent or reversible. Permanent primary hypoparathyroidism may be congenital or acquired.

1. Iatrogenic causes

1.1. The most common cause of primary hypoparathyroidism is excision of all parathyroid glands via surgery in the treatment of thyroid, laryngeal, or other neck malignancy. Patients with parathyroid hyperplasia, as observed in the multiple endocrine neoplasia (MEN) syndromes, are treated by surgical removal of the parathyroid glands. Attempts at restoring normal PTH levels and normocalcemia by autotransplantation of a fraction of one of the parathyroid glands sometimes are effective, but many patients become hypoparathyroid. Repeated neck explorations for primary hyperparathyroidism caused by parathyroid adenoma may also cause hypoparathyroidism.

1.2. Extensive irradiation to the face, neck, or mediastinum may cause destruction of all 4 parathyroid glands, with ensuing primary hypoparathyroidism and hypocalcemia.

1.3. The "hungry bone syndrome" develops after a parathyroidectomy for hyperparathyroidism. The body has been accustomed to high levels of PTH, causing hypercalcemia. Much of this hypercalcemic effect is because of resorption of bone. When the parathyroid gland or glands responsible for the hypersecretion of PTH are removed, the PTH level in the blood drops suddenly, and the patient experiences transient hypoparathyroidism. The bone, which has been starved of calcium, avidly retains it under the influence of osteoblasts. Without PTH and with bone now using calcium to remineralize, the ECF ionized calcium level falls. Postoperatively, patients require aggressive treatment with calcium for several hours to several days. Eventually, the hypoparathyroid state resolves, and calcium homeostasis is re-achieved.

2. Autoimmune causes

2.1. Type 1 autoimmune polyglandular syndrome (also referred to as HAM syndrome) includes primary hypoparathyroidism that is due to destruction of the parathyroid glands. On average, these patients develop primary hypoparathyroidism by age 10 years.

2.2. Autoimmune hypoparathyroidism may exist alone or in sporadic or familial forms. For patients with autoimmune primary hypoparathyroidism, the average age for development of hypocalcemia is 7 years, with a range of 6 months to 20 years.

3. Congenital causes

3.1. Numerous conditions are described in the literature that result in congenital agenesis or hypoplasia and, therefore, can produce primary hypoparathyroidism with symptomatic hypocalcemia at birth or in the new-born period. These conditions, which are summarized from Goltzman and Cole (1996), are as follows:

1. Isolated primary hypoparathyroidism.
2. X-linked primary hypoparathyroidism (band Xq26-Xq27).
3. X autosomal-recessive primary hypoparathyroidism.
4. Branchial dysgenesis (DiGeorge syndrome).

5. Chromosomal defects dup(1q), del(5p), dup(8q), del(10q), del(22q).

6. Monogenic hypoparathyroidism.

7. Isolated autosomal-dominant conditions.

8. Isolated autosomal-recessive conditions.

9. Velocardiofacial (Shprintzen) syndrome (CATCH 22 [for cardiac, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia with 22q deletion] is a mnemonic for the features of this syndrome).

10. Zellweger syndrome.

11. Retinoid embryopathy.

12. Associational arhinencephalia and/or DiGeorge syndrome and the coloboma, heart disease, choanal atresia, retarded growth and development, genital anomalies, ear anomalies (CHARGE) syndrome and/or DiGeorge syndrome

4. Causes related to metal overload (ion deficiency)

4.1. Hemochromatosis and thalassemia, both of which are associated with iron overload, may result in primary hypoparathyroidism.

4.2. Wilson disease, with copper overload, may also cause primary hypoparathyroidism.

4.3. Hypermagnesemia has been demonstrated to decrease PTH release. Correction of hypermagnesemia leads to correction of the primary hypoparathyroidism.

4.4. Aluminum deposition within the parathyroid glands may cause primary hypo-parathyroidism in patients with end-stage renal disease who are on hemodialysis.

5. Causes related to infiltration of the parathyroid glands

5.1. In addition to hemochromatosis and Wilson disease, parathyroid gland destruction has been reported as a result of metastatic disease, granulomatous disease, amyloidosis, syphilis, and progressive systemic sclerosis.

5.2. Of note, clinically significant hypocalcemia is not always apparent in these patients.

6. Neonatal causes

6.1. The unborn baby of a mother with hypercalcemia has chronic suppression of parathyroid gland function. In the worst circumstances, the parathyroid glands may become atrophic.

6.2. At birth, the maternal calcium excess is eliminated, and newborns are at risk of hypocalcemia caused by primary hypoparathyroidism.

6.3. Clinically significant hypocalcemia may develop within the first 3 weeks of life but may occur as late as 1 year after birth. The primary hypoparathyroidism in these patients is self-limited.

Pathophysiology. The ionized calcium concentration in the extracellular fluid (ECF) remains nearly constant, at a level of approximately 1 mM. Ionized calcium in the ECF is in equilibrium with ionized calcium in storage pools such as bone, proteins in the circulation, and within the intracellular fluid. The intracellular fluid concentration of calcium is more than 10,000-fold lower than in the ECF. Maintenance of ionized calcium concentrations in the intracellular and extracellular fluids is highly regulated. It modulates the functions of bone, renal tubular cells, clotting factors, adhesion molecules, excitable tissues, and a myriad of intracellular processes. An extracellular calcium-sensing receptor has been isolated from parathyroid, kidney, and brain cells. The extracellular calcium-sensing receptor is G protein coupled. Mutations in the extracellular calcium-sensing receptor have been demonstrated to result in hypercalcemic or hypocalcemic states. Normally, the extracellular calcium-sensing receptor is extremely sensitive and responds to changes in the ECF calcium ion concentration as small as 2 %.

In parathyroid cells, the extracellular calcium-sensing receptor regulates the secretion of PTH. Inactivating mutations of the extracellular calcium-sensing receptor lead to hypercalcemia, as observed in familial hypocalciuric hypercalcemia (heterozygous mutation) and neonatal severe hyperparathyroidism (homozygous mutation). Conversely, activating mutations of the extracellular calcium-sensing receptor lead to hypocalcemia, as observed in some families with autosomal-dominant hypocalcemia.

The intracellular mechanism(s) whereby activation of the extracellular calcium-sensing receptor leads to inhibition of PTH exocytosis is unknown. Because pertussis toxin blocks the inhibition of cyclic adenosine monophosphate (cAMP), but not PTH, in response to a high ECF ionized calcium concentration, cAMP is probably not an important second messenger for the extracellular calcium-sensing receptor. Candidate second messengers include protein kinase C, phospholipase A2, and intracellular calcium.

Conversely, a fall in ECF ionized calcium concentration leads to exocytosis of PTH.

1. PTH has the overall effect of returning the ECF ionized calcium concentration to the reference range by its effects on the kidneys and the skeleton.

2. PTH activates osteoclasts. Osteoclast activation results in bone resorption and a release of ionized calcium into the ECF. Evidence suggests that small pulse doses of PTH activate osteoblasts, with ensuing bone deposition. The effect of PTH on osteoclasts seems more important than the effect on osteoblasts.

3. PTH inhibits the proximal tubular transport of phosphate from the lumen to the interstitium. In conditions of primary PTH excess, hypophosphatemia tends to occur. Conversely, in hypoparathyroidism, the phosphate concentration in the plasma is within the reference range or slightly elevated.

4. PTH has a calcium-retaining effect on the distal tubule. The PTH-mediated calcium reabsorption is independent of any effects on sodium or water reabsorption. This effect of PTH is important in hypoparathyroidism because, in the absence of this distal tubular calcium reabsorption, the kidneys waste calcium. This depletes the ECF ionized calcium and increases the urinary calcium concentration.

5. PTH stimulates renal 1-alpha-hydroxylase, the enzyme that synthesizes formation of 1,25-dihydroxy vitamin D; 1,25-dihydroxy vitamin D allows for better dietary calcium absorption. Thus, 1,25-dihydroxy vitamin D has a synergistic effect with PTH; both contribute to a rise in the ECF ionized calcium concentration.

In absence of PTH, bone resorption, phosphaturic effect, renal distal tubular calcium reabsorption, and 1,25-dihydroxy vitamin D–mediated dietary calcium absorption cannot occur. Therefore, the consequence of PTH deficiency is hypocalcemia.

ADRENAL GLAND

ADDISON DISEASE (Primary or Chronic Adrenocortical Insufficiency)

Addison disease is an insidious, usually progressive hypofunctioning of the adrenal cortex. It causes various symptoms, including hypotension and hyperpigmentation, and can lead to adrenal crisis with cardiovascular collapse. Diagnosis is clinical and by finding elevated plasma ACTH with low plasma cortisol. Treatment depends on the cause but generally includes hydrocortisone and sometimes other hormones.

Addison disease develops in all age groups, about equally in each sex, and tends to become clinically apparent during metabolic stress or trauma. Onset of severe symptoms (adrenal crisis) may be precipitated by acute infection (a common cause, especially with septicemia). Other causes include trauma, surgery, and Na loss from excessive sweating. Even with treatment, Addison disease may cause a slight increase in mortality. It is not clear whether this increase is due to mistreated adrenal crises or long-term complications of inadvertent over-replacement.

Etiology. About 70 % of cases in the US are due to idiopathic atrophy of the adrenal cortex, probably caused by autoimmune processes. The remainder results from destruction of the adrenal gland by granuloma (eg, TB, histoplasmosis), tumor, amyloidosis, hemorrhage, or inflammatory necrosis. Hypoadrenocorticism can also result from administration of drugs that block corticosteroid synthesis (e.g, ketoconazole, the anesthetic etomidate). Addison disease may coexist with diabetes mellitus or hypothyroidism in polyglandular deficiency syndrome. In children, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia (CAH), but other genetic disorders are increasingly recognized as causes.

Pathophysiology. Both mineralocorticoids and glucocorticoids are deficient.

Mineralocorticoid deficiency. Because mineralocorticoids stimulate Na reabsorption and K excretion, deficiency results in increased excretion of Na and decreased excretion of K, chiefly in urine but also in sweat, saliva, and the GI tract. A low serum concentration of Na and a high concentration of K result. Urinary salt and water loss cause severe dehydration, plasma hypertonicity, acidosis, decreased circulatory volume, hypotension, and, eventually, circulatory collapse. However, when adrenal insufficiency is caused by inadequate ACTH production (secondary adrenal insufficiency), electrolyte levels are often normal or only mildly deranged.

Glucocorticoid deficiency. Glucocorticoid deficiency contributes to hypotension and causes severe insulin sensitivity and disturbances in carbohydrate, fat, and protein metabolism. In the absence of cortisol, insufficient carbohydrate is formed from protein; hypoglycemia and decreased liver glycogen result. Weakness follows, due in part to deficient neuromuscular function. Resistance to infection, trauma, and other stress is decreased. Myocardial weakness and dehydration reduce cardiac output, and circulatory failure can occur. Decreased blood cortisol results in increased pituitary ACTH production and increased bloodβ-lipotropin, which has melanocyte-stimulating activity and, together with ACTH, causes the hyperpigmentation of skin and mucous membranes characteristic of Addison disease. Thus, adrenal insufficiency secondary to pituitary failure does not cause hyperpigmentation.

CUSHING SYNDROME

Cushing syndrome is caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids. Individuals with Cushing syndrome can develop moon facies, facial plethora, supraclavicular fat pads, buffalo hump, truncal obesity, and purple striae, as shown in the image below. Individuals often complain of proximal muscle weakness, easy bruising, weight gain, hirsutism, and, in children, growth retardation. Hypertension, osteopenia, diabetes mellitus, and impaired immune function may occur.

In an emergency situation, it is important to remember that the most common cause of Cushing syndrome is the use of exogenous glucocorticoids. Exogenous steroids may cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis that can last for as long as a year after exogenous steroid administration has ended.

An individual with HPA-axis suppression cannot increase steroid production appropriately during a medical illness or other stress and would need to receive stress doses of steroids to avoid adrenal crisis. Thus, in an emergency, the potential for relative adrenal insufficiency should be considered in any patient with Cushing syndrome.

Causes

1. Exogenous steroid administration

1.1. Administration of exogenous steroids may lead to the development of Cushing syndrome.

1.2. Symptoms of glucocorticoid excess generally occur with the administration of oral steroids; however, occasionally injections of steroids into joints and the use of steroid inhalers can cause Cushing syndrome.

1.3. Patients with diseases that respond to steroid therapy are especially likely to receive steroids and thus develop Cushing syndrome. Such disorders include a wide variety of rheumatologic, pulmonary, neurological, and nephrologic diseases. Patients who have undergone organ transplants are also at risk for developing Cushing syndrome due to exogenous steroids required as part of graft antirejection medication regimens.

2. Endogenous glucocorticoid overproduction

2.1. ACTH-producing pituitary adenoma.

2.2. Pituitary adenomas that secrete ACTH are derived from corticotrophs in the anterior pituitary.

2.3. ACTH secreted by corticotrophs is released into the circulation and acts on the adrenal cortex to produce hyperplasia and stimulate the secretion of adrenal steroids.

2.4. These adenomas, if large, can result in loss of production of other anterior pituitary hormones (TSH, FSH, LH, growth hormone, and prolactin) and the posterior pituitary hormone vasopressin.

2.5. Pituitary tumors can also compress the hypophyseal stalk leading to hyperprolactinemia from loss of dopamine inhibition.

2.6. Nelson syndrome is caused by a large ACTH-secreting pituitary tumor; it is often locally invasive, difficult to cure, and associated with hyperpigmentation. In patients who undergo adrenalectomy without pituitary irradiation, the incidence of Nelson syndrome is about 20–25 %.

2.7. Large pituitary adenomas may press on the optic chiasm, causing visual-field deficiencies that often present as bitemporal field cuts.

2.8. Primary adrenal lesions.

2.9. Overproduction of glucocorticoids may be due to an adrenal adenoma, adrenal carcinoma, or macronodular or micronodular adrenal hyperplasia. The zona fasciculata and zona reticularis layers of the adrenal cortex normally produce glucocorticoids and androgens. Glucocorticoid-secreting tumors are derived from these cells and, thus, may secrete both glucocorticoids and androgens.

Pathophysiology. Excess levels of either exogenously administered glucocorticoids or endogenous overproduction of cortisol causes Cushing syndrome. Endogenous glucocorticoid overproduction or hypercortisolism that is independent of ACTH is usually due to a primary adrenocortical neoplasm (usually an adenoma but rarely a carcinoma). Bilateral micronodular hyperplasia and macronodular hyperplasia are rare causes of Cushing syndrome. ACTH-secreting neoplasms cause ACTH-dependent Cushing syndrome. They usually are due to an anterior pituitary tumor, that is, classic Cushing disease (80 %). Non-pituitary ectopic sources of ACTH, such as an oat cell carcinoma, small-cell lung carcinoma, or carcinoid tumor, cause the balance of ACTH-dependent disease. Ectopic corticotropin-releasing hormone (CRH) secretion leading to increased ACTH secretion comprise a very rare group of cases of Cushing syndrome.

PRIMARY ALDOSTERONISM (Conn Syndrome)

Primary aldosteronism is aldosteronism caused by autonomous production of aldosterone by the adrenal cortex (due to hyperplasia, adenoma, or carcinoma). Symptoms and signs include episodic weakness, elevated BP, and hypokalemia. Diagnosis includes measurement of plasma aldosterone levels and plasma renin activity. Treatment depends on cause. A tumor is removed if possible; in hyperplasia, spironolactone or related drugs may normalize BP and eliminate other clinical features.

Aldosterone is the most potent mineralocorticoid produced by the adrenals. It causes Na retention and K loss. In the kidneys, aldosterone causes transfer of Na from the lumen of the distal tubule into the tubular cells in exchange for K and hydrogen. The same effect occurs in salivary glands, sweat glands, cells of the intestinal mucosa, and in exchanges between ICFs and ECFs. Aldosterone secretion is regulated by the renin-angiotensin system and, to a lesser extent, by ACTH. Renin, a proteolytic enzyme, is stored in the juxtaglomerular cells of the kidneys. Reduction in blood volume and flow in the afferent renal arterioles induces secretion of renin. Renin transforms angiotensinogen from the liver to angiotensin I, which is transformed by ACE to angiotensin II. Angiotensin II causes secretion of aldosterone and, to a much lesser extent, secretion of cortisol and deoxycorticosterone; it also has pressor activity. Na and water retention resulting from increased aldosterone secretion increases the blood volume and reduces renin secretion.

Primary aldosteronism is caused by adenoma, usually unilateral, of the glomerulosa cells of the adrenal cortex or, more rarely, by adrenal carcinoma or hyperplasia. Adenomas are extremely rare in children but the syndrome sometimes occurs in childhood adrenal carcinoma or hyperplasia.

SECONDARY ALDOSTERONISM

Secondary aldosteronism is increased adrenal production of aldosterone in response to nonpituitary, extra-adrenal stimuli, including renal artery stenosis and hypovolemia. Symptoms are those of primary aldosteronism. Treatment involves correcting the cause.

Secondary aldosteronism is caused by reduced renal blood flow, which stimulates the renin-angiotensin mechanism with resultant hypersecretion of aldosterone. Causes of reduced renal blood flow include obstructive renal artery disease (e.g, atheroma, stenosis), renal vasoconstriction (as occurs in accelerated hypertension), and edematous disorders (e.g, heart failure, cirrhosis with ascites, nephrotic syndrome). Secretion may be normal in heart failure, but hepatic blood flow and aldosterone metabolism are reduced, so circulating levels of the hormone are high.

ADRENAL VIRILISM (Adrenogenital Syndrome)

Adrenal virilism is a syndrome in which excessive adrenal androgens cause virilization. Diagnosis is clinical and confirmed by elevated androgen levels with and without dexamethasone suppression; determining the cause may involve adrenal imaging. Treatment depends on the cause.

Adrenal virilism is caused by an androgen-secreting adrenal tumor or by adrenal hyperplasia. Malignant adrenal tumors may secrete excess androgens, cortisol, or mineralocorticoids (or all three), resulting in Cushing syndrome with suppression of ACTH secretion and atrophy of the contralateral adrenal as well as hypertension. Adrenal hyperplasia is usually congenital; delayed virilizing adrenal hyperplasia is a variant of congenital adrenal hyperplasia. Both are caused by a defect in hydroxylation of cortisol precursors; cortisol precursors accumulate and are shunted into the production of androgens. The defect is only partial in delayed virilizing adrenal hyperplasia, so clinical disease may not develop until adulthood.

PHEOCHROMOCYTOMA

A pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells typically located in the adrenals. It causes persistent or paroxysmal hypertension. Diagnosis is by measuring catecholamine products in blood or urine. Imaging tests, especially CT or MRI, help localize tumors. Treatment involves removal of the tumor when possible. Drug therapy for control of BP includes α-blockade, usually combined with β-blockade.

The catecholamines secreted include norepinephrine, epinephrine, dopamine, and dopa in varying proportions. About 90 % of pheochromocytomas are in the adrenal medulla, but they may also be located in other tissues derived from neural crest cells. Possible sites include the following:

1. Paraganglia of the sympathetic chain.
2. Retroperitoneally along the course of the aorta.
3. Carotid body.
4. Organ of Zuckerkandl (at the aortic bifurcation).
5. GU system.
6. Brain.

Pheochromocytomas vary in size but average 5 to 6 cm in diameter. They weigh 50 to 200 g, but tumors weighing several kilograms have been reported. Rarely, they are large enough to be palpated or cause symptoms due to pressure or obstruction. Regardless of the histologic appearance, the tumor is considered benign if it has not invaded the capsule and no metastases are found, although exceptions occur. Pheochromocytomas may be part of the syndrome of familial multiple endocrine neoplasia (MEN) types 2A and 2B, in which other endocrine tumors (parathyroid or medullary carcinoma of the thyroid) coexist or develop subsequently.

Date	Grade	Teacher’s signature

PATHOPHYSIOLOGY OF NERVOUS SYSTEM

Relevance. The nervous system is the highest regulatory system. It manages the functions of all its organs and systems, providing a perfect adaptation of the organism to the environment. The nervous system participates in numerous reactions designed to protect organism from damage or compensating those pathological changes that occur in case of diseases. Disorders of the nervous system can cause impairment of function of any other physiological system when the body becomes more sensitive to the action of pathogenic factors. Disorders of higher nervous activity does not allow an individual to fully implement its social function. In the pathogenesis of any disease on this or other stage of its development it is possible to find disorders of the nervous system function. All this underlines the relevance of the topic.

Overall Objective is to be able to describe disorders of higher nervous (conditioned reflex) activities, motor and other functions of the nervous system, explain their causes, main forms and manifestations.

The student should be able to (specific objectives):

1. Describe the etiology and pathogenesis of disorders of higher nervous activity and neuroses.
2. Classify the disorder of motor function of the nervous system.
3. Describe the concept of "hyperkinesis", "paralysis and paresis," "ataxia".
4. Explain the causes and mechanisms of hyperkinesis, paralysis and ataxia.
5. Discover the main features and manifestations of motor function disorders of the nervous system in hyperkinesia, ataxia and paralysis, to explain the mechanism of their development.
6. Differentiate central and peripheral paralysis.

The student should be able to (required knowledge and skills):

1. Describe the structure and functions of various parts of the central nervous system (Depart. of normal anatomy and physiology).
2. Explain the motor function of the nervous system, what nerve structures it carries out. What is the motor analyzer? (Depart. of normal physiology).
3. Describe the main motor nerve pathways (Depart. of normal physiology).
4. Evaluate the impact of the extrapyramidal system and cerebellum on motor function of the organism (Depart. of normal physiology).
5. Evaluate the structural organization of the connections of the spinal medulla and other parts of the central nervous system (Depart. of normal physiology).

QUESTIONS TO THE LESSON

1. The main function of the nervous system. The theory of "nervism" – the role of the nervous system pathology.
2. Risk factors of the nervous system damage. Etiology of the nervous system disorders. Levels of dysfunction of the nervous system. Typical forms of disorders of the nervous system.
3. Pathogenesis of the nervous system disorders. Disorders of neuron, interneuronal connections and systemic pathological phenomena.
4. Disorders of the motor functions of the nervous system. Movement disorders. Classes of typical forms neurogenic disorders of movement. Hypo- and hyperkinesia Types. Causes. Manifestation.
5. Disorders of sensitivity. Classification. Causes. Mechanisms. Manifestation.
6. Pain. Definition. Causes. Mechanisms of formation and development of pain. Clinical pain syndromes (thalamic pain, phantom pain, causalgia). Value of pain. Causes. Types of pain.
7. Neurogenic trophic disorders. Mechanisms of neurotrophic control. Neurodystrophic process. Denervation syndrome.
8. Neurosis. The role of higher nervous activity in the development of neuroses. The causes and conditions of neuroses development. The main types of neuroses and their manifestations. Common manifestations of neurotic states. The notion of vegetative neurosis.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

PATHOPHYSIOLOGY OF THE NERVOUS SYSTEM

Sensory Nervous System Disorders

The central nervous system (CNS) refers to the brain and spinal cord together. The peripheral nervous system refers to the cervical, thoracic, lumbar, and sacral nerve trunks leading away from the spine to the limbs. Messages related to function (such as movement) or dysfunction (such as pain) travel from the brain to the spinal cord and from there to other regions in the body and back to the brain again. The autonomic nervous system controls involuntary functions in the body, like perspiration, blood pressure, heart rate, or heartbeat. It is divided into the sympathetic and parasympathetic nervous systems. The sympathetic and parasympathetic nervous systems have links to important organs and systems in the body; for example, the sympathetic nervous system controls the heart, blood vessels, and respiratory system, while the parasympathetic nervous system controls our ability to sleep, eat, and digest food.

The peripheral nervous system also includes 12 pairs of cranial nerves located on the underside of the brain. Most relay messages of a sensory nature. Neuralgia, as in trigeminal neuralgia, is a term that refers to pain that arises from abnormal activity of a nerve trunk or its branches. The type and severity of pain associated with neuralgia vary widely.

The sensory nervous system is a major component of the body's overall nervous system function. It's a highly complex network of nerves, muscles and organs designed to delivery sensory input to the spinal cord and brain. Because of its complexity, diagnosing a disorder within this system can be a lengthy process.

Identification

The human body's central nervous system is made up of two subsystems – the peripheral system and the autonomic system. The brain and spinal cord are the components of the autonomic portion. The peripheral portion is made up of motor, sensory, autonomic and somatic systems. Sensory nervous system structures run along the skin in the form of receptors, in the muscles and other organs. Organs related to sight, sound and taste are also a part of this system. A disorder can develop within any one of these areas, and can affect other areas of the body as well.

Causes. Disorders can develop in the sensory nervous system in case of an injury, when blood flowing to a particular area is hampered or as the result of a disease. Blood flow impairment can occur because of a tumor, a genetic defect, or a condition which causes the blood to clog, or clot inside blood vessels. Nutritional deficiencies, or metabolic imbalances can also work to alter the chemical make-up of the blood. Trauma related disorders may result from a blow to an area of the body where nerve damage is caused. Sensory receptors can also become damaged when an infection is present, or when nerve endings begin to deteriorate.

Warning Signs

With so many different areas of the body involved in the sensory nervous system, symptoms of a disorder can vary depending on the area involved. Tingling sensations, or numbness along the arm or leg are possible. Sudden vision loss may also indicate some sort of sensory receptor damage is present. Individuals who experience a type of back pain that radiates out into other areas of the body may have a pinched nerve that can develop into a nerve disorder. It's essential to consult with a physician when any sudden change in the body's function or condition arises.

Types

Sensory nervous system disorders can affect large areas of the body or localized regions. Pain, tingling, weakness and numbness are usually present in affected areas. Polyneuropathies involve nerve damage that's occurred in the long peripheral nerves of the body. Distal symmetric sensory-motor polyneuropathy is a disorder that involves the nerves that run from the bottom of the spinal cord to the feet. Carpal tunnel syndrome is a localized condition that develops in the wrist area. Multiple mononeuropathy is a disorder in which inflammation destroys the small blood vessels in an area like the hand or the foot.

Brown-Séquard–plus syndrome

The pure Brown-Séquard syndrome reflecting hemisection of the cord is not often observed. A clinical picture composed of fragments of the syndrome or of the hemisection syndrome plus additional symptoms and signs is more common. These less-pure forms of the disorder are often referred to as Brown-Séquard–plus syndrome.

Interruption of the lateral corticospinal tracts, the lateral spinal thalamic tract, and at times the posterior columns produces a picture of a spastic, weak leg with brisk reflexes and a strong leg with loss of pain and temperature sensation. Note that spasticity and hyperactive reflexes may not be present with an acute lesion. Spinal cord anatomy accounts for the clinical presentation of Brown-Séquard syndrome. The motor fibers of the corticospinal tracts cross at the junction of the medulla and spinal cord. The ascending dorsal column, carrying the sensations of vibration and position, runs ipsilateral to the roots of entry and crosses above the spinal cord in the medulla. The spinothalamic tracts convey sensations of pain, temperature, and crude touch from the contralateral side of the body. At the site of spinal cord injury (SCI), nerve roots and/or anterior horn cells also may be affected.

Pathophysiology. Brown-Séquard syndrome results from damage to or loss of ascending and descending spinal cord tracts on one side of the spinal cord. Scattered petechial hemorrhages develop in the gray matter, enlarge and coalesce in an hour postinjury. Subsequent development of hemorrhagic necrosis occurs within 24–36 hours. White matter shows petechial hemorrhage in 3–4 hours. Myelinated fibers and long tracts show extensive structural damage.

Etiology. Brown-Séquard syndrome can be caused by any mechanism resulting in damage to one side of the spinal cord. Multiple causes of Brown-Séquard syndrome have been described in the literature. The most common cause remains traumatic injury, often a penetrating mechanism, such as a stab or gunshot wound or a unilateral facet fracture and dislocation due to a motor vehicle accident or fall. More unusual etiologies that have been reported include assault with a pen, removal of a cerebrospinal fluid drainage catheter after thoracic aortic surgery, and injury from a blowgun dart. Traumatic injury may also be the result of blunt trauma or pressure contusion.

Nontraumatic causes. Numerous nontraumatic causes of Brown-Séquard syndrome have also been reported, including the following:

1. Tumor (primary or metastatic).
2. Multiple sclerosis.
3. Disk herniation.
4. Cervical spondylosis.
5. Herniation of the spinal cord through a dural defect (idiopathic or posttraumatic).
6. Epidural hematoma.
7. Vertebral artery dissection.
8. Radiation.
9. Intravenous drug use.
10. Tuberculosis.
11. Meningitis, Empyema.
12. Herpes zoster, Herpes simplex.
13. Syphilis.
14. Ischemia.
15. Hemorrhage – Including spinal subdural/epidural and hematomyelia.
16. Chiropractic manipulation – Rare, but reported.

Race-, sex-, and age-related demographics

The SCI database indicates that since 2000, 63 % of cases of Brown-Séquard syndrome have occurred in white population; 22.7 %, in African Americans; 11.8 %, in Hispanics; and

2.4 %, in other racial/ethnic groups. Various demographic studies have consistently shown a greater frequency of SCI in males than in females. This finding primarily reflects traumatic injury data and may not reflect the frequency of nontraumatic etiologies.

Pain

Pain is a feeling triggered in the nervous system. Pain may be sharp or dull. It may come and go, or it may be constant. You may feel pain in one area of your body, such as your back, abdomen or chest or you may feel pain all over, such as when your muscles ache from the flu.

Pain can be helpful in diagnosing a problem. Without pain, you might seriously hurt yourself without knowing it, or you might not realize you have a medical problem that needs treatment. Once you take care of the problem, pain usually goes away. However, sometimes pain goes on for weeks, months or even years. This is called chronic pain. Sometimes chronic pain is due to an ongoing cause, such as cancer or arthritis. Sometimes the cause is unknown.

Fortunately, there are many ways to treat pain. Treatment varies depending on the cause of pain. Pain relievers, acupuncture and sometimes surgery are helpful.

The Two Faces of Pain: Acute and Chronic

1. Acute pain, for the most part, results from disease, inflammation, or injury to tissues. This type of pain generally comes on suddenly, for example, after trauma or surgery, and may be accompanied by anxiety or emotional distress. The cause of acute pain can usually be diagnosed and treated, and the pain is self-limiting, that is, it is confined to a given period of time and severity. In some rare instances, it can become chronic.

2. Chronic pain is widely believed to represent disease itself. It can be made much worse by environmental and psychological factors. Chronic pain persists over a longer period of time than acute pain and is resistant to most medical treatments. It can—and often does—cause severe problems for patients. A person may have two or more co-existing chronic pain conditions. Such conditions can include chronic fatigue syndrome, endometriosis, fibromyalgia, inflammatory bowel disease, interstitial cystitis, temporomandibular joint dysfunction, and vulvodynia. It is not known whether these disorders share a common cause.

Pain Management: Neuropathic Pain

Introduction. Neuropathic pain is a complex, chronic pain state that usually is accompanied by tissue injury. With neuropathic pain, the nerve fibers themselves may be damaged, dysfunctional or injured. These damaged nerve fibers send incorrect signals to other pain centers. The impact of nerve fiber injury includes a change in nerve function both at the site of injury and areas around the injury. One example of neuropathic pain is called phantom limb syndrome. This occurs when an arm or a leg has been removed because of illness or injury, but the brain still gets pain messages from the nerves that originally carried impulses from the missing limb. These nerves now misfire and cause pain.

Neuropathic pain often seems to have no obvious cause; but, some common causes of neuropathic pain include:

1. Alcoholism, Chemotherapy.
2. Back, leg, and hip problems.
3. Diabetes.
4. Facial nerve problems.
5. HIV infection or AIDS.
6. Multiple sclerosis.
7. Shingles.
8. Spine surgery.

Symptoms may include. Shooting and burning pain, tingling and numbness.

Unfortunately, neuropathic pain often responds poorly to standard pain treatments and occasionally may get worse instead of better over time. For some people, it can lead to serious disability.

The perception of pain

Pain is an unpleasant yet important function for survival: warning system (but not all pain is needed for survival).

There are two different pathways to the brain on which pain can travel – information brought from free nerve endings in the skin to the brain via two different systems:

1) **fast pathways** – registers localized pain (usually sharp pain) and sends the information to the cortex in a fraction of a second (cut your finger with a knife).

2) **slow pathways** – sends information through the limbic system which takes about 1–2 seconds longer than directly to the cortex (longer lasting, aching/burning).

Factors in Pain Perception – not an automatic result of stimulation:

✓ Expectations – research shown that our expectations about how much something will hurt can effect our perception.

✓ Melzack – indicated that believing that something will be very painful helps us prepare for it.

For example – child birth: Lamaze method falsely leads us to believe it won't be painful. Maybe if we know it will be bad we can adequately prepare to handle it.

another example – placebo effect – if we believe pain has stopped, it may.

personality – people with negative types of personalities often have more pain. For example – a very uptight person may experience muscle pains, back pains, etc.

mood – bad moods, angry, unhappy, etc, can lead to the experience of increased pain. For example – study manipulated moods of subjects then asked them to complete questionnaires of pain perception. Those in negative mood group reported significantly more pain than other subjects.So, it seems that our brains can regulate, control, determine, and even produce pain.

Theories of pain perception

Gate Control Theory (Melzack & Walls, 1965) - incoming pain must pass through a "gate" located in the spinal cord which determines what information about pain will be sent to the brain. So, it can be opened to allow pain through or closed to prevent pain from being perceived.

The Gate – actually a neural network controlled by the brain. Located in an area of the spinal cord called the Substansia Gelatinosa.

There are two types of nerve fibers in this area:

a) large – sends fast signals and can prevent pain by closing the gate.

b) small – sends slower signals which open the gate. Thus, when pain occurs, it is because the large fibers are off and the small are on, opening the gate.

Since the gate is controlled by the brain, the factors discussed earlier (expectations, mood, personality) influence the functioning of the gate.

Contradiction to Gate Control Theory:

1) endorphins – the body's own pain killers (morphine-like). May explain acupuncture, acupressure, pain tolerance during last two weeks of pregnancy, etc.

2) BUT– endorphins may work with the gate control theory - maybe pain is perceived, endorphins are released, so the brain no longer needs the signals and closes the gate.

Phantom limbs. Ability to feel pain, pressure, temperature, and many other types of sensations including pain in a limb that does not exist (either amputated or born without).

The feelings and the pain are sometimes so life-like that a person attempts to pick things up with phantom hand, step with phantom foot or leg, etc. Often person feels phantom moving in perfect coordination with the rest of the body – some report a missing arm extending outward at a 90 degree angle so they turn sideways when going through a doorway.

It may occur right after amputation or not until years later. It is often felt as part of the body (belonging to the rest of the body). For example, with a missing leg, some report having a phantom foot but not the rest of the leg. Still, the foot feels as though it is part of the body.

Explanations:

1. The neuroma explanation – remaining nerves in the stump grow into nodules (neuromas) at the end of the stump continue to fire signals. Signals follow the same pathways the brain as when the appendage existed.

2. The spinal cord explanation – neurons in the spinal cord that are no longer receiving information from the lost appendage continue to send information to the brain.

3. The brain explanation – signals in the somatosensory circuits of the brain change when the limb is lost which produce the phantom the brain compensates for the loss or altered signals. This has been expanded – brain contains a network of fibers that not only respond to stimulation but continually generates a pattern of impulses that indicate that the body is intact and functioning. Thus, the brain creates the impression that the limb exists and is al right. This system may be prewired.

4. The hardwired explanation - we may have a biological makeup to be born with all of our appendages. So, when we are born w/o one or lose one, the nerves are still there and are still going to send the information.

PHYSIOLOGICAL PRINCIPLES OF SENSATION AND PERCEPTION

Sensory receptor cells must be specialised to transduce different forms of environmental energy into common electrical signals. The breakdown of light-sensitive pigment within photoreceptors, and the vibrations of cilia in mechanoreceptors, both lead to neural impulses. Nerve impulses cannot differentiate between the senses; the cortical destination of the impulses determines the sensory experience (visual or auditory). This concept was first formalized in the law of specific nerve energy, which gains empirical support from electrical stimulation of the cortex in awake, anaesthetised patients.

Electrical signals travel from cell's dendrites, via its axon, to terminal buttons that synapse with the dendrites of receiving neurons. Signals are transmitted across synapses by either excitatory or inhibitory neurotransmitters (e.g. acetylcholine and gamma amino butyric acid, respectively). Between sensory receptor cells and cortical receiving areas, there are three synapses in the visual sensory pathway and five in the auditory sensory pathway. In all of the senses, except olfaction, receptor signals travel unidirectionally to the thalamus. From the thalamus the flow of information is bi-directional, to and from the primary cortex (receiving area), and subsequently to and from the secondary cortex (cortical association area). Each successive stage in the processing hierarchy refines and modifies the sensory signal.

All sensory systems respond to a selective range of stimuli that define their sensory space. Within this range, individual neurons have their own, highly selective stimulus preferences. The area in which a preferred stimulus must be presented to elicit a response is known as the cell's receptive field. At each level of sensory processing, neighbouring cells generally have similar stimulus preferences. Tootell et al used a physiological staining technique to identify active cells in cortex. Their illustration of the topographic map of the visual field in the striate cortex provides a striking example of cells being organised according to proximity of their receptive fields. Cortical maps are not necessarily scale representations. Cortical magnification, or exaggeration of part of a sensory dimension, often occurs.

Plasticity, or adaptability, is a feature of all sensory processing. Neural mechanisms can be modified to accommodate either short-term environmental changes, or long-term developmental changes.

DISORDERS OF THE NERVOUS SYSTEM AND SENSORY DISORDERS

Early recognition of drug-induced disorders of the nervous system is highly important because it can often prevent irreversible damage. **Drug-induced neurological disorders** (DINDs) can occur at initiation, during sudden withdrawal, or after many months or years of therapy.

Treatment is primarily concerned with controlled withdrawal, but some DINDs require urgent symptomatic treatment to avoid serious complications. Some DINDs can be reversed with certain vitamins and essential trace elements.

A chief mechanism in a number of DINDs is mitochondrial toxicity, a condition in which the "power plants" of certain cells become damaged or decline significantly in number. DINDs induced by statins (medications used to lower cholesterol levels) are more likely to become more prevalent. Increased use of newer humanized monoclonal antibodies may cause previously unrecognized DINDs. Antiretroviral agents are also commonly associated with DINDs. Drug interactions can also increase the toxicity of single agents.

Disorders of the nervous system and sensory disorders associated with the use of certain drugs include:

1. Seizures – often seen in drug-induced encephalopathy (see below)

1.1. Cerebrovascular disease – which can lead to stroke

1.2. Headache – drugs that cause headaches often do so by exacerbating pre-existing migraine, chronic daily headache, or tension headache

1.3. Encephalopathy – when drugs cause these diseases of the brain, they usually do so either by inducing metabolic disturbances, or by direct central nervous system toxicity

1.4. Dementia – several drugs can cause a reversible condition resembling dementia

1.5. Extrapyramidal disorders – symmetrical akinetic rigid syndromes, hyperkinetic syndromes acute dystonia-dyskinesia, choreo-athetosis, restless leg syndrome, and motor tics can all be caused by drugs

1.6. Cerebellar disorders and tremor – these include postural, kinetic and resting tremor, and a host of drug-induced syndromes which are occasionally irreversible

1.7. Myoclonus – this condition, in which muscles contract abnormally, may persist when the causative drug is withdrawn or reduced. This eventuality can be treated with other drugs, but alternative diagnoses should be considered

1.8. Eye movement disorders – nystagmus, external ophthalmoplegia, and internuclear ophthalmoplegia are among eye movement disorders that can be caused by drugs

1.9. Cranial neuropathies – several palsies have been shown to be drug-induced. Early withdrawal of the offending agent is critical.

2. Sensory disorders

2.1. Vision: while blurred vision is a common side effect of several medications, more serious, occasionally irreversible visual impairment is also possible. Examples include miosis, midriasis, refraction, cortical blindness, retinopathy, dyschromatopsia, xanthopsia and optic neuritis.

2.2. Ototoxicity: by definition, damage to the hearing or balance functions of the inner ear by drugs or chemicals

2.3. Disorders of the spinal cord and peripheral nervous system – drug-induced subacute myelo-opticoneuropathy is thought to occur by depletion of vitamins by the drug. Other than withdrawal, glutathione, B vitamin, and zinc supplements should be considered.

2.4. Inflammatory demyelinating diseases of the central nervous system - these include multiple sclerosis, transverse myelitis, and Progressive Multifocal Leukoencephalopathy (PML).

2.5. Inflammatory demyelinating diseases of the peripheral nervous system include aseptic meningitis, mononeuritis multiplex, polymyositis, vasculitis, bilateral anterior toxic optic neuropathy, orbital myositis, and CNS lupus, which may all be associated with anti-TNF treatment.

2.6. Immune reconstitution inflammatory syndrome (IRIS) – a recognized complication of highly active antiretroviral therapy (HAART) in HIV.

2.7. Propofol infusion syndrome – characterized by rhabdomyolysis, renal failure, bradyarrythmias, lipaemic plasma and metabolic acidosis, and is often fatal.

2.8. Reye's syndrome - associated with the use of aspirin during acute viral illnesses.

PARALYSIS

Paralysis also called palsy, is defined as "loss or impairment of voluntary muscular power".

In general, diseases that produce paralysis can be divided into two groups; those that involve changes in the makeup of nervous or muscular tissue or those that are the result of metabolic disturbances in the function of nerves or muscles. Some diseases affect the entire body while others hit only a small area of the body.

At times, only one side of the body may be involved, producing a condition known as hemiplegia. In other instances both sides of the body may suffer the effects leading to diplegia or bilateral hemiplegia. When only the lower limbs are affected by paralysis it is called paraplegia. When all four limbs are affected, it is referred to as quadriplegia. How much of the body is affected depends on the site of the neurological damage. Strokes, brain tumors, etc. classically cause such extensive loss of function. In instances of inflammation of nervous tissue such as occurs in polio, specific nerve cells are damaged, which leads to paralysis and muscle wasting.

Various diseases that affect muscle tissue are encountered much less often that those that affect nervous tissue. These are often hereditary, and due to a disturbance of muscle metabolism. Most cases of paralysis of muscular origin, therefore, usually begin early in life. However, other diseases can occur at any time of life, such as myasthenia gravis. Toxins such as alcohol can also affect muscle tissue, as well as abnormalities of hormonal production. The cause diagnosis of neuromuscular paralysis is made by careful evaluation of the nervous system, and the use of ancillary tests.

Table 40

Variants and appiarance of voluntary muscular power impairment

Term	Definition	Cause	Effect
Atony	A state in which muscles are floppy, lacking their normal elasticity	Many possible causes.	Muscles are floppy, lacking their normal elasticity
Atrophy	Generally, the **wasting away** of a normally developed organ or tissue due to degeneration of cells. In the case of muscle tissue, the individual muscle fibers decrease in size due to a progressive loss of myofibrils	Generally, possible causes include undernourishment, disuse or ageing. (a) **Disuse Atrophy**: muscles atrophy because they are not used. Bedridden individuals and people with casts that immobilize large muscle groups may experience disuse atrophy because the flow of nerve impulses to the inactive muscle is greatly reduced. (b) **Denervation atrophy**: occurs when a muscle's nerve impulses cease in it's motor neurons	(a) Need physiotherapy to gradually re-build the muscle. (b) In 6–24 months the denervated muscle will be one quarter of it's original size and the muscle fibers will be replaced by fibrous connective tissue. The transition to fibrous connective tissue, when complete, cannot be reversed
Cramp	Prolonged painful involuntary contraction of skeletal muscle	It is sometimes caused by an imbalance of the salts in the body, but is more often a result of fatigue, imperfect posture, or stress	Pain. Possibly inability to perform specific tasks (e.g. of 'occupational cramp' is 'writer's cramp')
Fibrositis	Inflammation of fibrous connective tissues in muscles. It often affects the muscles of the trunk and back	It may be a symptom of another disease, such as Sciatica, but in most cases the cause is unknown	Pain and stiffness
Muscle Fatigue	Tiredness following prolonged or intense activity	May be due to dehydration (loss of water and NaCl, that is "sodium chloride", or "common salt"), and the waste products of metabolism accumulating in the muscles faster than they can be removed by the venous blood	Tired/aching muscles
Myositis	**Inflammation of muscle fibers** / Any of a group of muscle diseases in which inflammation and degenerative changes occur	(A minority are caused by bacterial or parasitic infections)	
Spasm	A **sustained involuntary muscular contraction** (which may occur either as part of a generalized disorder such as spastic paralysis, or as a local response to an otherwise unconnected painful condition)	May occur either as part of a generalized disorder such as spastic paralysis, or as a local response to an otherwise unconnected painful condition	Painful. Lack of use of body parts normally moved by the muscle in spasm

Term	Definition	Cause	Effect
Spasticity	= Muscular Hypertonicity (i.e. an increase in the state of readiness of muscle fibers to contract; an increase in partial contraction) with an increased resistance to stretch. Moderate cases show movement requiring great effort and a lack of normal coordination, while slight cases show exaggerated movements that are coordinated. = Resistance to the passive movement of a limb that is maximal at the beginning of the movement and gives way as more pressure is applied	This is a symptom of damage to the cortiscospinal tracts in the brain or spinal cord. It is usually accompanied by weakness in the affected limb	Increase in the state of readiness of muscle fibers to contract with an increased resistance to stretch. Moderate cases show **movement requiring great effort and a lack of normal coordination**, while slight cases show **exaggerated movements that are coordinated**
Sprain	Injury to a ligament, caused by overstretching	Overstretching of ligament	As the ligament is not severed it gradually heals, but this may take several months
Strain	Excessive stretching or working of a muscle, resulting in pain and swelling of the muscle	Damage to muscle caused by overstretching	Pain

MUSCULAR DISORDERS

Movement disorders are a group of diseases and syndromes, affecting the ability to produce and control movement. Though it seems simple and effortless, normal movement in fact requires an astonishingly complex system of control. Disruption of any portion of this system can cause a person to produce movements that are too weak, too forceful, too uncoordinated, or too poorly controlled for the task at hand. Unwanted movements may occur at rest. Intentional movement may become impossible. Such conditions are called movement disorders.

Types of Muscle disorders

Abnormal movements themselves are symptoms of underlying disorders. In some cases, the abnormal movements are the only symptoms. Disorders causing abnormal movements include:

1. Parkinson's disease.
2. Parkinson-plus syndromes (progressive supranuclear palsy, multiple system atrophy, and cortical-basal ganglionic degeneration).
3. Huntington's disease.
4. Wilson's disease.
5. Inherited ataxias (Friedreich's ataxia, Machado-Joseph disease, and pinocerebellar ataxias).
6. Tourette syndrome and other tic disorders.
7. Essential tremor.
8. Restless Leg Syndrome.
9. Dystonia.
10. Stroke.
11. Cerebral palsy.
12. Encephalopathies.
13. Intoxication.
14. Poisoning by carbon monoxide, cyanide, methanol, or manganese.

Movement is produced and coordinated by several interacting brain centers, including the motor cortex, the cerebellum, and a group of structures in the inner portions of the brain called the basal ganglia. Sensory information provides critical input on the current position and velocity of body parts, and spinal nerve cells (neurons) help prevent opposing muscle groups from contracting at the same time.

To understand how movement disorders occur, it is helpful to consider a normal voluntary movement, such as reaching to touch a nearby object with the right index finger. To accomplish the desired movement, the arm must be lifted and extended.

The hand must be held out to align with the forearm, and the forefinger must be extended while the other fingers remain flexed.

THE MOTOR CORTEX

Voluntary motor commands begin in the motor cortex located on the outer, wrinkled surface of the brain. Movement of the right arm is begun by the left motor cortex, which generates a large volley of signals to the involved muscles. These electrical signals pass along upper motor neurons through the midbrain to the spinal cord.

Within the spinal cord, they connect to lower motor neurons, which convey the signals out of the spinal cord to the surface of the muscles involved. Electrical stimulation of the muscles causes contraction, and the force of contraction pulling on the skeleton causes movement of the arm, hand, and fingers.Damage to or death of any of the neurons along this path causes weakness or paralysis of the affected muscles.

ANTAGONISTIC MUSCLE PAIRS

This picture of movement is too simple, however. One important refinement to it comes from considering the role of opposing, or antagonistic, muscle pairs. Contraction of the biceps muscle, located on the top of the upper arm, pulls on the forearm to flex the elbow and bend the arm. Contraction of the triceps, located on the opposite side, extends the elbow and straightens the arm.

Within the spine, these muscles are normally wired so that willed (voluntary) contraction of one is automatically accompanied by blocking of the other. In other words, the command to contract the biceps provokes another command within the spine to prevent contraction of the triceps. In this way, these antagonist muscles are kept from resisting one another. Spinal cord or brain injury can damage this control system and cause involuntary simultaneous contraction and spasticity, an increase in resistance to movement during motion.

THE CEREBELLUM

Once the movement of the arm is initiated, sensory information is needed to guide the finger to its precise destination. In addition to sight, the most important source of information comes from the "position sense" provided by the many sensory neurons located within the limbs (proprioception).

Proprioception is what allows you to touch your nose with your finger even with your eyes closed. The balance organs in the ears provide important information about posture. Both postural and proprioceptive information are processed by a structure at the rear of the brain called the cerebellum. The cerebellum sends out electrical signals to modify movements as they progress, "sculpting" the barrage of voluntary commands into a tightly controlled, constantly evolving pattern. Cerebellar disorders cause inability to control the force, fine positioning, and speed of movements (ataxia). Disorders of the cerebellum may also impair the ability to judge distance so that a person under- or over-reaches the target (dysmetria). Tremor during voluntary movements can also result from cerebellar damage.

THE BASAL GANGLIA

Both the cerebellum and the motor cortex send information to a set of structures deep within the brain that help control involuntary components of movement (basal ganglia). The basal ganglia send output messages to the motor cortex, helping to initiate movements, regulate repetitive or patterned movements, and control muscle tone.

Circuits within the basal ganglia are complex. Within this structure, some groups of cells begin the action of other basal ganglia components and some groups of cells block the action. These complicated feedback circuits are not entirely understood. Disruptions of these circuits are known to cause several distinct movement disorders.

A portion of the basal ganglia, called the substantia nigra, sends electrical signals that block output from another structure called the subthalamic nucleus. The subthalamic nucleus sends signals to the globus pallidus, which in turn blocks the thalamic nuclei. Finally, the thalamic nuclei send signals to the motor cortex. The substantia nigra, then, begins movement and the globus pallidus blocks it.

This complicated circuit can be disrupted at several points. For instance, loss of substantia nigra cells, as in Parkinson's disease, increases blocking of the thalamic nuclei, preventing them from sending signals to the motor cortex. The result is a loss of movement (motor activity), a characteristic of Parkinson's.

In contrast, cell loss in early Huntington's disease decreases blocking of signals from the thalamic nuclei, causing more cortex stimulation and stronger but uncontrolled movements.

Disruptions in other portions of the basal ganglia are thought to cause tics, tremors, dystonia, and a variety of other movement disorders, although the exact mechanisms are not well understood.

MUSCLE TREMORS

Tremor is an unintentional (involuntary), rhythmical alternating movement that may affect the muscles of any part of the body. Tremor is caused by the rapid alternating contraction and relaxation of muscles and is a common symptom of diseases of the nervous system (neurologic disease).

Occasional tremor is felt by almost everyone, usually as a result of fear or excitement. However, uncontrollable tremor or shaking is a common symptom of disorders that destroy nerve tissue, such as Parkinson's disease or multiple sclerosis. Tremor may also occur after stroke or head injury. Other tremors appear without any underlying illness.

Causes and symptoms

Tremor can be a symptom of an underlying disease, and it may be caused by drugs. It may also exist as the only symptom (essential tremor).

Some types of tremor are signs of an underlying condition. About a million and a half Americans have Parkinson's disease, a disease that destroys nerve cells. Severe shaking is the most apparent symptom of Parkinson's disease. This coarse tremor features four to five muscle movements per second. The shaking is evident at rest but declines or disappears during movement. Other disorders that cause tremor are multiple sclerosis, Wilson's disease, mercury poisoning, thyrotoxicosis, and liver encephalopathy. A tremor that gets worse during body movement is called an "intention tremor". This type of tremor is a sign that something is amiss in the cerebellum, a region of the brain concerned chiefly with movement, balance and coordination.

Date	Grade	Teacher’s signature

PATHOPHYSIOLOGY OF EXTREME CONDITIONS. ETIOLOGY, PATHOGENESIS OF SHOCK. THE COLLARSE SIMILAR CONDITIONS

Relevance. Extreme (critical, urgent) state is caused by the influence of pathogenic factors expressed in strength or duration of exposureon the body. It is characterized by metabolic disorders of vital body functions. As a consequence, there is a direct threat to life, which requires immediate therapeutic measures. Knowledge of the etiology and pathogenesis of extreme states is necessary for treatment and prevention of these dangerous for life condition.

Overall Objective is to study basic kinds of extreme conditions, causes and mechanisms of their development, pathogenetic treatment.

The student should be able to (specific objectives):

1. Internalize the notion of "extreme conditions";
2. Know types of extreme conditions;
3. Know the causes of different types of collapse;
4. Know etiology of different types of shock;
5. Understand the mechanisms of shock.

The student should be able to (required knowledge and skills):

1. Explain the mechanisms for maintaining blood pressure and its regulation (Dep. of normal physiology).

2. Characterize the peculiarities of the energy providing brain neurons (Dep. of normal physiology).

3. Evaluate the role of the kidney and liver in the maintenance of homeostasis (Dep. of normal physiology)

QUESTIONS TO THE LESSON

1. Extreme states. Similarities and differences between extreme and terminal states.
2. Etiology and pathogenesis of extreme conditions.
3. Collapse. Risk factors. Types. Causes.
4. Pathogenesis of different types of collapse.
5. General manifestations of collapse.
6. Shock. Causes. Risk factors. Types.
7. Pathogenesis and stage of shock. Clinical manifestations.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

SHOCK

Shock, or cardiovascular collapse, is the final common pathway for a number of potentially lethal clinical events, including severe hemorrhage, extensive trauma or burns, large myocardial infarction, massive pulmonary embolism, and microbial sepsis. Regardless of the underlying pathology, shock gives rise to systemic hypoperfusion caused by reduction either in cardiac output or in the effective circulating blood volume. The end results are hypotension, followed by impaired tissue perfusion and cellular hypoxia. Although the hypoxic and metabolic effects of hypoperfusion initially cause only reversible cellular injury, persistence of shock eventually causes irreversible tissue injury and can culminate in the death of the patient. Shock may be grouped into three general categories.

The mechanisms underlying cardiogenic and hypovolemic shock are fairly straightforward, essentially involving low cardiac output. Septic shock, by comparison, is substantially more complicated and is discussed in further detail below.

Cardiogenic shock is recognized as a low cardiac output state secondary to extensive left ventricular infarction, development of a mechanical defect (e.g, ventricular septal defect or papillary muscle rupture), or right ventricular infarction. Disorders that can result in the acute deterioration of cardiac function and lead to cardiogenic shock include myocardial infarction (MI) or myocardial ischemia, acute myocarditis, sustained arrhythmia, severe valvular dysfunction, and decompensation of end-stage cardiomyopathy from multiple etiologies. Autopsy studies show that cardiogenic shock is generally associated with the loss of more than 40 % of the left ventricular myocardial muscle.

CARDIOGENIC SHOCK

Cardiogenic shock implies failure of the heart to pump blood adequately. Cardiogenic shock can occur relatively quickly because of the damage to the heart that occurs during myocardial infarction; ineffective pumping caused by cardiac arrhythmias; mechanical defects that may occur as a complication of myocardial infarction, such as ventricular septal defect; ventricular aneurysm; acute disruption of valvular function; or problems associated with open-heart surgery. Cardiogenic shock also may ensue as an end-stage condition of coronary artery disease or cardiomyopathy. The most common cause of cardiogenic shock is myocardial infarction. Most patients who die of cardiogenic shock have lost at least 40 % of the contracting muscle of the left ventricle because of a recent infarct or a combination of recent and old infarcts. Cardiogenic shock can follow other types of shock associated with inadequate coronary blood flow, or it can develop because substances released from ischemic tissues impair cardiac function. One such substance, myocardial depressant factor, is thought to be released into the circulation during severe shock. Myocardial depressant factor produces reversible (although often severe) myocardial depression, ventricular dilation, and decreased left ventricular ejection fraction and diastolic pressure.

In all cases of cardiogenic shock, there is a failure to eject blood from the heart, hypotension, and inadequate cardiac output. Increased systemic vascular resistance often contributes to the deterioration of cardiac function by increasing afterload or the resistance to ventricular systole. The filling pressure, or preload of the heart, also is increased as blood returning to the heart is added to blood that previously returned but was not pumped forward, resulting in an increase in end-systolic ventricular volume. Increased resistance to ventricular systole (i.e., afterload), combined with decreased myocardial contractility, causes the increased end-systolic ventricular volume and increased preload, which further complicate cardiac status.

HYPOVOLEMIC SHOCK

Hypovolemic shock is characterized by diminished blood volume such that there is inadequate filling of the vascular compartment. It occurs when there is an acute loss of 15 % to 20 % of the circulating blood volume. The decrease may be caused by an external loss of whole blood (e.g., hemorrhage), plasma (e.g., severe burns), or extracellular fluid (e.g., gastrointestinal fluids lost in vomiting or diarrhea). Hypovolemic shock also can result from an internal hemorrhage or from third-space losses, when extracellular fluid is shifted from the vascular compartment to the interstitial space or compartment.

Physiology of Hypovolemic Shock

Hypovolemic shock has been the most widely studied type of shock and usually serves as a prototype in discussions of the manifestations of shock. The effect of removing blood from the circulatory system during approximately 30 minutes. Approximately 10 % can be removed without changing the cardiac output.

Circulatory shock

Circulatory shock represents the inability of the circulation to adequately perfuse the tissues of the body.

1. It can result from a loss of fluid from the vascular compartment (hypovolemic shock), obstruction of flow through the vascular compartment (obstructive shock), or an increase in the size of the vascular compartment that interferes with the distribution of blood (distributive shock).

2. The manifestations of shock reflect both the impaired perfusion of body tissues and the body’s attempt to maintain tissue perfusion through conservation of water by the kidney, translocation of fluid from extracellular to the intravascular compartment, and activation of sympathetic nervous system mechanisms that increase heart rate and divert blood from less to more essential body tissues.

The average blood donor loses a pint of blood without experiencing adverse effects. As increasing amounts of blood (10 to 25 %) are removed, the cardiac output falls, but the arterial pressure is maintained because of sympathetic-mediated increases in heart rate and vasoconstriction. Blood pressure is the product of cardiac output and systemic vascular resistance (also known as the peripheral vascular resistance); thus, an increase in systemic vascular resistance can maintain the blood pressure in the presence of decreased cardiac output for a short period of time. Cardiac output and tissue perfusion decrease before signs of hypotension occur. Cardiac output and arterial pressure fall to zero when approximately 35 % to 45 % of the total blood volume has been removed.

Compensatory Mechanisms

Without compensatory mechanisms to maintain cardiac output and blood pressure, the loss of vascular volume would result in a rapid progression from the initial to the progressive and irreversible stages of shock. The most immediate of the compensatory mechanisms are the sympathetic-mediated responses designed to maintain cardiac output and blood pressure. Within seconds after the onset of hemorrhage or the loss of blood volume, tachycardia, increased cardiac contractility, vasoconstriction, and other signs of sympathetic and adrenal medullary activity appear. The sympathetic vasoconstrictor response affects the arterioles and the veins. Arteriolar constriction helps to maintain blood pressure by increasing the systemic vascular resistance, and venous constriction mobilizes blood that has been stored in the

capacitance side of the circulation as a means of increasing venous return to the heart. There is considerable capacity for blood storage in the large veins of the abdomen and liver. Approximately 350 mL of blood that can be mobilized in shock is stored in the liver. Sympathetic stimulation does not cause constriction of the cerebral and coronary vessels, and blood flow through the heart and brain is maintained at essentially normal levels as long as the mean arterial pressure remains above 70 mm Hg. During the early stages of hypovolemic shock, vasoconstriction causes a reduction in the size of the vascular compartment and an increase in systemic vascular resistance. This response usually is all that is needed when the injury is slight, and blood loss is arrested at this point. As hypovolemic shock progresses, there are further increases in heart rate and cardiac contractility, and vasoconstriction becomes more intense. There is vasoconstriction of the blood vessels that supply the skin, skeletal muscles, kidneys, and abdominal organs, with a resultant decrease in blood flow and conversion to anaerobic metabolism with lactic acid formation.

Compensatory mechanisms, designed to restore blood volume, include absorption of fluid from the interstitial spaces, conservation of salt and water by the kidneys, and thirst. Extracellular fluid is distributed between the interstitial spaces and the vascular compartment. When there is a loss of vascular volume, capillary pressures decrease, and water is drawn into the vascular compartment from the interstitial spaces. The maintenance of vascular volume is further enhanced by renal mechanisms that conserve fluid. A decrease in renal blood flow and glomerular filtration rate results in activation of the renin-angiotensin-aldosterone mechanism, which produces an increase in sodium reabsorption by the kidney.

The decrease in blood volume also stimulates centers in the hypothalamus that regulate ADH release and thirst. A decrease in blood volume of 5 to 10 % is sufficient to stimulate ADH release and thirst. ADH, also known as vasopressin, constricts the peripheral arteries and veins and greatly increases water retention by the kidneys. While more sensitive to changes in serum osmolality, a decrease of 10 to 15 % in blood volume serves as a strong stimulus for thirst. The compensatory mechanisms that the body recruits in hypovolemic and other forms of circulatory shock were not intended for long-term use. When injury is severe or its effects prolonged, the compensatory mechanisms begin to exert their own detrimental effects. The intense vasoconstriction causes a decrease in tissue perfusion, impaired cellular metabolism, release of vasoactive inflammatory mediators such as histamine, liberation of lactic acid, and cell death. After circulatory function has been reestablished, whether the shock will be irreversible or the patient will survive is determined largely at the cellular level.

Cellular Function. Shock ultimately exerts its effect at the cellular level with failure of the circulation to supply the cell with the oxygen and nutrients needed for production of adenosine triphosphate (ATP). The cell uses ATP for a number of purposes, including operation of the sodium potassium membrane pump that moves sodium out of the cell and potassium back into the cell. The cell uses two pathways to convert nutrients to energy. The first is the anaerobic (nonoxygen) glycolytic pathway, which is located in the cytoplasm. Glycolysis converts glucose to ATP and pyruvate. The second pathway is the aerobic (oxygen-dependent) pathway, called the citric acid cycle, which is located in the mitochondria. When oxygen is available, pyruvate from the glycolytic pathway moves into the mitochondria and enters the citric acid cycle, where it is transformed into ATP and the metabolic by-products carbon dioxide and water. Fatty acids and proteins also can be metabolized in the mitochondrial pathway. When oxygen is lacking, pyruvate does not enter the citric acid cycle; instead, it is converted to lactic acid. In severe shock, cellular metabolic processes are essentially anaerobic, which means that excess amounts of lactic acid accumulate in the cellular and the extracellular compartment. The anaerobic pathway, although allowing energy production to continue in the absence of oxygen, is relatively inefficient and produces significantly less ATP than does the aerobic pathway. Without sufficient energy production, normal cell function cannot be maintained, and the activity of the sodium-potassium

membrane pump is impaired. As a result, sodium chloride accumulates in cells, and potassium is lost from cells. The cells then swell, and their membranes become more permeable. Mitochondrial activity becomes severely depressed, and lysosomal membranes rupture.

Obstructive shock

The term obstructive shock is used to describe circulatory shock that results from mechanical obstruction of the flow of blood through the central circulation (great veins, heart, or lungs). Obstructive shock may be caused by a number of conditions, including dissecting aortic aneurysm, cardiac tamponade, pneumothorax, atrial myxoma, or evisceration of abdominal contents into the thoracic cavity because of a ruptured hemidiaphragm. The most frequent cause of obstructive shock is pulmonary embolism. The primary physiologic results of obstructive shock are elevated right heart pressure and impaired venous return to the heart. The signs of right heart failure are seen, including elevation of CVP and jugular venous distention. Treatment modalities focus on correcting the cause of the disorder, frequently with surgical interventions such as pulmonary embolectomy, pericardiocentesis (i.e., removal of fluid from the pericardial sac) for cardiac tamponade, or the insertion of a chest tube for correction of a tensionpneumothorax or hemothorax. In select cases of pulmonary embolus, thrombolytic drugs may be used to dissolve the clots causing the obstruction.

Distributive shock

Distributive or vasodilatory shock is characterized by loss of blood vessel tone, enlargement of the vascular compartment, and displacement of the vascular volume away from the heart and central circulation. With distributive shock, the capacity of the vascular compartment expandsto the extent that a normal volume of blood does not fill the circulatory system. Venous return is decreased in distributive shock, which leads to a diminished cardiac output but not a decrease in total blood volume; this type of shock is also referred to as normovolemic shock. Loss of vessel tone has two main causes: a decrease in the sympathetic control of vasomotor tone and the presence of vasodilator substances in the blood. It can also occur as a complication of vessel damage resulting from prolonged and severe hypotension due to hemorrhage, known as irreversible or late-phase hemorrhagic shock. Three shock states share the basic circulatory pattern of distributive shock: neurogenic shock, anaphylactic shock, and septic shock.

Neurogenic Shock

Neurogenic shock describes shock caused by decreased sympathetic control of blood vessel tone due to a defect in the vasomotor center in the brain stem or the sympathetic outflow to the blood vessels. Output from the vasomotor center can be interrupted by brain injury, the depressant action of drugs, general anesthesia, hypoxia, or lack of glucose (e.g., insulin reaction). Fainting due to emotional causes is a transient form of neurogenic shock. Spinal anesthesia or spinal cord injury above the midthoracic region can interrupt the transmission of outflow from the vasomotor center. The term spinal shock is used to describe the neurogenic shock that occurs in persons with spinal cord injury. Many general anesthetic agents can cause a neurogenic shock-like reaction, especially during induction, because of interference with sympathetic nervous system function. In contrast to hypovolemic shock, the heart rate in neurogenic shock often is slower than normal, and the skin is dry and warm. This type of distributive shock is rare and usually transitory.

Anaphylactic Shock

Anaphylaxis is a clinical syndrome that represents the most severe systemic allergic reaction. It results from an immunologically mediated reaction in which vasodilator substances such as histamine are released into the blood. These substances cause vasodilatation of arterioles and venules along with a marked increase in capillary permeability. The vascular response in anaphylaxis is often accompanied by life-threatening laryngeal edema and bronchospasm, circulatory collapse, contraction of gastrointestinal and uterine smooth muscle, and urticaria or angioedema.

Among the most frequent causes of anaphylactic shock are reactions to drugs, such as penicillin; foods, such as nuts and shellfish; and insect venoms. The most common cause is stings from insects of the order Hymenoptera (i.e., bees, wasps, and fire ants). Latex allergy has also caused life-threatening anaphylaxis in a growing segment of the population. Health care workers and others who are exposed to latex are developing latex sensitivities that range from mild urticaria, contact dermatitis, and mild respiratory distress to anaphylactic shock. Children with spina bifida are at extreme risk for this increasingly serious allergy. The onset of anaphylaxis depends on the sensitivity of the person and the rate and quantity of antigen exposure

Sepsis and Septic Shock

Septic shock, which is the most common type of vasodilatory shock, is associated with severe infection and the systemic response to infection. It is associated most frequently with gram-negative bacteremia, although it can be caused by gram-positive bacilli and other micro-organisms such as fungi, which carry an even greater risk for mortality. Unlike other types of shock, septic shock commonly is associated with pathologic complications, such as pulmonary insufficiency, disseminated intravascular coagulation, and multiple organ dysfunction syndrome. The growing incidence has been attributed to an increased awareness of the diagnosis, increased numbers of immunocompromised patients, increased use of invasive procedures, increased number of resistant organisms, and an increased number of elderly patients. Septic shock has been described in the context of what has been termed the systemic inflammatory response syndrome. Although usually associated with infection, the systemic inflammatory response syndrome can be initiated by noninfectious disorders such as acute trauma and pancreatitis.

Mechanisms. The mechanisms of sepsis and septic shock are thought to be related to mediators of the inflammatory response. Although the immune system and the inflammatory response are designed to overcome infection and eliminate bacterial breakdown products, the unregulated release of inflammatory mediators or cytokines may elicit toxic reactions, resulting in the potentially fatal sepsis syndrome.

The most widely investigated cytokines have been tumor necrosis factor-α (TNF-α), interleukin-1, and interleukin-8, which usually are proinflammatory, and interleukin-6 and interleukin-10, which tend to be anti-inflammatory. A trigger, such as a microbial toxin, stimulates the release of TNF-α and interleukin-1, which in turn promotes endothelial cell–leukocyte adhesion, release of cell-damaging proteases and prostaglandins, and activation of the clotting cascade. The prostaglandins, thromboxane A2 (a vasoconstrictor), prostacyclin (a vasodilator), and prostaglandin E2, participate in the generation of fever, tachycardia, ventilation-perfusion abnormalities, and lactic acidosis. Interleukin-8, a neutrophil chemotaxin, may have a particularly important role in perpetuating tissue inflammation. Interleukin-6 and interleukin-10, which have anti-inflammatory actions and perhaps are counter-regulatory, augment the acute-phase response and consequent generation of additional proinflammatory mediators.

In addition to inducing the release of inflammatory mediators, the sepsis-producing endotoxins may induce tissue damage by directly activating pathways such as the coagulation cascade, the complement cascade, vessel injury, or release of vasodilating prostaglandins.

Collapse

Collapse (from the Latin word collabor – to fall down) is characterised by a sharp diminution in all functions of the organism as a result of sudden reflex dilation of the vessels and acute depression of cardiac activity. It occurs most commonly in acute infections (during the crisis), after massive hemorrhages, in cachexia. The blood pressure drops, the pulse becomes fast and weak, the flow of blood to the heart sharply diminishes and the supply of the vital centers is disturbed. It is impossible to draw a clear line between shock and collapse.

Orthostatic Hypotension (collapse). Orthostatic or postural hypotension is an abnormal drop in blood pressure on assumption of the standing position. In the absence of normal circulatory reflexes or blood volume, blood pools in the lower part of the body when the standing position is assumed, cardiac output and blood pressure fall, and blood flow to the

brain is inadequate. Dizziness, syncope (i.e., fainting), or both may occur. Some authorities differentiate between orthostatic hypotension, which is characterized by a rapid decrease in blood pressure and the inability to stand for more than 1 to 2 minutes, and orthostatic intolerance, which generally occurs in younger persons and is characterized by a delayed decrease in blood pressure. Rather than inability to stand, persons with orthostatic intolerance complain of dizziness, visual changes, head and neck discomfort, poor concentration while standing, palpitations, tremor, anxiety, presyncope, and in some cases syncope. This text uses orthostatic hypotension to indicate both types of postural hypotension. After the assumption of the upright posture from the supine position, approximately 500 to 700 mL of blood is momentarily shifted to the lower part of the body, with an accompanying decrease in central blood volume and arterial pressure. Normally, this decrease in blood pressure is transient, lasting through several cardiac cycles, because the baroreceptors located in the thorax and carotid sinus area sense the decreased pressure and initiate reflex constriction of the veins and arterioles and an increase in heart rate, which brings blood pressure back to normal.

The initial adjustment to orthostatic stress is mediated exclusively by the ANS. Within a few minutes of standing, blood levels of antidiuretic hormone and sympathetic neuromediators increase as a secondary means of ensuring maintenance of normal blood pressure in the standing po position. Under normal conditions, the renin-angiotensinaldosterone system is also activated when the standing position is assumed, and even more so in situations of hypotensive orthostatic stress. The unconscious slight body and leg movement during standing (postural sway) is recognized as an important factor in moving venous blood back to the heart. Crossing the legs, which involves contraction of the agonist and antagonist muscles, has been shown to be a simple and effective way of increasing cardiac output and, therefore, blood pressure. When leg crossing is practiced routinely by persons with autonomic failure, standing systolic and diastolic pressures can be increased by approximately 20/10 mm Hg. In persons with healthy blood vessels and normal ANS function, cerebral blood flow usually is not reduced on assumption of the upright position unless arterial pressure falls below 70 mm Hg.

Classification. Although there is no firm agreement on the definition of orthostatic hypotension, many authorities consider a fall in blood pressure equal to or greater than 20 mm Hg systolic or 10 mm Hg diastolic as indicative of orthostatic hypotension. The presence of orthostatic symptoms (e.g., dizziness, syncope) may be more relevant to the diagnosis of orthostatic hypotension than the numeric decrease in blood pressure. A diagnosis of chronic orthostatic hypotension is characterized by signs of sympathetic activation, a heart rate increase of equal to or greater than30 beats/minute, and plasma norepinephrine equal to or greater than 600 pg/mL.

Reduced Blood Volume. Orthostatic hypotension often is an early sign of reduced blood volume or fluid deficit. When blood volume is decreased, the vascular compartment is only partially filled; although cardiac output may be adequate when a person is in the recumbent position, it often decreases to the point of causing weakness and fainting when the person assumes the standing position. Common causes of orthostatic hypotension related to hypovolemia are excessive use of diuretics, excessive diaphoresis, loss of gastrointestinal fluids through vomiting and diarrhea, and loss of fluid volume associated with prolonged bed rest.

Drug-Induced Hypotension. Antihypertensive drugs and psychotropic drugs are the most common cause of chronic orthostatic hypotension. In most cases, the orthostatic hypotension is well tolerated. However, if the hypotension causes light-headedness or syncope, the dosage of the drug is usually reduced or a different drug substituted.

Aging. Weakness and dizziness on standing are common complaints of elderly persons. The Cardiovascular Health Study reports a 16.2 % prevalence of asymptomatic orthostatic hypotension among persons 65 years of age and older. Orthostatic hypotension was associated with systolic hypertension, major electrocardiographic abnormalities, and carotid artery stenosis. Because cerebral blood flow primarily depends on systolic pressure, patients with

impaired cerebral circulation may experience symptoms of weakness, ataxia, dizziness, and syncope when their arterial pressure falls even slightly. This may happen in older persons who are immobilized for brief periods or whose blood volume is decreased owing to inadequate fluid intake or overzealous use of diuretics. Postprandial blood pressure often decreases in elderly persons. The greatest postprandial changes occur after a high-carbohydrate meal. Although the mechanism responsible for these changes is not fully understood, it is thought to result from glucose-mediated impairment of baroreflex sensitivity and increased splanchnic blood flow mediated by insulin and vasoactive gastrointestinal hormones.

Bed Rest. Prolonged bed rest promotes a reduction in plasma volume, a decrease in venous tone, failure of peripheral vasoconstriction, and weakness of the skeletal muscles that support the veins and assist in returning blood to the heart. Physical deconditioning follows even short periods of bed rest. After 3 to 4 days, the blood volume is decreased. Loss of vascular and skeletal muscle tone is less predictable but probably becomes maximal after approximately 2 weeks of bed rest.

Disorders of Autonomic Nervous System Function. The sympathetic nervous system plays an essential role in adjustment to the upright position. Sympathetic stimulation increases heart rate and cardiac contractility and causes constriction of peripheral veins and arterioles. Orthostatic hypotension caused by altered autonomic function iscommon in peripheral neuropathies associated with diabetes mellitus, after injury or disease of the spinal cord, or as the result of a cerebral vascular accident in which sympathetic outflow from the brain stem is disrupted.

The American Autonomic Society and Academy of Neurology have distinguished three forms of primary ANS dysfunction:

1) pure autonomic failure, which is defined as a sporadic, idiopathic cause of persistent orthostatic hypotension and other manifestations of autonomic failure such as urinary retention, impotence, or decreased sweating;

2) parkinson disease with autonomic failure;

3) multiple-system atrophy (Shy-Drager syndrome). Shy-Drager syndrome usually develops in middle to late life as orthostatic hypotension associated with uncoordinated movements, urinary incontinence, constipation, and other signs of neurologic deficits referable to the corticospinal, extrapyramidal, corticobulbar, and cerebellar systems.

SYNCOPE

Background: Syncope (faint – weakened), defined as a transient loss of consciousness and postural tone with spontaneous recovery, is an extremely common medical problem. Syncope affects patients of all ages, both with and without other medical conditions, and has a broad number of causes. Pathophysiology: Decreased cerebral perfusion is the final common pathway leading to syncope. In some patients, brainstem hypoxia triggers a posturing reflex that can appear seizurelike. A number of cardiac and noncardiac conditions can cause syncope (see Causes). The pathophysiology of neurocardiogenic syncope is interesting and poorly understood. With prolonged standing, the left ventricle may be underfilled. This triggers an increase in inotropy. The forceful contraction stimulates mechanoreceptors, located primarily on the floor of the left ventricle. This mechanical activation triggers a reflex similar to the Bezold-Jarisch reflex, which leads to sympathetic withdrawal and parasympathetic activation. The result is bradycardia (cardioinhibitory), vasodilatation (vasodepressor), or both (mixed response). Other stimuli can trigger a similar autonomic response. The best-known response is carotid sinus pressure. Other situational triggers to reflex syncope include cough, micturition, defecation, and deglutition (ie, swallowing).

Causes of Syncope

1. Bradycardia, Tachycardia, Aortic stenosis, Sick sinus syndrome, Ventricular tachycardia.
2. Hypertrophic cardiomyopathy, Atrioventricular (AV) block, Ventricular fibrillation.
3. Pulmonary embolus, Pulmonary hypertension.
4. Drug-induced.

5. Supraventricular tachycardia.
6. Acute myocardial infarction.
7. Atrial fibrillation /flutter Tamponade.

Seizure: Epileptic disorders are caused by excessive activity in the cortex or other area of the brain. Partial complex seizures may cause loss of consciousness without marked motor activity. Grand mal seizures are characterized by tonic-clonic motor activity. On the other hand, syncope can be accompanied by tonic posturing due to brainstem hypoxia. Syncope is rarely accompanied by incontinence or a prolonged period of confusion following the event (ie, postictal confusion).

Transient ischemic attack: While a vertebrobasilar transient ischemic attack can cause loss of consciousness, this is unusual in the absence of other vertebrobasilar symptoms (eg, dysarthria, difficulty swallowing).

Narcolepsy: This is an extreme tendency to fall asleep during the day. A patient who is found to have unexpectedly fallen asleep is sometimes diagnosed with syncope.

Pseudosyncope. This is a functional or psychiatric disorder, in which episodes are fabricated or faked.

Cataplexy: This rare condition is characterized by transient loss of postural tone without loss of consciousness.

Date	Grade	Teacher's signature

PATHOPHYSIOLOGY OF EXTREME CONDITIONS. ETIOLOGY AND PATHOGENESIS OF COMA

Relevance. Extreme (critical, urgent) state is caused by the influence of pathogenic factors expressed in strength or duration of exposure on the body, characterized by metabolic disorders of vital body functions. Consequently, there is direct threat to life, which requires immediate medical actions. Knowledge of the etiology and pathogenesis of extreme states is necessary for the treatment and prevention these dangerous for life condition.

Overall Objective is to study basic kinds of extreme conditions, causes and mechanisms of their development, pathogenetic treatment.

The student should be able to (specific objectives):

1. Internalize the notion of "extreme conditions".
2. Know the types of extreme conditions.
3. Explain the etiology and pathogenesis of uremia, hepatic, hypoglycemic and diabetic com.

The student should be able to (required knowledge and skills):

1. Explain the mechanisms for maintaining blood pressure and its regulation (Dep. of normal physiology).
2. Characterize the peculiarities of the energy providing of brain neurons (Dep. of normal physiology).
3. Evaluate the role of the kidney and liver in the maintenance of homeostasis (Dep. of normal physiology).

QUESTIONS TO THE LESSON

1. Coma. Changes and oppression of consciousness.
2. Causes of coma.
3. Classification of coma.
4. Pathogenesis coma.
5. Clinical manifestations, course and out of the coma.
6. Treatment of extreme conditions.

THEORETICAL MATERIAL FOR PREPARATION TO THE LESSON

COMA

The state of consciousness is characterized by the ability to get in contact with reality, to recognize objects that are part of it and to interact with it. Consciousness has two main components: wakefulness and content. The first relates to the degree of consciousness, i.e., it represents a quantitative aspect. The second, on the other hand, is a qualitative aspect and is made up of functions mediated by the cortex; these include cognitive abilities such as attention, sensory perception, explicit memory, language, the execution of tasks, temporal and spatial orientation and reality judgment. There can be wakefulness without the content of consciousness, as occurs in the vegetative state. However, the content of consciousness can only exist in the wakeful state.

Although the neurological and anatomical aspects of consciousness have been exhaustively studied, many aspects remain unexplained. Wakefulness is related to the reticular activating system, a structure that originates in the tegmentum of the pons and mesencephalon and has projections into the diencephalon and cortical areas. The content of consciousness, on the other hand, depends on various cortical structures and their subcortical connections.

The spectrum of alterations in the level of consciousness varies progressively from obtundation, through delirium, torpor and stupor to coma. The last of these is the complete absence of wakefulness and content of conscience, which manifests itself as a lack of response to any kind of external stimuli. A comatose state usually occurs in two circumstances: diffuse or extensive involvement of both hemispheres of the brain and situations in which there is a lesion in the brainstem. Unilateral focal lesions very rarely lead to coma.

Coma can be caused by structural lesions (lesions of the central nervous system, such as ischemic and hemorrhagic lesions) or nonstructural ones (such as exogenous intoxication and metabolic disorders). It is potentially fatal and must be investigated quickly and systematically using a standardized neurological examination. Certain clinical parameters can be used to correlate the anatomical and physiological aspects of coma with its etiology, such as state of consciousness, respiratory rhythmicity, pupillary size, eye movements, motor response, cranial nerves responses, evidence of trauma in neck or head, and optic fundi abnormalities.

Coma scales arose because of the need to standardize the language used and so make written and spoken communication of information related to coma between different health professionals easier. A further aim of coma scales is to provide a consistent system for following the evolution of the patient's level of consciousness.

Full Outline Un Responsiveness – FOUR Score

In 2005, Wijdicks et al. published a new coma scale, the FOUR score. It involves assessment of the following four components, each on a scale with a maximum of four: eye response, motor response, brainstem reflexes and respiration. This scale is able to detect conditions such locked-in syndrome and the vegetative state, which are not detected by the GCS. When assessing eye response, the best of three attempts is used. E4 indicates at least three voluntary movements in response to the examiner's commands (for example, asking the patient to look up, look down and blink twice). If the patient's eyes are closed, the examiner should open them and observe whether they track.

Diabetes and coma. Diabetes mellitus is a condition characterised by high blood glucose (sugar) levels. Uncontrolled diabetes may lead to a diabetic coma or unconsciousness. The three types of coma associated with diabetes include diabetic ketoacidosis coma, hyperosmolar coma and hypoglycaemic coma.

Diabetic ketoacidosis (coma)

Diabetic ketoacidosis coma is more common in people with type 1 diabetes, which was previously known as juvenile diabetes or insulin dependent diabetes mellitus (IDDM). This type of coma is triggered by the build-up of chemicals called ketones. Ketones are strongly acidic and cause the blood to become too acidic.

When there is not enough insulin circulating, the body cannot use glucose for energy. Instead fat is broken down and then converted to ketones in the liver. The ketones can build up excessively when there is insufficient insulin in the body.

Common causes of ketoacidosis include a missed dose of insulin or an acute infection in a person with type 1 diabetes. Ketoacidosis is a feature that may occur in people with newly diagnosed type 1 diabetes.

Diabetic hyperosmolar coma is caused by severe dehydration and very high blood glucose levels (hyperglycaemia).

Events that can lead to high blood glucose levels include:

1. Forgotten diabetes medications or insulin.
2. An infection or illness, such as the flu or pneumonia.
3. Increased intake of sugary foods or fluids.

Those at most risk of this type of coma are people with type 2 diabetes who have an infection or acute illness and have reduced their intake of fluids or are taking diuretic medication or steroids.

The **kidneys respond** to high levels of blood glucose by doing their best to remove it, along with a great deal of water. The person experiencing diabetic hyperosmolarity will be very thirsty, but they can't drink enough water to replace the lost fluids. They will become dehydrated and urgently need intravenous fluids. Without this kind of treatment, they may lapse into hyperosmolar coma.

Hyperosmolar coma develops slowly over several days or weeks, so if the high blood glucose levels or dehydration are detected and treated early, coma can be prevented.

Diabetic hypoglycaemic coma. Hypoglycaemia, or low blood glucose levels (below 3.5 mmol/l), may occur if a person on diabetes medication or insulin:

1. Takes an extra dose or an increased dose
2. Exercises strenuously without eating extra food or reducing their insulin intake
3. Misses a meal or snack
4. Drinks too much alcohol or drinks alcohol without eating food.

If the blood glucose falls to very low levels, the person may become unconscious (hypoglycaemic coma) and seizures may occur.

Portosystemic encephalopathy (PSE) or hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with hepatocellular failure or portal-systemic venous shunting.

There has been a lack of terminology standardization used to define hepatic encephalopathy. Acute hepatic encephalopathy referred to acute liver failure or acute decompensation in the setting of chronic liver failure. The term chronic was used to describe the hepatic encephalopathy seen in chronic liver failure.

In 2002, a working committee task force on hepatic encephalopathy standardized the definition and the classification of hepatic encephalopathy. According to the characteristics of neurological manifestations, hepatic encephalopathy is classified as episodic (previously acute), persistent (previously chronic), or minimal (previously subclinical).

Hepatic encephalopathy is classified into 3 types based on the disease state of the liver.

1. Type A: Hepatic encephalopathy associated with acute liver failure.
2. Type B: Hepatic encephalopathy associated with portal-systemic bypass with no intrinsic hepatocellular disease.
3. Type C: Hepatic encephalopathy associated with cirrhosis and portal hypertension or portal-systemic shunts. In cases of chronic liver disease, type C hepatic encephalopathy can be episodic or persistent. The term subclinical encephalopathy was replaced with minimal encephalopathy.

Portal-Systemic Encephalopathy

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Hepatic encephalopathy is a reversible metabolic encephalopathy with multifactorial pathogenesis. The widely accepted hypothesis is that encephalopathy is due to a failure of hepatic clearance of gut-derived toxins. Although the exact toxins involved remain controversial, ammonia remains the toxin of interest. This has led to many investigative and therapeutic efforts aimed at identifying and eliminating the putative toxins that originate from the gut lumen. A fluctuating level of consciousness is common, and progression to coma may occur rapidly.

A high index of clinical awareness is critical for anticipating and recognizing complications. A precipitating cause is usually discovered after clinical and laboratory evaluations. Although elevated plasma ammonia levels are often seen and therapy based on this observation is generally effective, poor correlation exists between the plasma ammonia levels and the degree of encephalopathy. Multiple mechanisms contribute to the pathogenesis of this disorder. Discrete neuropathological features are described in portosystemic encephalopathy but may represent epiphenomena. Although the exact pathophysiological mechanisms of hepatic encephalopathy remain unclear, 2 areas have received more attention: first, the gut-derived neurotoxins (mainly ammonia), and, second, the changes in astrocyte morphology and physiology.

Hyperammonemia and portosystemic shunting led to the hypothesis in 1877 that enteral production of ammonia is central to the pathogenesis of this disorder. Various other putative toxins, which also may be shunted to result in portosystemic encephalopathy, are described. Portosystemic shunting is a requisite for the development of portosystemic encephalopathy. Although disturbances in urea cycle metabolism may result in hyperammonemia, similar encephalopathy does not exist in patients with isolated hyperammonemia in the absence of other evidence of hepatic dysfunction.

Pathophysiology. The pathogenesis of portal hypertension is discussed in Portal Hypertension. This complex condition results in the flow of portal blood containing putative toxins produced in the gut to the systemic circulation and, ultimately, the brain via extrahepatic shunts (collateral flow).

A minority of patients with cirrhosis present with recurrent symptoms of hepatic encephalopathy often without any precipitating cause. These patients may have minimal or mild hepatocellular dysfunction but have significant neurological impairment. In one study, large portosystemic shunts were detected by CT in most patients. Shunting, in part, appears to be a response to increased hepatic vascular resistance in the setting of cirrhosis; however, shunting may result from other causes, including portal vein thrombosis or compression, congenital hepatic fibrosis, iatrogenic shunt placement, and congenital shunt formation. The latter is an important consideration in younger patients with otherwise unexplained hepatic encephalopathy (in the absence of cirrhosis or iatrogenic shunts or portosystemic shunts associated with splenic or portal vein thrombosis). These patients may present in middle age and respond to appropriate shunt-reversal surgery.

The intrahepatic shunt (transjugular intrahepatic portosystemic shunt [TIPS]) provides a conduit for portal venous blood flow directly into the hepatic vein while bypassing the hepatic parenchyma. TIPS is associated with the development of portosystemic encephalopathy in approximately 25 % of cases.

The proposed gut-derived toxins responsible for portosystemic encephalopathy include ammonia, phenols, thiols, and short-chain fatty acids. Other possible mediators include cytokines and bacterial endotoxins. The enteral production of gamma-aminobutyric acid (GABA) and endogenous benzodiazepines (BZPs) remains somewhat speculative, although alterations in GABA-receptor–mediated neurotransmission may play a role for other reasons. The GABA complex, when provided with an appropriate ligand, leads to the production of an inhibitory signal. Widespread inhibition of cortical function from excessive GABAergic signaling, therefore, has been postulated as a mechanism leading to portosystemic encephalopathy.

The thiols or mercaptans are small volatile molecules that characteristically are recognized by their pungent odor, which results from the inclusion of a sulfhydryl group. Accordingly, they may lead to the clinical presentation of fetor hepaticus; however, ammonia clearly is the best contender for the most significant gut-derived neurotoxin, and the ammonia hypothesis, therefore, justifies elaboration.

Most successful forms of therapy are based on the concept of ammonia neurotoxicity. Elimination of ammoniagenic luminal bacteria with nonabsorbed antibiotics (eg, neomycin), luminal acidification with nonabsorbed sugars fermented by luminal bacteria (eg, lactulose), avoidance of constipation, and reduction in ammoniagenic substrate intake (eg, protein-restricted diets) support the ammonia hypothesis.

The production of ammonia from the bacterial expression of urease and metabolism of colonic protein accounts for most ammoniagenesis. The bulk of extracolonic ammonia production occurs in the kidneys. Renal failure may promote ammoniagenesis as a consequence of uremia, which increases available substrate for urease. Ammonia is a neurotoxic compound that principally is eliminated from humans by its hepatic conversion to urea. Periportal hepatocytes in the liver primarily metabolize ammonia. Subsequently, urea is excreted in the urine. Residual ammonia in the hepatic sinusoidal circulation is converted to glutamine by perivenous hepatocytes expressing glutamine synthase.

Besides causing functional changes such as reduction in cerebral perfusion, ammonia may also be responsible for structural changes in the brains of patients with hepatic encephalopathy. In necropsy studies, brains of cirrhotic patients exhibit Alzheimer type II astrocytosis, characterized by swollen astrocytes with enlarged nuclei and chromatin displaced to the perimeter of the cell. Type II astrocytosis is hypothesized to be caused in part by the detoxification of ammonia. Astrocytes, the only cells in the brain that can metabolize ammonia, contain glutamine.

In vivo proton MRS (1H-MRS) shows that astrocyte swelling without increases in intracerebral pressure may occur early in the pathogenesis of portosystemic encephalopathy.

Ultimately, the development of advanced portosystemic encephalopathy may be accompanied by cerebral edema, which may contribute to neurological impairment. While cerebral edema has its most obvious manifestations in the patient with fulminant hepatic failure (FHF), osmotically active substances do accumulate in the brains of patients without overt cerebral edema. An osmotically sensitive pool of myoinositol is released from astrocytes in response to osmotically induced astrocyte swelling. A depletion of myoinositol is shown by 1H-MRS in patients with chronic portosystemic encephalopathy, and it appears to correlate with an increase in the signal for glutamine and glutamate.

With the use of magnetic resonance spectroscopy (MRS), low-grade cerebral edema has been demonstrated in patients with cirrhosis and chronic hepatic encephalopathy.

Despite the demonstration of astrocyte swelling and osmotic phenomena, treatment of hepatic encephalopathy does not include use of mannitol or hyperventilation unless cerebral edema is suspected, as in FHF. No established role currently exists for routine cerebral magnetic

resonance imaging or spectroscopy in the evaluation of portosystemic encephalopathy. The data supporting the ammonia hypothesis in the development of portosystemic encephalopathy, therefore, are impressive and follow multiple lines of evidence. Indeed, the past decade was remarkable for the recognition of ammonia as a key element in the pathogenesis of portosystemic encephalopathy. However, other small molecules also may contribute, and these theories are not mutually exclusive. Synergistic toxicity of ammonia and other agents likely is important

Production of the so-called false neurotransmitters may contribute significantly to the pathogenesis of portosystemic encephalopathy. Putative agents include octopamine and diazepam. Supplementation with branched-chain amino acids (BCAAs) such as isoleucine, leucine, and valine and avoidance of aromatic amino acids, such as phenylalanine, tryptophan, and tyrosine may lead to decreased production of false neurotransmitters; however, the clinical benefit of BCAA supplementation has never been demonstrated convincingly.

Increased production of endogenous BZPs has been proposed in patients with portosystemic encephalopathy. These agents may represent the best-defined false transmitters in portosystemic encephalopathy; however, their precise role is somewhat unclear. These substances are suggested to depress central nervous system (CNS) function by binding to specific high-affinity BZP sites on GABA-receptor complexes. The GABA complex, when provided with an appropriate ligand, leads to the production of an inhibitory signal. Therefore, widespread inhibition of cortical function from excessive GABAergic signaling has been postulated as a mechanism leading to portosystemic encephalopathy.

Broadly speaking, cytokines are substances produced and released by cells for communication with other cells. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-a) are important examples of immunomodulatory cytokines that are increased in the systemic circulation and possibly contribute to the pathogenesis of systemic hemodynamic events in portal hypertension. The rapidly diffusing NO is grouped with these substances for the purposes of this discussion. Although not a cytokine in the strictest sense, NO plays an important, if ill-defined, role in mediating some of the significant communication events resulting from cytokine activation in advanced liver disease.

Endotoxemia, presumably in part from gut mucosal permeability, is demonstrated in cirrhosis with portal hypertension. Associated increased IL-1 and TNF-a concentrations and metabolites of NO in the systemic circulation also are reported. This suggests that shunting of proinflammatory substances from the gut lumen contributes to or perhaps initiates a cascade of events culminating in the hyperdynamic circulation typical of advanced liver disease.

Cerebral ischemia is another mechanism that contributes to portosystemic encephalopathy, although it may represent a consequence of ammonia toxicity. A loss of cerebral blood flow autoregulation reflexes may accompany the development of FHF; however, cerebral autoregulation, in general, is preserved in patients with cirrhosis if mean arterial pressure is maintained above 70 mm Hg, even in severe cases of hepatic encephalopathy. In contrast, patients with advanced hepatic encephalopathy have reduced cortical blood flow and increased cerebral vascular resistance.

Myxedema Coma or Crisis

The term myxedema has been applied to several clinical entities and is often used interchangeably with severe hypothyroidism, the common clinical condition in which the thyroid gland produces abnormally low levels of hormones.

Myxedema also refers to 2 different dermatologic conditions. Pretibial myxedema, an uncommon skin disorder, occurs not in cases of hypothyroidism but in hyperthyroid states, including, most commonly, Graves' disease. The term pretibial is somewhat misleading, because the condition can affect other areas of the body and could more accurately be called localized dermopathy.

The other skin condition, called myxedema, occurs in severe, long-standing hypothyroid states and is caused by the deposition of mucopolysaccharides within the dermis.

This article discusses myxedema coma, an uncommon but life-threatening form of untreated hypothyroidism with physiological decompensation The condition occurs in patients with long-standing, untreated hypothyroidism and is usually precipitated by a secondary insult, such as climate-induced hypothermia, infection, or another systemic condition, or drug therapy. Patients with myxedema coma have changes in their mental status, including lethargy, stupor, delirium, or coma. A more appropriate term for myxedema coma is myxedema crisis; this article often uses the term myxedema coma/crisis.

Pathophysiology. Myxedema coma/crisis occurs most commonly in older women with long-standing, undiagnosed or undertreated hypothyroidism who experience an additional significant stress, such as infection, a systemic disease, certain medications, and exposure to a cold environment.

When hypothyroidism is long-standing, physiologic adaptations occur. Reduced metabolic rate and decreased oxygen consumption result in peripheral vasoconstriction, which maintains core temperature. The number of beta-adrenergic receptors is reduced, usually with preservation of alpha-adrenergic receptors and circulating catecholamines, causing beta/alpha-adrenergic imbalance, diastolic hypertension, and reduced total blood volume.

Myxedema coma/crisis is a form of decompensated hypothyroidism in which adaptations are no longer sufficient. Essentially, all organ systems are affected.

Metabolic. Thyroid hormones are critical for cell metabolism and organ function. With an inadequate supply, organ tissues do not grow or mature, energy production declines, and the action of other hormones is affected. Although weight gain is common, severe obesity is rarely secondary to hypothyroidism alone. However, long-standing, untreated hypothyroidism may result in years of inactivity, eventually with a large increase in weight.

Because of decreased drug metabolism, overdoses of medications (eg, morphine, hypnotics, anesthetic agents, sedatives) can occur and can even precipitate myxedema crisis.

Neurologic. Although the condition is called myxedema coma, absence of coma does not exclude the diagnosis of this disorder. The presenting mental status may be lethargy or stupor. The exact mechanisms causing changes in mental status are not known. Brain function is influenced by reductions in cerebral blood flow and oxygen delivery, a lack of thyroxine (T_4) and triiodothyronine (T_3), and reductions in oxygen and glucose consumption; all of these factors are probably involved. Hyponatremia brought on by renal dysfunction may be an additional cause of altered mental function.

Cardiovascular. The heart is profoundly depressed, with bradycardia and decreased contractility causing low stroke volume and cardiac output. These changes are caused by decreased production of myocyte contractile proteins and enzymes, including NA^+/K^+ adenosine triphosphatase (NA^+/K^+ ATPase), as a result of low levels of gene transcription in the absence of T_3. Increased systemic vascular resistance occurs; although the causes appear to be multifactorial, a study suggests that in many cases, the increase is secondary to decreased T_3 levels.Nonspecific ST- and T-wave inversion changes, low voltage, and ventricular arrhythmias may be noted. Plasma volume is decreased, and capillary permeability is increased, leading to fluid accumulation in tissue and spaces and possibly causing pericardial effusions.

Pulmonary. Typically, the lungs are not severely affected. Respiratory muscle dysfunction may be compromised, and depressed ventilatory drive and increased alveolar-arterial oxygen gradient are common. Fluid accumulation may cause pleural effusions and decreased diffusing capacity. Ventilation-perfusion mismatch is common, contributing to hypercapnia. Dysfunction of other organ systems may have profound effects. Severe obesity, if present, causes decreased lung volumes, diffusion capacity, and flow rates and may be the primary cause of the hypoventilation, hypoxia, hypercarbia, and depressed respiratory drive that is often noted in these patients. However, hypothyroidism may also have a direct impact, because the condition can cause obstructive sleep apnea that resolves with thyroid replacement (even without weight loss).

Renal. Kidney function may be severely compromised, partly because of low cardiac output and vasoconstriction that causes a low glomerular filtration rate. Reduced levels of NA^+/K^+ ATPase decrease sodium reabsorption and impair free water excretion, resulting in hyponatremia, which is usually present in myxedema coma.

Gastrointestinal. Severe or even mild hypothyroidism decreases intestinal motility. Patients with myxedema coma can present with gastric atony, megacolon, or paralytic ileus. Malabsorption has also been reported. Ascites, while uncommon, may occur due to increased capillary permeability, congestive heart failure, or other mechanisms.

Uric Acid Nephropathy. Uric acid is the relatively water-insoluble end product of purine nucleotide metabolism. It poses a special problem for humans because of its limited solubility, particularly in the acidic environment of the distal nephron of the kidney.[1] It is problematic because humans do not possess the enzyme uricase, which converts uric acid into the more soluble compound allantoin. Three forms of kidney disease have been attributed to excess uric acid: acute uric acid nephropathy, chronic urate nephropathy, and uric acid nephrolithiasis. These disorders share the common element of excess uric acid or urate deposition, although the clinical features vary.

Properties of uric acid. Uric acid, the product of the xanthine oxidase–catalyzed conversion of xanthine and hypoxanthine, is the final metabolite of endogenous and dietary purine nucleotide metabolism. It is a weak acid, with a p K_a of 5.75; at a physiologic pH of 7.40 in the extracellular compartment, 98 % of uric acid is in the ionized form as urate. In the collecting tubules of the kidneys, where the pH can fall to 5.0, uric acid formation is favored. The critical physical property of uric acid in the clinical setting is solubility. Uric acid is less soluble than urate; thus, an acidic environment decreases solubility. Plasma at a pH of 7.40 is saturated with urate at a concentration of 7 mg/dL. Because normal plasma levels of urate are 3–7 mg/dL for men and 2–6 mg/dL for women, the solubility limit apparently is approached under physiologic conditions. Of the uric acid produced daily, the biliary and gastrointestinal tracts excrete 30 % and the kidney excretes 70 %.

Renal handling of urate. Renal excretion of uric acid involves 4 pathways: filtration, reabsorption, secretion, and postsecretory reabsorption. Urate is freely filtered at the glomerulus. An active anion-exchange process in the early proximal convoluted tubule reabsorbs most of it. Most urinary uric acid appears to be derived from tubular secretion, possibly from the S2 segment of the proximal tubule. Overall, 98–100 % of filtered urate is reabsorbed; 6–10 % is secreted, ultimately appearing in the final urine.

Several factors influence the renal handling of urate. Many medications can affect the renal transport of uric acid through effects of proximal tubular absorption and secretion. Extracellular volume expansion or contraction, respectively, enhances or reduces uric acid excretion through the paired movement of sodium. Consequently, in cases of extracellular compartment depletion, urate excretion is diminished.

Physiologically, the major factors that affect urate excretion are the tubular fluid pH, the tubular fluid flow rate, and renal blood flow. The first 2 factors primarily diminish uric acid and urate precipitation in the collecting ducts, while the third is important in urate secretion. In disorders such as sickle cell disease, hypertension, and eclampsia, hyperuricemia out of proportion with decreases in glomerular filtration result from decreased renal blood flow. Organic acids, such as lactic acid and ketoacids, also can impair the proximal secretion of uric acid.

Acute uric acid nephropathy. Overproduction of uric acid occurs primarily when tissue breakdown is accelerated. Acute uric acid nephropathy is the term applied to the development of acute oligoanuric renal failure caused by renal tubular obstruction by urate and uric acid crystals. This is observed almost exclusively in the setting of malignancy, especially leukemia and lymphoma, in which rapid cell turnover or cell lysis occurs from chemotherapeutic agents or radiation therapy.

The release of intracellular nucleotides leads to severe hyperuricemia. When urate is filtered at exceedingly high concentrations from the plasma and is further concentrated through the course of the tubular system, with the pH becoming progressively more acidic, uric acid precipitation and obstruction in the tubules, collecting ducts, and even pelves and ureters may result. In animal models of uric acid nephropathy, the precipitation of uric acid and urate occurs primarily in the collecting duct system and, to some extent, in the vasa recta.

Crystal deposition causes increased tubular pressure, increased intrarenal pressure, and extrinsic compression of the small-diameter renal venous network. This causes an increase in renal vascular resistance and a fall in renal blood flow. The elevated tubular pressure and decreased renal blood flow cause a decline in glomerular filtration and can result in acute renal failure.

Chronic urate nephropathy. A widely accepted belief is that the overproduction of uric acid and presence of hyperuricemia can cause acute kidney failure; however, whether chronic hyperuricemia independently results in chronic interstitial nephritis and progressive kidney failure is less clear.

In patients with chronic hyperuricemia and gout, early studies revealed microtophi formation in the renal medullary interstitium. These deposits were found to contain monosodium urate monohydrate and to be surrounded by a giant cell reaction. Thus, the theory was that urate deposition triggers a foreign body reaction and leads to chronic inflammation and fibrosis. Chronic renal failure from this process was termed chronic uric acid nephropathy, or gouty nephropathy, and articles from the 1960s suggested that all patients with long-standing gout had gouty nephropathy. However, the existence of a chronic urate nephropathy has since been questioned.

In a study of 11,408 consecutive autopsies in Switzerland, only 37 revealed urate deposits in the kidney and only 3 of these cases had otherwise unexplained kidney failure. Investigators also found urate deposition in the kidneys of patients without gout, suggesting that this finding is not specific for gout. In another study, a long-term follow-up evaluation of 524 subjects with gout, the authors concluded that deterioration of kidney function could not be ascribed to hyperuricemia and gout alone. They found that in general, the decline in kidney function could be attributed to other known causes of chronic renal failure, such as nephropathy not associated with uric acid, renal stones, aging, or hypertension. In summary, little compelling evidence exists that chronic hyperuricemia leads to chronic urate nephropathy.

There continues to be considerable interest and debate, however, on the relationship between hyperuricemia, hypertension, and progressive kidney failure. In several prospective cohort trials, hyperuricemia was identified in subjects with normal kidney function at baseline as an independent risk factor for development of chronic kidney disease. A newer hypothesis proposes that hyperuricemia may cause impairment of renal autoregulation, leading to hypertension, microalbuminuria and overt albuminuria, and progressive kidney failure. Moreover, epidemiologic studies in Japan have supported a link between hyperuricemia and progressive kidney disease.

The use of allopurinolto lower uric acid levels has been proposed as a means of retarding the progression of chronic kidney disease and of preventing end-stage renal disease. It has been claimed that at least 1 small, prospective clinical trial demonstrated allopurinol's efficacy for this purpose. However, the routine use of allopurinol in chronic kidney disease and asymptomatic hyperuricemia is not yet considered to be the standard of care, primarily due to the risk and cost of therapy and the lack of a large, randomized, controlled trial demonstrating the efficacy of uric acid reduction in retarding the progression of chronic kidney disease.

There are 2 other situations in which there appears to be a link between elevated uric acid levels and chronic kidney disease. First, there is evidence that environmental lead exposure is associated with hyperuricemia, gout, hypertension, and chronic kidney disease. Lead exposure may affect urate excretion by the kidney, leading to chronic hyperuricemia and kidney disease. Whether hyperuricemia is the key mechanism for lead-related nephrotoxicity is not clear, however.

Additionally, there is a rare group of patients in which chronic hyperuricemia clearly leads to kidney failure. These are patients with a congenital absence of hypoxanthine guanine phosphoribosyltransferase (HGPRT), a condition that is also known as Lesch-Nyhan syndrome. This is an X-linked disorder that results in mental retardation, involuntary movement, self-mutilation, gout, and early kidney failure. In these patients, chronic uric acid overproduction causes hyperuricemia and uricosuria. The incidence of chronic kidney disease is high in these individuals, who have intratubular uric acid deposits and interstitial urate deposits.

Uric acid nephrolithiasis

Uric acid stones, which represent 5–10 % of all renal calculi in the United States, also result from uric acid precipitation in the collecting system. Uric acid stones are related to uric acid exceeding its solubility in the urine; thus, patients with hyperuricosuria have an increased risk of uric acid nephrolithiasis. Urine oversaturation with uric acid and subsequent crystal formation is determined largely by urinary pH. Individuals who form uric acid stones tend to excrete less ammonium, which contributes directly to low urinary pH. In addition, persons with gout and those who form stones, in particular, have a reduced postprandial alkaline tide (alkaline urinary pH).

Uremia is a clinical syndrome associated with fluid, electrolyte, and hormone imbalances and metabolic abnormalities, which develop in parallel with deterioration of renal function. The term uremia, which literally means urine in the blood, was first used by Piorry to describe the clinical condition associated with renal failure.

Uremia more commonly develops with chronic renal failure (CRF) or the later stages of chronic kidney disease (CKD), but it also may occur with acute renal failure (ARF) if loss of renal function is rapid. As yet, no single uremic toxin has been identified that accounts for all of the clinical manifestations of uremia. Toxins, such as parathyroid hormone (PTH), beta2 microglobulin, polyamines, advanced glycosylation end products, and other middle molecules, are thought to contribute to the clinical syndrome.

Pathophysiology. Normally, the kidney is the site of hormone production and secretion, acid-base homeostasis, fluid and electrolyte regulation, and waste-product elimination. In the presence of renal failure, these functions are not performed adequately and metabolic abnormalities, such as anemia, acidemia, hyperkalemia, hyperparathyroidism, malnutrition, and hypertension, can occur. Uremia usually develops only after the creatinine clearance falls to less than 10mL/min, although some patients may be symptomatic at higher clearance levels, especially if renal failure acutely develops. The syndrome may be heralded by the clinical onset of the following symptoms:

1. Nausea, Vomiting, Fatigue
2. Anorexia.'
3. Weight loss, Muscle cramps.
4. Pruritus.
5. Change in mental status.

Anemia. Anemia-induced fatigue is thought to be one of the major contributors to the uremic syndrome. Erythropoietin (EPO), a hormone necessary for red blood cell production in bone marrow, is produced by peritubular cells in the kidney in response to hypoxia. Anemia associated with renal failure can be observed when the glomerular filtration rate (GFR) is less than 50 mL/min or when the serum creatinine is greater than 2 mg/dL. Patients with diabetes may experience anemia with a GFR of less than 60 mL/min.

Anemia associated with chronic kidney disease is characteristically normocytic, normochromic, and hypoproliferative.

Anemia in chronic renal failure. In the setting of CRF, anemia may be due to other clinical factors or diseases, such as iron deficiency, vitamin deficiencies (eg, folate, vitamin B_{12}), hyperparathyroidism, hypothyroidism, and decreased red blood cell survival. Iron deficiency, which may occur as a result of occult GI bleeding or frequent blood draws, should be excluded in all patients.

Elevated PTH levels are thought to be associated with marrow calcification, which may suppress red blood cell production and lead to a hypoproliferative anemia. Parathyroid-induced marrow calcification tends to regress after parathyroidectomy.

Studies have shown that hepcidin, an acute phase protein involved with iron metabolism, plays a key role in erythropoiesis. Hepcidin, up-regulated in states of inflammation, prevents iron absorption in the small intestine, as well as iron release from macrophages.

Coagulopathy. Bleeding diatheses are characteristic findings in patients with end-stage renal disease (ESRD). The pathogenesis of uremic bleeding tendency is related to multiple dysfunctions of the platelets. The platelet numbers may be reduced slightly, while platelet turnover is increased.

The reduced adhesion of platelets to the vascular subendothelial wall is due to reduction of GPIb and altered conformational changes of GPIIb/IIIa receptors. Alterations of platelet adhesion and aggregation are caused by uremic toxins, increased platelet production of NO, PGI(2), calcium and cAMP, as well as renal anemia.

Correction of uremic bleeding is accomplished through treatment of renal anemia with recombinant human erythropoietin or darbepoetin alpha, adequate dialysis, desmopressin, cryoprecipitate, tranexamic acid, or conjugated estrogens.

Patients with ESRD are at significantly increased risk for bleeding if placed on oral anticoagulants or antiplatelet agents. Thus, these classes of medicines need to be prescribed with extreme caution.

Acidosis is another major metabolic abnormality associated with uremia. Metabolic acid-base regulation is controlled primarily by tubular cells located in the kidney, while respiratory compensation is accomplished in the lungs. Failure to secrete hydrogen ions and impaired excretion of ammonium may initially contribute to metabolic acidosis.

As kidney disease continues to progress, accumulation of phosphate and other organic acids, such as sulfuric acid, hippuric acid, and lactic acid, creates an increased anion-gap metabolic acidosis. In uremia, metabolic acidemia may contribute to other clinical abnormalities, such as hyperventilation, anorexia, stupor, decreased cardiac response (congestive heart failure), and muscle weakness.

In patients with CKD who are not yet on dialysis, treatment of the acidosis with oral bicarbonate supplementation has been demonstrated to help slow the progression of the renal disease.

Hyperkalemia. Hyperkalemia (potassium > 6.5 mEq/L) may be an acute or chronic manifestation of renal failure, but regardless of the etiology, a potassium level of greater than 6.5 mEq/L is a clinical emergency. As renal function declines, the nephron is unable to excrete a normal potassium load, which can lead to hyperkalemia if dietary intake remains constant. In addition, other metabolic abnormalities, such as acidemia or type IV renal tubular acidosis, may contribute to decreased potassium excretion and lead to hyperkalemia. (Most cases of hyperkalemia are multifactorial in etiology).

Hyperkalemia can occur in several instances, including the following:

Excessive potassium intake in patients with a creatinine clearance of less than 20 mL/min

Hyporeninemic hypoaldosteronism or type IV renal tubular acidosis in patients with diabetes, urinary obstruction, or interstitial nephritis.

Hyperparathyroidism. In the setting of renal failure, there are a number of abnormalities of the calcium-vitamin D metabolic pathway, such as hypocalcemia, hyperphosphatemia, and increased PTH levels that ultimately lead to renal bone disease (osteodystrophy).

After exposure to the sun, vitamin D_3 is produced in the skin and transported to the liver for hydroxylation (25[OH] vitamin D_3). Hydroxylated vitamin D_3 is then transported to the kidney, where a second hydroxylation occurs, and 1,25 $(OH)_2$ vitamin D_3 is formed.

As the clinically active form of vitamin D, 1,25 $(OH)_2$ vitamin D_3 is responsible for GI absorption of calcium and phosphorus and suppression of PTH. During renal failure, 1,25 $(OH)_2$ vitamin D_3 levels are reduced secondary to decreased production in renal tissue, as well as

hyperphosphatemia, which leads to decreased calcium absorption from the GI tract and results in low serum calcium levels. Hypocalcemia stimulates the parathyroid gland to excrete PTH, a process termed secondary hyperparathyroidism. Hyperphosphatemia occurs as excretion of phosphate decreases with progressive renal failure. Hyperphosphatemia stimulates parathyroid gland hypertrophy and stimulates increased production and secretion of PTH.

Elevated PTH levels have been associated with uremic neuropathy and other metabolic disturbances, which include altered pancreatic response, erythropoiesis, and cardiac and liver function abnormalities. The direct deposit of calcium and phosphate in the skin, blood vessels, and other tissue, termed metastatic calcification, can occur when the calcium-phosphate product is greater than 70.

Endocrine abnormalities. Other endocrine abnormalities that may occur in the setting of uremia include changes in carbohydrate metabolism, decreased thyroid hormone excretion, and abnormal sexual hormone regulation.

Reduced insulin clearance and increased insulin secretion can lead to increased episodes of hypoglycemia and normalization of hyperglycemia in diabetic patients. Glycemic control may appear to be improved; however, this may be an ominous sign of renal function decline. Consider appropriate decreases in doses of antihyperglycemic medications (ie, insulin and oral antihyperglycemic medications) as renal function declines to avoid hypoglycemic reactions.

Levels of thyroid hormones, such as thyroxine, may become depressed, while reverse triiodothyronine levels may increase because of impaired conversion of triiodothyronine to thyroxine.

Reproductive hormone dysfunction is common and can cause impotence in men and infertility in women. Renal failure is associated with decreased spermatogenesis, reduced testosterone levels, increased estrogen levels, and elevated luteinizing hormone levels in men, all of which contribute to impotence and decreased libido.

In women, uremia reduces the cyclic luteinizing hormone surge, which results in anovulation and amenorrhea. Infertility is common and pregnancy is rare in women with advanced uremia and renal failure, but this may be reversed with renal transplantation.

Cardiovascular abnormalities. Cardiovascular abnormalities, including uremic pericarditis, pericardial effusions, calcium and phosphate deposition–associated worsening of underlying valvular disorders, and uremic suppression of myocardial contractility, are common in patients with CRF. Left ventricular hypertrophy is a common disorder found in approximately 75 % of patients who have not yet undergone dialysis. Left ventricular hypertrophy is associated with increased ventricular thickness, arterial stiffening, coronary atherosclerosis, and/or coronary artery calcification. Patients are at increased risk for cardiac arrhythmias due to underlying electrolyte and acid-base abnormalities. Renal dysfunction may contribute to associated fluid retention, which may lead to uncontrolled hypertension and congestive heart failure.

Malnutrition. Malnutrition usually occurs as renal failure progresses; it is manifested by the following symptoms:

1. Anorexia, Weight loss
2. Loss of muscle mass, Low cholesterol levels
3. Low blood urea nitrogen (BUN) levels in the setting of an elevated creatinine level
4. Low serum transferrin levels, Hypoalbuminemia

However, the question of whether uremia stimulates protein catabolism directly remains controversial.

Comorbid diseases, such as diabetes and congestive heart failure, that require reduced food intake or restrictions of certain foods may contribute to anorexia.

Numerous epidemiologic studies have shown that a decreased serum albumin concentration is a very strong and independent predictor of mortality among dialysis patients. Thus, it is important that dialysis be initiated prior to the occurrence of significant malnutrition.

Etiology. The etiologies of CKD range from primary glomerular and tubular disorders (e.g, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, IgA nephropathy, polycystic kidney disease) to systemic disorders causing renal injury (e.g, diabetes, lupus, amyloidosis, Goodpasture disease, multiple myeloma, thrombotic thrombocytopenic purpura, haemolytic uremic syndrome). ARF may be caused by multiple etiologies, but it is associated with uremia when a rapid rise in urea or creatinine occurs.

Date	Grade	Teacher's signature

REFERENCES:

1. Stanley L. Robbins, M.D., Vinay Kumar, M.D.: Basic Pathology, 6th ed., W. B. Saunders Company, 1999.
2. Harsh Mohan: Textbook of Pathology 3rd ed., Jaypee Brothers Medical Publishers ltd, Delhi, India, 1998.
3. Stephen J. McPhee et al.: Pathophysiology of Disease, 2nd ed., Appleton & Lange, 1999.
4. Alpern D. Pathologic Physiology, Mir Publishers, Moscow, 1976.

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