ZAPORIZHZHIA STATE MEDICAL UNIVERSITY

DEPARTMENT OF HOSPITAL PEDIATRICS

DISEASES OF BLOOD AND ENDOCRINE SYSTEM IN CHILDREN

(educational and methodical manual for the 5 year English speaking students of medical faculty)

ZAPORIZHZHIA

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Zaporizhzhia State Medical University

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CONTENTS

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Pediatrics is one of important clinical disciplines, without deep knowledge of which the forming of modern specialist-physician is not possible.

Pediatrics as educational discipline is based on students knowledge of substantive provisions of anatomy, histology, physiology, physiopathology, pathoanatomy, propedeutics and infectious diseases

Acquisition of thorough knowledges and abilities from paediatrics allows to utillize them for the savation of clinical problems of diagnostics, prophylaxis and treatment of diseases.

Educational and methodical manual "Diseases of blood and endocrine system in children" for the 5 year students of medical faculty compiled in accordance to "Educational profesional programm for high education" after professional direction of „Medicine" , ratified by the Ministries of Education and Health of Ukraine. In developing of materials the long-term experience of pediatrics department of Zaporizhzhia State Medical University and the recommendations of supporting department of pediatrics is used (hospital pediatrics department of National Medical University).

Materials given in the Manual show by itself the guidance on the practical classes leadthrough for the 5 year students of medical faculty studying on speciality of Pediatrics and General Practitioner. Taking into account progressive development of pediatrics, change of requirements to the specialists the given educational methodical Manual will incompletely reflecs to the pedagogical and professional necessities, that is why will be perfected and complemented.

TEST CREDIT STRUCTURE OF THE MODULE 3. Diseases of blood and endocrine system in children.

Topic	Lectures	Pract. classes	Ind. prep.	Individual work
Semantic module 10. Diseases of blood in children.				.
1. Scarce anemias in children	**2**	4	2	
2. Hemoblastoses in children	2	4	2	
3. Hemorrhagic diseases in children	2	4	2	
Semantic module 11. Diseases of endocrine system in children				
4. Diabetes melltus in children	2	4	2	
5. Thyroid diseases in children	2	4	2	
6. Diseases of hypothalamus pituitary system in children		4	2	
Implementation of individual work			4	
Final module control		4	6	
Total: ECTS credits - 2,0; hours - 60	10	28	22	

TIMETABLE OF LECTURES. MODULE 3

Diseases of blood and endocrine system in children

#	Topic	Hours
1	Anemias in children	2
2	Hemoblastoses in children	2
3	Hemorrhagic diseases in children	2
4	Diabetes melltus in children	2
5	Thyroid diseases in children	2
	Total	10

TIMETABLE OF PRACTICAL CLASSES. MODULE 3.
Diseases of blood and endocrine system in children

#	Topic	Hours
1	Scarce anemias in children	4
2	Hemoblastoses in children	4
3	Hemorrhagic diseases in children	4
4	Diabetes melltus in children	4
S	Thyroid diseases in children	4
6	Diseases of hypothalamus, pituitary and sexual glands in children.	4
7	Final module control	4
	Total	28

TEMATIC PLAN OF STUDENTS INDIVIDUAL PREPARATION (SIP). MODULE 3.
Diseases of blood and endocrine system in children

№ п/п	Kind of SIP	Hours	Control types
1	Preparation to practical classes	12	Current control on the practical classes.
2	Working of themes which are not included in the plan of audience classes.		Final module control
3	SIP:case reports analysis, preparing of referates and the performancies in clinical meetings.	4	Final module control. Current control on the practical classes.
4	Preparing to the final module control	6	Підсумковий модульний контроль
	Total	20	Final module control.

POINTS DISTRIBUTION FOR THE ASSESMENT OF STUDENTS PERFORMANCIES. MODULE 3.МОДУЛЬ 3.

Diseases of blood and endocrine system in children

.Module 3 (volume of the estimated activity)	Maximal points are possible
Semantic module 10.	
Topic 1. Scarce anemias in children	**20**
Topic 2. Hemoblastoses in children	**20**
Topic 3. Hemorrhagic diseases in children	**20**
Semantic module 11	
Topic 1. Diabetes melltus in children	**20**
Topic 2.Thyroid diseases in children	**20**
Topic 3. Diseases of hypothalamus, pituitary and sexual glands in children.	**20**
Current perfomance in total	**120**
Final module control	**80**
SUMMARISED MODULE POINTS	**200**

Note: In mastering the topic after traditional system points gives to the a student as follows: «5» - 20 points, «4» - 16 points, «3» - 12 points, «2» - 0 points.. Maximal amount of points for current educational performance of student are 120.

A student is allowed to pass the final module control in terms of him performance according to the requirements of tutorial and in case of obtaining no less than 72 points for current performance during the practical classes. (12 x 6).

Final module control is setting off to the student if he get not less than 50 of 80 points.

Theme. Iron-, protein-and vitamin scarce anaemias.

Study time: 4 hours

Etiology, pathogenesis,classification, clinical presentation, diagnostics, differential diagnostics, treatment, prophylaxis. Emergency in haemorrhage. Prognosis.

I. **Actuality of the theme.**

Anemia is a frequent laboratory abnormality in children. As many as 20 percent of children in the United States and 80 percent of children in developing countries will be anemic at some point by the age of 18 years.

Childhood anaemia poses a major public health issue leading to an increased risk of child mortality, as well as the negative consequences of iron deficiency anaemia on cognitive and physical development.3 The United Nations General Assembly set a goal at its special session on children in 2003 to reduce the prevalence of anaemia by one third by 2010.Anemia (uh-NEE-me-eh) is a condition in which your blood has a lower than normal number of red blood cells. This condition also can occur if your red blood cells don't contain enough hemoglobin (HEE-muh-glow-bin). Hemoglobin is an iron-rich protein that gives blood its red color. This protein helps red blood cells to carry oxygen from the lungs to the rest of the body.If you have anemia, your body doesn't get enough oxygen-rich blood. As a result, you may feel tired and have other symptoms. With severe or long-lasting anemia, the lack of oxygen in the blood can damage the heart, brain, and other organs of the body. Very severe anemia may even cause death.Red blood cells are disc-shaped and look like doughnuts without holes in the center. They carry oxygen and remove carbon dioxide (a waste product) from your body. These cells are made in the bone marrow—a sponge-like tissue inside the bones. Red blood cells live for about 120 days in the bloodstream and then die.White blood cells and platelets (PLATE-lets) are also made in the bone marrow. White blood cells help to fight infection. Platelets stick together to seal small cuts or breaks on the blood vessel walls and stop bleeding. With some types of anemia, you may have low numbers of all three types of blood cells.Anemia has three main causes: blood loss, lack of red blood cell production, or high rates of red blood cell destruction. These causes may be due to a number of diseases, conditions, or other factors.Many types of anemia can be mild, short term, and easily treated. Some types can even be prevented with a healthy diet. Other types can be treated with dietary supplements.However, certain types of anemia may be severe, long lasting, and life threatening if not diagnosed and treated.

Concrete purposes:

1.To determine the etiological and pathogenetic factors in iron-,protein-and vitamin scarce anaemias in children .

2. To classify and analyze the typical clinical manifestation of iron-,protein-and vitamin scarce anaemias in children.

3.To make the plan of investigation and analyse the information about laboratory and instrumental data of iron-, protein-and vitamin scarce anaemias in children.

4. To demonstrate skills of treatment, rehabilitation and prophylaxis in iron-,protein-and vitamin scarce anaemias in children .

5. To diagnose and render an urgent help in haemorrhage.

6. To conduct differential diagnostics of iron-,protein-and vitamin scarce anaemias in children and make a preliminary diagnosis.

7. To determine the prognosis for life in iron-, protein-and vitamin scarce anaemias in children.

8. To demonstrate the skills of medical specialist moral and deontological principles and principles of professional subordination in pediatrics.

II. Classes (pointing of planned mastering level)

1. A student must know (to familiarize): α1

- About the place of iron-,protein-and vitamin scarce anaemias in the structure of haematology system diseases in children, widespread in different age-dependent and ethnic groups;

- About statistical information in relation to morbidity, frequencies of complications, lethality, the nearest and remote prognosis in patients with iron , protein-and vitamin scarce anaemias ;

- About history of scientific study and payment of domestic scientists;

2. A student must know : α2

- etiology of iron-,protein-and vitamin scarce anaemias
  in children;

- key links of iron-,protein-and vitamin scarce anaemias pathogenesis ;

- clinical classification of iron-,protein-and vitamin scarce anaemias;

- the classic clinical manifestation of iron-,protein-and vitamin scarce anaemias;

- laboratory diagnosis iron-,protein-and vitamin scarce anaemias;

- laboratory and instrumental diagnosis of iron-, protein-and vitamin scarce anaemias;

- complications of iron-,protein-and vitamin scarce anaemias in children;

- the treatment principles of iron-,protein-and vitamin scarce anaemias in children;

3. A student must seize: α3

By skills:

- collection of complaints and anamnesis of disease;

- examination of patients with iron-,protein-and vitamin scarce anaemias and revealing the main symptoms and syndromes.

- formulating and substantiating the preliminary diagnosis;

- determinat a laboratory and instrumental examination plan of patients investigation (with obedience of diagnostics standards);

By the abilities:
-   interpreting the results of laboratory and instrumental investigations.
-   conducting a differential diagnosis among different kinds of anaemias ;
-   giving recommendations in relation to the patient regimen and diet with anaemias- taking into account the stage of disease, severity of the state and concomitant pathology;
-   completing the treatment plan for anaemias according to standards taking into account the stage of disease, complications and concomitant pathology.
-   rendering the first aid in extreme situations and exigent states.

III. Aims of personality development (educative aims):

-   A student must learn to adhere to the rules of behaviour and principles of medical etiquette and deontology near a bed ridden patient with iron-, protein-and vitamin scarce anaemias -to try hands on ability to set a psychological contact with a patient and his family;
-   to master a sense of professional responsibility for a timely , adequate and skilled medicare.

IV. Interdisciplinary integartion:

Subject	To know	To be able
1. Previous (providing)		
Anatomy	Structure of blood in children	To determine the location of thyroid projection and palpation, of local lymphatic nodes.
Physiology	Physiology of hematopoietic system in newborns, normative indices of laboratory and instrumental investigational methods and their assesment.	To asses laboratory data and instrumental investigational methods.
Pathologic physiology	Key links of the pathogenesis of hematopoietic system	
Pathologic anatomy	Morphological features of the hematopoietic system in newborns development depending of disease stage.	To analyze and interpret the information about clinical examination and about additional methods of investigation
Pharmacology	Pharmacokinetics and pharmacodynamics, the side effects of preparations.	To prescribe: age dependent and individual patient's characteristics of treatment to identify the stage of disease and establish an individual

		prescription to take with the correct dosage. To be able to make a prescription.
Propedeutical pediatrics.	The basic stages and methods for the clinical examination of patients.	To collect complaints and anamnesis vitae et morbid- to find out the basic risk factors in disease of hematopoietic system , be able to coduct patient's examination, to reveal the clinical signs of anaemias and to be able to interpret the data about additional methods of investigation.
2. Followings (provided)		
Hospital pediatrics.	Clinical signs of anaemias, differential diagnosis and treatment tactics.	To reveal the clinical signs of anaemias and complications, to conduct differential diagnosis, be able to prescribe treatment.

V. Contens of the theme

When oxygen delivery by red cells to tissues is decreased, a variety of mechanisms, including expanded cardiac output, increased production of 2,3-diphosphoglycerate (2,3-DPG) in red cells, and higher levels of erythropoietin, help the body to modify the deficiency. Red cell production by the bone marrow in response to erythropoietin (EPO) may expand severalfold and may compensate for mild to moderate reductions in red cell life span. In a variety of anemias, the bone marrow loses its usual capacity for sustained production and expansion of the red blood cell mass. In these instances, absolute reticulocyte numbers in the peripheral blood are decreased. If the normal reticulocyte percentage of total red cells during most of childhood is about 1.0%, and the expected red cell count is approximately 4.0 r{times} 106/mm3, then the normal absolute reticulocyte number should be about 40,000/mm3. In the face of anemia, EPO production and the absolute number of reticulocytes should rise. A normal or low absolute number or percentage of reticulocytes in response to anemia indicates relative bone marrow failure or ineffective erythropoiesis (e.g., megaloblastic anemia, thalassemia). Measurement of the serum transferrin receptor (TfR) level or examination of the bone marrow will distinguish between these possibilities, because TfR is elevated with increased red blood cell (RBC) turnover in the marrow in ineffective erythropoiesis and is decreased in marrow RBC hypoproliferation.

Diamond-Blackfan Syndrome

This rare condition usually becomes symptomatic in early infancy, frequently with pallor in the neonatal period, but may first be noted later in childhood. About

50% of children are diagnosed by 2 mo of age, and 75% by 6 mo. The most characteristic features are macrocytic anemia, reticulocytopenia, and a deficiency or absence of red blood cell (RBC) precursors in an otherwise normally cellular bone marrow.

ETIOLOGY. Although in 20% of patients a hereditary basis is suggested by instances of familial occurrence, no distinct genetic defect has been identified and dominant and recessive patterns have been noted in different families. Males and females are affected in equal numbers. Erythropoietin (EPO) levels are elevated, even more than expected for the degree of anemia. Although immunologic mechanisms have been suggested as the cause of suppression of red cell precursors, the abnormalities are most likely due to sensitization by transfusions. Most evidence indicates that the primary defects are in the erythroid precursor and are not due to immunologic damage to normal stem cells. Cytokines and their receptors on red cells, such as those for EPO stem cell factor (SCF), interleukin-3 (IL-3), and granulocyte-macrophage{endash}–colony-stimulating factor (GM-CSF), are possible candidates for genetic defects in this disorder, but investigations thus far have not been positive. High levels of EPO are present in serum and urine. Chromosomes are usually normal. Although addition of SCF to marrow from many of these patients results in improved growth of erythroid colonies (burst-forming units{endash}–erythrocyte, BFU-E), no defects have been found in the genes in patients for SCF or its receptor, c-kit, nor does prednisone correct the anemias in mice with deficiencies of SCF or c-kit. Erythroid progenitors in this disorder have an unusual sensitivity to withdrawal of EPO with resultant increased apoptosis (programmed cell death) accompanied by accelerated DNA fragmentation.

CLINICAL MANIFESTATIONS. Many affected infants appear pale even in the first few days of life, but hematopoiesis must be generally adequate in fetal life. Profound anemia usually becomes evident by 2{endash}–6 mo of age, occasionally somewhat later. The liver and spleen are not enlarged initially. About one third of affected children have congenital anomalies, most commonly dysmorphic facies or defects of the upper extremities, including triphalangeal thumbs. The abnormalities are diverse, with no specific pattern emerging in the majority of those affected.

LABORATORY FINDINGS. The RBCs are usually macrocytic with elevated levels of folic acid and vitamin B12. Assay of RBCs reveals a pattern characteristic of a "young" erythrocyte population, including elevated fetal hemoglobin (Hb F) and increased expression of "i" antigen. Adenosine deaminase (ADA) activity is increased in RBCs of patients with this disorder. These findings may help distinguish congenital RBC aplasia from acquired transient erythroblastopenia of childhood Thrombocytosis and occasionally neutropenia may also be present initially. Reticulocytes are diminished, even when the anemia is severe. Red blood cell

precursors are markedly reduced in the marrow in most patients, while other marrow elements are usually normal. Serum iron levels are elevated. Bone marrow culture shows markedly reduced numbers of colony-forming units–erythrocyte (CFU-E) and BFU-E.

DIFFERENTIAL DIAGNOSIS. Congenital hypoplastic anemia must be differentiated from other anemias with low reticulocyte counts. The anemia of the convalescent phase of hemolytic disease of the newborn may, on occasion, be associated with markedly reduced erythropoiesis. This terminates spontaneously at 5–8 wk of age. Aplastic crises characterized by reticulocytopenia and by decreased numbers of RBC precursors, frequently caused by B19 parvovirus infections, may complicate various types of hemolytic disease, but usually after the first several months of life. Infection with this virus in utero may also cause pure red cell aplasia in infancy, even with hydrops fetalis at birth. The syndrome of transient erythroblastopenia of childhood may be differentiated from Diamond-Blackfan syndrome by its relatively late onset and by biochemical differences in RBCs (408).

PROGNOSIS. The outlook is best in those who respond to corticosteroid therapy. About one half of the patients are long-term responders. In the others, survival depends on transfusions. Some children in each group may eventually have spontaneous remissions (about 14%). By late childhood, children who do not respond to corticosteroids may have had 100 or more transfusions, and hemosiderosis may result unless adequate chelation therapy for excess iron is carried out appropriately. The liver and spleen enlarge, and secondary hypersplenism with leukopenia and thrombocytopenia may occur in children who are not chelated adequately or in those with chronic hepatitis acquired from transfusions. The complications of chronic transfusions are similar to those seen in b{beta}-thalassemia major, and prevention and treatment of iron overload should be equally aggressive in both groups of transfused patients .

TREATMENT. Corticosteroid therapy is frequently beneficial if begun early, with three fourths of patients responding initially. The mechanism of its effect is unknown.

Prednisone in three or four divided doses totaling 2 mg/kg/24 hr is used as an initial trial. Red blood cell precursors appear in bone marrow 1–3 wk after therapy is begun, and then normoblastosis and a brisk peripheral reticulocytosis occur. The hemoglobin may reach normal levels in 4–6 wk. The dose of corticosteroid may then be reduced gradually by tapering divided doses and then by eliminating all except a single, lowest effective daily dose. This dose should then be doubled, used on alternate days, and tapered still further while maintaining the hemoglobin level at 10 g/dL or above. In some patients, very small amounts of prednisone, as low as 2.5 mg, may be sufficient to sustain adequate erythropoiesis.

In patients who do not respond to corticosteroid therapy, transfusions at intervals of 4–8 wk are necessary to sustain life. Chelation therapy for iron overload with deferoxamine administered subcutaneously via a battery-powered portable pump should be begun when excess iron accumulation is reflected by serum ferritin levels >1,000 mg/dL, but preferably after 5 yr of age, because the medication may interfere with normal growth. A newer, oral iron chelator, deferiprone (L1), is in clinical trials in Canada and elsewhere, and may offer an easier alternative if it is shown to be effective and to have acceptable toxicity. Other therapies, including androgens, cyclosporin A, cyclophosphamide, antithymocyte globulin (ATG), high-dose intravenous immunoglobulins, erythropoietin, and IL-3 have not had a consistent beneficial effect and may have a high incidence of side effects. High-dose intravenous methylprednisolone has been beneficial in some patients. Splenectomy may decrease the need for transfusion if hypersplenism or isoimmunization has developed. Bone marrow transplantation has a role in children who do not respond to corticosteroids and who have a histocompatible donor, but the risks of death related to transplant and chronic graft-versus-host disease must be weighed against the risks and difficulties of chronic transfusion and iron chelation therapy. The rate of engraftment is high, providing further evidence that immunosuppression is not the primary cause of this disorder.

406.1. Pearson Marrow-Pancreas Syndrome

This form of congenital hypoplastic anemia may be initially confused with Diamond-Blackfan syndrome or transient erythroblastopenia of childhood. The marrow failure usually appears in the neonatal period and is characterized by a macrocytic normochromic anemia, elevated Hb F and red cell adenosine deaminase, vacuolated erythroblasts and myeloblasts in the marrow, and occasional neutropenia and thrombocytopenia. Other features are failure to thrive, insulin-dependent diabetes mellitus, and exocrine dysfunction due to fibrosis of the pancreas, lactic acidosis, renal Fanconi syndrome with vacuolated tubular cells, muscle and neurologic impairment, and, frequently, early death. This multiorgan disorder has been shown to be due to mitochondrial DNA (mtDNA) deletions, with heterogeneity in different tissues and between patients. This heterogeneity accounts for the variable clinical picture, and a change in proportions of mtDNA types in tissues over time may result in spontaneous improvement of red cell hypoproliferation.

ACQUIRED PURE RED BLOOD CELL ANEMIAS

A number of forms of acquired anemia with reticulocytopenia and reduced red blood cell (RBC) precursors in the marrow have been described. Most of these are rare in childhood, and the causes of most of them are uncertain. In some cases in adults, remission has followed removal of a tumor of the thymus. Association with

thymoma has been reported in a child. The presence of a complement-dependent antibody cytotoxic for erythroblasts in some adults, and rarely in children, has suggested the use of high-dose intravenous immunoglobulin (IVIG) or immunosuppressive therapy. The acquired pure RBC anemias may respond to therapy with corticosteroids, and a trial is indicated in any chronic case.

Large doses of chloramphenicol may inhibit erythropoiesis. Reticulocytopenia, erythroid hypoplasia, and vacuolated pronormoblasts in the marrow are reversible effects of this drug. This effect differs from the idiosynchratic and rare development of severe aplastic anemia in recipients of the drug.

Episodes of acute failure of erythropoiesis may follow various viral infections. B19 parvovirus is the best documented viral cause of red cell aplasia. This small, single-stranded DNA virus is the cause of fifth disease (erythema infectiosum), usually manifested in children by facial erythema and a maculopapular rash on the trunk and, occasionally, by joint pains or arthritis. It may also be associated with systemic necrotizing vasculitis in some children. The virus is particularly infective and cytotoxic for erythroid progenitor cells in the marrow, interacting specifically with the red cell P antigen as a receptor. Characteristic nuclear inclusions in erythroblasts and giant pronormoblasts can be seen with light microscopy of bone marrow. Hemophagocytosis may also be seen in the marrow, perhaps accounting for the occasional granulocytopenia and thrombocytopenia. Because infection with this virus is usually transient, with recovery usually occurring in less than 2 wk, anemia is not present or not noticed in otherwise normal children, in whom the life span of peripheral red cells is 110–120 days. In patients with hemolysis, such as that due to hereditary spherocytosis or sickle cell disease, in whom red cell life span is much shorter, a cessation of erythropoiesis due to parvovirus infection may cause severe anemia, the "aplastic crisis" seen in these diseases. Recovery from moderate to severe anemia is usually spontaneous, heralded by a wave of nucleated red cells and subsequent reticulocytosis in the peripheral blood. Occasionally, a red cell transfusion may be necessary for marked symptoms due to anemia. Rarely, persistence of parvovirus infection may occur in patients unable to mount an adequate antibody response to the virus, as in children with congenital immunodeficiency diseases, those being treated with immunosuppressive agents, and those with acquired immunodeficiency syndrome (AIDS). The resultant pure red cell aplasia may be severe. The viral infection in these chronically infected patients may be treated with high-dose IVIG, which contains neutralizing antibody to the virus. Different clinical manifestations of infection with this virus and destruction of erythroid precursors occur with infections in utero, in which there is increased fetal wastage in the first and second trimesters, and babies may be born with hydrops fetalis and viremia. Congenital infection may also cause congenital pure red cell

aplasia due to induction of tolerance. The presence of persistent congenital parvovirus infection needs to be detected by examination of bone marrow DNA because immunologic tolerance to the virus may prevent the usual development of specific antibodies

Other viruses causing suppression of erythropoiesis usually affect the production of at least one other hematopoietic cell as well and may also cause increased destruction of peripheral blood cells by immunologic mechanisms. These include hepatitis virus (non-A, non-B, non-C), Epstein-Barr virus, cytomegalovirus, and the human immunodeficiency virus.

TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD (TEC)

This syndrome of severe, transient hypoplastic anemia occurs mainly in previously healthy children between 6 mo and 3 yr of age, with most above 12 mo of age at onset; it is more common than congenital hypoplastic anemia. The cause of this acquired decrease in red cell production is not clear, although it frequently follows a viral illness. Parvovirus infections, which may cause hypoplasia in children with hemolytic anemia, does not appear to be commonly associated with TEC. Reticulocytes and bone marrow erythroid precursors are markedly decreased, while white blood cell and platelet numbers are usually normal. Mean corpuscular volume (MCV) is usually normal for age, and fetal hemoglobin (Hb F) levels are normal before the recovery phase. Red cell adenosine deaminase (ADA) levels are normal in this disorder, while they may be elevated in congenital hypoplastic anemia. Differentiation from the latter disease may be difficult, but differences in age of onset and in age-related MCV, Hb F, and ADA may be helpful.

Most children recover within 1–2 mo and recurrence is rare. Red cell transfusions may be necessary for severe anemia (Hb level <3.5 g/dL) in the absence of signs of early recovery. The anemia develops slowly, and marked symptoms usually only develop with severe anemia. Corticosteroid therapy does not appear to be of any value in this disorder.

ANEMIA OF CHRONIC DISORDERS AND RENAL DISEASE

Anemia complicates a number of chronic systemic diseases associated with infection, inflammation, or tissue breakdown. Examples of such conditions include chronic pyogenic infections, such as bronchiectasis and osteomyelitis; chronic inflammatory processes, such as rheumatoid arthritis, systemic lupus erythematosis, and ulcerative colitis; malignancies; and advanced renal disease. In the latter, an additional major component is decreased production of erythropoietin (EPO) due to damage of the cells producing this cytokine. Despite diverse underlying causes, the erythroid abnormalities are similar. Red blood cell (RBC) life span is moderately

decreased, reflecting increased RBC destruction by a hyperactive reticuloendothelial system. The increased hemolysis is less important, however, than a relative failure of bone marrow response, reflecting both hypoactivity of marrow and an EPO production inadequate for the degree of anemia. In addition, there are abnormalities of iron metabolism, including defective iron release from tissues into the plasma. Suppression of the erythroid response in the marrow appears to be primarily due to an increase in tumor necrosis factor (TNF) acting on bone marrow stromal cells to produce interferon (IFN)-b{beta} as a primary mediator and an increase in interleukin-1 (IL-1) acting on T cells to produce IFN-g{gamma} as a primary mediator. Recombinant human EPO (r-HuEPO) can overcome this effect if the EPO level in a patient is <500 mUnits/mL. TNF and IL-1 decrease EPO production in perfused kidneys and hepatoma cells, corresponding to the two sites of EPO production, accounting for the inadequate EPO response in this type of anemia. The specific stimulant of increased TNF and IL-1 production in these patients has not been identified.

CLINICAL MANIFESTATIONS. Although the important symptoms and signs are those of the underlying disease, the quality of life may be affected by the mild to moderate anemia present.

LABORATORY FINDINGS. Hemoglobin concentrations usually range from 6 to 9 g/dL. The anemia is usually normochromic and normocytic; in about one third of patients, modest hypochromia and microcytosis may be seen. Absolute reticulocyte counts are normal or low, and leukocytosis is common. Free erythrocyte protoporphyrin (FEP) levels are frequently elevated and provide a sensitive reflection of derangements of iron metabolism. They return to normal after successful treatment of the primary disease. The serum iron level is low, without the increase in total iron-binding capacity seen in iron deficiency. This pattern of low serum iron and low to normal iron-binding protein is a regular and valuable diagnostic feature. Serum ferritin may be elevated. The bone marrow has normal cellularity; the RBC precursors are low to adequate, marrow hemosiderin may be increased, and granulocytic hyperplasia may be present. A frequent clinical challenge is to identify concomitant iron deficiency in the patient with an inflammatory disease. A trial of iron therapy may be needed to resolve the issue, although there may not be a response, even with iron deficiency, when inflammation due to the primary disease persists. This is a common problem, particularly in disorders such as juvenile rheumatoid arthritis, in which treatment may result in gastrointestinal blood loss and consequent iron deficiency.

TREATMENT AND PROGNOSIS. Because these anemias are secondary to other disease processes, they do not respond to iron or hematinics unless there is concomitant deficiency. Transfusions raise the hemoglobin concentration only

temporarily and are rarely indicated. If the underlying systemic disease can be controlled, the anemia is corrected spontaneously. Recombinant human erythropoietin can increase the hemoglobin level and improve activity and the sense of well-being in patients with end-stage renal failure and in those with anemia of chronic inflammation. Treatment with iron is frequently necessary for an optimal EPO effect.

CONGENITAL DYSERYTHROPOIETIC ANEMIAS

These rare inherited normocytic or macrocytic anemias display multinuclearity and abnormal chromatin patterns in red blood cell precursors. Three major types have been distinguished, with considerable variation within each type and overlap among them. Type I (about 15% of cases) is defined by binuclearity of erythroblasts, thin internuclear chromatin bridges between separate erythroblasts, and megaloblastic morphology. Red cells are macrocytic. Type II (more than 60% of cases) has erythroblastic multinuclearity and a positive acidified serum (Ham) test, but only to 30% of sera. The sugar water test, frequently positive in paroxysmal nocturnal hemoglobinuria, where the Ham test is also positive, is negative in this disorder. Red blood cells in type II (HEMPAS: hereditary erythroblastic multinuclearity associated with a positive acidified serum lysis test) are strongly agglutinated by anti-i antibody. The primary defect in some patients with this variant is in a gene for enzymes involved in biosynthesis of asn-linked oligosaccharide chains of glycoproteins, including those in the red cell membrane and in transferrin. Types I and II appear to be inherited as autosomal recessive traits. Type III (about 15% of cases) has pronounced erythroid multinuclearity with DNA content up to 24 times normal in marrow. It appears to be inherited as an autosomal dominant trait in some families and as recessive in others. In each type there are variable degrees of anemia (sometimes first noted in adolescence or adult life), ineffective erythropoiesis, and increased intestinal uptake of iron. Findings of chronic hemolysis, such as intermittent jaundice, gallstones, and splenomegaly, are common. Blood transfusions may occasionally be needed for severe anemia. Splenectomy may help patients with anemia severe enough to require chronic transfusions. Restriction of iron intake and iron chelation therapy should be of value in patients with iron overload.

PHYSIOLOGIC ANEMIA OF INFANCY

The normal newborn has higher hemoglobin and hematocrit levels with larger red cells than older children and adults. Within the first week of life a progressive decline in hemoglobin level begins, which persists for approximately 6–8 wk. The result of this decline is generally referred to as physiologic anemia of infancy. Several factors are operative. First, there is abrupt cessation of erythropoiesis with onset of respiration at birth, when the arterial oxygen saturation rises toward 95%. Concomitantly, levels of erythropoietin (EPO) are low, perhaps due to the liver being

the major site of EPO production in the neonatal period, rather than the kidney, and the relative insensitivity of the liver to EPO release with tissue hypoxia. In addition, EPO has a decreased half-life and an increased volume of distribution in newborns. A shortened survival of the fetal red blood cell (RBC) also contributes to the development of physiologic anemia. Furthermore, the sizable expansion of blood volume that accompanies rapid weight gain during the first 3 mo of life adds to the need for increased red cell production. In addition, red cell function is influenced by the higher levels of serum phosphate in newborns than later on in infancy. Red cell phosphate and 2,3-diphosphoglycerate (2,3-DPG) increase, facilitating release of oxygen from the normal adult hemoglobin (Hb A) that is present and decreasing tissue hypoxia. When the hemoglobin level has fallen to 9–11 g/dL at 2–3 mo of age in full-term infants, erythropoiesis resumes. This "anemia" should be viewed as a physiologic adaptation to extrauterine life.

The premature infant also develops a physiologic anemia. The same factors are operative as in term infants, but they are exaggerated. The decline in hemoglobin level is both more extreme and more rapid. Minimal hemoglobin levels of 7–9 g/dL commonly occur by 3–6 wk of age, and in very small premature infants levels may be even lower.

In the preterm infant, the inability to produce compensatory amounts of EPO accounts in part for the greater decline in hemoglobin concentrations, but frequent phlebotomies in sick infants for diagnostic and monitoring purposes, particularly in very small infants, are a major cause of anemia and the need for repeated transfusions. When premature infants are transfused with adult blood containing Hb A, the shift of the oxygen dissociation curve as a result of the presence of Hb A facilitates delivery of oxygen to the tissues. Accordingly, the definition of anemia and the need for transfusion in the premature infant must be based not only on hemoglobin level but also on oxygen requirements and the ability of the infant's circulating hemoglobin to release oxygen.

The marginal erythropoietic equilibrium responsible for physiologic anemia can add to anemia accompanying processes with increased hemolysis, such as congenital hemolytic states, which may be associated with severe anemia in the early weeks of life. Late hyporegenerative anemia, with absence of reticulocytes, may occur in infants with rhesus factor (Rh) hemolytic disease, perhaps due to low serum EPO levels. Bone marrow hypoplasia may also occur following intrauterine transfusions, also accompanied by low EPO levels. Therapy with recombinant human EPO (r-HuEPO; 200 IU/kg tiw 200–250 IU/kg three times per week SC), 2–3 mg/kg/24 hr of iron and 0.5–1 mg/24 hr of folate, may accelerate recovery. Some infants with bronchopulmonary dysplasia may develop anemia associated with deficient production of EPO, and a trial of EPO in such patients may be warranted.

Dietary factors may also aggravate physiologic anemia. Deficiency of folic acid superimposed on the physiologic process may result in more severe anemia. Vitamin E deficiency and therapy do not appear to play a role in anemia of prematurity, despite early suggestions to the contrary. A controlled and blinded study of oral vitamin E administration (25 IU dl-a{alpha}-tocopherol, colloidal aqueous solution) to infants less than 1,500 g showed no difference in hemoglobin levels, reticulocytes, red cell morphology, or platelet counts. Breast milk and modern formulas appear to provide adequate vitamin E. Supplemental iron starting about at approximately 4 mg/kg/24 hr for preterm babies 4–8 wk old and by 4 mo in full-term infants should not cause significant hemolysis due to oxidation.

Unless there has been significant perinatal blood loss, iron deficiency should not be considered as a cause of anemia in the first 3 mo of life. Assuming an infant is born with adequate iron stores, dietary iron deficiency cannot be a cause of anemia until these iron stores have been exhausted. In the absence of blood loss, this does not occur until the birthweight has approximately doubled.

TREATMENT. As a developmental process, physiologic anemia usually requires no therapy other than ensuring that the diet of the infant contains the essential nutrients for normal hematopoiesis, especially folic acid and iron. A premature infant who is feeding well and growing normally rarely needs transfusion unless there has been significant iatrogenic blood loss. Assessment of the overall clinical condition, including growth rate, and monitoring of hematocrit are better guides to transfusion of red cells than are formulas regarding blood loss from phlebotomy. Red cell transfusions consistently do not appear to affect the course of apneic spells and bradycardia, and the beneficial effects noted in some reports are probably due to the effect of volume expansion. The number of donors for an infant should be minimized. The optimal level of hematocrit for premature infants is not settled. In general, raising the hemoglobin to about 30%, particularly if the red cells have a high percentage of Hb A, should suffice for adequate tissue oxygen delivery due to transfused blood. Anemia seen in very low birthweight preterm infants may be related to a relative deficiency of EPO, and clinical trials indicate that infants between 800 and 1,300 g who do not have severe illnesses who are treated with r-HuEPO and iron during the first 6 wk of life, at doses about 250 IU/kg three times per week subcutaneously, require fewer transfusions.

MEGALOBLASTIC ANEMIAS

The megaloblastic anemias have in common certain abnormalities of red blood cell (RBC) morphology and maturation. The RBCs at every stage of development are larger than normal and have an open, finely dispersed nuclear chromatin and an asynchrony between maturation of nucleus and cytoplasm, with the delay in nuclear progression being more evident with further cell divisions. Megaloblastic

morphology may be seen in a number of conditions; almost all cases in children result from a deficiency of folic acid, of vitamin B12, or of both. Both substances are cofactors required in the synthesis of nucleoproteins, and deficiencies result in defective synthesis of DNA and, to a lesser extent, RNA and protein. Ineffective erythropoiesis results from arrest in development or premature death of cells in the marrow. In the peripheral blood, red cells are large (increased mean corpuscular volume, MCV) and frequently oval, hypersegmented neutrophils appear, and giant platelets may also be found. In the marrow, the late nucleated megaloblastic red cell may appear well hemoglobinized but still retains an immature nucleus, rather than the usual clumped chromatin. Giant metamyelocytes and bands are also present in the marrow. Megaloblastic anemias due to malnutrition are relatively uncommon in the United States.

MEGALOBLASTIC ANEMIA OF INFANCY

This disease is caused by a deficient intake or absorption of folic acid. Folates are abundant in many foods, including green vegetables, fruits, and animal organs (liver, kidney). Folic acid is absorbed throughout the small intestine, after pteroylglutamate reacts with membrane-associated folate-binding proteins. Pteroylpolyglutamates, found in cabbage, lettuce, and other foods, are absorbed less efficiently than pteroylmonoglutamate (folic acid). Pterolypolyglutamate hydrolase activity in the brush border aids the conversion to the monoglutamate. The specific nature of folate receptors and transport through the intestinal cell is not clear. Surgical removal or disorders of the small intestine may lead to folate deficiency. There is an active enterohepatic circulation. Much of the folate in the plasma is loosely bound to albumin. Pteroylglutamate is not biologically active. It is reduced by dihydrofolate reductase to tetrahydropteroylglutamate (tetrahydrofolate), which is transported into tissue cells and polyglutamated. Dietary deficiency is usually compounded by rapid growth or infection, which may increase folic acid requirements. The normal adult daily requirement is about 100 m{mu}g/24 hr, which rises to 350 m{mu}g/24 hr in pregnancy. The requirements on a weight basis are higher in the pediatric age range in comparison to adults due to the increased needs of growth. The needs are also increased with accelerated tissue turnover, as in hemolytic anemia. Human and cow's milks provide adequate amounts of folic acid. Goat's milk is clearly deficient; folic acid supplementation must be given when it is the main food. Unless supplemented, powered milk may also be a poor source of folic acid.

CLINICAL MANIFESTATIONS. Mild megaloblastic anemia has been reported in very low birthweight infants, and routine folic acid supplementation is advised. Megaloblastic anemia has its peak incidence at 4–7 mo of age, somewhat earlier than iron deficiency anemia, although the two may be present concomitantly in infants with poor nutrition. Besides having the usual clinical features of anemia, affected

infants with folate deficiency are irritable, fail to gain weight adequately, and have chronic diarrhea. Hemorrhages due to thrombocytopenia occur in advanced cases. Folic acid deficiency may accompany kwashiorkor, marasmus, or sprue.

LABORATORY FINDINGS. The anemia is macrocytic (MCV >100 fl). Variations in RBC shape and size are common The reticulocyte count is low, and nucleated RBCs demonstrating megaloblastic morphology are often seen in the blood. Neutropenia and thrombocytopenia may be present, particularly in long-standing deficiencies. The neutrophils are large, some with hypersegmented nuclei; more than 5% of neutrophils have five or more nuclear segments. Normal serum folic acid levels are 5–20 ng/mL; deficiency is accompanied by levels less than 3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The normal RBC folate level is 150–600 ng/mL of packed cells. Levels of iron and vitamin B12 in serum are usually normal or elevated. Serum activity of lactic acid dehydrogenase (LDH) is markedly elevated. The bone marrow is hypercellular because of erythroid hyperplasia. Megaloblastic changes are prominent, although some normal RBC precursors may also be found. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolization are seen, as well as hypersegmentation of the nuclei of megakaryocytes.

TREATMENT. When the diagnosis is established, or in severely ill children, folic acid may be administered orally or parenterally in a dose of 1–5 mg/24 hr. If the specific diagnosis is in doubt, 50–100 m{mu}g/24 hr of folate may be used for a week as a diagnostic test, or 1 m{mu}g/24 hr of cyanocobalamin parenterally for suspected vitamin B12 deficiency. Because a hematologic response can be expected within 72 hr, transfusions are indicated only when the anemia is severe or the child is very ill. Folic acid therapy should be continued for 3–4 wk. If juvenile pernicious anemia is present or if the anemia recurs after therapy, the prolonged use of folic acid should be avoided, because in pernicious anemia folic acid may produce a partial response to the anemia without decreasing the neurologic abnormalities.

MEGALOBLASTIC ANEMIA OF PREGNANCY

Folate requirements increase markedly during pregnancy, in part to meet fetal needs. Decreases in serum and RBC folate levels occur in as many as 25% of pregnant women at term and may be aggravated by infection. Folate supplementation, 1 mg/24 hr, is often advocated, particularly during the last trimester. Mothers with folate deficiency may have babies with normal folate stores due to selective transfer of folate to the fetus via placental folate receptors.

FOLIC ACID DEFICIENCY IN MALABSORPTION SYNDROMES

Diffuse inflammatory or degenerative disease of the intestine may reduce intestinal pteroylpolyglutamate hydrolase activity as well as markedly impair absorption of folate. Celiac disease, chronic infectious enteritis, and enteroenteric

fistulas may lead to folic acid deficiency and megaloblastic anemia. Measurement of serum folate is used to assess small intestinal absorptive functions in malabsorptive disorders. Oral folic acid supplements of 1 mg/24 hr may be indicated in these states .

CONGENITAL FOLATE MALABSORPTION

An autosomal recessive defect in the intestinal absorption of folic acid and an associated inability to transfer folate from the plasma to the central nervous system has been associated with megaloblastic anemia, convulsions, mental retardation, and cerebral calcifications. Infants present at 2–3 mo of age with severe megaloblastic anemia. Early and intensive treatment with intramuscular folinic acid (5-formyltetrahydrofolate) is important to correct the hematologic defect and to try to prevent neurologic deterioration.

FOLIC ACID DEFICIENCY ASSOCIATED WITH ANTICONVULSANTS AND OTHER DRUGS

Many patients have low serum levels of folic acid during therapy with certain anticonvulsant drugs (e.g., phenytoin, primidone, phenobarbital), but they usually do not develop anemia. Frank megaloblastic anemia is rare and responds to folic acid therapy, even if administration of the offending drug is continued. Absorption of folic acid is impaired by anticonvulsant drugs, but there is also increased utilization of folate. Megaloblastic anemia has been seen in users of oral contraceptives, but the cause is not clear.

A number of drugs have antifolic acid activity as their primary pharmacologic effect and regularly produce megaloblastic anemia. Methotrexate binds to dihydrofolate reductase and prevents the formation of tetrahydrofolate, the active form. Pyrimethamine, used in the therapy of toxoplasmosis, and trimethoprim, used for treatment of a variety of infections, may induce folic acid deficiency and, occasionally, megaloblastic anemia. Therapy with folinic acid (5-formyl-tetrahydrofolate) is usually beneficial.

CONGENITAL DIHYDROFOLATE REDUCTASE DEFICIENCY

This has been reported in several patients who were unable to form biologically active tetrahydrofolate and who developed severe megaloblastic anemia in early infancy. These patients were successfully treated with large doses of folic acid or folinic acid. Deficiency of methylene tetrahydrofolate reductase has been described in some patients with homocystinuria who had no hematologic abnormalities.

Vitamin B12 (Cobalamin) Deficiency

Vitamin B12 is derived from cobalamin in food, mainly animal sources, secondary to production by microorganisms. Humans cannot synthesize vitamin B12. The cobalamins are released in the acidity of the stomach and combine there with R proteins and intrinsic factor (IF), traverse the duodenum, where pancreatic proteases break down the R proteins, and are absorbed in the distal ileum via specific receptors

for IF-cobalamin. In addition, some vitamin B12 from large doses may diffuse through mucosa in the intestine and mouth. In plasma, vitamin B12 is bound to transcobalamin (TC) II, the physiologically important transporter, as well as to TCI and TCIII. TCII-cobalamin enters cells by receptor-mediated endocytosis, and cobalamin is converted to active forms important in the transfer of methyl groups and DNA synthesis.

Vitamin B12 deficiency may therefore result from inadequate intake, surgery involving the stomach or terminal ileum, lack of secretion of intrinsic factor by the stomach, consumption or inhibition of the B12-intrinsic factor complex, abnormalities involving the receptor sites in the terminal ileum, or abnormalities of TCII. Although TCI binds 80% of serum cobalamin, a deficiency of this protein results in low serum B12 levels but not in megaloblastic anemia.

Because vitamin B12 is present in many foods, dietary deficiency is rare. It may be seen in cases of extreme dietary restriction (strict vegetarians: "vegans") in which no animal products are consumed. Vitamin B12 deficiency is not commonly seen in kwashiorkor or infantile marasmus. Cases occur in breast-fed infants whose mothers have deficient diets or pernicious anemia.

JUVENILE PERNICIOUS ANEMIA

This rare autosomal recessive disorder results from an inability to secrete gastric intrinsic factor or secretion of a functionally abnormal IF. It differs from the typical disease in adults in that the stomach secretes acid normally and is histologically normal.

CLINICAL MANIFESTATIONS. The symptoms of juvenile pernicious anemia become prominent at 9 mo to 11 yr of age. This interval is consistent with exhaustion of the stores of vitamin B12 acquired in utero. As the anemia becomes severe, weakness, irritability, anorexia, and listlessness occur. The tongue is smooth, red, and painful. Neurologic manifestations include ataxia, paresthesias, hyporeflexia, Babinski responses, clonus, and coma.

LABORATORY FINDINGS. The anemia is macrocytic, with prominent macro-ovalocytosis of the RBCs. The neutrophils may be large and hypersegmented. In advanced cases neutropenia and thrombocytopenia, simulating aplastic anemia or leukemia, are seen. Serum vitamin B12 levels are <100 pg/mL. Concentrations of serum iron and serum folic acid are normal or elevated. Serum LDH activity is markedly increased. Moderate elevations (2–3 mg/dL) of serum bilirubin levels may be seen. Excessive excretion of methylmalonic acid in the urine (normal amount, 0–3.5 mg/24 hr) is a reliable and sensitive index of vitamin B12 deficiency. In contrast to many adult cases with pernicious anemia, serum antibodies directed against parietal cells or intrinsic factor cannot be detected in children with this disorder. Gastric acidity may be reduced initially but returns to normal when vitamin B12

therapy is instituted. Intrinsic factor activity is absent in gastric secretion.

Absorption of vitamin B12 is usually assessed by the Schilling test. When a normal person ingests a small amount of vitamin B12 into which 57Co has been incorporated, the radioactive vitamin combines with the IF in stomach secretions and passes to the terminal ileum, where absorption occurs. Because the absorbed vitamin is bound to TCII and incorporated into tissues, little or none is normally excreted in the urine. If a large dose (1 mg) of nonradioactive vitamin B12 is injected parenterally after 2 hr ("flushing dose"), 10–30% of the previously absorbed radioactive vitamin appears in the urine in 24 hr. Children with pernicious anemia usually excrete 2% or less under these conditions. To confirm that absence of IF is the basis of the B12 malabsorption, 30 mg of IF is given with a second dose of radioactive vitamin B12. Normal amounts of radioactive vitamin should now be absorbed and flushed out in the urine. On the other hand, when vitamin B12 malabsorption results from absence of ileal receptor sites or other intestinal causes, no improvement in absorption is seen with intrinsic factor. Occasionally, gastric disorders may impair absorption of cobalamin incorporated in food but not the pure tracer. A food Shilling test, using labeled eggs produced by hens injected with radioactive vitamin B12, may be used to investigate the presence of such disorders. The Schilling test result remains abnormal in pernicious anemia, even when therapy has completely reversed the hematologic and neurologic manifestations of the disease.

TREATMENT. A prompt hematologic response follows parenteral administration of vitamin B12 (1 mg), usually with reticulocytosis in 2–4 days, unless there is concurrent inflammatory disease. The physiologic requirement for vitamin B12 is 1–5 m{mu}g/24 hr, and hematologic responses have been observed with these small doses, indicating that administration of a minidose may be used as a therapeutic test when the diagnosis of vitamin B12 deficiency is in doubt. If there is evidence of neurologic involvement, 1 mg should be injected intramuscularly daily for at least 2 wk. Maintenance therapy is necessary throughout the patient's life; monthly intramuscular administration of 1 mg of vitamin B12 is sufficient. Oral therapy may succeed because of mucosal diffusion with high doses, but it is not generally advisable due to uncertainty of absorption.

TRANSCOBALAMIN DEFICIENCY

Transcobalamin II is the principal physiologic transport vehicle for vitamin B12. The role of TCII in B12 transport is similar to that of transferrin (Tf) for iron; specific receptors for TCII and Tf exist on cells needing vitamin B12 or iron. A congenital deficiency is inherited as an autosomal recessive condition, with failure to absorb and transport vitamin B12. Severe megaloblastic anemia occurs in early infancy. Therapy requires massive parenteral doses of vitamin B12.

VITAMIN B12 MALABSORPTION DUE TO INTESTINAL CAUSES

Cases have been reported of familial occurrence of absence or defect of the receptor for IF-B12 in the terminal ileum, in some instances associated with proteinuria (Imerslund syndrome). Histology of the stomach is normal, and intrinsic factor and acid are present in gastric secretions. Parenteral treatment with vitamin B12 monthly corrects the deficiency.

Surgical resection of the terminal ileum, inflammatory diseases such as regional enteritis, neonatal necrotizing enterocolitis, and tuberculosis may also impair absorption of vitamin B12. When the terminal ileum has been removed, lifelong parenteral administration should be used if the Schilling test indicates that vitamin B12 is not absorbed.

An overgrowth of intestinal bacteria within diverticula or duplications of the small intestine may cause vitamin B12 deficiency by consumption of or competition for the vitamin or by splitting of its complex with intrinsic factor. In these cases hematologic response may follow appropriate antibiotic therapy. Similar mechanisms may operate when the fish tapeworm Diphyllobothrium latum infests the upper small intestine. When megaloblastic anemia occurs in these situations, the serum vitamin B12 level is low, the gastric juice contains intrinsic factor, and the abnormal Schilling test result is not corrected by addition of exogenous intrinsic factor.

VITAMIN B12 DEFICIENCY IN OLDER CHILDREN

In some cases of vitamin B12 malabsorption in adolescence, atrophy of the gastric mucosa, and achlorhydria have been noted. These cases may be related to the syndrome of malabsorption of vitamin B12 occurring in combination with cutaneous candidiasis, hypoparathyroidism, and other endocrine deficiencies. The serum contains antibodies against intrinsic factor and parietal cells. An abnormal Schilling test is corrected by addition of exogenous intrinsic factor. Parenteral vitamin B12 should be administered regularly to these patients.

Rare Megaloblastic Anemias

Oroticaciduria is a rare genetically determined defect in pyrimidine biosynthesis associated with severe megaloblastic anemia, neutropenia, failure to thrive, and crystalluria, caused by excretion of orotic acid . Physical and mental retardation are frequently present. The anemia is refractory to vitamin B12 or folic acid but responds promptly to administration of the pyrimidine uridine (100–150 m{mu}g/kg/24 hr). The basic defects, which involve many tissues, include deficiencies of orotate phosphoribosyl transferase and orotidine-5-phosphate decarboxylase, enzymes essential for the formation of uridine-5r{prime}-phosphate. Inheritance is autosomal recessive. Megaloblastic anemia can also occur in the Lesch-Nyhan syndrome, in which regeneration of purine nucleotides is blocked .

Cases of thiamine-responsive and thiamine-dependent megaloblastic anemia

have been reported. Administration of thiamine, 100 mg/day, produced a brisk reticulocyte response and a sustained increase in hemoglobin level. Sensorineural deafness and diabetes mellitus were associated.

Megaloblastic anemia has also been seen in a group of children with inability to convert cobalamin to its biologically active metabolites, adenosylcobalamin and methylcobalamin, perhaps due to a deficiency in a cobalamin reductase. The disorder is called the cobalamin C variant and is characterized by neurologic abnormalities, methylmalonic aciduria, and homocystinuria. Abnormalities are usually noted in the early weeks of life, and include failure to thrive, lethargy, hypotonia, macrocytosis with megaloblastic bone marrow changes and anemia or pancytopenia, and hepatic dysfunction. Serum cobalamin levels are elevated. The megaloblastic changes may reverse and other symptoms may improve with hydroxycobalamin treatment, 1 mg/24 hr IM initially, gradually changed to a dose every month.

IRON DEFICIENCY ANEMIA

Anemia resulting from lack of sufficient iron for synthesis of hemoglobin is the most common hematologic disease of infancy and childhood. Its frequency is related to certain basic aspects of iron metabolism and nutrition. The body of the newborn infant contains about 0.5 g of iron, whereas the adult content is estimated at 5 g. To make up for this discrepancy, an average of 0.8 mg of iron must be absorbed each day during the first 15 yr of life. In addition to this growth requirement, a small amount is necessary to balance normal losses of iron by shedding of cells. Accordingly, to maintain positive iron balance in childhood, about 1 mg of iron must be absorbed each day.

Iron is absorbed in the proximal small intestine, mediated in part by the duodenal protein mobilferrin. Because absorption of dietary iron is assumed to be about 10%, a diet containing 8–10 mg of iron is necessary for optimal nutrition. Iron is absorbed two to three times more efficiently from human milk than from cow's milk, perhaps due in part to differences in calcium content. Breast-fed infants may, therefore, require less iron from other foods. During the first years of life, because relatively small quantities of iron-rich foods are taken, it is often difficult to attain sufficient iron. For this reason the diet should include such foods as infant cereals or formulas that have been fortified with iron, both of which are very effective in preventing iron deficiency. Formulas with 7–12 mg Fe/L for full-term infants and premature infant formulas with 15 mg/L for infants <1,800 g at birth are effective. Infants breast fed exclusively should receive iron supplementation from 4 mo of age. At best, the infant is in a precarious situation with respect to iron. Should the diet become inadequate or external blood loss occur, anemia ensues rapidly.

Adolescents are also susceptible to iron deficiency because of high requirements due to the growth spurt, dietary deficiencies, and menstrual blood loss. In several

affluent countries about 40% of adolescent girls and 15% of boys have serum ferritin levels less than 16%, reflecting low bone marrow iron stores.

ETIOLOGY. Low birthweight and unusual perinatal hemorrhage are associated with decreases in neonatal hemoglobin mass and stores of iron. As the high hemoglobin concentration of the newborn falls during the first 2–3 mo of life, considerable iron is reclaimed and stored. These reclaimed stores are usually sufficient for blood formation in the first 6–9 mo of life in term infants. In low-birthweight infants or those with perinatal blood loss, stored iron may be depleted earlier, and dietary sources become of paramount importance. Anemia caused solely by inadequate dietary iron is unusual before 4–6 mo but becomes common at 9–24 mo of age. Thereafter, it is relatively infrequent. The usual dietary pattern observed in infants with iron deficiency anemia is the consumption of large amounts of cow's milk and of foods not supplemented with iron.

Blood loss must be considered a possible cause in every case of iron deficiency anemia, particularly in the older child. Chronic iron deficiency anemia from occult bleeding may be caused by a lesion of the gastrointestinal tract, such as a peptic ulcer, Meckel diverticulum, a polyp or hemangioma, or by inflammatory bowel disease. In some geographic areas hookworm infestation is an important cause of iron deficiency. Pulmonary hemosiderosis may be associated with unrecognized bleeding in the lungs and recurrent iron deficiency after treatment with iron. Chronic diarrhea in early childhood may be associated with considerable unrecognized blood loss. Some infants with severe iron deficiency in the United States have chronic intestinal blood loss induced by exposure to a heat-labile protein in whole cow's milk. Loss of blood in the stools each day can be prevented either by reducing the quantity of whole cow's milk to 1 pint/24 hr or less, by using heated or evaporated milk, or by a milk substitute. This gastrointestinal reaction is not related to enzymatic abnormalities in the mucosa, such as lactase deficiency, or to typical "milk allergy." Characteristically, involved infants develop anemia that is more severe and occurs earlier than would be expected simply from an inadequate intake of iron.

Histologic abnormalities of the mucosa of the gastrointestinal tract, such as blunting of the villi, are present in advanced iron deficiency anemia and may cause leakage of blood and decreased absorption of iron, further compounding the problem.

CLINICAL MANIFESTATIONS. Pallor is the most important clue to iron deficiency. Blue sclerae are also common, although also found in normal infants. In mild to moderate iron deficiency (hemoglobin levels of 6–10 g/dL) compensatory mechanisms, including increased levels of 2,3-diphosphoglycerate (2,3-DPG) and a shift of the oxygen dissociation curve, may be so effective that few symptoms of anemia are noted, although there may be increased irritability. Pagophagia, the desire to ingest unusual substances such as ice or dirt, may be present. In some children,

ingestion of lead-containing substances may lead to concomitant plumbism. When the hemoglobin level falls below 5 g/dL, irritability and anorexia are prominent. Tachycardia and cardiac dilatation occur, and systolic murmurs are often present.

The spleen is enlarged to palpation in 10–15% of patients. In long-standing cases, widening of the diploл{umlaut-e} of the skull similar to that seen in congenital hemolytic anemias may occur. These changes resolve slowly with adequate replacement therapy. The child with iron deficiency anemia may be obese or may be underweight, with other evidence of poor nutrition. The irritability and anorexia characteristic of advanced cases may reflect deficiency in tissue iron, because with iron therapy striking improvement in behavior frequently occurs before significant hematologic improvement.

Iron deficiency may have effects on neurologic and intellectual function. A number of reports suggest that iron deficiency anemia, and even iron deficiency without significant anemia, affect attention span, alertness, and learning of both infants and adolescents, but it is not absolutely clear whether iron deficiency is usually causal or whether it helps to identify infants whose suboptimal behavior has another basis. It is also not clear whether the defects that are observed persist after adequate treatment, because the results of controlled studies are conflicting.

Monoamine oxidase (MAO), an iron-dependent enzyme, plays a crucial role in neurochemical reactions in the central nervous system. Iron deficiency produces decreases in the activities of enzymes such as catalase and cytochromes. Catalase and peroxidase contain iron, but their biologic essentiality is not well established. It is not possible to measure iron in vivo in the enzymatic compartment easily and accurately, yet this is a vital area of iron metabolism.

LABORATORY FINDINGS. In progressive iron deficiency, a sequence of biochemical and hematologic events occurs. First, the tissue iron stores represented by bone marrow hemosiderin disappear. The level of serum ferritin, an iron-storage protein, provides a relatively accurate estimate of body iron stores in the absence of inflammatory disease. Normal ranges are age dependent, and decreased levels accompany iron deficiency. Next, there is a decrease in serum iron (also age dependent), the iron-binding capacity of the serum increases, and the percent saturation falls below normal (also varies with age). When the availability of iron becomes rate limiting for hemoglobin synthesis, a moderate accumulation of heme precursors, free erythrocyte protoporphyrins (FEP), results.

As the deficiency progresses, the red blood cells (RBCs) become smaller than normal and their hemoglobin content decreases. The morphologic characteristics of RBCs are best quantified by the determination of mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV). Developmental changes in MCV require the use of age-related standards for diagnosis of microcytosis (see Table 405–

1 Table 405–1). With increasing deficiency the RBCs become deformed and mis-shapen and present characteristic microcytosis, hypochromia, poikilocytosis, and increased red cell distribution width (RDW); see Fig. 405–1 Fig. 405–1C). The reticulocyte percentage may be normal or moderately elevated, but absolute reticulocyte counts indicate an insufficient response to anemia. Nucleated RBCs may occasionally be seen in the peripheral blood. White blood cell counts are normal. Thrombocytosis, sometimes of a striking degree (600,000–1,000,000/mm3), may occur or, in a few cases, thrombocytopenia. The mechanisms of these platelet abnormalities are not clear. They appear to be a direct consequence of iron deficiency, perhaps with associated gastrointestinal blood loss or associated folate deficiency, and they return to normal with iron therapy and dietary change. The bone marrow is hypercellular, with erythroid hyperplasia. The normoblasts may have scanty, fragmented cytoplasm with poor hemoglobinization. Leukocytes and megakaryocytes are normal. Hemosiderin cannot be demonstrated in marrow specimens by Prussian blue staining. In about a third of cases occult blood can be detected in the stools.

DIFFERENTIAL DIAGNOSIS. Iron deficiency must be differentiated from other hypochromic microcytic anemias. In lead poisoning associated with iron deficiency, the red cells are morphologically similar, but coarse basophilic stippling of the RBCs, an artifact of drying the slide, is frequently prominent. Elevations of blood lead, free erythrocyte protophyrin, and urinary coproporphyrin levels are seen (665). The blood changes of b{beta}-thalassemia trait resemble those of iron deficiency (419.9), and RDW is usually normal or only slightly elevated. a{alpha}-Thalassemia trait occurs in about 3% of blacks in the United States and in many Southeast Asian peoples. The diagnosis requires direct identification of DNA defects or difficult globin synthesis studies after the newborn period. The diagnosis can be assumed when a case of familial hypochromic microcytic anemia with normal levels of Hb A2 and Hb F, and normal hemoglobin electrophoresis, is refractory to iron therapy. In the newborn period infants with the a{alpha}-thalassemia trait have 3–10% Barts and the MCV is decreased (419.9). Thalassemia major, with its pronounced erythroblastosis and hemolytic component, should present no diagnostic confusion. Hb H disease, a form of a{alpha}-thalassemia with hypochromia and microcytosis, also has a hemolytic component due to instability of the beta-chain tetramers resulting from a deficiency of alpha globin. The RBC morphology of chronic inflammation and infection, though usually normochromic, may be microcytic, but in these conditions both the serum iron level and iron-binding ability are reduced, and serum ferritin levels are normal or elevated. Elevations of FEP level are not specific to iron deficiency and are observed in patients with lead poisoning, chronic hemolytic anemia, the anemia associated with chronic disorders, and some of

the porphyrias.

TREATMENT. The regular response of iron deficiency anemia to adequate amounts of iron is an important diagnostic and therapeutic feature. Oral administration of simple ferrous salts (sulfate, gluconate, fumarate) provides inexpensive and satisfactory therapy. There is no evidence that addition of any trace metal, vitamin, or other hematinic substance significantly increases the response to simple ferrous salts. For routine clinical use the physician should be familiar with an inexpensive preparation of one of the simple ferrous compounds. The therapeutic dose should be calculated in terms of elemental iron; ferrous sulfate is 20% elemental iron by weight. A daily total of 6 mg/kg of elemental iron in three divided doses provides an optimal amount of iron for the stimulated bone marrow to use. Better absorption may result when medicinal iron is given between meals. Intolerance to oral iron is uncommon. A parenteral iron preparation (iron dextran) is an effective form of iron and is usually safe when given in a properly calculated dose, but the response to parenteral iron is no more rapid or complete than that obtained with proper oral administration of iron, unless malabsorption is present.

While adequate iron medication is given the family must be educated about the patient's diet, and the consumption of milk should be limited to a reasonable quantity, preferably 500 mL (1 pint)/24 hr or less. This reduction has a dual effect: The amount of iron-rich foods is increased, and blood loss from intolerance to cow's milk proteins is prevented. When the re-education of child and parent is not successful, parenteral iron medication may be indicated. Iron deficiency can be prevented in high-risk populations by providing iron-fortified formula or cereals during infancy.

Within 72–96 hr after administration of iron to the anemic child, peripheral reticulocytosis is seen. The height of this response is inversely proportional to the severity of the anemia. Reticulocytosis is followed by a rise in the hemoglobin level, which may increase as much as 0.5 g/dL/24 hr. Iron medication should be continued for 8 wk after blood values are normal. Failures of iron therapy occur when the child does not receive the prescribed medication, when iron is given in a form that is poorly absorbed, or when there is continuing unrecognized blood loss, such as intestinal or pulmonary loss, or with menstrual periods. An incorrect original diagnosis of nutritional iron deficiency may be revealed by therapeutic failure of iron medication.

Because a rapid hematologic response can be confidently predicted in typical iron deficiency, blood transfusion is indicated only when the anemia is very severe or when superimposed infection may interfere with the response. It is not necessary to attempt rapid correction of severe anemia by transfusion; the procedure may be dangerous because of associated hypervolemia and cardiac dilatation. Packed or sedimented red cells should be administered slowly in an amount sufficient to raise

the hemoglobin to a safe level at which the response to iron therapy can be awaited. In general, severely anemic children with hemoglobins under 4 g/dL should be given only 2–3 mL/kg of packed cells at any one time (furosemide may also be administered as a diuretic). If there is evidence of frank congestive heart failure, a modified exchange transfusion employing fresh-packed RBCs should be considered, although diuretics followed by slow infusion of packed red cells may suffice.

OTHER MICROCYTIC ANEMIAS

SIDEROBLASTIC ANEMIAS

The sideroblastic anemias are a heterogeneous group of hypochromic, microcytic anemias whose basic defects may be abnormalities of heme metabolism. Serum iron levels are increased. In the bone marrow ringed sideroblasts are found; these are nucleated red blood cells with a perinuclear collar of coarse hemosiderin granules that represent iron-laden mitochondria.

Pearson syndrome, a combination of refractory sideroblastic anemia with vacuolization of marrow precursor cells and exocrine pancreatic dysfunction, is caused by a variety of deletions in mitochondrial DNA. Acquired sideroblastic anemias occur in adults with various inflammatory and malignant processes, or with alcoholism.

A form of sideroblastic anemia transmitted as an X-linked recessive trait becomes symptomatic by late childhood. Splenomegaly is usually present. Free erythrocyte protoporphyrin (FEP) levels are not elevated. Some cases of sideroblastic anemia are responsive to pyridoxine (vitamin B6) given in doses of 200–300 mg/24 hr, although other findings of vitamin B6 deficiency are not observed. In one kindred with X-linked pyridoxine-responsive sideroblastic anemia, a thr-to-ser substitution was identified at amino acid residue 388 of erythroid 5-aminolevulinate synthease (ALS), near the pyridoxal phosphate cofactor binding site, affecting heme precursor synthesis. In another kindred, with a son and daughter with pyridoxine-refractory sideroblastic anemia, the ALS gene on the X chromosome of the son was normal, and the children each received a different X chromosome, indicating a different autosomal defect.

LEAD POISONING

RARE TYPES OF HYPOCHROMIC MICROCYTIC ANEMIA

Isolated cases are known of hypochromic, microcytic anemia with other abnormalities of iron metabolism; some cases have had defects in iron mobilization or reutilization. Congenital absence of iron-binding protein (atransferrinemia) is associated with severe hypochromic anemia despite iron overload and requires lifelong transfusions. Iron is absorbed normally and is deposited in the visceral organs rather than in bone marrow.

Several patients have had refractory hypochromic anemia associated with

lymphatic tumors or lymphoid hyperplasia. Correction of the anemia followed removal of the abnormal lymphatic tissue in these patients.

Hemolytic Anemias

George B. Segel

Hemolysis is defined as the premature destruction of red cells. If the rate of destruction exceeds the capacity of the marrow to produce red cells, anemia results. The normal red cell survival is 110–120 days, and approximately 1% of the red cells (the senescent ones) are removed each day and replaced by the marrow to maintain the red cell count. During hemolysis the red cell survival is shortened, and increased marrow activity results in a heightened reticulocyte percentage and number. Hemolysis should be suspected as a cause of anemia if an elevated reticulocyte count is present in the absence of bleeding or administration of hematinic therapy. The marrow can increase its output two- to threefold acutely with a maximum of six- to eightfold if hemolysis is long-standing. The reticulocyte index quantifies the magnitude of the marrow production in response to hemolysis and is calculated as follows:

[observed hematocrit / normal hematocrit] $\times$ [1 / μ] $\times$ reticulocyte %, where μ is a maturation factor related to the severity of the anemia. In the absence of hemolysis the reticulocyte index is 1.0, representing normal marrow activity.

As anemia becomes more severe, there is more erythropoietin stimulation of erythropoiesis, and reticulocytes are released from the marrow earlier, spending more than one day as reticulocytes in the blood. In terms of quantifying the marrow response, it is inappropriate to count reticulocytes produced yesterday in today's calculation of the reticulocyte index. The maturation factor, μ, provides this correction. The usual marrow response in a chronic hemolytic anemia is reflected by a reticulocyte index of 3–4, with a maximum of 6–8 corresponding to maximal marrow output.

The erythroid hyperplasia resulting from chronic hemolytic anemia in children, especially thalassemia, may be so extensive that the medullary spaces may expand at the expense of the cortical bone. These changes may be evident on physical examination or on x-rays of the skull and long bones. A propensity to fracture long bones can occur also.

The direct assessment of the severity of hemolysis requires measurement of the red cell survival using red cells tagged with the radioisotope $Na_2^{51}CrO_4$. The normal value for the ^{51}Cr half-life is 25–35 days. This value is less than the expected halflife of 50–60 days because of the elution of ^{51}Cr from the labeled red cells at the rate of about 1% per day.

Several other plasma, urinary, or fecal chemical alterations reflect the presence of hemolysis. The degradation of hemoglobin results in the biliary excretion of heme pigments and increased fecal urobilinogen Elevations of serum unconjugated bilirubin also may accompany hemolysis.

Gallstones composed of calcium bilirubinate may be formed in children as young as 4 yr of age. There are three heme-binding proteins in the plasma that are altered during hemolysis Hemoglobin binds to haptoglobin and hemopexin, both of which are reduced. Oxidized heme binds to albumin to form methemalbumin, which is increased. When the capacity of these binding molecules is exceeded, free hemoglobin appears in the plasma and can be seen easily if the red cells are sedimented in a capillary hematocrit tube. If present, free hemoglobin in the plasma is prima-facie evidence of intravascular hemolysis. When the tubular reabsorptive capacity of the kidney for hemoglobin is exceeded, free hemoglobin appears in the urine. Even in the absence of hemoglobinuria, there may be iron loss resulting from reabsorbed hemoglobin and the shedding of renal epithelial cells containing hemosiderin. This may lead to secondary iron deficiency during chronic intravascular hemolysis. When hemoglobin is degraded an alpha-methene bridge is broken in the cyclic tetrapyrrole of the heme moiety with release of carbon monoxide (CO). The quantitation of CO in the blood or expired air provides a dynamic measure of the hemolytic rate. The end-tidal CO is being evaluated in several research laboratories but is not used in clinical laboratories to quantify hemolysis.

The hematocrit during hemolysis is dependent on the severity of the hemolysis and on the increased marrow production of red cells. The shortened red cell life span and heightened red cell production result in a marked susceptibility to "aplastic" or "hypoplastic" crises, characterized by erythroid marrow failure and reticulocytopenia, accompanied by a rapid fall in hemoglobin and hematocrit. The most common cause of aplastic crises is the parvovirus, which is erythrocytotropic in marrow culture in vitro. Aplastic crises may produce a precipitous and life-threatening fall in the hematocrit, which usually lasts 10–14 days. Such transient erythroid marrow failure has little effect in persons with a normal red cell life span but has a proportionately greater effect as the red cell life span is shortened by hemolysis. A second infection with parvovirus is uncommon, but other infections may compromise the erythroid marrow output, resulting in various degrees of hypoplasia or hypoplastic crises.

The hemolytic anemias may be classified as either cellular, resulting from intrinsic abnormalities of the membrane, enzymes, or hemoglobin; or extracellular, resulting from antibodies, mechanical factors, or plasma factors. Most of the cellular defects are inherited (paroxysmal nocturnal hemoglobinuria is acquired), and most of the extracellular defects are acquired (abetalipoproteinemia with acanthocytosis is inherited). HEREDITARY SPHEROCYTOSIS (HS)

Hereditary spherocytosis is a common cause of hemolysis and hemolytic anemia with a prevalence of approximately 1:5,000 in people of Northern European extraction. It is the most common familial and congenital abnormality of the red cell membrane. Affected individuals may be asymptomatic without anemia and with minimal hemolysis, or may have a severe hemolytic anemia. Hereditary spherocytosis has been described in most ethnic groups but is most common among persons of Northern European origin.

ETIOLOGY. Hereditary spherocytosis usually is transmitted as an autosomal dominant and, less frequently, as an autosomal recessive disorder. There is a high rate of new mutations, and as many as 25% of patients may have no previous family history. The most common molecular defect is an abnormality of spectrin, which is a major component of the cytoskeleton responsible for red cell shape. A recessive defect has been described in a{alpha}-spectrin; dominant defects in b{beta}-spectrin and in protein 3; and dominant and recessive defects in ankyrin. A deficiency in spectrin, protein 3, or ankyrin results in uncoupling in the "vertical" interactions of the lipid bilayer skeleton and the loss of membrane microvesicles). The loss of membrane without a proportional loss of volume causes sphering of the red cells and an associated increase in cation permeability, cation transport, and ATP utilization, and an increase in glycolytic metabolism. The decreased deformability of the spherocytic red cells impairs cell passage from the splenic cords to the splenic sinuses, and the spherocytic red cells are destroyed prematurely in the spleen. Splenectomy markedly improves the red cell life span and cures the anemia.

CLINICAL MANIFESTATIONS. Hereditary spherocytosis may be a cause of hemolytic disease in the newborn and present with anemia and hyperbilirubinemia sufficiently severe to require phototherapy or exchange transfusions. The severity in infants and children is variable. Some patients remain asymptomatic into adulthood, while others may have severe anemia with pallor, jaundice, fatigue, and exercise intolerance. In severe cases there may be expansion of the diploл{umlaut-e} of the skull and the medullary region of other bones, but to a lesser extent than seen in thalassemia major. After infancy the spleen is usually enlarged, and pigmentary (bilirubin) gallstones may form as early as age 4–5 yr. At least 50% of unsplenectomized patients ultimately form gallstones, although, for the most part, they remain asymptomatic. Because of the high red cell turnover and heightened erythroid marrow activity, children with hereditary spherocytosis are susceptible to aplastic crisis, primarily due to parvovirus, and to hypoplastic crises associated with a variety of other infections. Such erythroid marrow failure may result rapidly in profound anemia (hematocrit <10%), high output heart failure, hypoxia, cardiovascular collapse, and death.

LABORATORY FINDINGS. Evidence for hemolysis includes reticulocytosis

and hyperbilirubinemia. The hemoglobin level usually is 6–10 g/dL, but it can be in the normal range. The reticulocyte count often is heightened to 6–20%, with a mean of approximately 10%. The mean corpuscular volume is normal, while the mean corpuscular hemoglobin concentration often is increased (36–38 g/dL red cells). The red cells on the blood film vary in size and include polychromatophilic reticulocytes and spherocytes The spherocytes are smaller in diameter and on the blood film are hyperchromic as a result of the high hemoglobin concentration. The central pallor is less conspicuous than in normal cells. Spherocytes may be the predominant cell or may be relatively sparse depending on severity of the disease, but they usually comprise greater than 15–20% of the cells when hemolytic anemia is present. Erythroid hyperplasia is evident in the marrow aspirate or biopsy. The marrow expansion may be evident on routine roentgenographic examination. Evidence of hemolysis may include elevated indirect bilirubin, decreased haptoglobin, and the presence of gallstones by ultrasonography.

The diagnosis of hereditary spherocytosis usually is established clinically from the blood film, showing many spherocytes and reticulocytes, the family history, and splenomegaly. The presence of spherocytes in the blood can be confirmed with an osmotic fragility test. The red cells are incubated in progressive dilutions of an isoosmotic buffered salt solution. Exposure to hypotonic saline causes red cells to swell, and the spherocytes lyse more readily than biconcave cells in hypotomic solutions. This feature is accentuated by depriving the cells of glucose for 24 hr at 37ϵ{degree} C, a so-called incubated osmotic fragility test.

As a research tool, the specific protein abnormality can be established in 80% of these patients by red cell membrane protein analysis using gel electrophoresis and densitometric quantitation. Studies to define the underlying defects in the cytoskeleton require the assessment of protein synthesis, stability, assembly, and binding to the other membrane proteins.

DIFFERENTIAL DIAGNOSIS. The major alternative consideration when large numbers of spherocytes are seen on the blood film is immune hemolysis. Isoimmune hemolytic disease of the newborn, particularly due to ABO incompatibility, mimics hereditary spherocytosis. The detection of antibody on the infant's red cells using a direct Coombs test should establish the diagnosis of immune hemolysis. Other autoimmune hemolytic anemias also are characterized by spherocytes, and there may be evidence of a previously normal hemoglobin, hematocrit, and reticulocyte count. Rare causes of spherocytosis include thermal injury, clostridia septicemia with exotoxemia, and Wilson disease, each of which may present with a transient hemolytic anemia

TREATMENT. Since the spherocytes in hereditary spherocytosis are destroyed almost exclusively in the spleen, splenectomy eliminates most of the hemolysis

associated with this disorder. After splenectomy, the spherocytes may be more numerous, increasing the osmotic fragility, but the anemia, reticulocytosis, and hyperbilirubinemia resolve. Whether all patients with hereditary spherocytosis should undergo splenectomy has become controversial. Some hematologists do not recommend splenectomy for those patients whose hemoglobin values are >10 g/dL and whose reticulocyte counts are <10%. Folic acid, 1 mg/24 hr, should be administered to prevent secondary folic acid deficiency. For patients with more severe anemia and reticulocytosis or those with hypoplastic or aplastic crises, splenectomy is recommended after age 5–6 yr to avoid the heightened risk of postsplenectomy sepsis in younger children. Vaccines for encapsulated organisms such as pneumococcus, meningococcus, and Haemophilus influenzae should be administered prior to splenectomy, and prophylactic penicillin (age J{less than or equal}5 yr: 125 mg/12 hr; age >5 yr through adulthood: 250 mg/12 hr) administered thereafter. Postsplenectomy thrombocytosis is commonly observed but needs no treatment and usually resolves spontaneously. In one report partial splenectomy provided substantial increases in Hb and reductions in the reticulocyte count with potential maintenance of splenic phagocytic and immune function. This technique, if substantiated, would be particularly useful for those children less than 5 yr of age with severe disease and could be employed in older patients with mild disease.

Vertical and horizontal interactions of membrane proteins and the pathobiology of the red cell lesion in hereditary spherocytosis (HS) and hereditary elliptocytosis/hereditary pyropoikilocytosis (HE/HPP). Left: A defect of vertical or transverse interactions as exemplified by the red cell membrane lesion in HS. Partial deficiencies of spectrin, ankyrin (band 2.1), or band 3 protein lead to uncoupling of the membrane lipid bilayer from theunderlying skeleton (arrow) followed by a formation of spectrin-free microvesicles of approximately 0.2–0.5 m{mu}m in diameter (arrowheads). These vesicles can be visualized by transmission electron microscopy, but they are not seen during examination of blood films. The subsequent loss of cell surface and a decrease in the surface/volume ratio leads to spherocytosis. Right: Defect of horizontal or parallel interactions of skeletal proteins as exemplified by the membrane lesion in hemolytic forms of HE associated with a defect of spectrin heterodimer self-association. The molecular lesion involving a weakened self-association of spectrin heterodimers to tetramers represents a horizontal defect of the stress-supporting protein interactions. It leads to a disruption of the membrane skeletal lattice and, consequently, whole cell destabilization followed by red cell fragmentation and poikilocytosis. Such fragments are readily seen on stained blood films. (Modified from Palek J, Jarolim P: Clinical expression and laboratory detection of red blood cell membrane protein mutations. Semin Hematol

Morphology of abnormal red cells. A, Hereditary spherocytosis; B, hereditary

elliptocytosis; C, hereditary pyropoikilocytosis; D, hereditary stomatocytosis; E, acanthocytosis; F, fragmentation hemolysis.

HEREDITARY ELLIPTOCYTOSIS

Hereditary elliptocytosis is an uncommon disorder that varies markedly in severity. Mild hereditary elliptocytosis produces no symptoms, while more severe varieties may result in neonatal poikilocytosis and hemolysis, chronic or sporadic hemolytic anemias, or hereditary pyropoikilocytosis (HPP), which is a severe disorder with microspherocytosis and poikilocytosis. While hereditary elliptocytosis is rare in western populations, it is more commonly found in West Africa, where the abnormalities (spectrin mutations) may provide resistance to malarial infection.

ETIOLOGY. Hereditary elliptocytosis is inherited as a dominant disorder. In the rare instances wherein two abnormal alleles are inherited, the patient exhibits a particularly severe hemolytic anemia, HPP. A variety of molecular defects has been described in hereditary elliptocytosis that produce abnormalities of a{alpha}- and b{beta}-spectrin and defective spectrin heterodimer self-association. Such defects in the horizontal protein interactions result in gross membrane fragmentation, particularly in homozygous HPP. Less commonly, mutations in protein 4.1 and glycophorin C may produce elliptocytosis.

CLINICAL MANIFESTATIONS. Elliptocytosis may be noted as an incidental finding on a routine blood film and not be associated with clinically significant hemolysis. The diagnosis of hereditary elliptocytosis is established by the findings on the blood film, the autosomal dominant inheritance pattern, and the absence of other causes of elliptocytosis, such as iron, folic acid, or B12 deficiencies. Hemolytic elliptocytosis may produce neonatal jaundice, even though characteristic elliptocytosis may not be evident at that time. The blood of the affected newborn may show bizarre poikilocytes and pyknocytes. The usual features of a chronic hemolytic process with elliptocytosis are seen later as anemia, jaundice, splenomegaly, and osseous changes. Cholelithiasis may occur in later childhood, and aplastic crises have been reported. The most severe form is HPP, which is characterized by extreme microcytosis (mean corpuscular volume [MCV] 50–60 fl/cell), with extraordinary variation in the cell size and shape, and primarily microspherocytic rather than elliptocytic cells. These patients inherit a mutant spectrin from one parent, who has mild or no elliptocytosis, and a partial spectrin deficiency from the other parent, who is hematologically normal.

LABORATORY FINDINGS. The blood film is the most important test to establish hereditary elliptocytosis The red cells show various degrees of elongation and may actually be rod shaped. Ovalocytes, in contrast to elliptocytes, are less elongated and may reflect a condition termed Southeast Asian ovalocytosis (SAO), which is associated with a mutant protein 3 but does not cause hemolysis. In addition

to elliptocytosis, other abnormal red cell shapes may be present depending on the severity of hemolysis. They include microcytes, spherocytes, and other poikilocytes. The reticulocyte count reflects the severity of hemolysis, and erythroid hyperplasia and indirect hyperbilirubinemia may be present. Increased thermal instability is characteristic of HPP, wherein the abnormal spectrin denatures and the cells lyse at 45–46є{degree} C instead of the usual 49–50є{degree} C. The specific protein abnormality can be established by protein separation and analysis techniques.

TREATMENT. If hereditary elliptocytosis represents a morphologic abnormality on the blood film without hemolysis, no treatment is necessary. Patients with chronic hemolysis should receive folic acid 1 mg/24 hr to prevent secondary folic acid deficiency. Splenectomy decreases the hemolysis and should be considered if the Hb is <10 g/dL and the reticulocyte count is >10%. The red cells on the blood film may be more abnormal after splenectomy even though Hb increases and the reticulocytes decrease.

HEREDITARY STOMATOCYTOSIS

Hereditary stomatocytosis is a rare condition in which the red cells are cup-shaped. On stained blood film they present a mouthlike slit in place of the usual circular area of central pallor Acquired stomatocytosis may be seen in several conditions, especially liver disease. Hereditary stomatocytosis may be associated with alterations in red cell hydration status or with deficiency in Rh antigens. The hydrocytic or overhydrated variety is associated with abnormalities within the region of protein 7, but the basic pathophysiology has not been defined. There may be hemolytic anemia associated with hereditary stomatocytosis, but splenectomy is not consistently effective as treatment. Symptomatic thrombocytosis may complicate splenectomy if the hemolysis is not decreased. Furthermore, a subgroup of patients has developed the life-threatening tendency to in situ thrombosis postsplenectomy, which may be related to abnormal adherence of the stomatocytic red cells to vascular endothelium as well as to the thrombocytosis.

OTHER MEMBRANE DEFECTS

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

ETIOLOGY. Paroxysmal nocturnal hemoglobinuria reflects a clonal abnormality of a marrow stem cell that affects multiple blood cell lines. The disease is not inherited; it is an acquired disorder of hematopoiesis characterized by a defect in proteins of the cell membrane that renders the red cells (and other cells) susceptible to damage by serum complement. The deficient membrane–associated proteins include decay accelerating factor, the C8 binding protein, and other proteins that normally impede complement lysis at various steps. The underlying defect involves the glycolipid anchor that maintains these proteins on the cell surface, and various mutations in the PIG-A gene involved in glycolipid biosynthesis have been

identified in PNH patients.

CLINICAL MANIFESTATIONS. PNH is a rare disorder, particularly in children, but 26 patients with a mean age of 13 yr (0.8–21.4 yr) were diagnosed at Duke University Medical Center between 1966 and 1991. Approximately 60% of these patients presented with marrow failure, while the remainder had either intermittent or chronic anemia, often with prominent intravascular hemolysis. Nocturnal and morning hemoglobinuria are classic findings in adults if hemolysis is worse during sleep. However, chronic hemolysis is more common in PNH in spite of its name. In addition to chronic hemolysis, thrombocytopenia and leukopenia often are present. Pyogenic infection, thrombosis, and thromboembolic phenomena are serious complications. Abdominal, back, and head pain may be prominent complaints. Hypoplastic or aplastic pancytopenia may precede or follow the onset of PNH, and the clonal disorder rarely progresses to acute myelogenous leukemia. The predicted survival for children is 80% for 5 yr, 60% for 10 yr, and 28% for 20 yr, and the mortality is related primarily to the development of aplastic anemia and/or thrombotic complications.

LABORATORY FINDINGS. The diagnosis of PNH is established by a positive result in the acid serum (Ham) or the sucrose lysis test, which activate the alternate and classical pathways of complement lysis, respectively. Hemosiderinuria is seen frequently and reflects the intravascular hemolysis. Markedly reduced levels of red cell acetylcholinesterase activity are also found, and the reduced levels of decay accelerating factor are diagnostic.

TREATMENT. Splenectomy is not indicated. Glucocorticoids such as prednisone (2 mg/kg/24 hr) have been used to treat acute hemolytic episodes and should be tapered as soon as the hemolysis abates. Prolonged anticoagulation therapy may be of benefit when thromboses occur. Because there is chronic loss of iron as hemosiderin in the urine, iron therapy may be necessary. Androgens such as halotestin and danazol, and antithymocyte globulin, have been used to treat marrow aplasia. Bone marrow transplantation has been successful in treating some cases.

ACANTHOCYTOSIS

Acanthocytosis is characterized by red cells with irregular circumferential pointed projections This morphologic finding is seen with alterations in the cholesterol/phospholipid ratio in some patients with liver disease, and in congenital abetalipoproteinemia associated with malabsorption, neuromuscular abnormalities, and retinitis pigmentosa It also is associated with the rare X-linked McLeod syndrome with absence of the Kx (Kell) antigen, late onset myopathy, neurologic abnormalities, splenomegaly, and hemolysis with acanthocytosis.

HEMOGLOBIN DISORDERS

The clinical disorders that result from abnormalities of the globin genes

comprise a diverse group of hematologic diseases. Normal hemoglobins are tetrameric molecules containing pairs of a{alpha} or a{alpha}-like and b{beta} or b{beta}-like globin-heme subunits. The normal postnatal hemoglobins include hemoglobin (Hb) A (a{alpha}2b{beta}2), Hb F (a{alpha}2g{gamma}2), and Hb A2 (a{alpha}2d{delta}2). The embryonic hemoglobins, which usually disappear before birth, include Hb Gower-1 (z{zeta}2e{epsilon}2), Hb Gower-2 (a{alpha}2e{epsilon}2), and Hb Portland (z{zeta}2g{gamma}2) (see also Part XXI, Section 1). The genes for the a{alpha} and z{zeta} chains are encoded on chromosome 16; those for the b{beta} group have been localized to chromosome 11. The nucleotide sequences of all these genes have been determined, and many globin-gene abnormalities have been characterized at the molecular level.

The hemoglobin disorders are subdivided into three major groups. The structural abnormalities, including the hemoglobinopathies, result from changes in the amino acid sequences of the globin chains. Most have a single amino acid substitution; in others, however, amino acids may be deleted or inserted, or other, more complex, structural changes may be present. The thalassemias are expressed as quantitative defects, in which the synthesis of one or more of the globin chains is decreased or, in the most severe forms, is totally suppressed. The hereditary persistence of fetal hemoglobin (HPFH) syndromes is characterized by elevated levels of Hb F continuing throughout adult life. Almost all these abnormalities result from the same types of molecular defects: Nucleotides may be substituted, deleted, or inserted into globin-gene DNA.

HEMOGLOBIN STRUCTURAL ABNORMALITIES

(Hemoglobinopathies)

Approximately 600 structural variants of hemoglobin have been identified. Most are rare but a few, including some severely pathologic forms, occur with high frequency in certain populations. Many abnormal hemoglobins are readily identified by electrophoresis, but some are electrophoretically "silent" and require other laboratory studies for identification. Many hemoglobin variants that have abnormal electrophoretic mobility, including benign and pathologic forms, exhibit very similar electrophoresis findings and cannot be specifically identified by this means alone. Sickle Cell Hemoglobinopathies

Sickle hemoglobin (Hb S) differs from normal adult hemoglobin by a substitution of glutamic acid at the 6th position of its b{beta} chains by valine. In the oxygenated state Hb S functions normally. When this hemoglobin is deoxygenated, an interaction between the b{beta}6 valine and complementary regions on the b{beta} chains of an adjacent molecule results in the formation of highly ordered molecular polymers; these elongate to form filamentous structures, which aggregate into rigid, crystal-like rods. This process of molecular polymerization is responsible

for the spiny, brittle character of sickle erythrocytes under conditions of decreased oxygenation. Certain other abnormal hemoglobins, notably Hb C, Hb D Los Angeles, and Hb O Arab, participate in the molecular polymerization of deoxy-Hb S. Hb A does so to a smaller degree, but fetal hemoglobin (Hb F) does not.

Erythrocytes of heterozygous (sickle cell trait) individuals have been shown to resist invasion by malarial parasites, which appears to have provided protection against the frequently lethal Plasmodium falciparum form of the disease. The b{beta}s gene is found in high frequency in those living in regions in which P. falciparum malaria has been endemic, including many parts of Africa, the Mediterranean area, and parts of Turkey, the Middle East, and India. In individuals from several geographic areas, the sickle mutation has been shown to exist in genetic linkage with discrete sets of closely associated markers. Some of these Hb S "haplotypes" appear to be predictive of the degree of severity of the sickle cell disease. Those associated with particularly mild disease produce significantly higher levels of fetal hemoglobin. Patients with sickle cell disease who coinherit genes for a{alpha}-thalassemia may also have disease of modified severity.

Hb S is readily identified by electrophoresis. A confirmatory solubility test excludes other abnormal hemoglobins with similar electrophoretic mobility. Although affected newborns express only small quantities of Hb S, because of the predominance of Hb F at birth, the sickle cell syndromes can nevertheless be identified reliably in the newborn by electrophoretic methods. Neonatal screening programs for the detection of infants with sickle cell disease are widely established in the United States. These disorders can also be determined antenatally using amniocyte or chorionic villus DNA by methods that identify the specific b{beta}s nucleotide substitution.

SICKLE CELL ANEMIA

(Homozygous Hb S)

This disorder is characterized by severe chronic hemolytic disease resulting from premature destruction of the brittle, poorly deformable erythrocytes. Other manifestations of sickle cell anemia are attributable to ischemic changes resulting from vascular occlusion by masses of sickled cells. The clinical course of affected children is typically associated with intermittent episodic events, often referred to as "crises."

CLINICAL MANIFESTATIONS. Affected newborns seldom exhibit clinical features of sickle cell disease; hemolytic anemia gradually develops over the 1st 2–4 mo, parallelling the replacement of much of the fetal hemoglobin by Hb S. Other clinical manifestations are uncommon prior to 5–6 mo of age. Acute sickle dactylitis, presenting as the hand-foot syndrome, is frequently the 1st overt evidence that sickle cell disease is present in the infant. Its associated findings include painful, usually

symmetric, swelling of the hands and feet. The underlying abnormality is ischemic necrosis of the small bones, believed to be caused by a choking off of the blood supply as a result of the rapidly expanding bone marrow. Roentgenograms are not informative in the acute phase, but later show evidence of extensive bony destruction and repair.

Acute painful vaso-occlusive episodes represent the most frequent and prominent manifestation of sickle cell disease. Most patients experience some pain on a nearly daily basis. Episodes of severe pain that require hospitalization and parenteral analgesic administration average about one per year in children with Hb SS, but this interval varies considerably, with some patients never experiencing severe pain and others requiring hospital admission with such frequency as to become seriously disabled. In young children pain often involves the extremities; in older patients head, chest, abdominal, and back pain occur more commonly. In an individual patient pain tends to recur in a limited number of sites. Intercurrent illnesses accompanied by fever, hypoxia, and acidosis, all of which promote the deoxygenation of Hb S, may precipitate sickle pain episodes, but acute pain also develops frequently without an apparent antecedent event. Sickle-related abdominal pain may mimic that of an acute surgical condition.

More extensive vaso-occlusive events in these patients can produce gross ischemic damage. Acute pain episodes may progress to infarction of bone marrow or bone. Splenic infarcts are common in children between 6 and 60 mo, causing pain and contributing to the process of "autosplenectomy." Pulmonary infarction, often occurring in association with pneumonitis or microscopic fat emboli (from bone marrow infarction) may produce the severe clinical picture of acute chest syndrome. Strokes caused by cerebrovascular occlusion are among the most catastrophic acute events and are a frequent cause of hemiplegia. As many as 10% of children with sickle cell anemia, mainly pre-adolescent and older patients, exhibit sequelae of cerebrovascular occlusion. Ischemic damage may also affect the myocardium, liver, and kidneys. Renal function is progressively impaired by diffuse glomerular and tubular fibrosis, and hyposthenuria accompanied by polyuria are characteristic findings in patients over 5 yr of age. Renal papillary necrosis and nephrotic syndrome also develop occasionally. Priapism is a relatively frequent complication that results from the pooling of blood in the corpora cavernosa, causing obstruction of the venous outflow.

Young children with Hb SS may have splenic enlargement associated with their hemolytic disease, with progression to the syndrome of hypersplenism accompanied by worsening anemia and sometimes thrombocytopenia. Acute splenic sequestration is a distinct and episodic event that occurs in infants and young children with sickle cell anemia. For unknown reasons large amounts of blood become acutely pooled in

the spleen, which becomes massively enlarged, and signs of circulatory collapse rapidly develop. Blood transfusions in the acute phase may be lifesaving.

Altered splenic function in young children with sickle cell disease is a significant factor leading to their increased susceptibility to meningitis, sepsis, and other serious infections, mainly caused by pneumococci and Haemophilus influenzae. In the absence of specific antibody to the polysaccharide capsular antigens of these organisms, splenic activity is essential for removing these bacteria when they invade the blood. In spite of frequent enlargement of the spleen in young patients with Hb SS, its phagocytic and reticuloendothelial functions have been shown to be markedly reduced. As an additional risk factor, children with sickle cell disease have also been shown to have deficient levels of serum opsonins of the alternate complement pathway, against pneumococci. Children with sickle cell disease also have increased susceptibility to Salmonella osteomyelitis (due, in part, to bone necrosis).

In common with patients having other forms of chronic hemolytic anemia, children with Hb SS are at risk of developing a rapid, potentially life-threatening decrease in their hemoglobin level (aplastic episodes) in association with parvovirus infection .

An additional group of sickle cell sequelae is attributable primarily to the hemolytic anemia that accompanies this disorder. Hemolytic crisis may occur with concomitant G-6-PD deficiency Cardiomegaly is invariably present in older children, often caused partly by sickle-related cardiomyopathy. Increased iron absorption contributes to parenchymal damage of the liver, pancreas, and heart. Symptomatic gallstone formation is common in adolescent and adult patients, occasionally occurring in children as young as 5 yr of age.

By midchildhood most patients are underweight, and puberty is frequently delayed. Chronic leg ulcers are relatively uncommon in children, usually occurring only in late adolescence.

LABORATORY FINDINGS. Hemoglobin concentrations usually range from 5 to 9 g/dL. The peripheral blood smear typically contains target cells, poikilocytes, and irreversibly sickled cells). These findings allow Hb SS and most of the other forms of sickle cell disease to be readily distinguished from sickle cell trait and other clinically benign conditions. Reticulocyte counts usually range from 5% to 15%, and nucleated red cells and Howell-Jolly bodies are often present. The total white blood cell count is elevated to 12,000–20,000/mm3, with a predominance of neutrophils. The platelet count is usually increased; the sedimentation rate is slow. Other changes include abnormal liver function test results, hyperbilirubinemia, and diffuse hypergammaglobulinemia. The bone marrow is markedly hyperplastic and shows erythroid predominance. Roentgenograms show expanded marrow spaces and osteoporosis.

DIAGNOSIS. The diagnosis is established by hemoglobin studies. Electrophoresis at an alkaline pH demonstrates a characteristic mobility, intermediate between those of Hb A and Hb A2. To distinguish Hb S from other hemoglobins with similar electrophoretic properties, another (confirmatory) test is required, such as electrophoresis at an acidic pH, a sickle cell preparation in which sickling is observed when the cells are deoxygenated or, most commonly, a hemoglobin solubility test. In the Hb S solubility test a measured amount of hemoglobin is added to a concentrated buffer that contains a reducing agent; a turbid precipitate forms when more than about 15% Hb S is present. Beyond infancy, red cells from patients with Hb SS contain Hb with between 2% and 20% Hb F and normal quantities of Hb A2. Hb A is notably absent. The identification of Hb S in each parent provides additional supportive evidence for the diagnosis of sickle cell anemia.

DIFFERENTIAL DIAGNOSIS. The various clinical manifestations of sickle cell disease, including limb pain, heart murmurs, hepatosplenomegaly, and anemia, may suggest a number of other diagnoses, including rheumatic fever or rheumatoid arthritis, osteomyelitis, and leukemia. In patients who have a Hb SS electrophoresis pattern and concomitant microcytosis (MCV <78 fL), possibilities that require consideration include iron deficiency or a combination of Hb S with a{alpha}- or b{beta}o-thalassemia

TREATMENT. Measures directed toward the prevention of serious complications of sickle cell disease are among the most important elements of patient management. Maintaining full immunization status of these children is particularly important. Administration of a polyvalent pneumococcal vaccine may be beneficial, but unfortunately the forms of these vaccines currently available appear to be poorly immunogenic in children with Hb SS who are under the age of 5 yr. Haemophilus influenzae immunization has been shown to be efficacious in infants with sickle cell disease, and this as well as hepatitis B immunizations are indicated. Prophylactic penicillin G is highly effective in preventing serious pneumococcal infections and should be administered to all young children with sickle cell disease. The penicillin is given orally, twice daily, starting in early infancy and continuing at least to the age of 6 yr. Parents of these children also need to be aware of the need to bring the child promptly to medical attention for acute illness, especially with fever above 39ϵ{degree} C. Because of the substantial risk of life-threatening bacterial infections, prompt parenteral antibiotic therapy is generally indicated for infants and young children with an acute onset of high fever. Patients older than 6 mo, excluding those with temperatures above 40ϵ{degree} C or who appear seriously ill, generally can be managed effectively on an outpatient basis. In low-risk, well-appearing children, after blood cultures are obtained, intravenous ceftriaxone is given, and the dose is repeated the following day. Parents and caretakers of these children should also be informed

about the manifestations of acute splenic sequestration and the need for immediate medical attention for the child with rapid splenic enlargement and pallor.

Painful episodes can frequently be managed with oral acetaminophen, alone or with codeine. More severe episodes may require hospitalization and the parenteral administration of narcotics. Anti-inflammatory agents, ketorolac or, less often, corticosteroids, may decrease or eliminate the need for narcotic analgesics. Epidural analgesia has also been used to manage pain from severe vaso-occusive crisis. Any dehydration and/or acidosis should be rapidly corrected by the intravenous route. Blood transfusions are seldom indicated for painful episodes, and it is doubtful whether transfusion can ameliorate the course of a pain crisis. For patients with disabling chronic pain, for those with ischemic organ damage (acute chest, priapism) or stroke, or in preparation for major surgery, however, transfusions of normal red blood cells can provide symptomatic relief and prevent further ischemic complications. For patients with stroke, cardiomyopathy, and other severe complications, chronic long-term transfusion regimens are a mainstay of therapy. It is important to select the minimum amount of blood necessary to achieve the desired Hb S percentage. These patients also often require iron chelation treatment to prevent the development of hemosiderosis. Packed red blood cell transfusions are specifically indicated for acute splenic sequestration and aplastic episodes. Repeated episodes of splenic sequestration are also an indication for splenectomy.

Bone marrow transplantation from a normal donor can be curative in patients with sickle cell disease, but the risks and morbidity associated with this procedure limit its application to highly selected patients. European experience, from more than 40 young children without chronic organ damage, has shown a high success rate following transplantation. In the United States, fewer patients have been transplanted, most of whom had severe consequences of vaso-occlusive events; all were improved, but some have had neurologic complications post-transplantation.

Chemotherapy regimens that stimulate fetal hemoglobin synthesis have been employed with beneficial effect, on an experimental basis, in a number of children with sickle cell disease. These agents, which include hydroxyurea and butyrate, offer considerable promise of more effective means for treating these patients.

OTHER SICKLE CELL SYNDROMES

Sickling disorders of varying degrees of severity result from Hb S existing in combination with other abnormal hemoglobins or thalassemias (see Table 419–1 Table 419–1). Several of these syndromes, including Hb SD Los Angeles, Hb SO Arab, and Hb S–b{beta}o-thalassemia, present a clinical picture virtually indistinguishable from that of sickle cell anemia. Most of the others produce less severe manifestations.

Hb SC disease results from the concurrence of genes for Hb S and Hb C. Painful

episodes and other vaso-occlusive manifestations are usually less severe in this condition than those associated with Hb SS. Most affected children have persistent splenomegaly, and bone infarcts occur more frequently than in those with Hb SS. Septicemia may also occur. Retinal vascular changes, predominantly in adolescents and adults, may lead to hemorrhage with retinal detachment. The hemoglobin concentration averages 9–10 g/dL, with the blood smear showing target cells and characteristic spindle-shaped red cells.

Sickle Cell Trait

(Heterozygous Hb S; Hb AS)

Heterozygous expression of the sickle hemoglobin gene is usually associated with a totally benign clinical course. About 8% of American blacks have sickle cell trait, with 35–45% of their hemoglobin consisting of Hb S. This low level of Hb S is insufficient to produce sickling manifestations under usual circumstances, but under conditions of severe hypoxia vaso-occlusive complications may occur. Splenic infarcts and other ischemic sequelae may occur in Hb AS individuals after flying at high altitudes in unpressurized aircraft and from hypoxia associated with general anesthesia. Hyposthenuria is usually present in older children and adults. Occasionally, gross hematuria develops in otherwise well individuals. The hematologic findings in sickle cell trait are indistinguishable from normal . The diagnosis is established by hemoglobin electrophoresis, with confirmatory sickle testing.

Other Hemoglobinopathies

HEMOGLOBIN C

Hemoglobin C (a{alpha}2b{beta}26lysine) occurs in about 2% of American blacks. In the heterozygous state (Hb AC) no anemia or disease is present, but increased numbers of target cells are seen in the peripheral blood. In the homozygous individual (Hb CC disease) a moderately severe hemolytic anemia with hemoglobin levels from 8 to 11 g/dL, a reticulocytosis of 5−10%, and splenomegaly are regularly observed. The peripheral blood contains striking numbers of target cells and occasional spherocytes

HEMOGLOBIN E

Hemoglobin E (a{alpha}2b{beta}226lysine) is prevalent in populations from Southeast Asia, particularly Thailand and Cambodia. Homozygous Hb E disease is characterized by hemolytic anemia with prominent target cells, microcytosis, and moderate to severe splenomegaly. The syndrome of Hb E–b{beta}0-thalassemia may be expressed as a severe Cooley anemia–like disorder; electrophoresis shows the presence of only Hb E and Hb F.

Unstable Hemoglobin Disorders

(Congenital Heinz Body Anemia)

A substantial group of abnormal hemoglobins, most of which are uncommon or rare, are characterized by molecular instability, leading to denaturation and precipitation of hemoglobin within the red cells. In the more severe forms of these disorders, amorphous masses of the denatured hemoglobin, known as Heinz bodies, attach to the red blood cell membrane, damaging the cell and shortening its survival. The Heinz bodies, which are particularly prominent following splenectomy, can be visualized by supravital staining of the red blood cells with brilliant cresyl blue These hemolytic anemias are inherited in an autosomal dominant mode, but many of the severe forms apparently occur as new mutations.

Most of the severe types involve the hemoglobin b{beta} chains, and hemolysis first becomes apparent at 3–6 mo after birth, when Hb F is replaced by adult hemoglobin. Anemia with increased reticulocytes, jaundice, and splenomegaly are characteristically present, becoming more pronounced with infections or following exposure to oxidant drugs or chemicals. With some of the unstable b{beta}-chain abnormalities, hemolysis is accompanied by excretion of darkly pigmented dipyrrolic compounds in the urine. In contrast to the clinical picture of chronic hemolytic disease typically associated with the highly unstable hemoglobins, some of the less severe abnormalities (e.g., Hb Zurich and Hb Hasharon) produce mild and usually inapparent anemia. With fever, infections, or exposure to oxidant conditions, however, these individuals may experience acute hemolytic episodes similar to those associated with G-6-PD deficiency.

Some unstable hemoglobins can be detected by electrophoresis, but many of them comigrate with Hb A. Heating at 50є{degree} C or treating the hemolysate with a 17% buffered solution of isopropanol produces a precipitate of the unstable hemoglobin, and screening tests based on these methods are used to detect these abnormalities. Examples include Hb Koln, Hb Hammersmith, and Hb Abraham Lincoln. Splenectomy is sometimes of benefit in these patients, particularly those with severe splenomegaly.

Abnormal Hemoglobins with Increased Oxygen Affinity

Almost 100 different rare, abnormal hemoglobins have been identified that have increased oxygen affinity, as indicated by a leftward displacement of their oxygen dissociation curves. Because of their increased oxygen affinity, these hemoglobins release oxygen poorly to the tissues, resulting in hypoxia at the tissue level. The hypoxic stimulus increases erythropoietin production, with the development of secondary erythrocytosis. Hemoglobin levels in affected individuals typically range from 16 to 19 g/dL. Some of these variants can be demonstrated by electrophoresis, but many of them have normal electrophoretic properties (e.g., Hb Chesapeake, Hb Malmo, Hb Kempsey).

Abnormal Hemoglobins Causing Cyanosis

Several rare hemoglobin variants with markedly decreased oxygen affinity have been identified. The oxygen dissociation curves of blood from affected individuals are significantly displaced to the right. Examples of these abnormalities, which produce benign cyanosis, include Hb Kansas and Hb Beth Israel.

An additional group of abnormal hemoglobins that cause cyanosis is the Hb M group. These variants all have amino acid substitutions at positions in the molecule that are close to the heme groups. The structural changes in these hemoglobins have the effect of stabilizing the heme iron atoms in the ferric (Fe^{3+}) state, rendering them incapable of binding oxygen. The Hb M syndromes are characterized by a brown color of the blood, even when fully oxygenated, and by cyanosis. Two of the Hb M variants, Hb M Saskatoon and Hb M Hyde Park, are also unstable and produce chronic hemolytic anemia. The Hb M variants that result from b{beta}-chain substitutions, such as Hb M Saskatoon, have an onset of cyanosis beginning at 4–6 mo of age, whereas the a{alpha}-chain variants, such as Hb M Iwate, produce cyanosis that is apparent at birth. The autosomal dominant mode of inheritance of these abnormalities helps distinguish them from other causes of congenital cyanosis.

Methemoglobinemias resulting from Hb M can be differentiated from other forms of methemoglobinemia by characteristic changes in the spectral absorption patterns of hemoglobin solutions and by the presence of normal levels of methemoglobin reductase (diaphorase). Electrophoresis can demonstrate some (but not all) of the Hb M variants. These are clinically benign abnormalities, except for the hemolytic disease that accompanies two of the Hb M group, and no treatment is required.

Hereditary Methemoglobinemia

The iron of both oxygenated and deoxygenated hemoglobin is normally in the ferrous state, which is essential for its oxygen-transporting function. Oxidation of hemoglobin iron to the ferric state yields methemoglobin, which is nonfunctional and imparts a brown color to the blood; in sufficient concentration it causes cyanosis. The blood of healthy persons contains methemoglobin, but the intraerythrocytic methemoglobin-reducing system maintains its concentration at less than 2% of the total hemoglobin.

HEREDITARY METHEMOGLOBINEMIA WITH DEFICIENCY OF NADH CYTOCHROME b5 REDUCTASE. Four types of enzymopenic hereditary methemoglobinemia have been identified. All have a recessive mode of inheritance. In type I, the most frequent of these rare disorders, a deficiency of cytochrome b5 reductase is limited to erythrocytes, and cyanosis is the only consequence. Type II is a severe, progressive disorder that accounts for approximately 10% of patients with hereditary methemoglobinemia. In this disorder the deficiency of cytochrome b5 reductase is generalized to all tissues. Affected individuals present with

methemoglobinemia and severe encephalopathy, appearing before 1 yr of age, and with mental retardation, microcephaly, retarded growth, attacks of bilateral athetoid movements, strabismus, opisthotonos, and generalized hypertonia. In type III disease, the enzyme deficiency is demonstrable in erythrocytes, platelets, lymphocytes, and granulocytes. Clinically, cyanosis is the only manifestation. Type IV disease results from a deficiency of erythrocyte cytochrome b5 and is associated with chronic cyanosis.

Clinically, cyanosis may vary in intensity with season and diet. The time of onset of cyanosis also varies; in some patients it appears at birth, in others as late as adolescence. Although up to 50% of the total circulating hemoglobin may be in the form of nonfunctional methemoglobin, little or no cardiorespiratory distress occurs in these patients, except on exertion.

Daily oral treatment with ascorbic acid (200–500 mg in divided doses) gradually reduces the quantity of methemoglobin to about 10% of the total pigment and alleviates the cyanosis as long as therapy is continued. Chronic high doses of ascorbic acid have been associated with hyperoxaluria and renal stone formation. Methylene blue given intravenously (1–2 mg/kg) promptly eliminates both methemoglobin and cyanosis, and this effect can be maintained by the daily oral administration of methylene blue (3–5 mg/kg).

Syndromes of Hereditary Persistence of Fetal Hemoglobin (HPFH)

These disorders are characterized by the production of elevated levels of Hb F beyond the neonatal period. At least 20 distinct forms of HPFH have been identified, affecting many different ethnic groups. Various molecular abnormalities have been determined as the cause for these conditions; for example, the common African forms result from extensive DNA deletions that encompass the entire b{beta}-globin gene. The normal changeover from g{gamma}-globin synthesis to b{beta}-chain synthesis consequently cannot take place in individuals with these affected chromosomes. In heterozygotes for the common African types, the level of Hb F is 15–30%. These types are characterized by a uniform distribution of Hb F in the red cells (pancellular HPFH) as compared with some of the other forms, in which the Hb F is unevenly distributed (heterocellular HPFH). Rare homozygotes for the African deletion HPFH forms have 100% Hb F in their red blood cells. Except for mild microcytosis they have normal hematologic findings. Individuals who have genes for both sickle hemoglobin and African pancellular HPFH have levels of Hb S in their red blood cells that are similar to those in patients with sickle cell anemia. This combination, however, is clinically benign, presumably because the elevated Hb F in all the red blood cells inhibits the sickling process.

Thalassemia Syndromes

The thalassemias are a heterogeneous group of heritable hypochromic anemias

of varying degrees of severity. Underlying genetic defects include total or partial deletions of globin chain genes and nucleotide substitutions, deletions, or insertions. The consequences of these various changes are a decrease or absence of mRNA for one or more of the globin chains or the formation of functionally defective mRNA. The result is a decrease or total suppression of hemoglobin polypeptide chain synthesis. Approximately 100 distinct mutations are known that produce thalassemia phenotypes; many of these mutations are unique to localized geographic regions. In general, the globin chains synthesized in thalassemic red blood cells are structurally normal. In severe forms of a-thalassemia abnormal homotetramer hemoglobins ($\beta4$, or $\gamma 4$) are formed, but their component globin polypeptides have a normal structure. Conversely, a number of abnormal hemoglobins also produce thalassemia-like hematologic changes. In characterizing the expression of the various thalassemia genes, superscript designations are used to distinguish those that produce a demonstrable globin chain product, although at decreased levels (e.g., b+-thalassemia), from those in which the synthesis of the affected globin chain is totally suppressed (e.g., b0-thalassemia).

Thalassemia genes are remarkably widespread, and these abnormalities are believed to be the most prevalent of all human genetic diseases. Their main distribution includes areas bordering the Mediterranean Sea, much of Africa, the Middle East, the Indian subcontinent, and Southeast Asia. From 3% to 8% of Americans of Italian or Greek ancestry and 0.5% of black Americans carry a gene for b-thalassemia. In some regions of Southeast Asia as many as 40% of the population have one or more thalassemia genes. The geographic areas in which thalassemia is prevalent closely parallel the regions in which Plasmodium falciparum malaria was formerly endemic. Resistance to lethal malarial infections by carriers of thalassemia genes apparently represented a strong selective force that favored their survival in these areas of endemic disease.

HOMOZYGOUS b0-THALASSEMIA

(Cooley Anemia; Thalassemia Major)

CLINICAL MANIFESTATIONS. Homozygous b0-thalassemia usually becomes symptomatic as a severe, progressive hemolytic anemia during the 2nd 6 mo of life. Regular blood transfusions are necessary in these patients to prevent the profound weakness and cardiac decompensation caused by the anemia. Without transfusion life expectancy is no more than a few years. In untreated cases or in those receiving infrequent transfusions at times of severe anemia, hypertrophy of erythropoietic tissue occurs in medullary and extramedullary locations. The bones become thin and pathologic fractures may occur. Massive expansion of the marrow of the face and skull produces characteristic facies. Pallor, hemosiderosis, and jaundice combine to produce a greenish-brown complexion. The spleen and liver are enlarged

by extramedullary hematopoiesis and hemosiderosis. In older patients the spleen may become so enlarged that it causes mechanical discomfort and secondary hypersplenism. Growth is impaired in older children; puberty is delayed or absent because of secondary endocrine abnormalities. Diabetes mellitus resulting from pancreatic siderosis may also occur. Cardiac complications, including intractable arrhythmias and chronic congestive failure caused by myocardial siderosis, are common terminal events. With modern regimens of comprehensive care for these patients, many of these complications can be prevented and others ameliorated and delayed in their onset.

LABORATORY FINDINGS. The red cell morphologic abnormalities in untransfused patients with homozygous b0-thalassemia are extreme. In addition to severe hypochromia and microcytosis, many bizarre, fragmented poikilocytes and target cells are present. Large numbers of nucleated red blood cells circulate, especially after splenectomy. Intraerythrocytic inclusions, which represent precipitated excess a chains, are also seen after splenectomy. The hemoglobin level falls progressively to lower than 5 g/dL unless transfusions are given. The unconjugated serum bilirubin level is elevated. The serum iron level is high, with saturation of the iron-binding capacity. A striking biochemical feature is the presence of very high levels of fetal hemoglobin in the red blood cells . Dipyrrolic compounds render the urine dark brown, especially after splenectomy.

TREATMENT. Transfusions are given on a regular basis to maintain the hemoglobin level above 10 g/dL. This "hypertransfusion" regimen has striking clinical benefits; it permits normal activity with comfort, prevents progressive marrow expansion and cosmetic problems associated with facial bone changes, and minimizes cardiac dilatation and osteoporosis. Transfusions of 15–20 mL/kg of packed cells are usually necessary every 4–5 wk. Cross-matching should be performed to forestall alloimmunization and prevent transfusion reactions. The use of packed red blood cells that are relatively fresh (less than 1 wk in CPD anticoagulant) is desirable. Even with meticulous care, febrile reactions to transfusions are common. These can be minimized with the use of erythrocytes reconstituted from frozen blood or the use of leukocyte filters, and by the administration of antipyretics before transfusions.

Hemosiderosis is an inevitable consequence of prolonged transfusion therapy because each 500 mL of blood delivers about 200 mg of iron to the tissues that cannot be excreted by physiologic means. Myocardial siderosis is a significant contributing factor in the early death of these patients. Hemosiderosis can be decreased or even prevented with the parenteral administration of the iron-chelating drug, deferoxamine, which forms an iron complex that can be excreted in the urine. A sustained high blood level of deferoxamine is needed for adequate iron excretion. The

drug is administered subcutaneously over an 8- to 12-hr period using a small portable pump (during sleep), 5 or 6 nights/wk. Patients who adhere to this regimen can maintain serum ferritin levels of lower than 1,000 ng/mL, which is well below the toxic range. Lethal complications of hepatic and myocardial siderosis can thus be prevented or significantly delayed. An orally effective iron chelating agent, deferiprone, has been shown to have effectiveness similar to that of deferoxamine. Because of concerns about possible toxicity (agranulocytosis, arthritis, arthralgia), this drug is not currently available in the United States.

Hypertransfusion therapy prevents massive splenomegaly resulting from extramedullary erythropoiesis. Splenectomy eventually becomes necessary, however, because of the size of the organ or because of secondary hypersplenism. Splenectomy increases the risk of severe, overwhelming sepsis, and therefore the operation should be performed only for significant indications and should be deferred as long as possible. The most important indication for splenectomy is an increased need for transfusions, indicating an element of hypersplenism. A transfusion requirement exceeding 240 mL/kg of packed red blood cells/yr is usually evidence of hypersplenism and is an indication for considering splenectomy. Immunization of these patients with hepatitis B vaccine, H. influenzae type b vaccine, and pneumococcal polysaccharide vaccine is desirable, and prophylactic penicillin therapy is also advocated.

Bone marrow transplantation is curative in these patients and has been performed with increasing success, even in patients who have been transfused extensively. This procedure, however, carries considerable risks of morbidity and mortality and generally can only be used for patients who have nonaffected histocompatible siblings.

OTHER b-THALASSEMIA SYNDROMES

The homozygous expression of milder (b+) thalassemia genes produces a Cooley anemia–like syndrome of lesser severity ("thalassemia intermedia"; see Table 419–2 Table 419–2). Skeletal deformities and hepatosplenomegaly develop in these patients, but their hemoglobin levels are usually maintained at 6–8 g/dL without transfusion. Nevertheless, they may develop severe hemosiderosis, attributable to their greatly increased gastrointestinal iron absorption. For such patients, who do not receive deferoxamine chelation therapy, a low-iron diet is indicated.

Several structurally abnormal hemoglobins produce b-thalassemia–like hematologic changes and, when present in combination with a gene for b-thalassemia, also result in a thalassemia intermedia syndrome. The most prevalent are the Hb Lepore variants, which are composed of a chains and hybrid d{delta}b fusion globin chains. The Lepore hemoglobins are identified by electrophoresis, in which they exhibit Hb S–like mobility.

Most forms of heterozygous b-thalassemia are associated with mild anemia. The hemoglobin concentration typically averages 2–3 g/dL lower than age-related normal values. The red blood cells are hypochromic and microcytic, with poikilocytosis, ovalocytosis, and often basophilic stippling. Target cells may be present but usually are not prominent and are not specific for thalassemia. The mean corpuscular volume (MCV) is low, averaging 65 fL, and the mean corpuscular hemoglobin (MCH) values are also low (<26 pg). A mild decrease in red blood cell survival can be shown, but overt signs of hemolysis are usually absent. The serum iron level is normal or elevated.

Individuals with thalassemia trait are often misdiagnosed as having iron deficiency anemia and may be inappropriately treated with iron for extended periods. More than 90% of persons with b-thalassemia trait have diagnostic elevations of Hb A2 of 3.4–7%. About 50% of these individuals also have slight elevations of Hb F, about 2–6%. In a small number of otherwise typical cases, normal levels of Hb A2 with Hb F levels ranging from 5% to 15% are found, representing the d{delta}b type of thalassemia. The "silent carrier" form of b-thalassemia produces no demonstrable abnormality in heterozygous individuals, but the gene for this condition, when inherited together with a gene for b0thalassemia, results in a thalassemia intermedia syndrome.

A rare type of deletion defect, which involves the g{gamma}-, d{delta}-, and b{beta}-globin genes, produces a clinical picture similar to that of the d{delta}b{beta} thalassemia trait in heterozygous individuals. In the newborn period, however, this defect is accompanied by significant hemolytic disease with microcytosis, normoblastemia, and splenomegaly. The hemolytic process is self-limited, but supportive transfusions may be required.

α-THALASSEMIA

α -THALASSEMIA

Microcytic anemias resulting from deficient synthesis of α -globin chains are prevalent in Africa, Mediterranean area countries, and much of Asia. Deletions of α -globin genes account for most of these abnormalities. Four α -globin genes are present in normal individuals, and four distinct forms of α -thalassemia have been identified corresponding to deletions of one, two, three, or all four of these genes .

Deletion of a single α -globin gene produces the silent carrier α -thalassemia phenotype. No hematologic abnormality is usually evident, except for mild microcytosis. Approximately 25% of African-Americans have this form of α -thalassemia.

Individuals lacking two α -globin genes exhibit the features of α -thalassemia trait, with mild microcytic anemia. In affected newborns, small quantities of Hb Barts (γ}4) can be identified by hemoglobin electrophoresis. Beyond about 1 mo of age Hb

Barts is no longer detectable, and the levels of Hb A2 and F are characteristically normal. Inclusions of precipitated hemoglobin may be visualized in red blood cell smears, however, following supravital staining.

The deletion of three of the four α -globin genes is associated with a thalassemia intermedia–like syndrome, Hb H disease. Microcytic anemia in this condition is accompanied by abnormal red blood cell morphology , with prominent intracellular inclusions present in the red blood cells following supravital staining. Hemoglobin H (β4) is highly unstable; it can be readily identified by electrophoresis, but, unless special measures are taken to prevent its precipitation during sample preparation, it may escape detection.

The most severe form of α -thalassemia, resulting from deletion of all the a{alpha}-globin genes, is accompanied by a total absence of α -chain synthesis. Because hemoglobins F, A, and A2 all contain α chains, none of these hemoglobins are produced. Hb Barts (γ4) accounts for most of the hemoglobin in affected infants, and, because γ 4 has a high oxygen affinity and therefore cannot transport oxygen to the tissues, these infants are severely hypoxic. Their red blood cells also contain small quantities of the normal embryonic Hb Portland (z{zeta}2 γ 2), which functions as an oxygen transporter. Most of these infants are stillborn, and most who are born alive die within a few hours. These infants are severely hydropic, with congestive heart failure and massive generalized edema. Those that survive with aggressive neonatal management are also transfusion-dependent.

The types of a{alpha}-thalassemia genes vary among affected populations, and these differences account for the α -thalassemia syndromes that predominate in specific population groups. In African-Americans α -thalassemia genes are prevalent, with almost all affected individuals having the deletion arrangement (–{minus}, α) that produces a single α -locus chromosome. In this population, therefore, a{alpha}-thalassemia occurs mainly as the silent carrier phenotype (–, α / α , α) or as the a{alpha}-thalassemia trait (–,α /–},α). Chromosomes with deletions of both of the a{alpha} loci (–{minus},–) are prevalent in both Mediterranean and Asian populations, and Hb H disease (–},α /–,–) therefore occurs with significant frequency in both groups. The two a{alpha}-locus deletion defects in Asians are often accompanied by retention of the z{zeta}-globin genes (i.e., z{zeta},–{minus},–{minus}), whereas those from Mediterranean countries usually are not (–{minus},–{minus},–{minus}). The latter type of defect, therefore, cannot support the synthesis of Hb Portland (z{zeta}2g{gamma}2), which appears to be essential for the intrauterine survival of fetuses with the hydrops fetalis form of a{alpha}-thalassemia. Accordingly, the hydrops fetalis form is seen almost exclusively in infants of Asian ancestry. An acquired a{alpha}-thalassemia syndrome, which may be associated with a large deletion involving the a{alpha}-globin genes, includes Hb H disease

accompanied by mental retardation, microcephaly, and hypogonadism.

A number of abnormal hemoglobins also produce a{alpha}-thalassemia–like changes. The a{alpha}-chain variant Hb Constant Spring occurs commonly in Far Eastern populations and is frequently observed in patients with Hb H disease, who have the genotype (a{alpha}A,a{alpha}Co Sp/–{minus},–{minus}). The gene for Hb G Philadelphia, which is the most prevalent a{alpha}-chain abnormality of African-Americans, usually occurs on a single-locus chromosome (–{minus},a{alpha}G). Individuals who express this abnormal hemoglobin therefore also exhibit a{alpha}-thalassemia–like hematologic changes.

Hemochromatosis

Excessive storage of iron, primarily in the form of hemosiderin in parenchymal cells, can result in impairment of the structure and function of the liver, heart, gonads, skin, and joints. Idiopathic hemochromatosis, which has an autosomal recessive mode of inheritance, usually does not become clinically apparent until adult life. More severe forms, however, may present during childhood. The underlying metabolic defect in this disorder is unknown. Symptomatic individuals exhibit massive iron stores with the classical clinical triad of cirrhosis, bronzing of the skin, and diabetes mellitus. Serum ferritin levels are characteristically greatly elevated, with increased transferrin saturation. The gene for this disorder is frequently linked to HLA types A-3, B-7, and B-14, and, in families with an affected individual, this association provides an opportunity for screening sibs prior to the onset of symptomatic iron storage. With treatment by repeated phlebotomy, organ damage can be prevented.

Neonatal hemochromatosis is an acquired syndrome resulting from severe liver disease arising prenatally. A variety of forms of fetal hepatopathy can give rise to this clinical entity, which consists of severe liver dysfunction or liver failure, accompanied by massive iron stores and siderosis. Most of these infants have had a fatal outcome, although some have survived.

Transfusion-induced hemosiderosis, in patients chronically transfused for congenital or acquired anemia, can produce clinical and pathologic features quite similar to those of patients with thalassemia

VI. Plan and organizational structure of classes.

№	Basic stages of classes, their function and maintenance	Educational aims are in the levels of mastering	Methods of control and studies	Educational materials	Distributing of time in minutes
1	Preparatory stage Organizational measures Raising				3 min.
2	of educational aims and moti-	$\alpha2$		П. II «Educational aims» П. I «Actuality of	12 min.

	vation			theme»	20 min.
3	Control of basic knowledges and skills level: 1.Ethiology of anaemias in children 2.Key links of pathogenesis of anaemias. 3.Classification of anaemias in children; 4.Typical mani-festation of anae-mias in children. 5. Laboratory and instrumental diag-nosis of anaemias in children. 6.Clinical syndro-mes of anaemias in children. 7.Treatment prin-ciples of anaemi-as in children;	α2 α2 α2 α2	Individual questioning Test control of the second level Individual questioning Typical situational task of 2 level Typical situational task of 2 level Typical situational task of 2 level Test control of 2 level Typical situatioonal task of 2 level	The second level tests Typical situational task of 2 level Typical situational task of 2 level Tests of 2 level Typical situational tasks of 2 level Kit of medicines.	
4	Basic stages of professional skills and abilities forming: 1.To conduct the patient manage-ment with anaemias, to take complaints and anamnesis. 2.To conduct the pateint's examination and detect the main symptoms and syndromes of anaemias. 3.To formulate and substantiate the preliminary diagnosis 4.To compose the plan of patient laboratory and instrumental investigation.	α3 α3 α3	Practical professional training Practical professional training Practical professional training Practical professional training Practical professional training.Tests and third level control. The third level test control.The practical professional training is in the salvation of non standard clinical situations.	Patient Patient Case history A reference chart for forming of professional abilities. Case history. A reference chart for forming of professional abilities.Situatio-onal typical tasks of 3 level.The third level tests.	115 min.

		5. To interpret the results of laboratory and instrumental investigation.	α3	The third level test control.Practical professional training.	Prescribing chart	
		6.To conduct differential diagnosis for clinical conditions accompaied by anaemias.	α3	The third level test control.Practical professional training .	The third level non typical situational tasks. Treatment algorythm for the leucaemia.	
		7.To give recom-mendations for the regimen and diet of a patent.	α3	The practical professional training in solving of non typical clinical situations.	The third level non typical situational tasks. First aid algorythm in hemmorage syndrome.	
		8.To compose the plan of anaemia treatment taking into account the stage of disease and presence of complications.	α3	The third level test control. Practical professional training in solving of non typical clinical situations.		
		9.To be able to render the first aid in extreme situations	α3			
5 6 7		Concluding stage. Control and correction of professional abilities and skills. Working out the totals of class. Home work (basic and additional literature on the topic)		Analysis of clinical work performances Solving of non typical tasks and the third level tests. Estimation of clinical work performances.	Clinical work The third level non typical situational tasks. A reference chart for independent work with literature	30 min.

Methodical materials for the class basic stage supporting

The questions for the control of the primary knowledge level of abilities and skills:

1. What is the function of erythrocytes?
2. How can we use erythrocytic index ?
3. What is general for anaemias?
4. What is the typical triad for hemolytic anemia?
5. What are the specific clinical signs of hypoplastic anaemias?
6. What are the typical syndromes for iron-deficiency anemia?
7. What are the laboratory findings of pernicious anemia ?

8.　　　To explain the ferrotherapy in children with iron-deficiency anemia.

9.　　　To explain the pathogenesis of hereditary spherocytosis.

10.　　To explain the pathogenesis of anemia praematarorum.

11. What is the prophylaxis of iron-deficiency anemia in children?

12. To explain the clinical manifestation of Diamond-Blackfan syndrome.

Primary tests

1. The true reticulocytosis is:
 A. Rising of reticulocytes in bone marrow and in blood.
 B. Rising of reticulocytes in blood.
 C. Rising of reticulocytes in bone marrow.
 D. A high level of blood reticulocytes in normal amount in bone marrow.
 E. The reduced amount of reticulocytes in bone marrow in normal blood concentration.

2. Poikilocytosis is:
 A. Change of the form of separate erythrocytes.
 B. Change of the sizes of separate erythrocytes.
 C. Change of staining intensity of separate erythrocytes.
 D. Presence of inclusions in cytoplasm of erythrocytes.
 E. All answers are correct

3. Anemias are:
 A. Decrease of haemoglobin and erythrocytes in a unit of blood volume.
 B. Decrease of erythrocytes amount in a unit of blood volume.
 C. Decrease of haemoglobin in a unit of blood volume.
 D. Decrease of circulating blood volume.
 E. All answers are correct.

4. Time of revealing of laboratory signs in an acute posthemorrhagic anemia:
 A. 2-nd day.
 B. In 18 hours.
 C. In 12 hours.
 D. The first hours from the beginning of bleeding.
 E. 24 hours from the beginning of bleeding.

5. What is the occurrence time of reticulocytic crisis after an acute hemorrhage?
 A. 4-5 day.
 B. 10 day
 C. 1-2 day.
 D. The first hours.
 E. The first minutes

6. Urgent measures after an acute hemorrhage:
 A. Transfusion of hemocorrectors
 B. Transfusion of packed red cells.

C. Transfusion of an integral blood.
D. Disaggregate therapy.
E. A vitamin therapy.

7. What is the definition of hypochromic anemia concept?
A. Anemias in which rates of hemoglobin synthesis lag of erythrocyte formation.
B. Anemias at which decreasing of average erythrocytes volume is observed.
C. The anemias connected to disturbances of goblin synthesis.
D. The anemias connected to disturbances of heme synthesis..
E. All answers are correct

8. What is typical for an aregeneratory anemia?
A. Absence of reticulocytosis in blood and bone marrow.
B. Decreasing of reticulocytes in blood.
C. Decreasing of reticulocytes in bone marrow
D. The normal amount of reticulocytes in blood and risings of their amount in the bone marrow.
E. All answers are correct.

9 What is the manifestation of. sideropenic syndrome in an iron scarce anemia?
A. Trophic changes, partially to unusual food.
B. Weakness, giddiness, nausea.
C. Glossitis.
D. Lesion of the central nervous system.
E. All answers are correct

10.What are the changes in blood in chronic iron scarce anemia?
A. Essential decreasing of haemoglobin, of color parameter, of serumal Ferri lactas.
B. Decreasing of hemoglobin and erythrocytes.
C. Presence of anemia, leukocytosis, neutrocytosis.
D. Presence of anemia, leukocytosis, hyperthrombocytosis
E. All the above-stated takes place

11. The dimensions of erythrocytes in an iron scarce anemia:
A. Do not change.
B. Essentially diminished up to microcytes.
C. Essentially diminished up to schizocytes.
D. Enlarged up to megalocytes.
E. All answers are correct

12. The amount of iron in blood serum in chronic iron scarce anemia:
A. < 12,5 mcmol/l
B. < 15 mcmol/l
C. <22 mcmol/l
D. <30,4 mcmol/l

E. <20 mcmol/l

13. Daily requirement for iron in children of early age:
 A. 2 mg
 B. 20 mg
 C. 50 mg
 D. 10 mg
 E. 1mg

14. Daily requirement for iron in teenagers:
A. 15-20 mg.
B. 10 mg.
C. 100 mg.
D. 2 mg.
E. 40 mg

15. What kind of iron is better absorbed?
 A. 2 valent.
 B. 3-valent.
 C. Iron in a complex with proteins.
 D. Iron chlorine.
 E. Iron in a complex with polivitamines

16. Whom a juvenile chlorosis inherent is the most often to?
 A. Girls of 15-20 years old.
 B. Young men of 17 years old.
 C. Women of genital age.
 D. Newborns
 E Children of early age

17.What is the cell –color index in juvenile chlorosis ?
A. 0,44-0,5
B. 0,7-0,85
C. 0,82-1,65
D. 1,1-1,3
E. More than 1,3

18. What is the basic prominent feature of a peripheral blood in newborns?
 A. Limphopenia
 B. Neutrophile leukocytosis .
 C .Erhythrocytosis
 D. Anemia.
 E. Limphocytosis

19. Is there a possibility of iron deficiency correction with a diet?
 A. No
 B. Yes.
 C. Possible with the help of using vegetable products.

D. Possible with the help of animal parentage products.

E. Possible with the help both of vegetable and animal parentage products

20. Are hemotransfusions indicated in iron scarce anemia?

 A. No.

 B. Yes.

 C. Indicated in hemoglobin amount lower than 100 g/l.

 D. Indicated in hemoglobin amount lower than 90g/l

 E. Indicated in hemoglobin amount lower than 80 g/l.

Answers: 1-B, 2-A, 3-D, 4-C, 5-A, 6-A, 7-B, 8-C, 9-D,A, 10-A, 11-B, 12-E, 13-B, 14-C, 15-C, 16-A, 17-E, 18-D, 19-A, 20-A.

Typical situational tasks of 2 level

1. On a routine-screening complete blood count, a 1-year-old is noted to have a microcytic anemia. A follow-up hemoglobin electrophoresis demonstrates an increased concentration of hemoglobin A2.

a. Iron deficiency

b. β-thalassemia trait

c. Sickle cell anemia

d. Chronic systemic illness

e. Lead poisoning

Task

 -What is the preliminary diagnosis?

2. A 4-year-old previously well boy develops pallor, dark urine, and jaundice. There has been no apparent exposure to a jaundiced person or to any toxins. He is taking trimethoprim-sulfamethoxazole for otitis media. You consider the possibility of a hemolytic crisis caused by glucose-6-phosphate dehydrogenase (G6PD) deficiency.

a. African American

b. Greek

c. Chinese

d. Middle Eastern

e. Scandinavian

Task

- Which of the following ethnic groups is the lowest incidence in?

- Key links of pathogenesis of disease

3. A 2950-g black baby boy is born at home at term. On arrival at the hospital, he appears pale, but the physical examination is otherwise normal. Laboratory studies reveal the following: mother's blood type A, Rhpositive; baby's blood type O, Rh-positive; hematocrit 38%; reticulocyte count 5%. Which of the following is the most likely cause of anemia?

a**. Fetomaternal transfusion**

b. ABO incompatibility

c. Physiologic anemia of the newborn

d. Sickle cell anemia

   Task

 -What is the preliminary diagnosis?

4. A preterm black male infant was found to be jaundiced 12 h after

birth. At 36 h of age, his serum bilirubin was 18 mg/dL, hemoglobin concentration

was 12.5 g/dL, and reticulocyte count 9%. Many nucleated red

cells and some spherocytes were seen in the peripheral blood smear.

a. Pyruvate kinase deficiency

b. Hereditary spherocytosis

c. Sickle cell anemia

d. Rh incompatibility

e. Polycythemia

Task Which of the following should the differential diagnosis include?

5. Having performed a complete history and physical examination of the patient, you proceed with a diagnostic workup. Initial laboratory results are as follows: hemoglobin 8 g/dL; hematocrit 24%; leukocyte count 11,000/□L with 38% neutrophils, 7% bands, 55% lymphocytes; hypochromia on smear; free erythrocyte protoporphyrin (FEP) 110 □g/dL; lead level 7 □g/dL whole blood; platelet count adequate; reticulocyte count 0.5%; sickle cell preparation negative; stool guaiac negative; and mean corpuscular volume (MCV) 65fl.

   Task You would most appropriately recommend

   a. Blood transfusion

   b. Oral ferrous sulfate

   c. Intramuscular iron dextran

   d. An iron-fortified cereal

   e. Calcium EDTA

6. On a routine well-child examination, a 1-year-old boy is noted to be

pale. He is in the seventy-fifth percentile for weight and the twenty-fifth percentile for length. Results of physical examination are otherwise normal. His hematocrit is 24%., which of the following questions is the most likely to be helpful in making a diagnosis?

   a. What is the child's usual daily diet?

   b. Did the child receive phototherapy for neonatal jaundice?

   c. Has anyone in the family received a blood transfusion?

   d. Is the child on any medications?

   e. What is the pattern and appearance of his bowel movements?

7. A girl of 12 years old, is admitted to hospital. Laboratory findings: macrocytic anaemia, serum vitamin B12 levels are 80 pg/mL. Concentrations of serum iron and serum folic acid are elevated.

   What is the preliminary diagnosis?

a. Iron deficiency

b**. vitamin B12 deficiency**

c. vitamin B12 hypervitaminosis

d. thalassemia

e. Minkowsky-Shauffard disease

8. A child of 4 years old is hospitalized with complaints to be pale. On examination the liver and spleen are not enlarged,congenital anomalies (dysmorphic facies). Laboratory findings : macrocytic anaemia with elevated levels of folic acid and vitamin B12,elevated fetal hemoglobin (Hb F) and increased expression of "i" antigen. Bone marrow culture shows markedly reduced numbers of colony-forming units–erythrocyte (CFU-E) and BFU-E.

What is the preliminary diagnosis?

a. Iron deficiency

b**.** vitamin B12 deficiency

c. **Diamond-Blackfan syndrome**

 d. thalassemia

e. Minkowsky-Shauffard disease

9. A girl of 11 years old firstly hospitalized in the depatment with complains of weakness, irritability, anorexia. The tongue is smooth, red, and painful. Neurologic manifestations include ataxia, paresthesias, hyporeflexia. The anemia is macrocytic, with prominent macro-ovalocytosis of the RBCs. Serum vitamin B12 levels are <100 pg/mL. Concentrations of serum iron and serum folic acid are normal.

What is the preliminary diagnosis?

Prescribe treatment.

10. A girl of 10 years old firstly hospitalized in the depatment with complaints of pagophagia. On examination tachycardia and cardiac dilatation occur, and systolic murmurs are present. The spleen is enlarged. Laboratory findings: microcytosis with increasing deficiency the RBCs, hypochromia, poikilocytosis, and increased red cell distribution width (RDW). Reticulocytes are moderately elevated. White blood cell counts are normal. The bone marrow is hypercellular, with erythroid hyperplasia. Leukocytes and megakaryocytes are normal.

What is the preliminary diagnosis?

Prescribe treatment.

Standard of answer

1. The concentration of hemoglobin A2 is increased in □-thalassemia trait. In severe iron deficiency, hemoglobin A2 may be decreased. In mild-to-moderate iron deficiency, the level of hemoglobin A2 is normal. The level is also normal in sickle cell anemia, chronic systemic illness, and lead poisoning.

2.Synthesis of the red cell enzyme glucose-6-phosphate dehydrogenase (G6PD) is determined by genes on the X chromosome, and the pattern of inheritance is X-linked recessive. The enzyme found in most populations is termed G6PDB1. There are over 380 deficient variants of the enzyme affecting over 100 million people

worldwide,among them G6PDA1, a mutant enzyme affecting about 13% of African American males and 2% of African American females; G6PDB or Mediterranean, a deficient mutant occurring among Middle Eastern, African,and Asian groups; and G6PD Canton occurring in 5% of Chinese. In people with G6PDB1, enzyme activity is reduced to 50% during the 120-day life span of the erythrocyte. In persons affected with all G6PD deficiency variants, enzyme activity is always 10% of normal or less. Deficiency of G6PD compromises the generation of reduced glutathione, and upon exposure to oxidant agents such as sulfa drugs, antimalarials, nitrofurans, naphthalene mothballs, or infection, a hemolytic episode usually occurs. The degree of hemolysis depends on the nature of the oxidant and severity of the enzyme deficiency. In African Americans, the older, more G6PD-deficient cells are destroyed, but since young cells have sufficient enzyme to prevent further red cell destruction even if the inciting factor is still present, the hemolytic crisis is usually self-limited. Blood transfusion may be unnecessary.In African Americans, premature testing for the enzyme immediately after a hemolytic episode can lead to a false negative result since the newly produced red cells in the circulation have a higher G6PD enzyme activity.The older red cells containing Heinz bodies (insoluble precipitates resulting from oxidation), the "bite cells" (red cells after the removal of the Heinz bodies), and cell fragments are removed from the circulation within 3 to 4 days. In the severe Mediterranean type, young as well as old red cells are enzyme-deficient. Recovery is signalled by the appearance of reticulocytes and a rise in hemoglobin.

3.The absence of a major blood-group incompatibility and the finding of a normal reticulocyte count argue strongly in favor of a recent fetomaternal transfusion, probably at the time of delivery. A Betke-Kleihauer stain for fetal hemoglobin-containing red cells in the mother's blood would confirm the diagnosis. After birth, erythropoiesis ceases, and the progressive decline in hemoglobin values, reaching a nadir at 6 to 8 weeks of age, has been termed physiologic anemia of infancy. Iron-deficiency anemia is common in the term infant between 9 and 24 months of age when the iron stores derived from circulating hemoglobin have been exhausted and an exogenous dietary source of iron has not been provided. The manifestations of sickle cell disease do not appear until 4 to 6 months of life, coincident with the replacement of fetal hemoglobin with sickle hemoglobin.

4.Spherocytosis can be seen in hyperthermia, hereditary spherocytosis, G6PD deficiency, or ABO incompatibility. Hyperbilirubinemia has been associated with black preterm infants with G6PD deficiency. The blood smear of the affected infant usually reveals nucleated red cells, spherocytes, poikilocytes, "blister" cells, and fragmented cells. Neonatal hyperbilirubinemia occurs in about 50% of patients with hereditary spherocytosis. Spherocytosis occurs in ABO incompatibility but not in Rh incompatibility. The hemolytic manifestations of ABO incompatibility and hereditary spherocytosis are very similar. The blood types of the mother and of the infant should be determined along with the results of a direct Coombs test of the infant and the presence or absence of a family history of hemolytic disease (spherocytosis). Sickle cell disease would not be expected to cause problems in newborns due to the protection by fetal hemoglobin.

5. Response to a therapeutic trial of iron is an appropriate and cost-effective method of diagnosing irondeficiency anemia. A prompt reticulocytosis and rise in hemoglobin and hematocrit follow the administration of an oral preparation of ferrous sulfate.

Intramuscular iron dextran should be reserved for situations in which compliance cannot be achieved. This is because this treatment is expensive, painful, and less effective than oral iron. Dietary modifications, such as limiting the intake of cow's milk and including iron-fortified cereals along with a mixed diet, are appropriate as long-term measures, but they will not make enough iron available to replenish iron stores. The gradual onset of iron-deficiency anemia enables a child to adapt to surprisingly low hemoglobin concentrations. Transfusion is rarely indicated unless a child becomes symptomatic or is further compromised by a superimposed infection.

When the iron available for production of hemoglobin is limited, free protoporphyrins accumulate in the blood. Levels of erythrocyte protoporphyrin

(EP) are also elevated in lead poisoning. Iron-deficiency anemia can be differentiated from lead intoxication by measuring blood lead, which

should be less than 10 □g/dL.

6.Iron-deficiency anemia is the most common nutritional deficiency in children between 9 and 15 months of age. Low availability of dietary iron, impaired absorption of iron related to frequent infections, high requirements for iron for growth, and, occasionally, blood losses, favor the development of iron deficiency in infants. A history regarding anemia in the family, blood loss, and gestational age

and weight can help to establish the cause of an anemia. The strong likelihood is that anemia in a 1-year-old child is nutritional in origin, and its cause will be suggested by a detailed nutritional history.

7. The anemia is macrocytic, with prominent macro-ovalocytosis of the RBCs (see Fig. 405–1 Fig. 405–1B). The neutrophils may be large and hypersegmented. In advanced cases neutropenia and thrombocytopenia, simulating aplastic anemia or leukemia, are seen. Serum vitamin B12 levels are <100 pg/mL. Concentrations of serum iron and serum folic acid are normal or elevated. Serum LDH activity is markedly increased. Moderate elevations (2–3 mg/dL) of serum bilirubin levels may

be seen. Excessive excretion of methylmalonic acid in the urine (normal amount, 0–3.5 mg/24 hr) is a reliable and sensitive index of vitamin B12 deficiency.

8. Diamond-Blackfan Syndrome

This rare condition usually becomes symptomatic in early infancy, frequently with pallor in the neonatal period, but may first be noted later in childhood. About 50% of children are diagnosed by 2 mo of age, and 75% by 6 mo. The most characteristic features are macrocytic anemia, reticulocytopenia, and a deficiency or absence of red blood cell (RBC) precursors in an otherwise normally cellular bone marrow.

9. JUVENILE PERNICIOUS ANEMIA

TREATMENT. A prompt hematologic response follows parenteral administration of vitamin B12 (1 mg), usually with reticulocytosis in 2–4 days, unless there is concurrent inflammatory disease. The physiologic requirement for vitamin B12 is 1–5 m{mu}g/24 hr, and hematologic responses have been observed with these small doses, indicating that administration of a minidose may be used as a therapeutic test when the diagnosis of vitamin B12 deficiency is in doubt. If there is evidence of neurologic involvement, 1 mg should be injected intramuscularly daily for at least 2 wk. Maintenance therapy is necessary throughout the patient's life; monthly intramuscular administration of 1 mg of vitamin B12 is sufficient. Oral therapy may succeed because of mucosal diffusion with high doses, but it is not generally advisable due to uncertainty of absorption.

10. Iron-deficiency anemia

Oral administration of simple ferrous salts (sulfate, gluconate, fumarate) provides inexpensive and satisfactory therapy. There is no evidence that addition of any trace metal, vitamin, or other hematinic substance significantly increases the response to simple ferrous salts. For routine clinical use the physician should be familiar with an inexpensive preparation of one of the simple ferrous compounds. The therapeutic dose should be calculated in terms of elemental iron; ferrous sulfate is 20% elemental iron by weight. A daily total of 6 mg/kg of elemental iron in three divided doses provides an optimal amount of iron for the stimulated bone marrow to use. Better absorption may result when medicinal iron is given between meals. Intolerance to oral iron is uncommon. A parenteral iron preparation (iron dextran) is an effective form of iron and is usually safe when given in a properly calculated dose, but the response to parenteral iron is no more rapid or complete than that obtained with proper oral administration of iron, unless malabsorption is present.

Metohodical materials for the class

A professional algorythm of patients management implementation (reference chart) for the practical skills and abilities forming .

№	Task	Sequence of implementation	Remarks and warnings related to self-control
1	To conduct patient's	1.To conduct complaints	To pay attention to

	examination for anaemias.	and disease's anamnesis gathering. 2.To gather thoroughly the patient's life anamnesis. 3.To conduct examination of the patient. 4.To investigate cardiovascular system of the patient (palpation, percussion).	features of disease course , underlying factors, concomitant diseases etc. To establish the risk factors which can cause the development of disease. To assess patient general condtion, position in bed, color and humidity of skin and mucouse, presence of neck veins and extermities swelling. To pay regard to pulse rhytm, it's tension and size on both hands, apex shove, its properties, margins of absolute and relative cardiac dullness, its changes, HR(tachi-or bradicardia, extrasystole),BP.
		5.To conduct heart and main vessels auscultation. 6.To investigate the pulmonary system (percussion, bronchophony). 7.To conduct lungs auscultation. 8.To investigate the system of digestion. 9. To conduct examination and palpation of thyroid gland and local lymphatic nodes.	To pay regard to heart tones weakening or amplifying, appearance of murmurs and additional III, IV tones. To pay attention to features of percussion and auscultation in children of different age.
2	To formulate the preliminary diagnosis.	1.To formulate the preliminary diagnosis 2.To substantiate all the components of preliminary diagnosis based on complaints,anamnesis, and examinations.	To formulate the preliminary diagnosis of anaemias and subtantiate each component of it.
3	To evaluate the parameters of additional laboratory investigations.	1.To evaluate the blood count data. 2. To evaluate the	To pay attenttion to the signs of anemia, reticulo-cyte count iron, ferritin

		biochemistry data. 3.To evaluate the blood hormonal profile.	and total iron binding capacity levels, leucocyto-sis, changing of formula, blood film, red cell enzy-me studies, folate, vitamin B12 levels , elevation of sedimentation rate. To pay attention to cholesterol, lipids and glucouse levels.
4	To undersrtand the data of additional and laboratory investigation.	To undersrtand the data of bone marrow puncture.	
5.	To conduct differential diagnosis.	1.Consistently to find the common signs in com-plaints,life and disease anamnesis, data of exami-nation, data of laboratory and instrumental investiagtions in patient and in similar states. 2.To find differences between complaints, infor-mation of life and disease anamnesis, examination data, information about the laboratory and instrument-tal methods of research and in similar nosology. 3.On the basis of the differences found to exclude similar diseases from the list of possible diagnoses. 4. To conduct differential diagnostics according to the above mentioned algorithm among all the nosologies having the similar signs, among other kinds of anaemias 5.Taking into account the impossibility to exclude the diagnosis of anaemias from the list of credible diagnoses to draw a con-clusion about the probabi-lity of such a diagnosis.	Special attention must be paid to differential diagnosis among the leucaemias

6	To formulate the final clininical diagnosis.	1.To formulate the final clininical diagnosis. 2.Basing on the preliminary diagnosis, additional investigations data, conducted differential diagnosis, substantiate all elements of the final clininical diagnosis.	Basing on modern classification of anaemias , formulate the diagnosis, complications of disease and the presence of concomitant diseases.
7	To pescribe treatment for patients.	1.To prescribe no medicinal treatment 2.To prescribe medicinal treatment.	Specify the regimen and detalized diet according to a disease. Taking into account the age, severity of patient's state, the stage of disease, the presence of complications and concomitant pathology, to prescribe modern medicinal treatment in accordance with the standards of anaemias therapy.

The material for the control of the secondary level of abilities and skills:

The secondary tests

1.The dimensions of erythrocytes in an iron scarce anemia:
 A. Do not change.
 B. Essentially diminished up to microcytes.
 C. Essentially diminished up to schizocytes.
 D. Enlarged up to megalocytes.
 E. All answers are correct

2. The amount of iron in blood serum in chronic iron scarce anemia:
A. < 12,5 mcmol/l
B. < 15 mcmol/l
C. <22 mcmol/l
D. <30,4 mcmol/l
E. <20 mcmol/l

3. Daily requirement for iron in children of an early age:
 A. 2 mg
 B. 20 mg
 C. 50 mg
 D. 10 mg
 E. 1mg

4. Daily requirement for iron in teenagers:
A. 15-20 mg.
B. 10 mg.
C. 100 mg.
D. 2 mg.
E. 40 mg

5. What kind of iron is better absorbed?
 A. 2 valent.
 B. 3-valent.
 C. Iron in a complex with proteins.
 D. Iron chlorine.
 E. Iron in a complex with polivitamines

.6. Who is a juvenile chlorosis inherent to the most often?
 A. Girls of 15-20 years old.
 B. Young men of 17 years old.
 C. Women of genital age.
 D. Newborns
 E Children of early age

7.What is the cell –color index in juvenile chlorosis?
A. 0,44-0,5
B. 0,7-0,85
C. 0,82-1,65
D. 1,1-1,3
E. More than 1,3

8. What is the basic prominent feature of a peripheral blood in newborns?
 A. Limphopenia
 B. Neutrophile leukocytosis .
 C .Erhythrocytosis
 D. Anemia.
 E. Limphocytosis

9. Is there a possibility of iron deficiency correction with a diet?
 A. No
 B. Yes.
 C. Possible with the help of using vegetable products.
 D. Possible with the help of animal parentage products.
 E. Possible with the help both of vegetable and animal parentage products

10. Are hemotransfusions indicated in iron scarce anemia?
 A. No.
 B. Yes.
 C. Indicated in hemoglobin amount lower than 100 g/l.
 D. Indicated in a hemoglobin amount lower than 90g/l

E. Indicated in hemoglobin amount lower than 80 g/l.

11. In what age the Diamond-Blackfan syndrome develops the most frequently?
A. 1 -2
B. 2-6
C. 8
D. 10-15
E. The first month of life

12. What are the blood parameters in the Diamond-Blackfan syndrome?
A. Microspherocytosis, anemia, reticulocytosis.
B. Anisocytosis, decreasing of erythrocytes, thrombocytopenia.
C. Makroanisocytosis, poicilocytosis of erythrocytes, decreasing of hemoglobin.
D. Normocytosis, decreasing of erythrocytes.
E. Macrocytosis, elevated fetal hemoglobin (Hb F), thrombocytosis

13. What is the diameter of erythrocytes in the case of macrocytic [megalocytic] anemia ?
A. 7,2-8,3 mkm
B. 10-12 mkm
C. <12 mkm
D. >7 mkm
E 7-12 mkm

14. What is the name of erythrocytes with thorns?
A. macrocyt
B. acanth(r)ocyte
C. spherocyt
D. stomatocyt
E. microcyt

15. What is the cell –color index in B12 deficiency anaemia ?
A. 0,44-0,5
B. 0,7-0,85
C. 0,82-1,05
D. >1,05
E. <0,44

16. What are the blood parameters in the drepanocytic anemia?
A. drepanocytosis
B. elliptocytosis
C. target cell anemia
D. acanth(r)ocytosis
E. spherocytosis

17. In what kind of anaemias can we find Heinz's bodies?
A. Iron deficiency
B. vitamin B12 deficiency

C. Diamond-Blackfan syndrome
D. thalassemia
E. Minkowsky-Shauffard disease

18. Where is erythropoietin synthesized?
A. marrow
B. juxteglomerular complex
C. plasma
D. hypothalamus
E. red corpuscle

19. The Etiology of hemolytic anemia
A. snake venom
B. sulfonamide
C. blood transfusion
 D. becoming too cold
E. all listed above

20. The stimulator of eritropoesis….
A. vasopressin
B. aldosterone
C. insulin
D. thyroxin
E. all listed above
Answers: 1-B, 2-A, 3-D, 4-C,5-A, 6-A, 7-B, 8-C, 9-D, 10-A, 11-B, 12-E,13-C,14-B, 15-D, 16-, 17-D, 18-B, 19-E,20-E.

Materials of the medical support for the students independent training: a reference chart for organization of students independent work with educational literature.

Tasks	Instructions
To study the etilogy and pathogenesis of iron-,protein-and vitamin scarce anaemias in children	To select the key links of anaemias pathogenesis.
To study the clinical manifestations of iron-,protein-and vitamin scarce anaemias in children.	To establish the symptoms and gather it to clinical syndromes which enable to make the credible diagnosis of anaemias.
To study diagnostic criteria of anaemias.	To make the structural plan of disease
To study the additional methods of research (laboratory, instrumental)	To work out a plan of patient's examination.
To study the changes in additional investigational methods which are pathognomonic for anaemias.	To enumerate the basic diagnostic cri-teria of anaemias according to the data of additional investigational methods.

To conduct differential diagnostics, to establish a final diagnosis	To substantiate the basic components of diagnosis in accordance with the modern classification, and to conduct a differential diagnosis.
To prescribe the individual holiatry to patient with anaemias. To be able to render the first aid in haemorrhage for children.	To make the prescribing chart specifying the regimen, diet, medicinal treatment, taking into account the age, severity of patient state, stage of disease, presence of complications and concomitant diseases.

Basic literature:

1.Nelson Textbook of Pediatrics, ed 16.2000.

2.Дитячі хвороби. За ред. В.М. Сідельникова, В.В.Бережного. К.:Здоров'я, 1999.- 734 с.

3.Медицина дитинства. За редакцією П.С. Мощича. - К.Здоров'я, 1994. -Т. 1-4.- 2350 с.

4.Майданник В.Г. Педиатрия. Учебник (2-е издание, испр. и доп.) - Харьков: Фолио, 2002. - 1125 с.

Theme: Leukemias in children.

Leukemias and lymphadenomas in children: etiology, pathogenesis, classification, diagnostics, differential diagnostics among other diseases of the blood system and diseases with hyperplastic syndrome, treatment. The first aid in hemorragic syndrome and in syndromes of prelum. Prognosis.

I. Actuality of the theme.

Leukemias are the most common childhood cancers, accounting for about 33% of pediatric malignancies. Acute lymphoblastic leukemia (ALL) represents about 75% of all cases, with a peak at the age of 4 yr. Acute myeloid leukemia (AML) accounts for about 20% of leukemias, with an incidence that is stable from birth through the age of 10 yr, increasing slightly during adolescence. Most of the remaining leukemias are the chronic myeloid form; chronic lymphocytic leukemia is rarely seen in children. The overall annual incidence of leukemia is 42.1 per million white children and 24.3 per million black children. The difference is due mainly to the lower incidence of ALL among black children. General clinical features of the leukemias are similar because all involve and severe disruption of bone marrow function. Specific clinical and laboratory features differ, however there is marked variability in responses to therapy and in prognosis.

Concrete purposes:

1. To determine the etiologic and pathogenetic factors in diffuse leukemias and lymmhoadenomas in children.

2. To classify and analyse the typical clinical manifestation of leukemias and lymphoadenomas in children.

3. To determine the features of leukemias and lymmhoadenomas in children and put the initial clinical diagnosis.

4. To make the plan of examination and analyse the information about laboratory and instrumental data in the classic course of leukemias and lymmhoadenomas in children.

5. To demonstrate skills of treatment, rehabilitation and prophylaxis of leukemias and lymmhoadenomas in children.

6. To diagnose and render an urgent help in cell lysis crisis in children.

7. To conduct differential diagnostics among leukemias and lymmhoadenomas and put the final diagnosis.

8. To determine the prognosis for life in leukemia and lymmhoadenoma in children.

9. To demonstrate the skills of medical specialist's moral and deontological principles and principles of professional subordination in pediatrics.

II. Classes (pointing of planned mastering level)

1. A student must have a notion (to familiarize): α1

- About the place of leukemia in the structure of blood system's diseases in children, dependent on different age and ethnic groups;
- About statistical information in relation to morbidity, frequency of complications, lethality, immediate and long-term prognosis for patients;
- About the history of scientific studying and the contribution of domestic scientists;

2. A student must know (to master): α2

- etiology of leukemia;
- key links of leukemia's pathogenesis;
- citochemical and immunologic classification of leukemias;
- classical clinical manifestation of leukemia;
- classical clinical manifestation of lymphoadenoma;
- laboratory and instrumental diagnosis of leukemia;
- complications of leukemia and lymphoadenoma;
- treatment principles of leukemias and lymphoadenias in children;

3. A student must master: α3

Skills:

- Complaints and anamnesis taking;
- Examination of patient with leukemia and revealing the main symptoms and syndromes.
- To formulate and substantiate the initial diagnosis;
- Determination of laboratory and instrumental examination, to make the plan of patient's investigation (according to diagnostics' standards).

Abilities:

- To interpret the results of laboratory and instrumental tests;
- To conduct differential diagnostics with a mielodysplastic syndrome, lymphogranulomatosis, non-Hodjkin lymphadenomas, and other clinical states which are accompanied by the increase of lymphatic nodes, increase of temperature, bleeding and other signs of disease;
- To give recommendations in relation to the patient's regimen and diet in leukemia and lymphadenoma, taking into account the stage of disease, severity of the state and the concomitant pathology;
- Taking into account the stage of disease to specify the severity of the state and concomitant pathology;

- To complete the treatment plan in leukemia and lymphoadenomas according to the standards taking into account the stage of the disease, complications and concomitant pathology;
- To render the first aid in extreme situations and exigent states.

III. Aims of personality development (educative aims):
- A student must learn to adhere to the rules of behaviour and principles of medical etiquette and deontology near a patient's bed;

Be able to set a psychological contact with a patient and his family;
- To master the sense of professional responsibility for a timeliness and adequacy of skilled medicare.

IV. Interdisciplinary integration:

Subject	To know	To be able
1. Previous (providing)		
Anatomy	Structure of the human's haemopoetic and lymphatic systems	
Histology	Structure of haemopoetic organs, their morphological features during the process of maturation	
Physiology	Physiology of haemopoetic organs and normal process of bone marrow maturation, normative indices of laboratory and instrumental methods and their value	To interpret the data of laboratory and instrumental investigational methods.
Pathologic physiology	Key links of leukomogenesis	
Pathologic anatomy	Morphological features of leukemias developing depend on the stage of the process	To analyse and interpret the information of clinical examination and about additional methods of investigation
Pharmacology	Pharmacokinetics and pharmacodynamics, preparations side effects	To prescribe age-dependent treatment of patient, taking into account individual

	(antibiotics, chemotherapy drugs, etc.), used in the treatment of patients with leukemias	features and period of disease, to establish the individual regimen of taking the preparations and their dosage. To prescribe recipes.
Propedeutical pediatrics.	Basic stages and methods of patient's clinical examination	To take complaints, anamnesis vitae et morbi, to find out the basic risk factors of leukemia, to conduct patient's examination, to reveal the clinical signs of leukemia, to interpret the data on additional methods of investigation.
Sternal puncture	Normative indices of sternal puncture	To interpret the information of sternal puncture
3. Intradiscipline integration		
Lymphogranulomatosis	Clinical signs of lymphogranulomatosis	To reveal the characteristic clinical signs of lymphogranolomatosis and differential diagnostics of the signs of leukemia
Non–Hodgkin disease	The signs of Non – Hodgkin disease	To reveal the main clinical signs of Non –Hodgkin disease and differential diagnostics among the signs of leukemia
Trombocitopenia	The signs of trombocitopenia	To reveal the characteristic clinical signs of trombocitopenia and differential diagnostics of the signs of leukemia.

V.   Contents of the theme:

Childhood ALL was the first disseminated cancer shown to be curable with chemotherapy and irradiation. ALL occurs slightly more frequently in boys than in girls. Reports of geographic clusters of childhood leukemia have suggested some shared environmental factor. However, careful review has not supported most of the proposed associations. Lymphoid leukemias occur more often than expected in

patients with immunodeficiency (congenital hypogammaglobulinemia, ataxia-telangiectasia) or with constitutional chromosomal defects (trisomy 21).

PATHOLOGY. Cases of ALL are subclassified according to morphologic, immunologic, and genetic features of the leukemic blast cells. Definitive diagnosis is generally based on examination of a bone marrow aspirate. The cytologic appearance of the blast cells is so variable, even within a single specimen, that no completely satisfactory morphologic classification has been devised. The French-American-British (FAB) system distinguishes three morphologic subtypes, L1 to L3. L1 lymphoblasts are predominantly small, with little cytoplasm; L2 cells are larger and pleomorphic with increased cytoplasm, irregular nuclear shape, and prominent nucleoli; and L3 cells have finely stippled and homogeneous nuclear chromatin, prominent nucleoli, and deep blue cytoplasm with prominent vacuolization Because of the subjective distinction between L1 and L2 blasts and a poor correlation with immunologic and genetic markers, only the L3 subtype is clinically meaningful.

Classification of ALL depends on a combination of cytologic, immunologic, and karyotypic features. With monoclonal antibodies that recognize lineage-associated cell surface and cytoplasmic antigens, the immunophenotype can be determined in most cases. Most are derived from B-progenitor cells; about 15% derive from T-progenitor cells; and 1% are from relatively mature B cells. These immunophenotypes have both prognostic and therapeutic implications. The subtypes of ALL, certain clinical characteristics, and their relative incidence rates are shown in Table 449–1 Table 449–1. A few cases cannot be readily classified because they demonstrate antigen expression associated with several different cell lineages (mixed lineage or biphenotypic ALL). Chromosomal abnormalities can be identified in at least 80–90% of childhood ALLs. The karyotypes of leukemic cells have diagnostic, prognostic, and therapeutic significance. They pinpoint sites for molecular studies to detect genes that may be involved in leukemic transformation. Childhood ALL can also be classified by the number of chromosomes per leukemic cell (ploidy) and by structural chromosomal rearrangements such as translocations.

Another biologic marker with potential usefulness is terminal deoxynucleotidyl transferase (TdT) activity, which is generally demonstrable in B-progenitor–cell and T-cell ALL. Because this enzyme is absent in normal lymphocytes, it can be useful in identifying leukemic cells in difficult diagnostic situations. For example, TdT activity in cells from cerebrospinal fluid may help to distinguish early central nervous system (CNS) relapse from aseptic meningitis. Most patients with leukemia have disseminated disease at diagnosis, with widespread bone marrow involvement and the presence of leukemic blast cells in circulating blood. Spleen, liver, and lymph nodes are also usually involved. Hence, there is no staging system for ALL.

CLINICAL MANIFESTATIONS. About 66% of children with ALL have had signs

and symptoms of their disease for less than 4 wk at the time of diagnosis. The first symptoms are usually nonspecific and include anorexia, irritability, and lethargy. There may be a history of viral respiratory infection or exanthem from which the child has not appeared to recover fully. Progressive bone marrow failure leads to pallor (anemia), bleeding (thrombocytopenia), and fever (neutropenia, malignancy)—{emdash}the features that usually prompt diagnostic studies.

On initial examination, most patients are pale, and about 50% have petechiae or mucous membrane bleeding. About 25% have fever, which may be ascribed to a specific cause such as upper respiratory infection or otitis media. Lymphadenopathy is occasionally prominent, and splenomegaly (usually extending less than 6 cm below the costal margin) is found in about 66%. Hepatomegaly is less common. About 25% present with significant bone pain and arthralgia caused by leukemic infiltration of the perichondral bone or joint or by leukemic expansion of the marrow cavity. Rarely, signs of increased intracranial pressure, such as headache and vomiting, indicate leukemic meningeal involvement. Children with T-cell ALL are likely to be older and are more often male; 66% have an anterior mediastinal mass, a feature that is strongly associated with this subtype of the disease

DIAGNOSIS. On initial examination, most have anemia, although only about 25% have hemoglobin levels below 6 g/dL. Most patients also have thrombocytopenia, but as many as 25% have platelet counts greater than 100,000/mm3. About 50% of patients have white blood cell counts less than 10,000/mm3; about 20% have counts greater than 50,000/mm3. The diagnosis of leukemia is suggested by the presence of blast cells on a peripheral blood smear but is confirmed by examination of bone marrow, which is usually completely replaced by leukemic lymphoblasts. Occasionally, the marrow is initially hypocellular. Cytogenetic studies in these cases may be useful in identifying specific abnormalities associated with preleukemic syndromes. If the marrow cannot be aspirated or the specimen is hypocellular, bone marrow biopsy is required. A chest radiograph is necessary to determine whether there is a mediastinal mass. Bone radiographs may show altered medullary trabeculae, cortical defects, or subepiphyseal bone resorption. These findings lack clinical or prognostic significance, and a skeletal survey is usually unnecessary. Cerebrospinal fluid should be examined for leukemic cells because early involvement of the CNS has important prognostic implications. Uric acid level and renal function should be determined before treatment is started

DIFFERENTIAL DIAGNOSIS. The diagnosis of ALL is usually straightforward once the possibility has been considered. Inclusion of ALL in the differential diagnosis may be delayed if a child has been sick and febrile with adenopathy for several weeks. The diseases included in the differential diagnosis are those also associated with bone marrow failure, such as aplastic anemia and myelofibrosis.

Infectious mononucleosis produces a somewhat similar clinical picture, but careful examination of the blood smear should identify atypical lymphocytes. If doubt remains, a bone marrow aspirate can demonstrate a normal cell population. Infiltration of the marrow by other types of malignant cells can occasionally produce pancytopenia. Pediatric tumors that can infiltrate marrow include neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and rarely retinoblastoma. These tumor cells are usually found in clumps scattered throughout normal marrow tissue but may occasionally replace the marrow completely. There is usually evidence of a primary tumor in some other site in these cases.

TREATMENT. Contemporary treatment of ALL is based on clinical risk features; there is no universal definition of risk groups. In general, patients with a standard or average risk of relapse are between the ages of 1 and 10 yr, have a white blood cell count under 100,000/mm3, lack evidence of mediastinal mass or of CNS leukemia, and have a B-progenitor–cell immunophenotype. The presence of certain specific chromosomal translocations should be ruled out. The treatment program for standard-risk patients includes administration of induction chemotherapy until the bone marrow no longer shows morphologically identifiable leukemic cells, "prophylactic" treatment of the CNS, and continuation chemotherapy. A combination of prednisone, vincristine (Oncovin), and asparaginase should produce remission in about 98% of children with standard-risk ALL, typically within 4 wk. Fewer than 5% of patients require another 2 wk of induction therapy. Systemic continuation therapy, usually consisting of the antimetabolites methotrexate and 6-mercaptopurine (Purinethol), should be given for 2.5–3 yr. In the absence of prophylactic treatment, the CNS is the initial site of relapse in more than 50% of patients. Leukemic cells are usually present in the meninges at diagnosis, even if they are not identifiable in the cerebrospinal fluid. These cells survive systemic chemotherapy because of the drug's poor penetration of the blood-brain barrier. Cranial irradiation prevents overt CNS leukemia in most patients but produces late neuropsychologic effects, particularly in younger children. Therefore, standard-risk patients typically receive intrathecal chemotherapy alone to prevent clinical CNS involvement. Most patients with T-cell ALL relapse within 3–4 yr if treated with a standard-risk regimen. With more intensive multidrug regimens, 50% or more of these patients achieve long-term remission. A goal is to develop targeted therapy that exploits the unique characteristics of leukemic T cells. As an example of this approach, monoclonal antibodies to T-cell–associated surface antigens can be conjugated to immunotoxins. The antibody-immunotoxin complex would then attach to T lymphoblasts, undergo endocytosis, and kill the cells. B-cell cases with L3 morphology and surface immunoglobulin expression once had a poor prognosis. Such patients are best treated with short (3–6 mo) but very intensive regimens developed for advanced B-cell

lymphoma. With this approach, cure rates have improved dramatically, from 20% a decade ago to 70% or more.

RELAPSE. The bone marrow is the most common site of relapse, although almost any site can be affected. In most centers, bone marrow is examined at regular intervals to confirm continued remission. If bone marrow relapse is detected, intensive retrieval therapy that includes drugs not used previously may achieve cures in 15–20% of patients, especially those who have had a long first remission (18 mo or more). For patients who experience bone marrow relapse during treatment, intensive chemotherapy followed by bone marrow transplantation from a matched sibling donor offers a better chance of cure. Autologous, mismatched related, or matched unrelated donor transplants are options for those without histocompatible sibling donors . The most important extramedullary sites of relapse are the CNS and the testes. The common early manifestations of CNS leukemia are due to increased intracranial pressure and include vomiting, headache, papilledema, and lethargy. Chemical meningitis secondary to intrathecal therapy can produce the same symptoms and must be considered. Convulsions and isolated cranial nerve palsies may occur with CNS leukemia or as side effects of vincristine. Hypothalamic involvement is rare but must be suspected in the presence of excessive weight gain or behavioral disturbances. In most cases, cerebrospinal fluid pressure is elevated, and the fluid shows a pleocytosis due to leukemic cells. If the cell count is normal, leukemic cells may be found in smears of cerebrospinal fluid specimens after centrifugation. Patients with CNS relapse should be given intrathecal chemotherapy weekly for 4–6 wk until lymphoblasts have disappeared from the cerebrospinal fluid. Doses should be age-adjusted because cerebrospinal fluid volume is not proportional to body surface area Cranial irradiation is the only treatment that completely eradicates overt CNS leukemia and should be given after intrathecal therapy. Systemic treatment should also be intensified because these patients are at high risk of subsequent bone marrow relapse. Finally, preventive CNS therapy should be repeated in any patient whose disease has relapsed in the bone marrow or in any extramedullary site. Testicular relapse generally produces painless swelling of one or both testicles. The patient is often unaware of the abnormality, mandating careful attention to testicular size at diagnosis and during follow-up. The diagnosis is confirmed by biopsy. Treatment should include irradiation of the gonads. Because a testicular relapse usually signals impending bone marrow relapse, systemic therapy should be reinforced for patients who are still undergoing treatment or reinstituted for those who have a relapse after treatment. As noted above, CNS-directed therapy should also be repeated.

PROGNOSIS. Numerous clinical features have emerged as prognostic indicators, only to lose their significance as treatment improves. For example,

immunophenotype is important in assigning risk-directed therapy, but its prognostic significance has largely been eliminated by contemporary treatment regimens. Hence, treatment is the single most important prognostic factor. The initial leukocyte count has a consistent inverse linear relationship to the likelihood of cure. Age at diagnosis is also a reliable predictor. Patients older than 10 yr, and those younger than 12 mo who have a chromosomal rearrangement involving the 11q23 region, fare much worse than children in the intermediate age group. Several chromosomal abnormalities influence treatment outcome. Hyperdiploidy with more than 50 chromosomes is associated with a favorable outcome and responds well to antimetabolite-based therapy. Two chromosomal translocations—{emdash}the t(9;22), or Philadelphia chromosome, and the t(4;11)—{emdash}confer a poor prognosis. Several investigators advocate bone marrow transplantation during initial remission in patients with these translocations. B-progenitor–cell ALL with the t(1;19) has a less promising prognosis than other cases with this immunophenotype; only 60% of patients will be in remission after 5 yr unless very intensive therapy is used.

Acute Myeloid Leukemia

AML has an annual incidence of five to six cases per million in children younger than 15 yr. In the United States, this is 350–500 new cases each year. AML constitutes 15–20% of all childhood leukemias but is the predominant neonatal or congenital leukemia. There are no clear racial or gender differences in incidence and, except for a slight increase during adolescence, the distribution of cases by age is consistent throughout childhood. The incidence of AML exceeds expected rates in certain genetic disorders, including trisomy 21, Fanconi anemia, Diamond-Blackfan anemia, Kostmann syndrome, and Bloom syndrome. Children previously treated for another malignancy are also at increased risk; the incidence of secondary AML approaches 5% after treatment of some malignancies. The incidence of secondary AML peaks within 10 yr of the initial malignancy. Its occurrence is associated with specific therapies (alkylating drugs such as cyclophosphamide, agents that inhibit DNA repair such as etoposide). Radiation therapy given with chemotherapy also increases the risk of secondary leukemia.

CLINICAL MANIFESTATIONS. AML typically presents with signs and symptoms attributable to bone marrow failure. AML must be considered in the evaluation of any patient with pallor, fever, infection, or bleeding. Bone pain is less common than in ALL. Liver and spleen enlargement is common; lymphadenopathy may be present. Unexplained gingival hypertrophy or parotid gland swelling are uncommon but suggestive findings. A localized mass of leukemic cells (chloroma), may develop at any site, but retro-orbital and epidural locations are most likely. Chloroma may precede leukemic cell infiltration of bone marrow. Blood counts are usually

abnormal; anemia and thrombocytopenia are often profound. The white blood cell count may be high, low, or normal. Leukemic blasts may be evident on the blood smear. AML can develop in children who present initially with only anemia, leukopenia, or thrombocytopenia. This presentation, which is more common among adults, is typically termed myelodysplastic syndrome. Characteristic features include abnormal morphology of blood and bone marrow cells and the presence of blast cells in the bone marrow. The natural history of myelodysplastic syndrome in children is not well characterized, but most cases evolve into AML. Like secondary AML, myelodysplastic syndrome can develop in children treated for a prior malignancy.

DIAGNOSIS. The presence of at least 30% leukemic blast cells in the bone marrow is necessary for the diagnosis of AML. The morphology and cytochemical analysis (histochemical stain positive for myeloperoxidase, Sudan black, or nonspecific esterase) of the leukemic blasts usually suffice to distinguish AML from ALL. Within the AML category, however, morphology may be variable. For contemporary classification and treatment of AML, leukemic blast cells must be characterized by their expression of cell surface antigens (immunophenotype) and by chromosomal analysis (karyotype). The FAB system divides AML into eight subtypes, M0 to M7, which broadly correspond to normal hematopoietic lineages. Among children, the number of patients with the M0, M1, and M2 subtypes approximates the number of M4 and M5 cases; together, these FAB types account for 80% of childhood AMLs. The M3 and M7 subtypes are less common, and M6 is rare. This classification system facilitates study of the clinical course and allows comparisons of various therapies. Specific molecular events underlie some FAB types. Although hemorrhagic diathesis (disseminated intravascular coagulation at presentation or later) may occur in any of the FAB groups, patients with acute promyelocytic leukemia (M3) are especially at risk. An almost invariant finding in this subtype is translocation of genetic material between chromosomes 15 and 17, producing a fusion gene that includes the gene encoding the a{alpha}-retinoic acid receptor. Retinoic acid can effectively induce remission in these patients. Translocation between chromosomes 8 and 21, typically present in the M2 subtype, is closely associated with chloroma. Inversion of genetic material in chromosome 16 can be found in M4 AML, in which eosinophilia is a prominent feature.

Myelodysplastic syndrome bears some resemblance to AML, but the bone marrow contains a lower percentage of blast cells and has characteristic dysplastic features, including megaloblastosis. Patients may not be ill at presentation and isolated anemia or leukopenia may bring them to medical attention. Chromosomal changes, including trisomy 8 and complete or partial deletion of chromosome 5 or 7, may be present. Deletion of chromosome 5 or 7 is particularly common in secondary myelodysplastic syndromes and secondary AML. Juvenile chronic myelogenous leukemia (JCML) is

unlike adult-type CML but may have features similar to those of AML and myelodysplastic syndrome. The Philadelphia chromosome is not present in JCML. Nonspecific signs and symptoms include fever, malaise, liver and spleen enlargement, and adenopathy. A chronic desquamative maculopapular skin eruption often predates the diagnosis. Striking elevation of hemoglobin F, which may exceed 50%, and leukocytosis (primarily blood and bone marrow monocytosis) are the predominant findings. JCML is rare in patients older than 5 yr of age and may be more common among children with type 1 neurofibromatosis; familial or hereditary cases have been documented.

TREATMENT. Therapy for AML has improved but remains unsatisfactory. Between 70–80% of patients achieve remission after treatment with chemotherapeutic regimens that include an anthracycline (daunomycin, idarubicin) and cytarabine. Optimal supportive care is critical to afford patients sufficient time to respond to treatment because most nonresponding patients die from infections or chemotherapy-related toxicity. Remission may occur within 2–3 wk after treatment is started but can also take 8–12 wk or longer and may require several courses of chemotherapy. Patients who do not respond to induction therapy are candidates for allogeneic transplantation. Hemorrhage secondary to pathologic activation of clotting and/or fibrinolytic factors is a particular problem in acute promyelocytic leukemia, but laboratory studies to detect disseminated intravascular coagulation should also be performed for other AML variants. Transfusion of platelets and fresh frozen plasma is mandatory for patients with disseminated intravascular coagulation; the need for heparin or antifibrinolytic therapies is less certain. Retinoic acid as initial treatment for acute promyelocytic leukemia may reduce the risk of hemorrhage but is not curative. Multiagent chemotherapy given as remission induction and consolidation may cure most patients, however. Once patients achieve remission, the optimal continuation therapy is undefined. Options include autologous or allogeneic bone marrow transplantation or intensive chemotherapy; none of these approaches has demonstrated an absolute survival advantage. Allogeneic bone marrow transplantation during first remission is limited to patients with a suitable sibling donor. Intrathecal chemotherapy is necessary to prevent CNS relapse. Intrathecal chemotherapy can usually clear leukemic cells from the cerebrospinal fluid in patients who have CNS leukemia at diagnosis (~10% of cases) or who have a CNS relapse, but CNS irradiation may be required to eradicate leukemia permanently.

Because myelodysplastic syndrome is likely to evolve into leukemia, patients are usually treated on AML protocols. If the patient is relatively asymptomatic, therapy may be delayed until symptoms progress. Remission induction is less successful in myelodysplastic syndrome than in AML. Because of this treatment resistance and other considerations, allogeneic marrow transplantation is often the preferred

treatment. For similar reasons, allogeneic BMT is recommended for patients with JCML. When a histocompatibility antigen (HLA) genotype-matched donor is not available, a partially matched relative or a matched unrelated donor may be considered.

PROGNOSIS. With aggressive therapy, 40–50% of patients who achieve remission will be long-term survivors (30–40% overall cure rate). Patients who have relapses after receiving chemotherapy or autologous transplantation may be treated with allogeneic transplantation as salvage therapy. Some morphologic and genetic subtypes of AML have a better prognosis.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal malignancy of the hematopoietic stem cell characterized by a specific translocation, the t(9;22)(q34;q1), known as the Philadelphia chromosome. This translocation juxtaposes the bcr gene on chromosome 22 with the abl gene on chromosome 9, producing a fusion gene that encodes the bcr-abl fusion protein. CML is more common in adults and accounts for only 3% of cases of childhood leukemia. In most cases, there are no predisposing features. CML has a biphasic or triphasic course. During the chronic phase, which lasts for 3–4 yr, white blood cell counts are easily controlled with low-dose chemotherapy. Progression to a myeloid or lymphoid blast crisis that resembles acute leukemia may occur rapidly or may follow an accelerated phase wherein blood counts become difficult to control and additional cytogenetic abnormalities may develop.

PATHOLOGY. CML is characterized by myeloid hyperplasia with increased numbers of differentiating myeloid cells in blood and bone marrow. The pathognomonic Philadelphia chromosome is easily detectable in more than 95% of cases; in most of the remaining patients, Southern blot analysis or polymerase chain reaction techniques reveal the bcr-abl rearrangement.

CLINICAL FEATURES. The onset of symptoms is generally insidious, and the diagnosis is often made when a blood count is performed for another reason. Patients may present with splenomegaly (which can be massive) or with symptoms of hypermetabolism, including weight loss, anorexia, and night sweats. Symptoms of leukostasis, such as visual disturbance or priapism, occur rarely.

DIAGNOSIS. Laboratory abnormalities are usually confined initially to elevated white blood cell counts, which may exceed 100,000/mm3, with all forms of myeloid cells seen in the blood smear. Platelet counts may also be abnormally high. Other laboratory abnormalities include elevated serum levels of vitamin B12 and uric acid and reduced or absent leukocyte alkaline phosphatase activity. The bone marrow is hypercellular, with normal myeloid cells in all stages of differentiation; megakaryocytes may be more numerous. Cytogenetic or molecular studies showing the Philadelphia chromosome confirm the diagnosis.

TREATMENT. In the chronic phase, leukocytosis and symptoms can be controlled by chemotherapy with busulfan (Myleran) or hydroxyurea, but the Philadelphia chromosome is not suppressed. In addition to controlling the leukocytosis, interferon-a{alpha} also suppresses the Philadelphia chromosome completely, in about 20% of cases, and it appears to lengthen the chronic phase. However, the only curative treatment at present is allogenic bone marrow transplant. The long-term survival rate of pediatric patients who receive an allograft from an HLA-identical sibling in early chronic phase is around 80%. This is the preferred therapy if an appropriate donor is available. When the donor is a partially matched family member or a matched unrelated individual, the transplant-related mortality rate is higher, and the survival rate is around 50–60%. Lymphoid blast crisis can usually be reverted to the chronic phase with standard ALL therapy, whereas myeloid crisis is generally refractory to standard AML chemotherapy; the median survival is only 3–4 mo. If bone marrow transplant is delayed until blast crisis occurs, the survival rate is only 10–20%.

Congenital Leukemia

Congenital leukemia is an extremely rare disease, diagnosed within the first month of life at a rate of 4.7 per million live births. Myeloid leukemia appears to be predominant in this group. Generally, cases present with marked leukocytosis, petechiae, ecchymoses, and extramedullary involvement, with massive hepatosplenomegaly, cutaneous nodules, and CNS leukemia. Neuroblastoma and leukemoid reactions secondary to erythroblastosis fetalis and severe congenital bacterial or viral infection may mimic congenital leukemia, but these can be ruled out by appropriate laboratory studies. More difficult to differentiate is transient myeloproliferative disorder, which occurs primarily in neonates with trisomy 21 or chromosome 21 mosaicism. Most transient myeloproliferative disorders undergo spontaneous remission within a few weeks. Thus, patients should receive only supportive measures initially but require careful follow-up because some will have leukemia months or years later.

Congenital leukemia has a poor prognosis, especially in cases with leukemic cell chromosomal rearrangements affecting the q23 region of chromosome 11. Although the short latency period suggests genetic predisposition, studies suggest that intrauterine exposure to carcinogens is responsible for at least some cases of leukemia in very young children. Examples of FAB morphologic subtypes of ALL. A, L1 blasts are small with scanty cytoplasm; B, L2 blasts are larger with more cytoplasm, irregular nuclear membranes, and prominent nucleoli; C, L3 blasts have basophilic cytoplasm with vacuolization.

LYMPHOMA

Lymphoma is the third most common cancer in children in the United States, with an annual incidence rate of 13.2 per million children. The two broad categories of

lymphoma, Hodgkin disease and non-Hodgkin lymphoma (NHL), have different clinical manifestations, treatments, and prognoses.

Hodgkin Disease

EPIDEMIOLOGY. The age-associated incidence of Hodgkin disease is bimodal. In industrialized countries, the early peak occurs in the middle to late 20s and the 2nd peak after the age of 50 yr. Other epidemiologic features include a higher frequency in males, whites, and patients with underlying immunodeficiency. Familial occurrence has been noted, particularly in same-sex siblings; the reasons for this are unclear. Increasing evidence suggests that Epstein-Barr virus (EBV) may be implicated in pathogenesis, as evidenced by detection of the EBV genomes in some histologic subtypes of Hodgkin disease.

PATHOLOGY. The cardinal histologic feature is the Reed-Sternberg cell . The cell of origin may be an activated antigen-presenting cell such as a lymphoid cell of B- or T-cell origin or even a cell of monocytic lineage. There are four histologic subtypes of Hodgkin disease, each with special clinical and prognostic features. The distribution of subtypes varies with age.

The nodular sclerosing variety is the most common form, accounting for 50% of cases in children and 70% in adolescents. Broad bands of collagen divide the involved lymph node into nodular cellular areas. A special cytologic feature is clear spaces surrounding "lacunar cells," variants of the Reed-Sternberg cell. Because of the amount of collagen, the radiographic appearance of these lesions may be slow to normalize, even when the patient responds to therapy. Hodgkin disease of mixed cellularity is the second most common form, affecting 40–50% of patients. It is characterized by an inflammatory background of lymphocytes, plasma cells, eosinophils, histiocytes, and malignant reticular cells; Reed-Sternberg cells are usually abundant. Patients with this subtype are more likely to present with advanced disease and extranodal extension. In the lymphocyte predominance variety, most of the cells appear to be mature lymphocytes or a mixture of lymphocytes and benign histiocytes, with only occasional Reed-Sternberg cells. This type affects 10–20% of patients with Hodgkin disease, is more common in males and younger patients, usually presents with clinically localized disease, and has the best prognosis. The least common and least favorable form is the lymphocytic depletion variety, which affects fewer than 10% of patients overall but is a common histologic type in patients infected with the human immunodeficiency virus. Numerous bizarre malignant reticular cells are found, along with Reed-Sternberg cells and relatively few lymphocytes. Patients with this histologic type commonly present with widespread disease involving the bones and bone marrow. Hodgkin disease usually arises in lymph nodes. Adjacent lymph node areas are the first site of spread, presumably as a result of direct anatomic extension along lymphoid channels. The most common sites

of extranodal involvement are lung, bone, bone marrow, and liver.

CLINICAL MANIFESTATIONS. The most common presenting feature is painless enlargement of lymph nodes in cervical, supraclavicular, or occasionally axillary or inguinal areas. The affected nodes are firm, nontender, and usually discrete. Characteristically, there is no evidence of regional inflammation that would explain the lymphadenopathy. Mediastinal lymph node enlargement is common and can produce a cough or other symptoms of airway compression. In younger children, the nodes can be difficult to distinguish from a large, normal thymus, although computed tomography (CT) or magnetic resonance imaging (MRI) of the mediastinum may reveal differences in texture. About 33% of patients with Hodgkin disease have nonspecific systemic manifestations that include fatigue, pruritus, urticaria, pain that worsens with ingestion of alcohol, lethargy, and anorexia. The specific symptoms of unexplained fever, weight loss of at least 10% in the previous 6 mo, and night sweats are thought to be of prognostic significance and are incorporated in staging assignment by the "B" designation (whereas "A" indicates the absence of any of these symptoms). Extranodal involvement occurs in 10–15% of patients at diagnosis and is seen most commonly in intrathoracic structures (lung, pleura, pericardium). Lung involvement may be represented radiographically by diffuse fluffy infiltrates that can be difficult to distinguish from disseminated fungal infection. Fever and tachypnea are common with intrathoracic disease, and pulmonary insufficiency may develop.

Rare presentations include intrahepatic biliary obstructive disease. With progression, signs of hepatocellular disease may develop. Extremely advanced bone marrow involvement may result in neutropenia, thrombocytopenia, and anemia. Extradural tumor masses in the spinal canal can cause spinal cord compression. A variety of immune disorders have also been observed, such as autoimmune hemolytic anemia, and thrombocytopenia, and the nephrotic syndrome. Cellular immunity is impaired by Hodgkin disease and its treatment. Affected patients are at increased risk of infections characteristically seen in immunosuppressed patients (see Table 448–3 Table 448–3). Varicella-zoster infections occur in up to 33% of patients and should be treated with intravenous acyclovir (Zovirax); fungal infections, such as cryptococcosis, histoplasmosis, and candidiasis, may become disseminated. Humoral immune function may also be transiently depressed after treatment.

DIAGNOSIS. Hodgkin disease should be suspected in patients with persistent unexplained lymphadenopathy. The disease is more common in late childhood and adolescence, when cervical lymphadenopathy resulting from infection is also common. Lymph node biopsy is indicated for persistent lymphadenopathy without evidence of an underlying inflammatory process. Some patients have a history of relatively recent, serologically proved infectious mononucleosis. Hence, enlarged nodes that do not regress after infectious mononucleosis should also be considered

for biopsy. Before biopsy is performed, a chest radiograph should be done to explore the possibility of mediastinal involvement and to examine airway patency. Changes in the white blood cell count can include a neutrophilic leukocytosis, lymphopenia, or sometimes eosinophilia and monocytosis. Anemia and thrombocytopenia occur only in patients with disseminated disease. Elevated acute-phase reactants, such as erythrocyte sedimentation rate and serum copper and ferritin levels, may be useful, albeit nonspecific, markers of disease activity.

Once the diagnosis is confirmed, extensive staging procedures are performed to establish the extent of the disease. Most patients first present with evidence of lymph node enlargement above the diaphragm; therefore, a radiograph and CT scan of the chest should be performed. CT scans may show disease when radiographs appear normal and can also evaluate the extent of pericardial and chest wall involvement.

Abdominal imaging studies (CT or MRI) can indicate the presence of focal lesions in the liver or spleen and node enlargement but cannot define the nature of the underlying process. Liver function tests are unreliable indicators of hepatic disease, and the size of the spleen correlates poorly with splenic involvement. Lymphangiography is generally accurate in indicating lymph node involvement below the level of the second lumbar vertebra; involved lymph nodes above that level may not take up contrast material because of lymphatic drainage into the thoracic duct. Although lymphangiography can provide useful information about nodal size and architecture, the examination is technically difficult in children, carries some degree of risk, and is available only in selected centers. Traditionally, a staging laparotomy was performed to determine the presence and extent of abdominal disease. At laparotomy, the spleen is removed, a biopsy is done of the liver, and samples are taken of retroperitoneal and pelvic nodes. For female patients, if radiotherapy to the pelvis is contemplated, the ovaries are moved to a midline position posterior to the uterus to minimize exposure. In about 33% of cases, the clinical disease stage is revised on the basis of such anatomic findings. However, in view of the potential morbidity of the surgery and the long-term risks of splenectomy, there is a growing opinion that staging laparotomy is indicated only when the findings will significantly alter therapy. Bone marrow biopsies should be done in all patients with advanced-stage disease. A bone scan and correlating plain films of abnormal areas define the presence of skeletal metastases and should be considered in patients with bone pain, elevated alkaline phosphatase levels, or extranodal disease identified by other staging modalities.

TREATMENT. Both radiation and chemotherapy are highly effective in the treatment of Hodgkin disease. The goal is to achieve cure while lessening treatment toxicity. For localized (stage I or IIA) disease in patients who have achieved their full growth, radiation to standard fields with doses of 3,500–4,406 cGy may be the

treatment of choice. However, as many as 15% of such patients will have recurrences and require combination chemotherapy. Multiagent chemotherapy with nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone (MOPP), or with doxorubicin (Adriamycin), bleomycin (Blenoxane), vinblastine (Velban), and dacarbazine (ABVD) can produce long-term disease-free periods for patients with advanced disease. The use of alternating noncross-resistant regimens (MOPP/ABVD) in combination with low-dose (2,000–2,500 cGy) radiotherapy has produced cure rates of 70–90% in pediatric patients with advanced-stage disease. This approach is favored by pediatric oncologists for three reasons: (1) potential growth defects and the risk of second solid tumors are reduced by limiting the radiotherapy dose and volume, (2) the risk of infertility and leukemogenesis is decreased by reduced exposure to alkylating agents, and (3) exposure to drugs with potential cardiopulmonary toxicity is limited. Combined-modality regimens with localized radiotherapy and fewer cycles of chemotherapy are being studied to determine whether currently excellent cure rates can be maintained.

PROGNOSIS. With modern treatment, more than 90% of patients with Hodgkin disease achieve an initial complete remission. The likelihood of prolonged remission or cure is related to disease stage at diagnosis. Most patients with stage I/II disease are cured, as are 75–90% of those with stage III disease treated with both chemotherapy and radiation, and 60–85% of those with stage IV disease treated with chemotherapy with or without radiotherapy. The longer survival of patients has generated concern about late sequelae of treatment (see Table 448–4 Table 448–4). Complications of irradiation depend on site, dosage, volume, and age at treatment. Supradiaphragmatic irradiation may lead to restrictive lung capacity, cardiac dysfunction, late-onset breast cancer, or hypothyroidism. Pelvic irradiation can cause sterility despite ovarian and testicular shielding. In the younger child, growth of the vertebral column, clavicles, and breast buds can be affected. Because of concerns regarding growth, standard-dose radiation is rarely given to children. Late pulmonary and cardiac toxicity may also develop after treatment with bleomycin or doxorubicin, respectively. MOPP and other regimens that contain alkylators can cause sterility in male or premature menopause in female patients. Second malignant tumors are a major concern. The most common second malignant neoplasm in Hodgkin survivors is acute myeloid leukemia (AML). The reported risk of secondary AML ranges from 1.2–13% at 10 yr, with most cases diagnosed 5–10 yr after treatment. The risk of a second malignant solid tumor increases with time after diagnosis, ranging from 13–20% at 15 yr. These tumors usually occur in or at the margins of the radiotherapy field A fraction of patients (1–2%) who have undergone splenectomy may have overwhelming sepsis caused by Streptococcus pneumoniae or Haemophilus influenzae. The risk of this complication has been substantially reduced by routine

immunization with pneumococcal and H. influenzae B vaccines and by the use of prophylactic antibiotics. Abdominal adhesions may also develop in patients who have had laparotomy, particularly if the abdomen has been irradiated.

Non-Hodgkin Lymphoma

The NHLs are malignant clonal proliferations of primarily T or B lymphocytes that present with varying degrees of tumor burden. These malignancies should not be confused with polyclonal lymphoproliferative disorders. Both groups of diseases occur with increased frequency in children with inherited immunodeficiency states such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, combined immune deficiencies, and the X-linked lymphoproliferative (XLP) syndrome. The XLP syndrome is characterized by marked sensitivity to EBV-induced diseases, including fatal infectious mononucleosis, which occurs in approximately 57% of cases. NHL that involves the bone marrow is distinguished from acute lymphoblastic leukemia by the degree of marrow involvement. Patients with greater than 25% marrow replacement are included with acute lymphoblastic leukemia (ALL), and the remaining cases are designated as having NHL with marrow involvement.

PATHOLOGY. The NHLs of childhood, in contrast to those of adults, are usually diffuse, extranodal, high-grade tumors. To eliminate the confusion created by multiple classification schemes, the National Cancer Institute developed a histologic system, which defines three primary subtypes of high-grade NHL: small noncleaved cell (SNCC), lymphoblastic, and large cell. The SNCC NHLs (Burkitt and non-Burkitt subtypes) are B-cell tumors that express surface immunoglobulin and contain one of three characteristic chromosomal translocations each of which involves the c-myc oncogene and an immunoglobulin gene (mu heavy chain, kappa light chain, and lambda light chain, respectively). Lymphoblastic lymphomas are usually of T-cell origin and may contain a translocation involving a T-cell receptor gene. Large cell NHLs occur as T-cell, B-cell or non-B, non-T-cell phenotypes; the t(2;5)(p23;q35) may be present in association with CD30 expression.

CLINICAL MANIFESTATIONS. The presenting signs and symptoms of NHL in children are largely determined by disease site and extent. The most frequent primary sites are the abdomen (31.4%), mediastinum (26%), and the head/neck region, including Waldeyer ring and/or cervical lymph nodes (29%). Noncervical lymph nodes are the primary sites in 6.5% of cases with skin, thyroid, epidural space, and bone accounting for the remainder (7%).

There is a striking association between histologic subtype and disease site. Lymphoblastic NHL usually occurs in the head and neck region or the anterior mediastinum; SNCC primary tumors arise in the abdomen and/or the head and neck; and large cell NHL may present in any anatomic location. Head and neck primaries are usually painless masses arising from cervical lymph nodes or tonsils. Mediastinal

masses may be associated with pleural effusions, respiratory distress, or superior vena cava syndrome (swelling of arms, neck, and face). Abdominal masses usually arise from the ileocecal region and may be associated with abdominal distention, nausea, vomiting, or change in bowel habits, a clinical picture similar to appendicitis or intussusception. Bone marrow involvement may cause anemia or thrombocytopenia and central nervous system disease may result in headache, increased intracranial pressure, or cranial nerve palsies.

DIAGNOSIS. The diagnostic and staging workup of a child with suspected NHL must be expeditious because of the rapid growth rate of these tumors. A tissue diagnosis is necessary before treatment is started. Excisional biopsy or fine-needle aspirate is usually sufficient to evaluate an isolated peripheral node. A mediastinal mass can be evaluated by thoracotomy or mediastinoscopy, parasternal fine-needle aspiration, or thoracentesis (if there is an associated pleural effusion). An open biopsy is usually necessary for abdominal masses, although percutaneous needle biopsy is occasionally feasible.

Once the diagnosis is established, a staging workup must be completed. The most widely used staging system is noted in Table 450–2 Table 450–2. The evaluation includes a complete history, physical examination, and numerous laboratory studies (complete blood count and levels of electrolytes, blood urea nitrogen, lactate dehydrogenase [LDH], calcium, phosphorus, and uric acid). Bone marrow and cerebrospinal fluid examinations must be performed. Diagnostic imaging studies include CT of the primary site, chest, abdomen, and pelvis, bone scan, and (in some settings) gallium-67 scan. Staging laparotomy and lymphangiography are not part of the standard evaluation.

TREATMENT. With the development of effective multiagent chemotherapy, most children with NHL are cured. Tumor lysis syndrome is common. A randomized trial comparing two of the first successful treatment regimens (the cyclophosphamide-based COMP regimen and the intensive multiagent LSA2L2 regimen) demonstrated that the prognosis for limited-stage disease was excellent with either treatment. However, among patients with advanced-stage disease, those with lymphoblastic NHL had a better outcome when treated with LSA2L2; those with SNCC histologic type had a better outcome with COMP.

Current strategies for patients with limited-stage disease focus on reducing morbidity without compromising cure rates. For advanced-stage disease, clinical trials focus on improving treatment outcome with histology-directed therapy that incorporates adequate CNS prophylaxis. The most effective treatments for lymphoblastic disease derive from multiagent regimens designed for the treatment of ALL, delivered over 1–2.5 yr. Cyclophosphamide remains an important component of the highly intensive regimens for SNCC NHL, which are delivered over 2–12 mo. The most effective

protocols for large cell NHL usually contain cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), given for 12–24 mo. Surgery plays little role in management unless there is a completely resected abdominal mass. Involved field radiation is generally not included in the primary therapy.

PROGNOSIS. With modern therapy, the 2-yr event-free survival (EFS) is approximately 90% for children with limited-stage disease and approximately 70% for those with stage III and IV disease. Improvements in the treatment of advanced-stage SNCC NHL have resulted in a 90% 2-yr EFS (70% for those with central nervous system disease). The stage of disease and the log of the serum LDH level at diagnosis have independent prognostic significance. Reed-Sternberg cell that contains two nuclei, each with a prominent nucleolus and distinct nuclear membrane. The cytoplasm of this cell is relatively abundant. Other cells present are lymphocytes, plasma cells, and tissue mononuclear cells. Presence of these cells in lymph node tissue is diagnostic of Hodgkin disease.

VI. Plan and organizational structure of classes.

№	Basic stages of classes, their function and maintenance	Edu-cational aims are in the levels of mastering	Methods of control and studies	Educational materials	Distri-buting of time in mi-nutes
1	Preparatory stage Organizational measures	α2		I «Actuality of the theme»	3 min.
2	Raising of educational aims and motivation	α2		II «Educational aims» The second level tests Typical situational	12 min.
3	Control of basic knowledge and skills level:	α2	Individual (oral) questioning	tasks of 2 level Typical situational tasks of 2 level	20 min.
	1. Etiology of leukemias in children.	α2	Test control of second level	The second level tests Typical situational tasks of 2 level	
	2. Key links of leukemias patho-genesis.	α2	Individual (oral) questioning Typical situational	Kit of medicines.	
	3. Cytomorpholo-gical and im-munological classi-fication of leukemias in children.	α2	task of 2 level Typical situational task of 2 level Typical situational task of 2 level		
	4. Acute lympho-blast leukemia-as, the features of diagnostics.	α2	Test control of		

	5. Chronic myelo-blast leukemia, the features of clinic and diagnostics.	α2	second level Typical situational task of 2 level		
	6. Laboratory and insrtumental diagnosis of leukemias in children.	α2			
	7. Complications of leukemias in children.	α2			
	8. The treament of leukemias in children.	α2			
4	Basic stage of professional skills and abilities forming				115 min.
	1. To conduct the patient's management, to take complaints and anamnesis.	α3	Practical professional training.	Patient.	
	2. Conducting of patient's examination to reveal the main symptoms and syndromes of leukemia.	α3	Practical professional training.	Case history. A reference chart for forming professional abilities. Case history. A reference chart for forming professional skills.	
	3. To formulate and substantiate the provisional diagnosis.	α3	Practical professional training.	Situational typical tasks of the third level/the third level tests.	
	4. To compose the plan of patient's laboratory and instrumental investigation.	α3	Practical professional training.	A reference chart for forming of professional abilities. Situational typical tasks of the third level. The third level tests.	
	5. To make a differential diagnosis among clinical conditions accompanied by lymphatic nodes enlargement, rising in body temperature,	α3	Practical professional training. Third level test control. The practical professional training is in the salvation of non	Prescribing chart. Non typical situational tasks and the third level tests. Treatment algorythm of the leukemia's treatment. Non typical situational tasks. The first aid algorythm	

			standard clinical situations. Third level test control. Practical professional training.	in leukemias.	
	6. To give recommendations for regimen and diet of a patient with leukemia.	α3			
	7. To compose the plan of patient's treatment taking into account the stage of disease and the presence of complications.	α3	The practical professional training is in the salvation of non standard clinical situations.		
	8.To be able to render the first aid in extreme situations	α3	The third level test control. The practical professional training in solving of non typical clinical situations.		
5 6 7	Concluding stage. Control and cor-rection of pro-fesssional abili-ties and skills. Working out the totals of class. Home work (ba-sic and additional literature on the topic)		Analysis of clinical work. Salving of non typical tasks and third level tests. Estimation of the clinical work.	Clinical work. The third level non typical situational tasks. A reference chart for independent work with literature.	30 min.

Methodical materials for the class basic stage supporting

A professional algorythm of patient's management (reference chart) for the practical skills and abilities forming.

№	Task	Sequence of implementation	Remarks and warnings related to self-control
1	To conduct an examination of a patient with leukemia	1.To conduct the complaints and disease's anamnesis taking. 1.To conduct the complaints and disease's anamnesis taking. 3.To conduct examination of the patient.	To pay attention to the features of disease course, underlying factors, concomitant diseases etc. To establish the risk factors of the disease occurrence. To assess patient's

			general condition, position in bed, color and wetness of skin and mocouses, presence of neck veins and extremities swelling.
		4.To examine lymphatic nodes system of the patient (palpation).	To pay regard to the rhythm of pulse, it tension and size on both hands, apex shove, its properties, margins of absolute and relative cardiac dullness, its changes, HR (tachi or bradicardia, extrasystole), BP.
		5.To conduct condition of heart and main vessels auscultation.	To pay regard to heart tones weakening or amplifying, appearance of murmurs and additional III, IV tones.
		6.To investigate the pulmonary system (percussion, bronchophony). 7.To conduct lungs auscultation. 8.To investigate the digestion system.	To pay attention to the features of percussion and auscultation in different aged children.
2	To formulate the initial diagnosis.	1.To formulate the initial diagnosis 2.To substantiate all the components of initial diagnosis, based on complaints,anamnesis, and examinations.	Taking the classifyca- tion as a starting point to formulate the initial diagnosis of leukemia and to substantiate each component of it.
3	To evaluate the parameters of additional laboratory investigations.	1.To evaluate the blood count data. 2.To interpret the data of CSF.	To pay attention to the presence of leucocyto- sis, shifting of formula, increasing of SR, pre- sence of blasts. To pay attention to the presence of blasts and their morphology, fea- tures of red stem in SP. To pay attention to

			agent and sensitiveness to antibiotics.
4	To understand the data of additional and laboratory investigation.	To understand the chest X-Ray data, SP, ECG, and ultrasound.	To pay special attention to the signs of pneumonia, lungs infiltration, to additional formations in lungs etc., ECG signs, hepatosplenome by ultrasound.
5	To conduct differential diagnosis.	1.Consistently to find the common signs in complaints,life and disease anamnesis, data of the examination, data of laboratory and instrumental examination of the patient and in similar states. 2.To find out the differences between complaints, information of life and disease anamnesis, examination data, information about the laboratory and instrumental methods of research and in similar nosology. 3.On the basis of the differences to found out similar diseases from the list of probable diagnoses. 4. To conduct differential diagnostics according to the mentioned algorithm among all the nosologies which have the similar signs. 5.Taking into account the impossibility to exclude the diagnosis of leukemia from the list of probable diagnoses to draw a conclusion about the highest degree of probability of such diagnosis.	Special attention must be payed to differential diagnosis among the lymphogranulo-matosis, non–Hodgkin disease and hemorrhagic syndromes.
6	To formulate the concluding clinical diagnosis.	1. To formulate the final clinical diagnosis. 2. Taking as a starting point the provisional diagnosis, additionnal investigations data, conducted differential diagnosis to substantiate all the elements of concluding clinical diagnosis.	Taking as a starting point the classification of leukemia to formulate a provisional diagnosis, complications of the disease and the presence of concomitant diseases.

7	To prescribe treatment for patient.	1.To prescribe non medicinal treatment. 2.To prescribe the medicinal treatment	Expressly to specify the regimen and detalized diet according to the disease. Taking into account the age, severity of the patient's state, the stage of the disease, the presence of complications and concomitant pathology, to prescribe modern medicinal treatment in accordance with the standards of leukemia's therapy.

VII. Material for the control and medical providing of the class.

A question for initial level control of knowledge, skills and abilities:

Definition of hemoblastoses.

1. To determine an etiology of acute and chronic leukemias in children.
2. To specify the key links of leukogenesis.
3. Basic statements of modern cytomorphologic and immunologic classification of leukemias.
4. To call the facilitating factors for leukemias origin.
5. To call the typical clinical manifestation of acute and chronic leucemia in children.
6. To compose the plan of laboratory and instrumental investigation of the patient.
7. To specify the most typical complications of leukoses in children.
8. To specify the principle of acute leucoses therapy. BFM protocols.
9. To specify the main groups of chemopreparations in the treatment of children with leukemia.
10. Prognosis and sensitivity to chemotherapy based on the most typical chromosome abberations in acute and chronic leukemias in children.

The first level tests

1. To the child sick with acute lymphoblast leukemia, for correction of anemia the hemotransfusion with packed red cells was performed. What laboratory investigations should be done necessarily after a hemotransfusion?

A. Determine hemoglobin, RBC, urine tests.

B Coombs test, functional liver tests.

C Proteinogramme, coagulogramme.

D Electrolytes in a blood and urine.

E Urinary acid of blood, acid and alkaline condition of blood.

2. The family of a child having been diagnosed with acute lymphoblastic leukemia applied for information about the

child's prognosis. Which of the following included is a poor prognostic sign?
a. Presence of a mediastinal mass
b. Hyperdiploidy with more than 50 chromosomes
c. White blood cell count at diagnosis of less than 50 x10/9l
d. Age between 1 and 10 years
e. Early pre-B-cell variety of the disease

3. A boy of 12 years old, has been admitted to the clinic with complaints on short wind, cough, increasing of body temperature up to 37, 0C. He's been falling sick during 3 months. On thorax X-ray a "pipe"-like mediastinal shadow with presence of polycyclic contoursy has been revealed. What preliminary diagnosis is the most probable?
     A. Leukemia
     B Tubercular bronchadenitis
     C Lungs cancer
     D Lymphogranulomatosis
     E Sarcoidosis

4. A boy of 4 years old, has been admitted with complaints of fever, itch, raised sweating, enlarged cervical and axillary lymph nodes. On examination of the patient the lymph nodes conglomerate (like potatoes in the bag) in the left site of the neck and in the right axillary area are palpated. The liver and lien are enlarged. What are the most typical signs of lymphogranulomatosis in the patient?
     A. Splenomegaly
     B Itch
     C Fever
     D Hepatomegalia
     E Conglomerate of lymphonoduses

5. A patient of 7 years old has been admitted to the hospital with complaints of weakness, fatigue, fever, short wind and cough, decreasing of body weight. On X-ray of the thorax the enlargement of mediastinum shadow and the presence of polycyclic contours were revealed. What disease is the most probable?
     A. Non Hodgkin lymphome
     B Dermoid cyst
     C Tumour of thymus gland
     D Tuberculosis
     E Lymphogranulomatosis

6. A girl of 12 years old during 6 months has been complaining of growing thin, labored respiration and dry cough. On X-ray of the thorax there are considerably enlarged mediastinal lymph nodes. Mantoux test is negative. Hemogramme: Hb-90 g/l, erhythrocytes. - 2,9 x 10^{12}/l , thrombocytes - 94x 10^9/l , leucocytes - 12 x 10^9/l, relating to stab neutrophiles - 12 %, segmented - 70 %, blood sedimetation rate is 18 mm / hour. What is the prime test for establishing of diagnosis?
     A. Morphological investigation of bone marrow
     B Histological investigation of mediastinal lymphonoduses
     C Computer tomography of abdominal cavity
     D Spirographic tests with Metacholine and Salbutamolum
     E Thermometry in each 3 hours during a week

7. A girl of 5 years old, that has been healthy before, during 3 months has being treated for pneumonitis. Body temperature is 37-37,50C, generalized lymphodenopathy, liver + 4 cm, lien +5 cm, ossalgies. Antibiotic therapy was ineffective. Hemogramme: Hb - 90 g/l, erhythrocytes. - 2,9 x 10^{12}/l, thrombocytes. - 80 10^9/l, leucocytes. - 56 g/l, blastes - 20 %, relating to stab neutrophiles - 12 %, segmented - 26 %, lymphocytes - 41 %. What is your subsequent tactics?
     A. To conduct sternal puncture and to investigate bone marrow
     B To direct to genetic center and to investigate karyotype
     C To conduct spirographic tests and analysis of sputum
     D To investigate the biopsy of the most enlarged lymph nodes
     E To hospitalize for urgent plasmapheresis

8. A girl of 6 years old, was taken to hematology department in a serious state: a high fever, all groups of lymph nodes are enlarged, hemorrhagic syndrome, hepatosplenomegalia. Blood count: RBC - 2,0 10 9/L , Нв - 84 g/l, CI: 0,75, WBC-24,0 10 9/L, eosinophiles.-3 %, relating to stab neutrophile -1 %, segmented neutrofiles.-16 %, lymphocytes-75 %, monocytes -5 %, a thrombocytes.-150 10 9/l, ESR-56 mm/h . In a myelogram the blasts is 92 %. Which of the listed parameters plays the main role for the establishing of a diagnosis?

     A. Blastosis in a myelogram

B. Leukocytosis
C. Thrombocytopenia
D. Lymphocytosis
E. Anemia

9. A child of 4 years old. During the last 4 months asthenia, dermal hemorrhages admitted. Nasal bleedings, paleness, hyperthermia. On the routine blood analysis : haemoglobin - 45 g/L, erythrocytes - 1,2 x109 /L, a color index - 0,9, leucocytes 1,5x109 /L, relating to stab neutrophile - 1 %, segmented - 25 %, eosinocytes - 1 %, lymphocytes - 5 %, monocytes - 4 %, blood sedimentation rate 50 mm / h, thrombocytes - 40x109/L. What is the preliminary diagnosis?
    A.   Aplastic anemia
    B. Iron deficiency anemia
    C.   B12 - deficiency anemiamaculae
    D.   Hemolytic anemia
    E. Acute leukosis

10. An 8-year-old child being treated with a combination of chemotherapy
agents develops very red, inflammed sores in the mouth and esophagus.
He has difficulty at eating and drinking food and liquids. Which of the following
antineoplastic agents is the most likely etiology?
    A. Cephasoline
    B. Prednisone
    C. Methotrexate
    D. Antifungal drugs
    E. Dexametasone

11. What are the most distinctive features of peripheral blood and bone marrow changes that allow to suspect a myelodisplastic syndrome?

A. WBC increasing, normal or decreased elements in bone marrow.

B. PLTC incresing and increased bone marrow elements.

C. WBC increasing with simultanously decreased thrombocytes and erhythrocytes and the signs of elements differentiation impairment in the bone marrow.

D. RBC, WBC, PLTC decreasing and simultanously increasing bone marrow elements and the signs of impaired bone marrow elements differentiation.

E. Decreasing of blood elements (RBC, WBC, PLTC) in simultanously significant decreasing of bone marrow elements

12. Basic criteria for the diagnostics of acute leucosis are:
    A. Rejuvenation of lucocytes blood formula.
    B. Anemia.
    C. Pancytopenia.
    D. Blasts in bone marrow (>30%).
    E. Thromocytopenia.

13. Research method for the diagnostics of acute leucosis is:
    A. Citogic.
    B. Histological.
    C. Citochemical.
    D. Immunological.
    E. Radiological.

14. What are the changes in the blood in aleukemic acute leucosis type?:

A. Nrutrophilosis

B. Anaemia, thromboctyopenia..

C. Absence of blasts, lymphocytosis.

D. Eosinophilia.

Å. Mielocytes, metamyelocytes.

15. Cytochemical criteria of acute lymphoblastic leucosis:

    A. Positive reaction to myeloperoxidase.

    B. Positive reaction to hepatin.

    C. Positive reaction to acid phoshatase.

    D. Positive reaction to heterospecific esterase.

    E. Positve reaction to lipids.

16. In what types of acute lymhoblastic leucemia leucemides on the skin is the most common sign?

    A. Lymphoblast

    B. Myeloblast

    C. Monoblast.

    D. Promyelociytic.

    E. Megacariocytic.

17 In what type of lecosis leukemic infiltration of gums is the most common sign?

    A. Myeloblastic

    B. lymphoblastic.

    C. Monoblastic.

    D. Promyeloctytoblastic

    E. Megakaryocytic

18. Neuroleucemia most often complicates the course of acute leucosis:

    A. Myeloblast.

    B. Monoblast.

    C. Lymphoblast.

    D. Erhythromyelos.

    E. Megakaryoblast.

19. Diagnostic criteria for nurolecosis:

    A. Headache, nausea, vomiting.

    B. Stiffed neck

    C. Kernig syndrom.

    D. Cytosis of neurolymph more than >10/iml, presence of blasts.

    E. Blood in a neurolymph

20. The increase of lymphatic nodes and spleen is the most common sign in:

    A. Mieloblast leucosis.

    B. Promyelocytic leucosis.

    C. Monoblast leucosis.

    D. Lymphoblastic leucosis.

E. Erhythromyelosis.

Answers: 1-a, 2-a, 3-d, 4-e, 5-e, 6-b, 7-a, 8-d, 9-a, 10-c.11-e, 12-d, 13-c, 15- c, 16-b, 17-b, 18-c, 19-d, 20-d.

Tasks:

1. Patient D.7 years, transferred to children department from ophtalmololologic department, where he had stayed because of lacrimal saccus phlegmone.

On examination: general condition is mild, skin pallor, some hemorrhages on the upper extremities. On cheek mucoses there is a hemorrhagic rash. Enlarged lymph nodes palpated (up to 2 cm in diameter): subsculled, retrocervical, supraclavicular, subinguinal, inguinal are painful and elastic in consistency

The breathing under lungs is unchanged. Pulse rate is 74 per min.BP 144 to 90 mm Hg. Tongue is clear. Hemorrhages on cheek mucous and palate. Gums are pale. Throat is red. Glands are uneven, enlarged.Liver and spleen are unchanged.

Blood count: Er.2.1 *10 x12/l, Hв 74 g/l,CI 1, polichromathophilia, anisocytosis, poicilocytosys, reticulocytosys 30%, leuc. 4.5*10x 9л, , bands: 6%, s: 10%, lymph..80%, blasts 4%, tr. 33*10x9/ l, SR 55 mm. per hour. Urine count is unchanged.

1. Establish the diagnosis.
2. What additional investigational methods are needed?
Acute leucosis. Bone marrow punction.

2. A patient, 4 years, old, had syptoms of an acute disease: fever, relapse vomiting. Next 2-3 days a considerable general weakness appeared. He was admitted to the hospital with a diagnosis of Botkin's disease to infectious department and after examination and blood count taking was transferred to children department. From the anamnesis it was reported that the child was born healthy, in the past he hadn't been ill. The parents are healthy.

On examination: the general condition is grave, the skin is pale with a rather yellow tint, scleres are subicteric. Pereferic lymphonodes are palpated up to the kidney bean dimensions, dense, painless. Pulse is 76 beats per minute, rhythmic, filled satisfactory, Heart margins are normal, on auscultation the systoloic murmur over all the sites of auscultation. Liver is 2 cm under the costal arch, painless and soft. Spleen is 4-5 cm under the costal arch, soft and painless. Body temperature is 37.8- 39.8 C. Blood count: erh.0.98*10x12/l, Hв 28 g/ l, L: 3.8*10x9/l, neutrophilosis without shifting in formula. In the blood smear there is a big amount of normoerhythroblasts. In blood data Tr.12*10x9/l, reticulocytes 22%, General bilirubin is 102 mcmol/l, indirect bilirubin 96 mcm/l. Urine is darkly brown color with big sediment of urates. Urobilin test is very positive.

1.Establish preliminary diagnosis.
2.What additional methods of investigation are necessary?
Hemolytic anemia.
Osmotic resistance of erhythrocytes.

3.A patient, 6 years old, was admitted to the hospital in a severe condition. A month ago she had had some disease with fever, treated with sulphadimesin and penicillin. A week ago the pain on swallowing occured, gum pain, increasing of body temperature up to 39C. On the mucosa of the mouth and glands the ulcerations were found. The treatment was prescribed: oral cavity lavage with furacillinum, enterally sulphadimetoxinum, levomycetin, but the state was unchanged and the patient was hospitalized.

4. On examination general condition is grave, body temperature is 39,0C, tongue is dry: on the mucosa of gums, hard and soft palate, tongue and tonsils the necrotising ulcers covered with grey scurf are found.

Blood count: Er.3.2*10x12/l, Hв 100 g/l, L: 0.8*10x9/l, eos: 0%, bands .0%, s;22%, lymph; 73%, monocytes 3%, blasts 2%, SR 2 mm/year.

1.Establish preliminary diagnosis.
2.What additional investigational are need?
Acute leukemia
Bone marrow puncture.

5.Boy U. was admitted to the clinic with complaints on enlargement of subjaw and paraauricular lymphatic nodes, increased body temperature. He has been feeling seek during a month, was treated in the outpatient department for the diagnosis of epidemic parotitis without any effect. Besides, the hemorrhages on skin and pallor appeared. In the outpatient department the blood count was taken where the leucocytes consists of 3,7x 10/l, lymphocytes were 90 %, SR 70 mm/h.

From the anamnesis it was reported: from the first pregnancy, normal development. In admission to the hospital the general state is mild, pallor, ecchymomas on the extremities, enlargement of cervical and subjaw lymphnodes up to 2-3 cm in diameter, dyspnea, weakened breathing on lungs auscultation, no rales. On heart auscultation the systolic murmur over the fifth site was heard with mild intesivity. Liver is 4 cm under the costal arch, spleen is 3 cm, dense and painless.

Blood count: erh. 2.56*10x12/l, Hв 60 g/l, anysocytosis. Leucocytes: 3,5 *10x9/l, e: 1%, bands: 5%, s: 9%,

lymph 11%, mon:1%, lymphoblasts 73 %, SR 2 mm/h.

What disease could be suggested?

What are the additional investigations?

What test will confirm the clinical diagnosis?

Acute lymphoblast leucosis

Bone marrow punction.

The presence of lymphoblasts, anemia in the hemogramme, lymphadenopathy, hepatolienal syndrome.

6. Five years old boy who's taking supportive chemotherapy because of acute lymphoblast leukemia, has fever with chills of 39C for one day. Thus, headache, symptoms of viral infection, the signs of dyspepsia, stomach pain are not observed.

On examination: his general state is severe, tachicardia, no presense of any infection, hyperemia of skin, longterm white dermographism. Blood count: leuc.: 1.0 x 10^9/l, Hb: 85 g/l, trombocytes: 90 x 10^9/l, absolute neutrophiles count is 200/mm^3.

What agent is the most likely cause of this condition?

Prescribe the apropriate therapeutic correction due to the agent assumed?

Fungal sepsis

Antifungal drugs must be included in complex therapy.

6. Patient L., 4 years old, fell ill nearly 4 months ago. The gradual onset of disease occurred, presented with pain in the right coxofemoral joint and due to it the girl experienced difficulties in moving. Tuberculous coxitis was suspected, therefore the pelvic bones and coxofemoral joints were X-rayed where the destructive changes were revealed. The patient was consulted by traumatologist and phthisiatrician who diagnosed tuberculosis of joints and bones. The patient was directed to the sanatorium. Despite the severe pallor and general weakness, the blood count first time was conducted on the third month of the disease: erh.1.3*10x12/l, Hв 48 g/l (significant anemia), thrombocytopenia 6.58x10x9/l, leucocytosys 30,08x10 x 9/l, in leucogramme: significant rejuvenascence of cells- 88.5% of blasts, SR significantly increased.

1.To establsh the initial diagnosis.

2. To compose the plan of investigation and therapy.

Chronic mieloblast leucemia.

Bone marrow puncture, clotting tests.

Chemotherapy according to the protocol.

7. Patient G., 6 years, was admitted to the hospital with complaints of stomach-ache, general weakness, bad appetite. Stomach-ache and general weakness had appeared 2 months ago, an the appetite disappeared then. To these phenomena pallor and fever were added. In the hospital the state of the child is severe, the child is flaccid, the paleness progresses: periferal lymphnodes are enlarged, insignificant pain on pattering the thorax, single hemorrhages. The spleen is considerably enlarged (lower pole palpated near the pelvis) and dense in consistency.

The liver is 4 cm under the edge of costal arc. Blood count: er.2.5*10x12/l, Leuc: 44*10x9/l, 77% of blasts are the myelocites, 1% are the bands, 1% are segmented cells, 2% are lymphocites, 19% are normoblasts -2:100, SR - 18 mm/ h

1. To establish the initial diagnosis.

2. Why can't given the data allow to establish the final diagnosis?

3. Work out a plan of examination.

Acute leucosis

Because, there is a requirement for the determination of blasts type.

Bone marrow punction, clotting tests, ultrasound of the heart, spleen and hepatobiliar system, chest X-ray.

8. A patient K., 6 years old, was admitted to the hospital with an exudative pleurisy. The disease began with a cough without the increase of body temperature. Then dyspnea occured, cyanosys, general weakness, therefore the child was hospitalized. On chest X-ray examination: increase of mediastinum shade and decline in transparency of pulmonary tissue on all the length with middle intensity on the left, heart margins are not determined. The liver and spleen are enlarged.

Blood count: er.4.8*10x 12/l, Hb 123 g/l, Leuc: 15.2*10x9/l, retikulocites 7%, neutrofiles, SR is 21mm/h. Pleuropneumonia on the left and mediastenitis were diagnosed. The treatment was carried out: antibiotics, vitamins and cardiac preparations. Up to 5 day of treatment the state of the child became better considerably: dyspnea and cyanosis diminished, the dimensions of liver diminished. In a week cough and dyspnea occurred again with cyanosis and general weakness. In the lungs on the left from the middle of the shoulder-blade the shortened percussion sound appeared, which passed in the lower parts to a dull sound marked, breathing was weakened. At the repeated X-ray: the expansion of middle shade, to the left of 4 rib there is the intensive darkening, left dome of diaphragm is not seen. The state of the child is severe : expressed dyspnea, cyanosis, pulsation of neck veins, pallor of the skin. Considerable system increase of lymphatic nodes. The cardiac shove is not palpated, right margin of relative cardiac dullness- to the right of parasternal line, upper- 1 rib, left – the margin limit of the heart is not determined. Tones considerably muffled,

tachycardia, liver and spleen are under 5cm to the edge of costal arc. Blood count: er.4.6*10x12/l, Hb-150 g/l, CI- 0.9, retikulocites 0.5%, tr.294.8*10x9/l, Leuc: 5.28*10x9/l, blasts 2%, eosinophils- 2%, bands-5%, segmented-36%, lymph.-1%, SR -15 mm/h. On mielogramme - 78 % blast elements of trombocitic type. Chest X-ray: to right of the heart shade – the impure shade which is in the lower part of mediastinum, on the left in the low lateral part the shade is due to exudate. Vascular shade is considerably extended on both sides. The heart is significantly extended in the diameter. Retro-cordial space is narrowed by all the length, retrosternal space is in the lower part. Kimogramm of the heart: the indents is not seen by countour. ECG : considerable decline of voltage, sinus tachichardia.

1. To establish the initial diagnosis.

2. What is the cause of thorax organs' injuries?

3. Work out a plan of examination and therapy.

Acute leucosis.

Leucemoid infiltration of mediastinal organs.

Bone marrow puncture, clotting tests, heart, hepatobiliar system and spleen ultasound. Chest X-ray, chemotherapy according to BFM protocol.

9. Patient O., 5 years old, disease began with elevated body temperature and catarrhal signs, then the feet pain appeared. After 2 weeks from the beginning of disease there was loin pain, the child stopped walking and even sat badly. He was treated in the local outpatient department, where various neurological diagnoses were made. During hospitalization the state of the child is severe: significant pallor, septic type of fever, periferal lymphnodes like kidney bean. On the right in the area of the lower jaw – dense infiltrate, there are the single hemorhages on the skin. The boy did not stand on his feet and did not sit. He comlplains of acute pain alongside the spine, the pain increased in the root area in palpaition. Knee and acchill reflexes are high, their area is extended, feet klonuses, Babinski sign is positive to the right, there is tremor in upper the extremities. Vesicular breathing in the lungs. Tones of the heart are muffled, sistolic murmur is heard over all sites of auscultation, tachicardia. The liver is under 2 cm of costal arc, the spleen is not enlarged.

Blood count: er.2.18*10x12/l, Hb 74 g/l, CI-1.0, retikulocytes 0.4%, tr.65.4*10x9/l, Leuc:-8.7x10x9/l, blasts 29%, mielocites -1%, bands-10%, lymph-54%, mon.-4%, normoblasts - 1:100, SR-60 mm/h. In mielograme: blasts 92%, depressing of erhythro-trombopoesis.

On X-ray of lumbar-sacral part of the spine in the bones of pelvis and upper parts of hips there is unsignificant osteoporosis.

1. To make a previous diagnosis.

2. To work out the plan of examination and therapy.

Acute leucosis.

Bone marrow puncture, clottinng test, heart, hepatobiliar system and spleen ultasound. Chest X-ray, chemotherapy according to BFM protocol.

The questions for the control of secondary knowledge level of abilities and skills:

1. Definiton of hemoblastoses.

2. To determ an etiology of acute and cronic leukemias in children.

3. To specify the key links of leukomogenesis.

4. Basic statements of modern cytomorphologic and immunologic classification of leukomias.

5. To define the facilitating factors for leukemias origin.

6. To define the typical clinical manifestation of acute and chronic leucemia in children.

7. To compose the plan of laboratory and instrumental investigation of leukemic child patient.

8. To specify most typical complication of leukoses in children.

9. To specify the principle of acute leucoses therapy. BFM protocols.

10. To specify the main groups of chemoreparations in treatment children with leukemia.

11. Prognosis and sensitivity to chemotherapy based on the most typical chromosome abberations in acute and chronic leukemias in children.

VII. Materials of the medical support for the students independent training: a reference chart for organization of students independent work with educational literature.

Tasks	Instructions
To study the etiology and pathogenesis of leukemia and lymphoadenoma in children. To be able to detect the risk group for the severity of leukemia.	To enumerate basic etiologic factors, select the key links of leukemia, pathogenesis.
To study clinical manifestations of leukemias and lymphoadenomas in children.	To establish the symptoms and gather it to clinical syndromes which enable to put the credible diagnosis of leukemia.
To study diagnostic criteria of leukemia.	To make the flow diagram of the disease
To study the additional methods of research (laboratory, instrumental)	To work out a plan of patient's investigation.
To study the changes in additional investigational methods which are pathognomonic for leukemias.	To enumerate the basic diagnostic criteria of leukemia according to the data of additional investigational methods.
To conduct differential diagnostics, to establish a final diagnosis	To substantiate the basic components of diagnosis in accordance with the modern classification, and to conduct a differential diagnosis.
To prescribe the individual poliatry to patient with the leukemia. To be able to render the first aid in cell lysis crisis for children.	To make the prescribing chart specifying the regimen, diet, medicinal treatment, taking into account the age, severity of patient's state, the stage of the disease, the presence of complications and concomitant diseases.

Tests–2

1**.** During a routine-screening CBC, a 1-year-old is noted to have eosinophilia. Which of the following most commonly causes increased eosinophilia in the peripheral blood smear?
a. Bacterial infections
b. Chronic allergic rhinitis
c. Fungal infections
d. Helminth infestation
e. Tuberculosis

2**.** The otherwise healthy 17-year-old complains of swollen glands in his neck and groin for the last 6 months and an increasing cough for the previous 2 weeks. He also reports some fevers, especially at night, and possibly some weight loss. On examination, you notice that he has nontender cervical, supraclavicular, axillary, and inguinal nodes, no hepatosplenomegaly, and otherwise looks to be fairly healthy. Which of the following would be the appropriate next step?

a. Urine tests

b. Complete and differential blood counts

c. Trial of antituberculous drugs

d. Chest radiograph

e. Cat-scratch titers

3. The child of 5 years old was admitted to the hospital with complaints of nasal bleedings and ecchymomas on the trunk. In the anamnesis 2 weeks ago the child had transferred viral infection. On the routine blood count anemia (Hb 85 g/l) and thrombocytopenia. What is necessary to administer for the acute management?

A. Epsilon Acidum aminocapronicum

B. Thrombocytes packed cells

C. Chilled plasma

D. Cryoprecipitate

E. Red packed cells.

4. Having performed a complete history and physical examination on the patient aged 7, you proceed with a diagnostic workup. Initial laboratory results are as follows: hemoglobin 60 g/L; hematocrit 24%; leukocyte count 11 x10 9/L with 38% neutrophils, 7% , bands, 55% lymphocytes; hypochromia on smear; platelet count adequate; reticulocyte count 0.5%; sickle cell preparation negative; stool guaiac negative; and mean corpuscular volume (MCV) 65 fl. You would most appropriately recommend

a. Blood transfusion

b. Oral ferrous sulfate

c. Intramuscular iron dextran

d. An iron-fortified cereal

e. Calcium EDTA

5. A child of 8 years old. Increasing paleness, weakness, hemorrhagic eruption on the skin have appeared. On bone marrow puncture the depression of hemopoiesis was marked. What basic method of therapy is indicated for this case?

A. Corticosteroids +bone marrow transplantation

B. Splenectomy

C. Haemotransfusion + cytotoxic agents

D. Cytotoxic agents + bone marrow transplantation

E. Antibiotics + a hemotransfusion

6. Most favourable variant of acute lymphoblast luecemia:

A. O-cell

B. Pre-B-cell.

C. T-cell

D. Variant with translocations (9;22)

E. B-cell

7. Most effective method of remission induction in ALL with good prognosis is:

A. Combinations of vincristine and prednisolone

B. Combination of monochemotherary with cranial irradiation.

C. combination of vincristine, prednisolone, asparaginase and any anthracyclic preparation.

D. Using of anthracyclic antibiotics.

E. Using of immunomodulations.

8. The most effective method of remission induction in ALL with unfouvarable prognosis is:

A. Combinations of vincristine and prednisolone

B. Combination of monochemotherary with cranial irradiation.

C. Combination of vincristine, prednisolone, asparaginase and any anthracyclic preparation.

D. Using of anthracyclic antibiotics.

E. Using of immunomodulation.

9. Prophylaxis of neuroleucemia is conducted by intralumbar administration of the following preparations:

A. Metotrexat 12,5 mg/m^2; citosar 20-30 mg/m^2; dexamethason 4 mg/m^2.

B. Metotrexat 10,0 mg/m^2; citosar 20-30 mg/m^2; dexamethason 4 mg/m^2.

C. Metotrexat 5,0 mg/m^2; citosar 20-30 mg/m^2; dexamethason 4 mg/m^2.

D. Metotrexat 30,0 mg/m^2; citosar 20-30 mg/m^2; dexamethason 4 mg/m^2.

E. Metotrexat 50 mg/m^2, ; citosar 20-30 mg/m^2; dexamethason 4 mg/m^2.

10. The complete remission criteria in acute leucemia:

A. Absence of complete remission in acute leucosis.

B. Normal blood count, in bone marrow smear not more than 5% of blasts, normal liquor count,

C. Satisfactory general condition and normal blood count.

D. Normal blood count, spleen enlargement.

E. Normal blood count, diminished spleen dimensions.

11. Prophilaxis of neuroleucemia in children's ALL includes:

A. High doses of metothrexat in combiation with prophylactic cranial irradiation.

B. Intrathecal and i.v. metothrexat administration in combination with prophylactic

cranial irradiation.

C. High doses of citosar in combination with average high doses of metothrexat.

D.High doses of metothrexat in combiation with high doses of citosar.

E. Cranial irradiation.

12. From what age is prophylactic cranial irradiation conducted for children in acute leucosis?:

A. After 10 years

B. After 3 years

C. After 1 year.

D. After 5 years

E. In 1 year.

13. Concept of "hybrid" leucosis is:

A. Two clones of lymphoid or mieloid blasts at different stage of differentiation belong to one cell line.

B. Two clones of blasts belong to mieloid line only (mieloblasts and monoblasts).

C. Two clones of blasts belong only to lymphoid line but to different cell lines (T- and B- lymphocytes).

D. The presence of the tumor substrate cells of chronic and acute leucoses at the same time.

E. The presence on the blast cells the markers of lymphoid and mieloid lines at the same time.

14. The signs of real policytemia are:

A. Splenomegaly, anemia, leucocytosis, neutrophilosis , bone marrow phybrosis.

B. Erhythrocytosis, thrombocytosis.

C. Myelofibrosis, leucopenia, basophilia.

D. Minimal clinical manifestation, mild erhythrocytosis, the amount of lymphocytes elevated insignificantly, neutrophylosis, in bone marrow elevated mielokaryocytes and megakaryocytes.

E. All answers are correct.

15. Hematologic signs of 2 stage (stable) true polycytemia.

A. Hepato-, -splenomegaly, -mielofibrosis.

B. Hepato-, -splenomegaly, thromboses, hemorrhages, hyperplasia of all stems in the born marrow.

C. Hepato-, -splenomegaly, hemorrhagic syndrome.

D. Anemia, leucocytosis, thrombocytopenia.

E. All answers are correct.

16. A test with a plural choice. What of following factors can cause development of leucosis:

A. benzol

B. antibiotics

C. ionized radiation

D. viruses

E. bacteria

17. Finding of belonging by the elements of two rows of information
To choose chemopreparations which belong to the proper group:

Antimetabolites	prednisolon
Alkalised agents	methotrexat
Alkaloids of plants	L-asparaginase
Enzymic preparations	cyclophosphanum
Hormonal preparations	vinkristin

Answer:

Antimetabolites   prednisolon

Alkalised agents	methotrexat
Alkaloids of plants	L-аспарсгіназа
Enzymic preparations	cyclophosphanum
Hormonal preparations	vinkristin
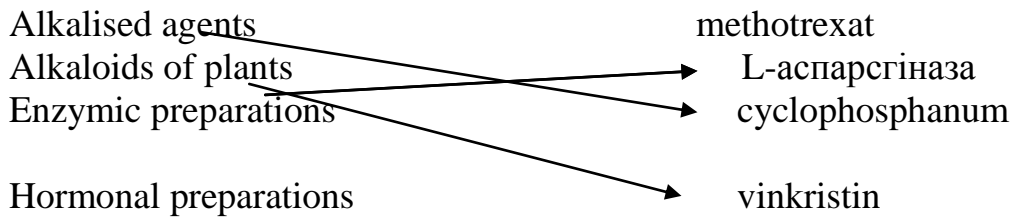
18. Test which foresees the determination of correct sequence of procedures from the set of arbitrary ones. Name the sequence of doctor's procedures in the examinations of a child patient with acute leucosis:

A. Clinical examinations

B. Drafting of examinations plan

C. Anamnesis taking.

D. Administration of additional examination.

E. Administration of treatment.

19. Test "on a substitution" or with an answer which is independently made:

Name the signs of lungs injuries and intrathoracic lymph nodes in children's acute leucosis:

A.

B.

C.

D.

E.

Answer: A- is specific tumours of front mediastinium; B- specific leukemic infiltration of pulmonary tissue; C- pneumonia; D-medicamentous pulmonitis (toxic alveolitis); E-hemorrhages in the lungs.

20. Prognostic signs of ALL.

Factor of prognosis	Favourable	Unfavorable
A period is from the beginning of illness to establishing of diagnosis		
Patient's age		
Increase of peripheral lymph nodes.		
Increase of liver		
Increase of spleen		
Damage of CNS.		
Leykocytosis		
Haemoglobin		
Thrombocytes		
Immunoproteins		

Morphology of blasts by FAB classification

Immunology of blasts.

Cytochemic signs: acid phosphatase

Shick-reaction

1-d, 2-d, 3-d, 4-a, 5-a, 6-c, 7-c, 8-c, 9-a, 10-b, 11-b, 12-a, 13- e, 14-d, 15-b, 16-a,c,d, 18- c,a,d,e.

VIII. ЛІТЕРАТУРА

Основна література

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Teme: Haemorrhagic diseases in children. Haemophilia, thrombopathy, thrombopenia. Etiology. Pathogenesis. Classification. Diagnostics. Differential diagnostics between haemorrhagic diseases in children. Treatment. The first aid in case of haemorrhage. Prognosis.

The amount of studying hours – 4 academic hours.

I. Actuality of the theme. Haemorrhagic syndrome can manifest itself as an indepent disease or can be manifestation of other pathology. A course of haemorrhage is damage in haemostasis, which can be primary in case of congenital haemorrhagic diseases and secondary in case of complications. Bleeding cessation occurs in compliance with interaction of three haemostasis links: vascular, platelets and coagulatory. Isolated or combined breaking in one or several hemostasis links can lead to haemorrhagic syndrome.

II. Classes (pointing planned mastering level with)

1. A student must have conception (to familiarize): α1

- the place of haemorrhagic disaeses in the structure of diseases in children;
- statistical information in relation to morbidity, frequencies of complications, lethality, the nearest and remote prognosis;
- the history of scientific studying and assessments of domestic scientists.

2. A student must know (master): α2

-risc factors of manifestation and pathogenesis of haemorrhagic diseases in children;

-modern scheme of coagulation and anticoagulative systems, thrombocyte haemostasis;

-key links of haemorrhagic diseases' pathogenesis;

-clinical classification of haemorrhagic diseases in children;

-classic clinical manifestation of haemophilia;

-classic clinical manifestation of thrombopenia;

-classic clinical manifestation of thrombopathia;

-laboratory diagnosis of haemophilia;

-laboratory and instrumental diagnostics of haemorrhagic diseases;

-complications of haemorrhagic diseases in children;

-treatment principles of haemorrhagic diseases in children;

-preventive measures of haemorrhagic diseases in children, rehabilitation methods of patients and their dispensary observation.

3. A student must master: α3

Skills:

- Collection of complaints and anamnesis morbi;

- Examination of patient with haemorrhagic disease and revealing the main symptoms and syndromes;
- To formulate and substantiate preliminary diagnosis;
- Determination of laboratory and instrumental plan of patient's examination (according to diagnostics standards);
- Giving the first aid in case of acute bleeding, haemorrhagic shock in children;
- To realize life prognosis of a patient with haemophilia, thrombopathy and thrombopenia.

Abilities:

- to interpret the result of laboratory and instrumental tests;
- to conduct differential diagnosis among haemophilias, thrombopenias and thrombopathias;
- to conduct differential diagnosis among diseases with bleeding;
- to give recommendations in relation to the regimen and diet of a patient with haemorrhagic disease,according to the stage of disease, severity of the state and concomitant pathology;
- to complete the treatment plan in haemorrhagic disease according to standards taking into account the stage of disease, complications and concomitant pathology;
- to render the first aid in extreme situation and exigent states.

   III.   Aims of personality development (educative aims):
   - A student must adhere rules of behaviour and principles of medical etiquette and deontology, to develop bedside manner;
   - to set a psychological contact with patient and his family;
   - to master the sense of professional responsibility for a timely and adequate medicare.

 Interdisciplinary integartion:

Subject	**To know**	To be able
1. Previous (providing)		
Physiology and pathologic physiology	Coagulating factors of blood system, platelets haemostasis. Modern scheme of blood clotting.	To determine ethiologic factors of possible bleeding.

Pharmacology	Pharmacokinetics and pharmacodynamics, the side effects of hemostyptic therapy.	To prescribe treatment dependent on age and patient's individual features, period of disease, to establish individual regimen of taking the preparations and its dosage. To prescribe recipes.

Propedeutical pediatrics.	Clinical and laboratory diagnostic methods of haemorrhagic syndromes. Principles of accomplishment of platelet count, bleeding time, prothrombin time, and activated partial thromboplastin time (APTT), the tourniquet test, whole blood clotting time, prothrombin consumption time, and thromboplastin generation test. Basic stages and methods of patient's clinical examination.	To collect complaints, anamnesis vitae et morbi, to find out the basic risk factors of haemorrhagic diseases, to conduct patient's examination, to reveal clinical signs of diseases of blood system, to interpret the data of additional investigative methods. To lay out medical report, to evaluate severity of child's condition.
2. Followings (provided)		
Hospital pediatrics.	Etiology, pathogenesis, clinical signs of haemorrhagic disease, differential diagnosis and treatment tactics.	- To reveal clinical signs and complications of haemorrhagic diseases; - to conduct survey design and medical plan; - to conduct differential diagnosis, to be able to prescribe treatment.
3. Interdiscipline integration		
Hypoplastic and aplastic anaemia	Clinical manifestations of transient hypoplastic and aplastic anaemia	To establish specific clinical signs of hypoplastic and aplastic anaemias. To conduct differential diagnosis between haemophilias, thrombopenias and thrombopathias.
Purpura rheumatica	Clinical manifestations of purpura rheumatica	To establish specific clinical signs of purpura rheumatica. To conduct differential diagnosis between haemophilias, thrombopenias and thrombopathias.
Acute leucosis	Clinical manifestations of acute leucosis	To establish specific clinical signs of acute leucosis. To conduct differential diagnosis between haemophilias, thrombopenias and thrombopathias.
DIC-syndrome	Clinical manifestations of DIC-syndrome	To establish specific clinical signs of DIC-syndrome. To conduct differential diagnosis between haemophilias, thrombopenias and thrombopathias.

III. Contents of theme

The blood is in dynamic equilibrium between fluidity and coagulation. This balance must be precisely maintained to ensure that neither excessive bleeding nor thrombosis occurs spontaneously or following trivial trauma. The hemostatic mechanism is complex: It involves local reactions of the blood vessels, the several activities of the platelet, the interaction of specific coagulation factors, inhibitors, and the fibrinolytic proteins that circulate in the blood. The vascular endothelium is the primary barrier against hemorrhage. When small blood vessels are transected, active vasoconstriction and local tissue pressure control minute areas of bleeding, even without mobilization of the coagulation process. The platelet, however, is essential for maintenance of small blood vessels and for the control of hemorrhage from small-vessel injury. More extensive injury and involvement of larger blood vessels require the participation of the coagulation system to provide a firm, stable, fibrin clot. Within this process natural inhibitors in plasma and a competent fibrinolytic system are needed to prevent excessive clot formation and to remove the clot.

HEMOSTASIS

SCHEMA OF HEMOSTASIS

The classic schema of hemostasis includes vascular response and platelet plug formation (the primary hemostatic mechanism) and the formation of a stable fibrin clot (the secondary hemostatic mechanism). Coagulation proceeds in three phases: In phase I, thromboplastin is formed by the interaction of certain coagulation factors, phospholipids, and tissue juice (which contains tissue factor); in phase II prothrombin (factor II) is converted to thrombin (factor IIa); and in phase III, soluble fibrinogen is converted by thrombin to fibrin. This simple scheme has been expanded, but retention of the concept as a basic three-phase reaction has merit lists the more common coagulation factors and their synonyms. A comprehensive representation of hemostasis is depicted

Following vascular injury, vasoconstriction occurs and a platelet plug forms. The platelets must first stick to the injured endothelium (adhesion). They require a plasma factor (von Willebrand factor) to be adhesive. After adhesion, the platelets undergo a release reaction in which certain intraplatelet factors (e.g., adenosine diphosphate [ADP], thromboxane A2) are released into the surrounding area. These materials cause aggregation of platelets and the eventual formation of the platelet plug. In phase I of the coagulation scheme there are two pathways to the formation of thromboplastin (factor Xa, and factor V plus phospholipid complex) called the intrinsic (or plasma) and extrinsic (or tissue) pathways. The intrinsic pathway involves the successive enzymatic conversion of the inactive forms of factors XII, XI, and IX. (Two other plasma proteins are also involved in the activation of factor XII and factor XI—{emdash} prekallikrein for factor XII and high-molecular-weight kininogen for

factor XI.) The activated factor IX (factor IXa) interacts with factor VIII, calcium, and phospholipid to activate factor X. Factor Xa interacts with factor V, calcium, and phospholipid, and becomes the active complex that converts prothrombin (factor II) to thrombin. This active complex has been called prothrombinase (preferred), prothrombin activator, and thromboplastin. The extrinsic pathway involves the conversion of factor VII to factor VIIa by tissue factor (a phospholipid protein complex). In the extrinsic pathway factor VIIa activates factor X directly.

Phase II of coagulation involves the enzymatic cleavage of factor II into smaller molecules, one of which is thrombin (factor IIa). This step requires factor II as substrate for the factor Xa-factor V-phospholipid-calcium complex.

In phase III thrombin splits four small peptides (two fibrinopeptide A and two fibrinopeptide B) from fibrinogen, producing fibrin monomers. These monomers then polymerize spontaneously to form fibrin. Factor XIIIa (formed by the action of thrombin on factor XIII) causes covalent bonding of the fibrin strands, which produces a stable clot.

There are at least three clinically important, naturally occurring coagulation inhibitors: antithrombin III, protein C, and protein S. Antithrombin III inhibits active-ted coagulation factors that have a serine moiety in their active site, such as thrombin, factor Xa, factor IXa, factor XIa, and factor XIIa. Protein C, when activated (protein Ca), inhibits factor V and factor VIII, using protein S as its cofactor.

The fibrinolytic system is composed of plasminogen, activators, and inhibitors. Plasminogen must be converted to plasmin, which is the active proteolytic enzyme, by activators (such as tissue-type plasminogen activator and urinary-type plasmino-gen activator). This reaction is modulated by plasminogen activator inhibitors (PAIs) and by a{alpha}2-antiplasmin (a{alpha}2-plasmin inhibitor). Plasmin's function is to lyse fibrin, a process that produces soluble fibrin degradation (split) products.

EVALUATION OF THE PATIENT WITH A SUSPECTED HEMOSTATIC DEFECT. HISTORY AND PHYSICAL EXAMINATION. The focus of the history and physical examination is to determine whether the suspected defect is acquired or congenital (inherited) and which mechanism appears to be affected (primary or secondary hemostatic mechanism). The history should determine the site or sites of bleeding, the severity and duration of the hemorrhage, the age of onset, what was done to control the bleeding, whether the bleeding was spontaneous or induced, the family history, a drug history, the patient's experiences with prior trauma (e.g., surgical procedures, biopsies, venipunctures, dental extraction) and, in females, a detailed menstrual history. The physical examination should determine the characteristics of the bleeding (e.g., petechiae, ecchymoses, hematomas, hemarthroses, mucous membrane bleeding) and identify signs of a primary systemic disease. The characteristic bleeding manifestations in a patient with a defective

primary hemostatic mechanism (platelet–blood vessel interaction) are mucous membrane bleeding (e.g., epistaxis, hematuria, menorrhagia, gastrointestinal), petechiae in the skin and mucous membranes, and multiple, small, ecchymotic lesions. The typical bleeding signs in a patient with a defective secondary hemostatic mechanism (coagulation system) are deep bleeding into joints and muscles, large spreading ecchymotic lesions, and hematomas.

LABORATORY TESTS. Patients who are hemorrhaging or who have a history suggestive of a hemostatic disorder should have a platelet count, bleeding time, prothrombin time, and activated partial thromboplastin time (APTT) performed. These screening studies should identify most hemostatic defects, although there are exceptions. More specific tests may be needed to define the defect more precisely.

Certain previously used tests are no longer employed either because they lack sensitivity and specificity or because the current techniques are less cumbersome and the results are easier to interpret. Tests that are now rarely used are the tourniquet test, whole blood clotting time, prothrombin consumption time, and thromboplastin generation test.

Bleeding Time. The bleeding time is the best test for assessing the vascular and platelet phases of hemostasis. It has been standardized by the use of a template that regulates the length and depth of the skin incision. A blood pressure cuff is applied to the arm and inflated to 40mm Hg for children, 30mm Hg for term newborns, and 20mm Hg for preterm babies, and an incision is made using a template and scalpel blade. At 30-sec intervals drops of blood are blotted from the margin of the incision. Normally, blood flow stops within 4–8min.

Platelet Count. A platelet count is essential in the evaluation, because thrombocytopenia is the most common cause of a defective primary hemostatic mechanism that produces a significant bleeding diathesis in children. There is a linear relationship between the bleeding time and the platelet count, that is, the lower the platelet count, the more prolonged the bleeding time. Using a template, bleeding time in this relationship can be determined as

Bleeding time (min) ={equals} 30.5 −{minus} [Platelet count (per uL) / 3,850].

If the bleeding time is disproportionate to the platelet count, a qualitative platelet defect should be suspected. Patients with a platelet count above 50g{times} 109/L rarely have significant bleeding.

Platelet Aggregation and Other Tests. If a platelet function defect is detected, further in vitro studies can be carried out, including platelet aggregation tests using activators (e.g., ADP, collagen, epinephrine, thrombin, and/or ristocetin), clot retraction, prothrombin consumption test (for platelet factor 3), ATP and serotonin release, and others.

The three phases of coagulation can be individually assessed by simple, reliable

tests.

Thrombin Time. Phase III can be evaluated by the thrombin time, the time required for plasma to clot after the addition of bovine or human thrombin (factor IIa). The normal thrombin time ranges from 15 to 20sec in most laboratories. Prolongation of the thrombin time occurs with hypofibrinogenemia, or dysfunctional fibrinogen (dysfibrinogenemia), or by substances that interfere with fibrin polymerization (e.g., heparin, certain fibrinolytic degradation products). If heparin contamination is the cause, the heparin can be inactivated by various neutralizing agents and the test repeated, or the thrombin time can be determined using a snake venom (reptilase) in place of the thrombin. Reptilase is a thrombin-like enzyme that is not affected by heparin. Fibrinogen also can be measured by chemical, immunologic, and heat precipitation methods.

Prothrombin Time. Phase II of coagulation is assessed by the prothrombin time, the time taken for plasma to clot after the addition of exogenous thromboplastin (tissue factor) and calcium. The normal prothrombin time ranges from 11.5 to 14sec. If phase III is intact, a prolonged prothrombin time indicates a deficiency involving factors II, V, VII, and/or X. Specific assays are available for all these factors. The prothrombin time, however, does not reflect the activity of factors XII, XI, IX, VIII, or XIII.

Activated Partial Thromboplastin Time. Phase I, the most complex part of the coagulation mechanism, is evaluated by the activated partial thromboplastin time (APTT). The APTT is the time required for the clotting of plasma that has been activated by incubation with an inert activator (e.g., kaolin, celite, ground glass, ellagic acid) when calcium and platelets (or a lipid substitute for platelets) are added. The normal APTT ranges from 25 to 40sec. This test is a simple, inexpensive, and reliable way to assess the adequacy of factors XII (and prekallikrein, high-molecular-weight kininogen), XI, IX, and VIII. The APTT does not assess factor VII or factor XIII activity. If phase III and phase II are intact, a prolonged APTT represents either a deficiency or an inhibitor in the intrinsic pathway.

Mixing Study. The next test to be performed is a mixing study. In this study, normal plasma is added to the patient's plasma and the APTT is carried out on the mixture. If the resulting APTT is normal (i.e., the patient's abnormal APTT is corrected), then a deficiency state is present. If, however, the mixture's APTT remains prolonged, an inhibitor is present. Correction of the abnormal APTT in the mixing study in a patient with a bleeding disorder indicates a deficiency of factor VIII, IX, or XI or, in a patient without a bleeding disorder, indicates a deficiency of factor XII, prekallikrein, or high-molecular-weight kininogen. If the mixing study does not correct (or worsens with incubation) and the patient has a bleeding disorder, an inhibitor against factors VIII, IX, or XI should be suspected. If the patient has no

hemorrhagic manifestations, the inhibitor is probably the lupus anticoagulant. Assays for each coagulation factor are available and are needed to identify the specific factor involved and the severity of the defect. Severity is graduated as follows: severe—{emdash} activity less than 1% of normal (also reported as less than 1 unit/dL or less than 0.01 unit/mL); moderate—{emdash}activity greater than 1% but less than 5% of normal (or 1–5 units/dL); and mild—{emdash}activity greater than 5% of normal (or greater than 5 units/dL). Normal levels in most laboratories for these factors are between 50% and 150% (50–150 units/dL).

Other Tests. There are no screening tests for the natural inhibitors of the coagulation mechanism. Specific functional and immunologic assays are available for measuring the plasma levels of antithrombin III, protein C, and protein S.

Screening tests for overall fibrinolysis are insensitive. Such tests include the whole blood clot lysis time and the plasma clot lysis time. The euglobulin clot lysis time (ELT) is used by most laboratories to assess fibrinolysis. In this test a euglobulin fraction of plasma is made (usually by acetic acid precipitation) and the fraction is clotted with calcium or thrombin. The time for clot lysis is determined (usually from 2 to 4 hr). The euglobulin fraction has clotting factors, fibrinogen, plasminogen, and plasminogen activators, but no inhibitors. A short ELT can be a result of increased activators and/or reduced fibrinogen; a prolonged ELT is seen with reduced plasminogen, reduced activator, or with extremely increased fibrinogen concentration. Other tests for assessing the fibrinolytic mechanisms include assays for plasminogen, plasminogen activators and inhibitors, and immunologic assays for fibrinolytic split (degradation) products.

PHASE I DISORDERS: THE HEMOPHILIAS

The hemophilias are the most common and serious of the congenital coagulation disorders. They are associated with genetically determined deficiencies of factors VIII, IX, or XI.

Factor VIII Deficiency

(Classic Hemophilia; Hemophilia A; Antihemophilic Factor [AHF] Deficiency)

About 80% of cases of hemophilia are hemophilia A, which is caused by a defective gene carried on the X chromosome. About 75% of patients with hemophilia A have a proportionate reduction in factor VIII activity and factor VIII antigen (protein). They are classified as CRM (cross-reacting material) negative (CRM–{minus}) or reduced (CRMred). The remaining 25% of patients have reduced factor VIII activity, but the antigen is present and these patients are classified as CRM+{plus}. Numerous mutations in gene structure have been described. The most common are large deletions and missense mutations. The others include small deletions, insertions, internal gene segment duplications, splice-site mutations, and

nonsense point mutations. Except for the missense mutations, most of these appear to prevent the synthesis of factor VIII antigen. In the mis-sense mutations the factor VIII protein is synthesized with variable functional activity of Factor VIII. To date, it is estimated that deletions account for 2.5–10% of mutations causing hemophilia A. The remaining mutations are mostly single nucleotide substitutions.

This deficiency results in a profound depression of the level of factor VIII coagulation activity in the plasma. Factor VIII is complexed with von Willebrand protein (called the factor VIII–von Willebrand complex) in plasma, with the von Willebrand protein acting as a carrier protein. Patients with hemophilia A and women who are carriers for the disorder have reduced factor VIII activity but normal plasma levels of the von Willebrand protein (in contrast to classic von Willebrand disease, in which both levels are reduced). In the normal population the plasma ratio of factor VIII activity to von Willebrand protein is 1:0. Thus, most female carriers have a ratio of less than one, which can be used for carrier detection and genetic counseling. Carrier and fetal detection has become more precise. The methods employed for the genetic analysis of hemophilia A are based on the detection of DNA sequence variations within or near the gene. An affected male and a heterozygotic mother are used to define the defect(s). Fetal samples can be obtained from DNA extracted from chorionic villi (8–11 wk) or from cells aspirated by amniocentesis (midtrimester). A combination of DNA-based methods and assays of factor VIII activity is usually used for carrier detection and prenatal diagnosis. However, it is estimated that 6–20% of women are still misclassified.

In 80% of cases the family history is positive for the disease. Sporadic cases may represent a new mutation. The clinical severity depends on the level of factor VIII activity in the plasma: Severe cases have less than 1% (1 unit/dL) of normal activity; moderate cases have 1–5% (1–5 units/dL); and mild cases have 6–30% (6–30 units/dL). The degree of severity tends to be consistent within a given family.

CLINICAL MANIFESTATIONS. Because factor VIII does not cross the placenta, a bleeding tendency may be evident in the neonatal period. Hematomas after injections and bleeding from circumcision are common, but many affected newborns exhibit no clinical abnormalities. As ambulation begins, excessive bruising occurs. Large intramuscular hematomas result from minor trauma. A relatively minor traumatic laceration, as of the tongue or lip, which bleeds persistently for hours or days, is frequently the event that leads to diagnosis. Of patients with severe disease, 90% have had clear clinical evidence of increased bleeding by 1 yr of age.

The hallmark of hemophilia is hemarthrosis. Hemorrhages into the elbows, knees, and ankles cause pain and swelling and limit movement of the joint; these may be induced by relatively minor trauma but often appear to be spontaneous. Repeated hemorrhages may produce degenerative changes, with osteoporosis, muscle atrophy

and, ultimately, a fixed, unusable joint. Spontaneous hematuria is a troublesome but not usually serious complication. Intracranial hemorrhage and bleeding into the neck constitute life-threatening emergencies.

Patients with factor VIII activities greater than 6% (6 units/dL) do not have spontaneous symptoms. These patients, with "mild hemophilia," may experience only prolonged bleeding following tooth extractions or dental work, surgery, or injury.

LABORATORY FINDINGS. The only significant laboratory abnormalities occur in coagulation tests and reflect a serious deficiency of factor VIII. The partial thromboplastin time (PTT) is greatly prolonged. The platelet count, bleeding time, and prothrombin time are normal. Mixing studies using normal plasma show a correction of the PTT. A specific assay for factor VIII activity confirms the diagnosis.

TREATMENT. Prevention of trauma is an important aspect of care for the hemophilic child. During early life the crib and playpen should be padded, and the child should be carefully supervised while learning to walk. As he or she becomes older, physical activities that do not entail a risk of trauma should be encouraged. It is important that a course between overprotection and permissiveness be followed. Aspirin and other drugs that affect platelet function may provoke hemorrhage and must be avoided by hemophilic patients. Because children with severe hemophilia are exposed to blood products throughout life, they should be immunized against hepatitis B virus. The vaccine may be given in the newborn period.

Replacement Therapy. When bleeding episodes occur, replacement therapy is essential to prevent pain, disability, or life-threatening hemorrhage. The aim of therapy is to increase factor VIII activity in the plasma to a level that secures hemostasis. Currently, this can be done only by the intravenous infusion of fresh frozen plasma or of plasma concentrates.

Therapy of the hemophilic patient has been considerably facilitated by the development of factor VIII concentrates; these permit fairly precise estimation of the dosage necessary to attain hemostatic levels. By definition, 1 mL of normal plasma contains 1 unit of factor VIII. Because the plasma volume is about 45 mL/kg, it is necessary to infuse 45 units/kg of factor VIII to increase its level in the hemophilic recipient from 0–100% (0–100 units/dL). A dose of 25–50 units/kg of factor VIII is usually given to raise the recipient's level to 50–100% (50–100 units/dL) of normal. Because the half-life of factor VIII in the plasma is about 8–12 hr, repeated infusions can be given, as necessary, to maintain the desired level of activity.

Several factor VIII concentrates are available. The most inexpensive of these is cryoprecipitate, which can be prepared in the blood bank from fresh plasma. The yield from 250 mL of fresh plasma is one bag of cryoprecipitate, which usually contains 75–125 units of factor VIII; there may, however, be marked variability in the content of bags. One bag of cryoprecipitate/5 kg of body weight raises the recipient's

level to about 50% (50 units/dL) of normal. Because cryoprecipitate is produced from single units of whole blood, the risk of blood-borne diseases such as hepatitis B and AIDS is lower than with concentrates prepared from large plasma pools. Factor VIII concentrates that are produced by recombinant technology and those that are prepared by monoclonal antibody techniques are more expensive than cryoprecipitate but are safer with regard to the transmission of infectious organisms. These concentrates are dispensed as lyophilized powders in bottles of 250–500 units that can be reconstituted just prior to use; they are tremendously useful and convenient. Their potency and relatively low protein content permit rapid restoration of normal hemostatic levels with very small volumes. Commercial factor VIII concentrates also contain anti-A and anti-B isohemagglutinins; when massive amounts are given to persons of blood group A or B, hemolysis may occur.

When the hemophilic child has significant bleeding, replacement therapy should be promptly instituted. First-aid measures should include application of cold and pressure, but these should not substitute for adequate replacement therapy. For ordinary hemarthroses, it is necessary to raise the factor VIII level to about 50% (50 units/dL) and to maintain it at least above 5% (5 units/dL) for 48–72 hr. A single infusion of 20–30 units/kg of factor VIII concentrate suffices, permitting the "one-shot" therapy of ordinary bleeding episodes. Immobilization is initially indicated, but passive exercise should be started within 48 hr to prevent joint stiffness and fibrosis. The need for aspiration of blood from the joint is controversial. When the skin overlying the joint is tense because therapy has been delayed the aspiration of blood, after

Adequate factor VIII has been given, may provide relief of pain. Replacement therapy is the most important aspect of the management of hemarthrosis, because equally good results have been obtained by some who routinely practice joint aspiration and by others who do not. Aggressive replacement therapy with factor VIII and careful orthopedic management of hemarthroses can prevent much severe deformity and crippling, which are now less common than in the past.

When hemorrhage occurs in vital areas such as the brain or neck, or when major surgery is contemplated, intensive therapy using factor VIII concentrates for 2 wk is indicated to maintain the plasma level above 50% (50 units/dL). e{epsilon}-Amino-caproic acid, 50–100 mg/kg every 6 hr, may be indicated in conjunction with replacement therapy for oral mucous membrane hemorrhage and dental extraction. Venipuncture should be performed only from superficial veins; aspiration from femoral or internal jugular veins is hazardous and has led to several deaths. There is compelling evidence that early treatment with factor VIII concentrates reduces disability and deformity as well as the amount and duration of replacement treatment necessary for bleeding episodes. Parents, or the older patient, can be trained to give intravenous infusions or concentrates at home, with substantial decreases in

hospitalization, morbidity, and risk of blood-transmitted diseases.

Home treatment with periodic assessment and counsel from the physician represents optimal or ideal management for the hemophilic child and family, and this enlightened management may permit the present generation of hemophilic children to enter adult life without major physical or psychologic crippling. On the other hand, some long-term complications may result from modern therapy. Abnormalities of hepatic enzyme activities are found in 50% of patients. Instances of chronic active hepatitis and cirrhosis have been reported. A high proportion of patients now have antibodies against hepatitis B and C viruses, and many older patients have antibodies against the AIDS virus (human immunodeficiency virus, HIV). These findings are the basis for recommending active immunization against HBV. Hypertension and renal disease with hematuria occur in many adult patients; their causes have not been defined.

Desmopressin (DDAVP; Stimate) causes an increase in factor VIII in patients with mild hemophilia A and in some patients with moderate disease. The recommended dose is 0.3m{mu}g/kg body weight, which raises the factor VIII level 25–50% above the baseline. It should only be given once every 1–2 days and only for minor bleeding episodes, such as oral bleeding, dental extractions, and small hematomas. It is ineffective in hemarthrosis, central nervous system bleeding, and for sustaining factor VIII levels after major surgery.

Factor VIII Inhibitors. Ten to 15% of patients with hemophilia become refractory to factor VIII therapy because a circulating inhibitor or antibody develops. The development of inhibitors is not related to the number of plasma transfusions, and replacement therapy should not be withheld in hope of avoiding this. These inhibitors are IgG globulins and are specifically active against factor VIII. The inhibitors may be of low titer and transient, or of extremely higher titer and very persistent. The "Bethesda unit" of inhibition is the amount of inhibitory activity in 1 mL of plasma that reduces the factor VIII level in 1 mL of normal plasma from 1 to 0.5unit. It is almost impossible to overpower a high-titer inhibitor but, when life-threatening hemorrhage occurs, massive doses of factor VIII concentrates or plasmapheresis with replacement with factor VIII should be given and may be of temporary benefit. Immunosuppressive therapy is of no value.

Another attempt at therapy of the hemophilic child who has developed a factor VIII inhibitor involves the use of factor IX concentrates (Konyne; Autoplex; Feiba), which apparently contain amounts of a factor VIII bypassing principle. These activated coagulants enter the coagulation cascade distal to the level of factor VIII and thus bypass the effects of the inhibitor. The activities of various preparations, however, and even of different lots of the same preparation, vary markedly. Thrombosis is a possible complication.

Porcine factor VIII (Hyate: C) is effective in hemophilia A patients with inhibitors. This animal factor VIII provides adequate factor VIII activity in patients with less than 50 Bethesda units of inhibitor. The usual starting dose is 100–150 porcine units/kg. Reported side effects include mild fever, nausea, headache, flushing, and occasional vomiting.

Immune tolerance may potentially be achieved with combined therapy including intravenous immunoglobulin, cyclophosphamide, and factor VIII.

PRENATAL DIAGNOSIS. Each male fetus of a mother who carries hemophilia has a 50% risk of having the disease. Prenatal diagnosis is possible through examination of the blood of the (male) fetus, which can be obtained at fetoscopy at 20–22 wk of gestation. Fetal plasma is assayed for von Willebrand protein and for factor VIIIc; as in the older patient, a markedly higher von Willebrand protein level compared to the factor VIIIc level identifies an affected male. It is now possible to identify a fetus with hemophilia by examining DNA polymorphisms in amniotic fluid fibroblasts. Trophoblastic biopsy in fetuses at risk may permit the diagnosis of hemophilia as early as 10–12 wk of gestation.

Christmas Disease; Hemophilia B

Factor IX is produced by the liver and is one of the vitamin K–dependent coagulation factors. About 12–15% of the hemophilias result from a genetically determined deficiency of factor IX.

CLINICAL MANIFESTATIONS. This disease is clinically indistinguishable from factor VIII deficiency (hemophilia A); joint and muscle hemorrhages are characteristic. It is transmitted as an X-linked recessive trait, and the severity is related to the level of coagulant activity of the factor in plasma.

Hemophilia B patients are classified as CRM+{plus}, CRM−{minus}, or CRMred; the majority (75%) are CRM−{minus}. More than 230 mutations have been described. The CRM−{minus} mutations tend to be large gene deletions, frameshift mutations, splice-site mutations, and nonsense mutations. The CRM+{plus} mutations (having normal or excess factor IX antigen) have had prevention of propeptide cleavage, mutations within the Gla (gamma carboxy glutamic acid) domain, and mutations within the growth factor domain or activation peptide region.

Factor IX is normally reduced in the plasma of newborns and slowly increases into the adult range after several months. Thus, unlike factor VIII, which is at normal or above-normal levels at birth, mild or moderate hemophilia B is difficult to diagnose in the newborn period, but severe hemophilia B (less than 1% factor IX activity) can be diagnosed in the newborn. Although female carriers can be identified by factor IX coagulation assays, detection is more specific by using monoclonal antibody or DNA analysis techniques. As with hemophilia A, the best method is the

detection of DNA sequence variations.

LABORATORY FINDINGS. The partial thromboplastin time is usually abnormally prolonged. The bleeding time and prothrombin time are normal. Specific factor IX assay is necessary to distinguish the deficiency from that of hemophilia A and to define the severity of the defect.

TREATMENT. Replacement of factor IX is accomplished by infusions of fresh frozen plasma (FFP) or a factor IX concentrate. Because the half-life of factor IX is longer than factor VIII (about 24 hr), it may be administered less frequently. Also, the dose-response relationship to factor IX is different than that for factor VIII. One unit of factor IX/kg raises the plasma factor IX from 1–1.2% of normal (factor VIII, 1 unit/kg, can raise the plasma factor VIII by 2%). Thus, to achieve 100% (100 units/dL) activity in a patient with severe hemophilia B, an infusion of 100 units of factor IX/kg is needed. Fresh frozen plasma has about 1 unit of factor IX/mL, whereas the concentrates contain considerably more factor IX in less volume. Concentrates that are heat-treated continue to have the risk of transmitting hepatitis B and C viruses. Their use is preferred when levels of factor IX greater than 30% (30 units/dL) are needed. All patients with hemophilia B should receive the hepatitis B vaccine.

Episodes of thrombosis have occurred after use of the concentrates, especially in the postoperative patient with underlying liver disease, presumably because the concentrates contain coagulants.

Factor XI Deficiency. Hemophilia C

Factor XI deficiency is the least common type of hemophilia and is found in 2–3% of all hemophilia patients. Factor XI deficiency is transmitted as an incomplete autosomal recessive disease that affects males and females. Only homozygous patients have a bleeding diathesis.

Postoperative and post-trauma hemorrhage is characteristic. Patients may also have epistaxis, hematuria, and menorrhagia. Spontaneous bleeding is rare.

Homozygous patients with factor XI deficiency have a prolonged partial thromboplastin time, and normal bleeding and prothrombin times. The factor XI level is 1–10% (1–10 units/dL), whereas heterozygous patients have factor XI levels of 30–65% (30–65 units/dL).

The half-life of factor XI in vivo is 40–80 hr. Replacement therapy for bleeding episodes is carried out with fresh frozen plasma. Plasma therapy in a dose of 10–15 mL/kg every 24 hr is effective.

Factor XII Deficiency. Hageman Factor Deficiency

Homozygous occurrence of an autosomal gene results in a profound deficiency of factor XII. Despite markedly abnormal test results of the 1st phase of coagulation (PTT and clotting times), affected persons have no clinical abnormalities of bleeding;

in fact, some patients have a thrombotic tendency.

Von Willebrand Disease (Vascular Hemophilia)

This disease is not as common as hemophilia A (factor VIII deficiency) but is probably more frequent than hemophilia B (factor IX deficiency). It occurs in both sexes and is inherited as an autosomal dominant trait. A few families with severe disease have been described in which the genetic transmission was autosomal recessive. The disease is caused by underproduction of von Willebrand protein or, in some families, by the synthesis of a dysfunctional protein. The von Willebrand protein contains a platelet-adhesive component (von Willebrand factor) and also the protein functions to carry factor VIII in the plasma.

There are at least three major varieties of von Willebrand disease, based on genetic and laboratory studies). Types I and II are autosomal dominant and type III is autosomal recessive. Types I (classic von Willebrand disease) and III show reduced factor VIII activity, reduced von Willebrand protein and function, and usually a normal multimer structure of the von Willebrand protein on gel electrophoresis. Type II can have normal or reduced factor VIII activity, normal or reduced von Willebrand protein, reduced von Willebrand factor activity, and a loss of large and intermediate-sized multimers on electrophoresis.

CLINICAL MANIFESTATIONS. These include nosebleeds, bleeding from gums, menorrhagia, prolonged oozing from cuts, and increased bleeding after trauma or surgery. Spontaneous hemarthroses are very rare.

LABORATORY FINDINGS. The bleeding time is prolonged in all von Willebrand syndromes. The platelet count and prothrombin time are normal. The partial thromboplastin time may be normal but usually is mildly to moderately prolonged. Type I patients (classic von Willebrand disease) have reduced plasma levels of von Willebrand protein, von Willebrand factor activity, and factor VIII activity. The platelets in von Willebrand disease have decreased adhesiveness and do not aggregate when the antibiotic ristocetin is added to platelet-rich plasma (because von Willebrand factor is missing), unlike platelets from normal individuals. Rare patients may show increased reactivity to ristocetin (type II B).

TREATMENT. Therapy consists of replacement of the von Willebrand factor using fresh frozen plasma or cryoprecipitate. Cryoprecipitate is the preferred form of therapy for serious bleeding or for preparation for surgery. The recommended dose is two to four bags of cryoprecipitate/10 kg, which can be repeated every 12–24 hr, depending on the bleeding episode to be treated or prevented. Patients with mild to moderate type I von Willebrand disease who have minor bleeding manifestations (e.g., epistaxis), or who are to undergo certain surgical procedures (e.g., dental extraction), may be given DDAVP as for those with hemophilia A.

PHASE II DISORDERS

Factors II (prothrombin), V, VII, and X are involved in the 2nd phase of coagulation and are designated the prothrombin complex. These factors are produced in the liver, and all except factor V require vitamin K for normal synthesis. The vitamin is necessary for the g{gamma}-carboxylation of glutamic acid residues, which converts the inactive precursors into their biologically active forms. These precursors are also known as PIVKA (protein induced by vitamin K absence) and preprotein. For example, factor II's precursor is called PIVKA-II, or prefactor II.

Deficiency of a factor in the prothrombin complex is rare and is inherited in an autosomal recessive manner. The production of a functionally abnormal factor II (dysprothrombinemia) is inherited as an autosomal dominant trait. Patients with a deficiency in one or more of these factors have.

Bleeding manifestations similar to those of the hemophilias, except that there is a high prevalence of spontaneous central nervous system bleeding in those with factor VII deficiency.

LABORATORY FINDINGS. The laboratory tests reveal a prolonged prothrombin time in these patients. Patients with factor II, V, and X deficiency also have a prolonged partial thromboplastin time (PTT). In contrast, patients with factor VII deficiency have a normal PTT. Bleeding time, platelet count, and platelet function tests are normal.

TREATMENT. Therapy consists of replacement of the deficient factor or factors with fresh frozen plasma. There is no factor concentrate available for factor V replacement. Severe cases of factor II, VII, or X deficiency may need a prothrombin complex concentrate (Proplex g{gamma}, Konyne) for control of hemostasis. These deficiencies are refractory to vitamin K therapy.

PHASE III DISORDERS. CONGENITAL AFIBRINOGENEMIA

This rare hemorrhagic disorder is caused by an autosomal recessive gene. Despite totally incoagulable blood, these patients usually do not have severe spontaneous hemorrhages or hemarthroses, but trauma or surgery may be followed by severe bleeding. Therapy with 100 mg/kg of fibrinogen provides a hemostatic plasma level. Because the plasma half-life of fibrinogen is 3–5 days, frequent infusions are not necessary. Cryoprecipitate contains fibrinogen and is used effectively for therapy. Each cryoprecipitate bag contains between 225 and 250mg of fibrinogen/bag. Thus, four to five bags provide 1g of fibrinogen.

CONGENITAL DYSFIBRINOGENEMIAS

A number of abnormal fibrinogens with defective function may be associated with thrombotic and bleeding states. Inheritance is as a dominant trait. The thrombin time is prolonged, but chemical or immunologic methods reveal normal levels of fibrinogen.

FACTOR XIII DEFICIENCY

(Fibrin-Stabilizing Factor Deficiency)

Deficiency of factor XIII has its onset most often in infancy, with bleeding after separation of the umbilical cord stump. Gastrointestinal, intracranial, and intra-articular hemorrhages are the most common clinical manifestations. Routine coagulation studies are normal. Factor XIII deficiency is diagnosed by finding an abnormal solubility of the clot in 5M urea solution. These patients can be treated with fresh frozen plasma or cryoprecipitate.

POSTNEONATAL VITAMIN K DEFICIENCY

Vitamin K deficiency rarely occurs after the neonatal period, although "late" hemorrhagic disease has been reported in breast-fed children. Intestinal malabsorption of fats and prolonged administration of broad-spectrum antibiotics may result in vitamin K deficiency; cystic fibrosis and biliary atresia may be complicated by disorders of the prothrombin complex. Prophylactic administration of water-soluble vitamin K orally is indicated in these situations (2–3 mg/24 hr for children and 5–10 mg/24 hr for adolescents and adults). In those with advanced liver disease synthesis of the factors of the prothrombin complex may be compromised by hepatocellular damage, so vitamin K therapy is often ineffective in correcting these disorders in these individuals. The anticoagulant properties of dicumarol and related anticoagulants depend on interference with vitamin K and the formation of factors II, VII, and X. Rat poison (superwarfarin) produces a similar deficiency. Vitamin K is a specific antidote.

The laboratory manifestations of vitamin K deficiency are prolonged prothrombin and partial thromboplastin times. The platelet count, bleeding time, and plasma fibrinogen level are normal. If needed, specific assays for factors II, VII, IX, and X or for detecting the noncarboxylated protein precursors of the vitamin K-dependent coagulation factors can be performed.

 LIVER DISEASE.

Coagulation abnormalities are common in patients with liver disease, estimated to be as high as 85%. Only 15% of patients, however, have significant clinical bleeding states. The severity of the coagulation abnormality appears to be directly proportional to the extent of hepatic cell damage.

The most common mechanism causing the defect is decreased synthesis of the coagulation factors. Almost all the coagulation factors are produced only in the liver except, apparently, factor VIII, which can be produced in other organs. Severe liver disease characteristically has normal to increased (not reduced) levels of factor VIII activity in plasma. Rare causes of coagulation defects in hepatic disease are disseminated intravascular coagulation or hyperfibrinolysis.

The treatment of the coagulopathy of liver disease consists of replacement with

fresh frozen plasma and cryoprecipitates. Fresh frozen plasma (10–15 mL/kg) can be expected to correct all clotting factor defects except fibrinogen. For fibrinogen correction, cryoprecipitates are recommended (four to five bags/10 kg). Because a reduction in the vitamin K dependent coagulation factors is common in those with acute and chronic liver disease, vitamin K therapy can be given a trial. The vitamin K can be given orally, subcutaneously, or intravenously (not intramuscularly) in a dose of 1 mg/24 hr for infants, 2–3mg for children, and 5–10mg for adolescents and adults. An inability to correct the coagulopathy indicates that the coagulopathy may be caused by a reduction in one or more of the non–vitamin K dependent proteins, or because the liver is severely impaired and cannot produce the precursor vitamin K proteins.

INHIBITORS

Acquired circulating anticoagulants (inhibitors) are defined as abnormal endogenous components of blood that inhibit the coagulation of normal blood. These anticoagulants are usually specific types of gamma globulin and may represent autoantibodies. The circulating anticoagulant may affect coagulation, either by neutralizing a specific coagulation factor directly or by acting against certain reaction sites in the coagulation pathway. When the anticoagulant acts against a specific coagulation factor (e.g., factor VIII or IX), the patient has a clinical bleeding picture similar to that of the congenital deficiency state. Usually no or minimal bleeding is noted in patients in whom the anticoagulant is directed toward a reaction site.

Circulating anticoagulants are uncommon in otherwise normal children. They are found in patients with systemic lupus erythematosus (SLE) or lymphomas, or in those with penicillin or other drug reactions. Spontaneous inhibitors have been reported in children following incidental viral infections.

LABORATORY FINDINGS. Inhibitors against specific coagulation factors usually affect factor VIII, IX, or XI (a phase I defect). The partial thromboplastin time (PTT) is prolonged and the test does not correct with the addition of normal plasma. The prothrombin time is normal. Specific factor assays determine which factor is involved.

The most common inhibitor against a reaction site is the so-called lupus anticoagulant. Although this inhibitor is found in patients with SLE, it may also occur spontaneously and in other disease states. This anticoagulant does not cause bleeding but paradoxically has been reported to be associated with a thrombotic tendency. It produces a prolonged PTT and it may also result in a prolonged prothrombin time. The addition of normal, platelet-poor plasma does not correct the abnormal tests, but the addition of platelets neutralizes the anticoagulant. On rare occasions there can be an associated hypoprothrombinemia (reduced factor II).

TREATMENT. Management of the patient with an inhibitor against a coagulation

factor is the same as for the hemophilia patient who develops an alloantibody against factor VIII or IX. Infusions of a prothrombin complex concentrate (Konyne) or activated prothrombin complex concentrate (Autoplex; Feiba) may be needed to control significant bleeding manifestations. Spontaneous inhibitors, usually following a viral infection, tend to disappear with a few weeks to months. Inhibitors seen with an underlying disease disappear when the primary disease is treated.

CONSUMPTION COAGULOPATHY (DISSEMINATED INTRAVASCULAR COAGULATION SYNDROMES)

Consumption coagulopathy refers to a large group of conditions, including disseminated intravascular coagulation (DIC). Consequences of this process include widespread intravascular deposition of fibrin, which may lead to tissue ischemia and necrosis, a generalized hemorrhagic state, and hemolytic anemia.

ETIOLOGY. A number of pathologic processes may incite episodes of DIC, including hypoxia, acidosis, tissue necrosis, shock, and endothelial damage Accordingly, it is not surprising that a large number of diseases have been reported to be associated with DIC, including incompatible blood transfusions, septic shock (especially gram-negative), rickettsial infections, snakebite, purpura fulminans, giant hemangioma, malignancies, and acute promyelocytic leukemia.

CLINICAL MANIFESTATIONS. Most frequently DIC accompanies a severe systemic disease process. Bleeding frequently first occurs from sites of venipuncture or surgical incision, with associated petechiae and ecchymoses. Tissue thrombosis may involve many organs and can be most spectacular as infarction of large areas of skin and subcutaneous tissue or of kidneys. Anemia caused by hemolysis may develop rapidly.

LABORATORY FINDINGS. There is no well-defined sequence of events. The consumption coagulation factors (II, V, VIII, and fibrinogen) and platelets may be consumed by the ongoing intravascular clotting process, with prolongation of the prothrombin, partial thromboplastin, and thrombin times. Platelet counts may be profoundly depressed. The blood contains fragmented burr and helmet-shaped red blood cells (schizocytes), changes referred to as microangiopathic. In addition, because the fibrinolytic mechanism is activated, fibrin split products (FSP) appear in the blood The D-dimer assay is equally sensitive and more specific for DIC than the fibrin degradation product (FDP) test. D-dimer is a neo-antigen formed following the thrombin-initiated generation of fibrin from fibrinogen, followed by cross-linking of fibrin by factor VIII and plasmin digestion of the cross-linked fibrin.

TREATMENT. The most important component of therapy is control or reversal of the process that initiated the DIC. Infection, shock, acidosis, and hypoxia must be treated promptly and vigorously. If the underlying problem can be controlled bleeding quickly ceases, and there is improvement of the abnormal laboratory

findings. Blood components are used for replacement therapy in patients who have hemorrhage. This may consist of platelet infusions (for thrombocytopenia), cryoprecipitates (for hypofibrinogenemia), and/or fresh frozen plasma (for replacement of other coagulation factors and natural inhibitors).

In some patients the treatment of the primary disease may be inadequate or incomplete, or the replacement therapy may not be effective in controlling the hemorrhage. When this occurs the DIC may be treated with anticoagulants to prevent ongoing consumption of factors. Heparin is the drug of choice and can be administered on an intermittent or continuous intravenous treatment schedule. Using the intermittent intravenous schedule, heparin is given in a dose of 75–100 units/kg every 4 hr. With the continuous schedule, 50–75 units of heparin/kg is given as a bolus followed by a continuous infusion of 15–25 units/kg/hr. The duration and effectiveness of heparin therapy can be judged by serial measurements of the platelet count and plasma fibrinogen concentration.

Heparin has been found to be an effective drug in children with DIC associated with purpura fulminans and promyelocytic leukemia. Lower doses (10–15 units/kg/hr without a loading dose) are used for those with progranulocytic leukemia. Heparin is not indicated and has been reported to be ineffective in septic shock, snake envenomation, heat stroke, massive head injury, and incompatible blood transfusion reaction.

PLATELET AND BLOOD VESSEL DISORDERS

Platelets are non-nucleated, cellular fragments produced by the megakaryocytes of the bone marrow. The large size of the megakaryocyte reflects its polyploidy. As the megakaryocyte reaches maturity, fragmentation of the cytoplasm occurs and large numbers of platelets are liberated. In the circulation they have a life span of 7–10 days. The platelet has a number of intrinsic antigens, which are distinct from those of the red blood cell, and some are shared by the leukocytes.

The platelets are intimately involved in both the vascular and clotting aspects of hemostasis. They are necessary for integrity of the vascular endothelium; when small blood vessels are transected, platelets accumulate at the site of injury, forming a hemostatic plug. Platelet adhesion is initiated by contact with extravascular components such as collagen. Release of thromboxane (a prostaglandin derivative) and endogenous ADP causes firm aggregation. Serotonin and histamine liberated during these processes increase local vasoconstriction. Platelets have a phospholipid with partial thromboplastin activity, which makes an important contribution to coagulation. They also transport other blood coagulation factors through absorption to the platelet surface. Finally, the platelet is necessary for normal clot retraction.

The normal platelet count is 150–400 g{times} 109/L. Lower counts indicate thrombocytopenia, either caused by inadequate production or by excessive

destruction or removal of platelets. Inadequate production is almost always a result of marrow dysfunction, with decreases in the number of megakaryocytes. By contrast, in the thrombocytopenias caused by increased destruction, the megakaryocytes are quantitatively normal or increased. The hypomegakaryocytic thrombocytopenias result from aplasia of the marrow or from its infiltration by abnormal or neoplastic tissue. Because of the grave prognosis of such disorders, bone marrow aspiration is indicated in those with significant, unexplained thrombocytopenia. Bone marrow aspirations can usually be performed without serious bleeding, even in patients with severe thrombocytopenia, because thromboplastins in tissue juice usually effect hemostasis.

Congenital Thrombocytopenias WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome consists of eczema, thrombocytopenic hemorrhage, and increased susceptibility to infection because of an immunologic defect that is transmitted as an X-linked recessive trait. The bone marrow contains a normal number of megakaryocytes, but many have bizarre nuclear morphology. Homologous platelets survive normally when transfused into these patients, but autologous platelets have a shortened life span and are small in size. Wiskott-Aldrich syndrome may represent an unusual circumstance in which thrombocytopenia results from abnormal platelet formation or release, despite quantitatively adequate numbers of megakaryocytes. Splenectomy has often been followed by overwhelming sepsis and death, but significant improvement in thrombocytopenia occurs after splenectomy. Prophylactic use of penicillin is essential postsplenectomy. About 5% of patients with Wiskott-Aldrich syndrome develop lymphoreticular malignancies. A few cases have been reported to benefit from the administration of transfer factor or from bone marrow transplantation.

OTHER INHERITED THROMBOCYTOPENIAS

Other types of inherited thrombocytopenias have been described. Some are X linked and some have autosomal transmission. Responses to therapy, including splenectomy, have usually been disappointing. The inordinately high mortality of young males splenectomized for presumed idiopathic thrombocytopenic purpura (ITP) suggests that, even without other stigmata, X-linked thrombocytopenia may represent a variant of Wiskott-Aldrich syndrome. Thus, the young thrombocytopenic male must be carefully studied before a diagnosis of ITP is made. A platelet survival study may be indicated in such patients.

THROMBOPOIETIN DEFICIENCY

A few patients have had chronic thrombocytopenia attributed to deficiency of a megakaryocyte maturation factor contained in normal plasma. Plasma infusions repeatedly produced a sustained rise in the platelet count. In somewhat similar cases, episodic thrombocytopenia and microangiopathic hemolysis were reversed by

infusions of plasma.

THROMBOCYTOPENIA WITH CAVERNOUS HEMANGIOMA

(Kasabach-Merritt Syndrome)

Some infants with large, cavernous hemangiomas of the trunk, extremities, or abdominal viscera have severe thrombocytopenia and other evidence of intravascular coagulation. Histologic and isotopic studies indicate that platelets are trapped and destroyed within the extensive vascular bed of the tumor. The peripheral blood reveals thrombocytopenia and red blood cell fragments, and the bone marrow contains adequate numbers of megakaryocytes. Spontaneous thrombosis within the tumor may lead to obliteration of the vascular channels and spontaneous recovery; radiation therapy in a single dose of 600–800 rad (6–8 Gy) may accelerate this process, but repeated courses may be necessary. When anatomically feasible, external compression or total excision may be attempted, but surgery can be associated with uncontrollable hemorrhage. Corticosteroids and interferon may hasten involution and warrant trial, especially in the young infant. Splenectomy is contraindicated.

CONGENITAL HYPOPLASTIC THROMBOCYTOPENIA WITH ASSOCIATED MALFORMATIONS

(Thrombocytopenia Absent Radius [TAR] Syndrome)

Severe thrombocytopenia associated with aplasia of radii and thumbs, and with cardiac and renal anomalies, occurs as a familial condition. Severe hemorrhagic manifestations are evident in the first days of life. Hemoglobin levels are normal; leukocytosis and even leukemoid reactions have been found in some patients. Megakaryocytes are absent from the bone marrow.

The anomalies in this disease are similar to those observed in Fanconi pancytopenia, in which the hematologic abnormalities are not usually observed until the 3rd to 4th year of life. In this disorder chromosomes do not reveal the abnormalities found in Fanconi syndrome. No infants with congenital hypoplastic thrombocytopenia have been reported to develop full-blown Fanconi syndrome, nor have both conditions been observed in the same family.

Congenital Platelet Function Defects

Hemorrhagic disease resulting from congenital disorders of platelet function are not common. The inheritance pattern is not known for many of these disorders. The defects can be in adhesion, aggregation, and platelet coagulant activity.

CLINICAL MANIFESTATIONS. The clinical manifestations are similar to those encountered in patients with thrombocytopenia and consist of mucous membrane bleeding (epistaxis, oral cavity bleeding, menorrhagia, gastrointestinal and genitourinary hemorrhage), skin petechiae, and small ecchymoses.

LABORATORY FINDINGS. The laboratory test results are variable and reflect the functional defect, but all functional defects have a prolonged bleeding time,

normal prothrombin time, normal PTT, and either a normal or moderately reduced platelet count. The defects can be defined by specific in vitro platelet function tests. Patients with platelet factor 3 deficiency, however, have a normal bleeding time but an abnormal prothrombin consumption test.

TREATMENT. Treatment of the bleeding disorders in these patients is difficult. Platelet transfusions are usually required to control significant hemorrhage.

BERNARD-SOULIER SYNDROME

This autosomal recessive inherited platelet adhesion defect is characterized by moderate thrombocytopenia, large platelets, and decreased ristocetin-induced platelet agglutination (aggregation) that is not corrected by the addition of von Willebrand factor.

GLANZMANN THROMBASTHENIA

This autosomal recessive inherited platelet disorder is characterized by a normal platelet count, absent in vitro aggregation with all agonists, and absent clot retraction.

OTHER DEFECTS

Defects in the normal platelet release reaction have been described, caused by platelet granule deficiency, impaired platelet arachidonic acid metabolism, or an impaired secretion of intraplatelet agonists. Laboratory studies reveal a normal platelet count and abnormal in vitro aggregation. The deficient granule variety can be detected by using electron microscopic techniques.

Inherited Blood Vessel Defects

Bleeding secondary to defective blood vessels is uncommon in childhood. Disorders such as hereditary hemorrhagic telangiectasia and Ehlers-Danlos syndrome can cause significant mucous membrane and skin bleeding. All laboratory tests for hemostasis are usually normal in these patients.

Acquired Thrombocytopenias. IDIOPATHIC THROMBOCYTOPENIC PURPURA

Acute idiopathic thrombocytopenic purpura (ITP), the most common of the thrombocytopenic purpuras of childhood, is associated with petechiae, mucocutaneous bleeding, and, occasionally, hemorrhage into tissues. There is a profound deficiency of circulating platelets, despite adequate numbers of megakaryocytes in the marrow.

ETIOLOGY. The disease often appears to be related to sensitization by viral infections; in about 70% of cases there is an antecedent disease such as rubella, rubeola, or viral respiratory infection. The interval between infection and onset of purpura averages 2 wk. As with the adult form, it seems probable that an immune mechanism is the basis for the thrombocytopenia. Platelet antibodies can be detected in some acute cases. Increased amounts of IgG have been found bound to platelets and may represent immune complexes absorbed on the platelet surface. No

consistently reliable test currently exists for the serologic diagnosis of ITP.

CLINICAL MANIFESTATIONS. The onset is frequently acute. Bruising and a generalized petechial rash occur 1–4 wk after a viral infection or in some cases without antecedent illness. The bleeding is typically asymmetric and may be most prominent over the legs. Hemorrhages in mucous membranes may be prominent, with hemorrhagic bullae of the gums and lips. Nosebleeds may be severe and difficult to control. The most serious complication is intracranial hemorrhage, which occurs in fewer than 1% of cases. The liver, spleen, and lymph nodes are not enlarged. Except for the signs of bleeding, the patient appears clinically well. The acute phase of the disease associated with spontaneous hemorrhages lasts for only 1–2 wk. Thrombocytopenia may persist, but spontaneous mucocutaneous hemorrhages subside. Sometimes the onset is more insidious, with moderate bruising and few petechiae.

LABORATORY FINDINGS. The platelet count is reduced below 20 g{times} 109/L. The few platelets observed on blood smear are large (megathrombocytes) and reflect increased marrow production. Those tests that depend on platelet function, such as the bleeding time and clot retraction, yield abnormal results. The white count cell count is normal, and anemia is not present unless significant blood loss has occurred.

Bone marrow aspiration, if indicated, reveals normal granulocytic and erythrocytic series and, frequently, modest eosinophilia. Normal or increased numbers of megakaryocytes are seen. Some of these are immature, with deep basophilic cytoplasm; platelet budding may be scanty, but there is no pathognomonic or diagnostic megakaryocyte morphology. The changes seen reflect increased megakaryocytic turnover.

DIFFERENTIAL DIAGNOSIS. ITP must be differentiated from aplastic or infiltrative processes of the bone marrow. Marrow aplasia or replacement is unlikely if the physical examination and blood count are normal, except for thrombocytopenia. Significant enlargement of the spleen suggests primary liver disease with congestive splenomegaly, lipidosis, or reticuloendotheliosis. Thrombocytopenic purpura may be an initial manifestation of systemic lupus erythematosus, AIDS, or lymphoma, but this sequence is unusual in young children. In adolescents the possibility is greater, and serologic studies for systemic lupus erythematosus and AIDS are indicated. Genetically determined thrombocytopenias must be considered in infants (particularly males) found to have low platelet counts.

TREATMENT. ITP has an excellent prognosis, even when no specific therapy is given. Within 3 mo 75% of patients recover completely, most within 8 wk. Severe spontaneous hemorrhages and intracranial bleeding (<1% of patients) are usually confined to the initial phase of the disease. After the initial acute phase, spontaneous

manifestations tend to subside. About 90% of affected children have regained normal platelet counts 9–12 mo after onset, and relapses are unusual.

Fresh blood or platelet concentrates have transient benefit because transfused platelets survive only briefly, but they should be administered when life-threatening hemorrhage occurs.

When the disease is mild and hemorrhages of the retina or mucous membranes are not present, no specific therapy may be indicated. The affected child should be protected from falls or trauma. Vitamins K and C have no therapeutic effect.

Gamma Globulin. Infusions of intravenous gamma globulin (Sandoglobulin; Gamimune N) are followed by sustained rises of platelet count. Large doses of intravenous gamma globulin (400 mg/kg for 5 days) induce remission of many cases of acute and, occasionally, chronic ITP. A randomized control trial demonstrated the effectiveness of intravenous immune globulin G (IVIG), 1 g/kg/24 hr for 1 or 2 consecutive days, in reducing the frequency of severe thrombocytopenia (platelet count J{less than or equal}20 r{times} 109/L).

Corticosteroid Therapy. Although corticosteroid therapy has not decreased the number of chronic cases, it is beneficial because it reduces the severity and shortens the duration of the initial phase. In more severe cases, therapy with a corticosteroid, such as prednisone in a dose of 1–2 mg/kg/24 hr in divided doses or its equivalent, is indicated. Some authorities recommend an examination of bone marrow to exclude leukemia prior to initiating prednisone. The necessity for corticosteroid therapy in mild cases has been debated, although the platelet count returns to a hemostatic level more rapidly with such therapy. This therapy is continued until the platelet count is normal or for 3 wk, whichever comes first. At this point steroid therapy should be discontinued, even if the platelet count remains low. Prolonged corticosteroid therapy is not indicated and may depress the bone marrow, in addition to producing cushingoid changes and growth failure. If thrombocytopenia persists for 4–6 mo, a 2nd short course of corticosteroid therapy or intravenous immunoglobulin may be given.

Whether the initial therapy of choice in acute ITP is no therapy, intravenous gamma globulin, or corticosteroids is now being reassessed. Splenectomy should be reserved for chronic patients, defined as thrombocytopenia persistent for more than 1 yr, and for severe cases that do not respond to corticosteroids. Considerable improvement can usually be expected. If the hemorrhagic manifestations are severe, or if intracranial hemorrhage is suspected, larger doses of prednisone (5–10 mg/kg/24 hr) and intravenous gamma globulin can be used. Platelet transfusions may provide temporary control of bleeding, but sustained platelet counts are rarely achieved.

DRUG-INDUCED THROMBOCYTOPENIAS

A number of drugs can cause thrombocytopenia, either as a result of an immune-mediated process (with the drug functioning as a hapten) or of megakaryocyte injury.

Drugs commonly used in pediatrics that can cause thrombocytopenia include carbamazepine (Tegretol), phenytoin (Dilantin), sulfonamides, trimethoprim-sulfamethoxazole, and chloramphenicol.

HEMOLYTIC-UREMIC SYNDROME

This acute disease of infancy and early childhood usually follows an episode of acute gastroenteritis. Shortly thereafter signs and symptoms of hemolytic anemia, thrombocytopenia, and acute renal insufficiency develop.

LABORATORY FINDINGS. The hemolytic anemia is associated with characteristically bizarre red blood cell morphology. Many of the red blood cells are contracted and distorted, with a prominence of spherocytes, burr cells, and helmet-shaped forms. A depressed platelet count, despite normal numbers of megakaryocytes in the marrow, indicates excessive peripheral destruction. Tests of the coagulation mechanism are usually normal. Protein, red blood cells, and casts are present in the urinary sediment, and grave renal damage is reflected by anuria and azotemia.

TREATMENT. For a discussion of the management of uremia and anuria. Transfusions are indicated for severe anemia. Corticosteroid and heparin therapy do not affect survival or prognosis.

THROMBOTIC THROMBOCYTOPENIC PURPURA

This rare and serious disease is similar to the hemolytic-uremic syndrome. Diffuse embolism and thrombosis of the small blood vessels of the brain are evidenced by shifting neurologic signs such as aphasias, blindness, and convulsions. The prognosis is grave. Laboratory findings include thrombocytopenia and a hemolytic anemia associated with distorted and fragmented red blood cell microangiopathy. Plasmapheresis and plasma infusions are effective in 60–70% of cases. Corticosteroids and splenectomy are reserved for refractory cases.

Other Causes

Thrombocytopenia is a common complication of viral and bacterial (especially septicemia) infections, disseminated intravascular coagulation, and, rarely, heparin therapy.

NEONATAL THROMBOCYTOPENIA

Thrombocytopenia of the newborn may indicate primary disease in the infant's hematopoietic system or may be a result of the transfer of abnormal factors from the mother.

Association with Infection

Thrombocytopenia may occur in various fetal and neonatal infections and may be responsible for serious spontaneous bleeding. These include viral infections (especially rubella and cytomegalic inclusion disease), protozoal infections (e.g., toxoplasmosis), syphilis, and bacterial infections, especially those caused by gram-negative bacilli. Hemolysis is usually also present in infants with prominent anemia

and jaundice. The liver and spleen are considerably enlarged. The bone marrow changes are variable, but reduced numbers of megakaryocytes may be seen.

Immune Neonatal Thrombocytopenia

About 30% of infants born of mothers with active idiopathic thrombocytopenic purpura have thrombocytopenia resulting from the transplacental transfer of antiplatelet antibodies. Rarely, infants with neonatal disease have been born of mothers with past histories of ITP (but who had splenectomy) who have normal platelet counts and whose disease has been inactive for many years. Petechiae are not present initially but appear in a generalized distribution within a few minutes after birth. Bleeding from the bowel or kidney and intracranial hemorrhage may occur. In mild cases there may be few abnormal findings. Hepatosplenomegaly is not present. The duration of the thrombocytopenia is 2–3 mo.

Therapy is not strikingly successful, but intravenous immunoglobulin, exchange transfusions, or platelet transfusions may be of temporary value in arresting acute bleeding. Corticosteroid therapy has not been proved beneficial. Because of the self-limited nature of the disease, splenectomy is contraindicated. Corticosteroid therapy given to the mother 1 wk prior to delivery or administration of intravenous gamma globulin to the mother late in pregnancy may reduce the severity of the disease in the mother and perhaps in the infant.

When the fetus has platelet antigens that the mother does not have, alloimmunization may occur. If maternal antibodies to fetal platelet antigens reach a sufficiently high titer, enough may cross the placenta to produce thrombocytopenia in the fetus. The disease may be familian, and first-born infants are frequently affected. Clinical signs include petechiae and other hemorrhagic manifestations. Antiplatelet antibodies can be demonstrated in about 50% of cases using sensitive tests. The PLA-1 antigen is most frequently involved. Infants born to mothers with antiplatelet alloantibodies are the most severely affected. Exchange transfusion is temporarily effective in stopping bleeding. Intravenous gamma globulin given to the affected newborn may be helpful. If compatible platelets can be obtained (these are most easily procured by preparing washed platelet concentrates from the mother), they offer specific, effective therapy. Infants born of successive pregnancies may be affected. Elective cesarean section has been advocated to spare the infant's head the trauma of delivery. Percutaneous umbilical blood sampling will diagnose fetal thrombocytopenia and permits fetal platelet transfusions with maternal platelets.

When the mother has drug-induced thrombocytopenia, both antibody and drug may cross the placenta and cause neonatal thrombocytopenia. Corticosteroid therapy, and especially exchange transfusions, should be considered when bleeding manifestations are severe.

Acquired Platelet Function Disorders

Acquired disorders of platelet function are caused by toxic metabolic products (e.g., in uremia), autoantibodies, immune complexes, fibrin split (degradation) products (FSPs), and drugs. These patients have a prolonged bleeding time and abnormalities in platelet aggregation tests.

The most common acquired defect is caused by drugs. Some drugs produce an irreversible reduction of prostaglandin synthesis within the platelet by inhibition of cyclo-oxygenase enzymes. This prevents the release of endogenous ADP and of the prostaglandin derivative thromboxane, which are essential for platelet aggregation. The abnormality can be most easily demonstrated with a platelet aggregometer, by which an ablation of the so-called secondary wave of platelet aggregation can be demonstrated. The most important drug that produces this effect is aspirin. The effect is not dose related. Abnormal platelet aggregation can be demonstrated in adults within 1 hr of ingestion of as little as 300 mg of aspirin. The abnormality persists for 4–6 days, or until the platelets that have been exposed to the drug have been replaced. Usually the effects of these drugs produce no clinical problems, although prolongation of bleeding time is frequently seen. If the patient has an underlying bleeding disorder such as hemophilia or undergoes surgery, however, hemorrhage may occur. Aspirin or other drugs that inhibit platelet aggregation are contraindicated in these circumstances and should be replaced with other agents, such as acetaminophen, when indicated. Aspirin may have transplacental effects on platelet function in the newborn, producing, rarely, neonatal hemorrhage; maternal aspirin consumption should be avoided during the last trimester of pregnancy.

Acquired Vascular Disorders

The most common cause of a vascular type of nonthrombocytopenic purpura is Schenlein-Henoch syndrome or anaphylactoid purpura. This acute inflammatory process of unknown origin involves the small blood vessels of the skin, joints, gut, and kidney. The striking centrifugal distribution of the rash and involvement of the legs and buttocks are characteristic, particularly when combined with arthritis, nephritis, or gastrointestinal bleeding. The petechiae should be differentiated from those of early meningococcemia or of septicemia caused by other microorganisms. Toxic vasculitis may produce a hemorrhagic rash as a reaction to drugs such as arsenicals and iodides. Similar findings may occur during viral or rickettsial infections.

Treatment of this self-limited condition is supportive. Corticosteroids can be effective in controlling the painful edema, gastrointestinal pain, and arthritis, but not the vasculitic skin rash.

Thrombocytosis

Platelet counts in excess of 750 g{times} 109/L may be designated as thrombocytosis. Markedly elevated counts may accompany hemorrhage, iron deficiency anemia, hemolytic anemias, and primary myeloproliferative disorders.

Acute and chronic inflammatory states may be accompanied by elevated platelet counts. Platelet counts exceeding 600 g{times} 109/L are regularly observed in those with Kawasaki disease. Persons with asplenia and children with sickle cell anemia often have somewhat elevated platelet counts. After splenectomy for ITP or hemolytic anemia, the platelet count often rises precipitously and may exceed 1,000 g{times} 109/L 10–14 days postoperatively. Generally, no specific therapy such as anticoagulation is necessary because thrombosis is extremely rare. The use of aspirin (or dipyridamole), which inhibits platelet function, may be considered if factors predisposing to thrombosis are present.

A case of primary thrombocytosis associated with thrombotic episodes and myocardial infarction has been described.

THROMBOTIC DISORDERS

CLINICAL MANIFESTATIONS AND DIAGNOSIS. The occlusion of a blood vessel with a platelet plug or fibrin clot may occur in vessels of any size. Capillary and small-vessel occlusion are seen in vasculitic diseases and as complications of disseminated intravascular coagulation; in medium-sized vessels, in homocystinuria, cyanotic congenital heart disease, dehydration, and polyarteritis nodosa; and in larger vessels, in aortic thrombosis, superior vena cava thrombosis in the newborn, deep venous thrombosis, sickle cell anemia, and pulmonary embolism. The mechanism leading to the thrombosis is vessel injury in addition to one or all of the following: abnormal platelet adhesiveness-aggregation; an activated coagulation mechanism; an inactive inhibitor system; an inactive fibrinolytic mechanism and reduced blood flow. Arterial thrombosis appears to depend on vascular injury and platelet activation, whereas venous thrombosis generally occurs in low-flow conditions associated with activation of the coagulation mechanism or with an impaired inhibitor-fibrinolytic system.

The clinical manifestations reflect organ or tissue injury resulting from the absentce or a severe reduction in blood perfusion. In general, vascular occlusive events in children have an acute or sudden onset. The diagnosis is made by angiography. Ultrasound and radionuclide scanning techniques can be used for screening purposes. Other laboratory studies are rarely helpful in diagnosing a thromboembolic event except in two settings: when the event is a result of disseminated intravascular coagulation (in which case the patient demonstrates thrombocytopenia, hypofibrinogenemia, reduced factors II, V, and VIII, and positive fibrin split products (FSPs) and, in rare patients, of congenital deficiencies of natural inhibitors.

CONGENITAL AND INHERITED DEFECTS

The formation of a fibrin clot is regulated by a complex inhibitor system that involves antithrombin III, protein C, a cofactor (probably factor V) for activated protein C (APC), and protein S. By regulating clot formation, these plasma inhibitors

prevent spontaneous intravascular coagulation, limit the thrombotic response of the body to injury, and control the extension of existing clots. Reduced plasma levels of any one of these inhibitors leads to a propensity to excessive thrombosis. Also, a reduced ability to remove fibrin clots (congenital hypoplasminogenemia and dysplasminogenemia) and the formation of an unusual fibrin clot (congenital dysfibrinogenemia) can lead to thrombotic diseases. The thromboembolic diseases reported in deficient patients predominantly affect the venous system; arterial forms are rare. Deep vein thrombosis of the legs, pulmonary embolism, thromboses of the pelvic veins and mesenteric veins, and sagittal sinus thrombosis are frequent manifestations. The 1st thromboembolic event usually occurs from 10 to 25 yr of age. A severe neonatal form (see later) has been reported.

Antithrombin III Deficiency

Antithrombin III (AT III) is a plasma inhibitor protein that blocks the enzymatic activity of some serine protease coagulation factors. The activity of this inhibitor is increased by heparin (formally called heparin cofactor activity). AT III is therefore necessary for heparin's anticoagulant activity. AT III is synthesized in the liver, is not vitamin K dependent, and can be consumed during the process of extensive intravascular clotting. Patients with AT III deficiency have AT III activity levels between 20 and 60% of normal. Normal newborns have reduced AT III activity.

Congenital AT III deficiency is an autosomal dominant trait that affects both sexes and has been observed in all races. Homozygous patients have not been described. Diagnosis is by detection of reduced AT III activity in plasma. There are at least two types of hereditary AT III deficiency: type I patients (most common) lack both AT III functional activity and protein, and type II patients lack functional activity but have the protein (a dysfunctional protein).

Treatment of thrombotic events in these patients can be difficult. Mildly deficient patients may respond to intravenous heparin but patients with severe deficiency do not. An infusion of plasma (as a source of AT III) plus heparin can be tried for acute therapy. Early initiation of long-term warfarin therapy is recommended for such patients. Danazol, a synthetic weak androgen, may raise AT III levels in selected patients. The efficacy and safety of this drug have not been established in children. Two AT III concentrates are available for clinical use (ATnativ, Kabi Vitrum, Stockholm; Thrombate III, Miles, Cutter Biological, West Haven, CT). An international unit per kilogram of body weight will raise the plasma activity level by 2–2.5% of normal. The drug must be given by the intravenous route.

Protein C Deficiency

Protein C is a plasma inhibitor protein that, once activated, inhibits clot formation and enhances fibrinolysis. It is synthesized in the liver and is vitamin K dependent.

Protein C is converted into an active enzyme by a thrombin-thrombomodulin complex on the endothelial cell surface. Activated protein C (protein Ca or APC) inhibits a plasminogen activator inhibitor, which results in enhanced fibrinolysis and, with protein S as a cofactor, inhibits the clotting ability of factors V and VIII by limited proteolysis. APC thus controls the conversion of factor X to Xa and of prothrombin to thrombin. Thromboembolic disease has been reported in patients with levels that are from 38 to 49% of normal, but not all patients with protein C deficiency have thromboembolic disease. Clinical thrombotic events appear in adolescence.

Congenital protein C deficiency is an autosomal dominant trait. Diagnosis is by detection of reduced protein C activity in plasma. There are two types: Type I patients (most common) have both activity and protein reduced, and type II patients have functionally reduced activity but a normal amount of protein. Acquired deficiency may occur in association with infection.

Treatment includes heparin anticoagulation for thrombosis and chronic oral anticoagulation with warfarin to prevent recurrence of thrombosis. Androgenic drugs (e.g., danazol) have been shown to increase the protein C protein level to normal levels within 10–20 days, but the functional activity remains significantly lower than the antigenic level. Thus, its efficacy has not been established.

Purpura Fulminans Neonatalis

Homozygous protein C–deficient infants are characterized by the abrupt, early onset of subcutaneous ecchymoses and necrosis and by the widespread thrombosis of blood vessels. The thrombosis is accompanied by evidence of disseminated intravascular coagulation. These patients have undetectable levels of protein C, and the parents have values consistent with the heterozygous state. Treatment of this rare, severe condition includes fresh frozen plasma and long-term anticoagulation with warfarin. A similar condition has occurred in an infant with homozygous protein S deficiency.

Protein S Deficiency

Protein S, a vitamin K–dependent plasma protein, is synthesized in the liver and by endothelial cells. It functions as a cofactor for the anticoagulant effect of activated protein C. Protein S exists in the protein-bound and free forms in the plasma; the free form is biologically active. Protein S–deficient patients have been identified by immunologic and functional assays. Patients with recurrent thrombosis have protein S free levels of 15–37% of normal. Transient acquired deficiency may occur during infection.

Congenital protein S deficiency is inherited as an autosomal dominant trait. Homozygous deficiency has been described. Thromboembolic disease may or may not occur in the heterozygotes. Treatment consists of heparin anticoagulation for thrombosis and oral anticoagulants for the prevention of further thrombosis.

Resistance to Activated Protein C (APC)

This disorder occurs due to a deficiency of a cofactor to APC that is inherited as an autosomal dominant trait. Factor V is the cofactor and demonstrates both procoagulant and anticoagulant functions. The latter activity is reduced in patients having resistance to APC by a molecular defect in the protein. The prevalence is about 5%, and the frequency in patients with venous thrombosis ranges from 21% to 64%. Anticoagulant therapy should be individualized.

Plasminogen and Fibrinogen Abnormalities

Both qualitative and quantitative plasminogen abnormalities have been observed in rare patients with thromboembolic disorders. Many abnormal fibrinogens (dysfibrinogenemia) have been discovered that form abnormal clots; the dysfibrinogens appear to be inherited as an autosomal dominant trait. Treatment of thromboses in these disorders consists of the administration of heparin and long-term warfarin to prevent subsequent thrombotic events. Anticoagulants

Heparin

Heparin enhances the rate by which antithrombin III neutralizes the activities of several of the activated clotting proteins, especially thrombin. The average half-life of intravenously administered heparin is about 60 min in adults and can be as short as 30 min in the newborn. Heparin does not cross the placenta. The half-life of heparin is dose dependent, that is, the higher the dose, the longer the circulating half-life. In thrombotic disease the half-life may be shorter than normal in patients with significant TED (such as pulmonary embolism) and longer than normal in patients with cirrhosis and uremia.

Anticoagulation with heparin is contraindicated in the following circumstances: a pre-existing coagulation defect or bleeding abnormality; a recent central nervous system hemorrhage; bleeding from inaccessible sites; malignant hypertension; bacterial endocarditis; recent surgery of the eye, brain, or spinal cord; and current administration of regional or lumbar block anesthesia. Despite these precautions, the frequency of bleeding in patients given heparin anticoagulation is about 5–10%.

Heparin can be given as an intravenous or subcutaneous injection. It is not effective when taken orally and should not be given as an intramuscular injection. Two techniques can be used to administer the drug intravenously, intermittent bolus or continuous infusion. Using the intermittent schedule, the patient is given 75–100 units/kg of heparin intravenously by bolus every 4 hr. Using the continuous infusion schedule, the patient is given a bolus injection of 50–75 units/kg followed by a continuous infusion of 10–25 units/kg/hr. Both schedules provide adequate anticoagulation, but the continuous method has been reported to have the effect of less anticoagulant-related bleeding.

Various coagulation tests are available to measure the action of heparin, including

the APTT, the thrombin clotting time (TCT), and the factor Xa inhibition assay. The APTT is the most frequently used test for monitoring heparin therapy. It is sensitive to small amounts of heparin, is rapid and reproducible, and can be performed in most clinical laboratories. Clinical studies suggest that the APTT should be maintained at 1.5–2 times the patient's own preheparin control APTT.

After initiation of heparin therapy, an APTT should be performed periodically to ensure that adequate anticoagulation has occurred and that the patient's requirements for the drug have not changed. In patients receiving the intermittent bolus schedule, the APTT should be determined 1 hr after the initial infusion and should be greatly prolonged at that time. The next APTT should be performed at the 4th hr, that is, just prior to the next dose of heparin; at that time it should be 5–10 sec longer than the normal control time for the laboratory. If the APTT is very prolonged, the dose of the drug should be reduced by 10%, or, if the APTT is within the normal range, the dose of the heparin should be increased 10% and the test repeated 4 hr later. Using the continuous schedule, the APTT can be performed at any time 4 hr after the continuous infusion has begun. The desired result is an APTT 1.5–2 times the patient's pretreatment value. Dose adjustments of 5–10% can be made during this period to achieve adequate anticoagulation.

Heparin can be neutralized immediately by using protamine sulfate. Because of the rapid clearance rate of heparin, however, most patients can be treated by stopping the infusion. As a general rule, 1 mg of protamine sulfate neutralizes between 90 and 110 units of heparin. Because heparin has a rapid in vivo metabolic decay, only half of the total dose of protamine should be administered. A clotting test is performed to determine whether adequate neutralization has occurred; if not, the additional protamine can be given. Protamine itself is an anticoagulant, thus if too much is given the clotting time may be prolonged. Although excess protamine has an anticoagulant effect, it rarely (if ever) is a cause of clinical bleeding.

Warfarin

The coumarin derivatives are oral anticoagulant drugs that act by decreasing the rate of synthesis of the vitamin K–dependent coagulation factors II, VII, IX, and X. In addition, protein C and protein S (the vitamin K–dependent anticoagulants) are also affected. These drugs inhibit vitamin K–dependent carboxylation of the precursor coagulation proteins. Warfarin probably acts by competitively inhibiting vitamin K metabolism. Following the administration of warfarin, the levels of factors II, VII, IX, and X decrease gradually, according to their half-life. Because factor VII has the shortest half-life, its level is the first to decrease, followed by factor IX, X, and finally II. It generally takes about 4–5 days to provide a reduction in all four coagulation factors to a level consistent with anticoagulation.

The prothrombin time (PT) is the clotting test used to assess warfarin

anticoagulation. The previously recommended therapeutic range of maintaining the patient's PT at 2.0–2.5 times the normal control should not be used when commercial rabbit brain is used as the clotting reagent. Current recommendations for mechanical prosthetic heart valves and recurrent systemic embolism are 1.5–2.0; for treatment of deep vein thrombosis or pulmonary embolism, 1.3–1.5; and for prevention of systemic embolism in patients with atrial fibrillation, valvular heart disease, or tissue heart valves, 1.3–1.5 times the control plasma.

The most serious side effect of warfarin is hemorrhage. This is often related to changes in the dose or metabolism of the drug. The addition or removal of certain drugs to the patient's therapeutic regimen can have significant effects on oral anticoagulation. For example, warfarin's effect can be enhanced by the administration of antibiotics, salicylates, anabolic steroids, chloral hydrate, laxatives, allopurinol, vitamin E, and methylphenidate HCl; its effect can be diminished by barbiturates, vitamin K, oral contraceptives, phenytoin, and others. Warfarin-induced bleeding is treated by discontinuation of the drug and the administration of vitamin K. Generally the amount of vitamin K given is equal to the amount of the daily warfarin dose. The vitamin can be administered orally, subcutaneously, or intravenously (not intramuscularly). Correction of the coagulopathy begins within 6–8 hr and should be complete in 24–48 hr. If the patient is having a significant bleeding problem, fresh frozen plasma (15 mL/kg) should be given at the same time the vitamin K is administered.

Coumarin anticoagulants are contraindicated in essentially the same circumstances as those for heparin therapy. The oral anticoagulants cross the placenta and should not be given during pregnancy. Although breast milk contains warfarin, the quantity is insignificant and the drug can be used in the lactating mother.

Thrombolytic Therapy

Thrombolytic therapy involves the removal of blood clots by enzymatic digestion. It is accomplished by the in vivo generation of plasmin through the administration of plasminogen activators such as streptokinase, urokinase, and tissue-type plasminogen activator (TPA). Urokinase and TPA act as direct activators, whereas streptokinase acts by binding to plasminogen, and the streptokinase-plasminogen complex becomes the plasminogen activator. For this therapy to be effective, the patient must have a relatively fresh clot (<7–10 days old), the clot must be accessible to the lytic agent, there must be an adequate amount of plasminogen, and the fibrinolytic inhibitors must not interfere with the reaction. Once plasmin has been formed, it lyses fibrin. The plasmin generated by urokinase and streptokinase can produce a systemic hyper-fibrinolytic state; when this occurs, the plasmin can degrade other plasma proteins, including fibrinogen, and factors V and VIII, resulting in a hemorrhagic disorder. TPA is fibrin specific—it acts as an activator within or on a fibrin clot. Clinical trials

with TPA suggest that a systemic hyperfibrinolytic state is rarely produced.

Thrombolytic therapy has been reported to be beneficial in those with pulmonary embolism, deep venous thrombosis, certain arterial occlusive events, and occluded access shunts. However, there are few published studies on its use in the pediatric age groups.

VI. Plan and organizational structure of classes.

№ п/п	Basic stages of classes, their function and maintenance	Educational aims are in the levels of mastering	Methods of control and studies	Educational materials	Distributing of time in minutes
1	**Preparatory stage** Organizational measures Raising of educational aims and motivation Control of basic knowledges and skills level:			p. II «Educational aims» p. I «Actuality of theme»	3 min. 12 min.
	1. Ethiology of haemophilias, thrombopenias and thrombopathias in children;	α2	Individual oral questioning Test control of the second level	Second lelevel tests the table «classification of haemorrhagic diseases»	20 min.
	2.Key links of haemorrhagic diseases pathogenesis;	α2	Individual oral questioning Typical situatioonal task of 2 level	Structurally logical chart of haemorrhagic diseases	
	3. Clinical classification of haemorrhagic diseases;	α2	Typical situatioonal task of 2 level	Typical situatioonal task 2 level	
	4. Features of clinic and diagnostic of different haemorrhagic disaeses in children.	α2	Typical situatioonal task of 2 level	Typical situatioonal task of 2 level	
	5. Laboratory and instrumental diagnosis of haemorrhagic disaeses in children;	α2	Test control of 2 level Typical situatioonal task of 2 level	Tests of 2 level Typical situatioonal tasks of 2 level	
	6. Differential diagnostic of haemorrhagic disaeses in children;	α2		Kit of medicines.	
	6.Complication of haemophilias, thrombopenias and thrombopathias in children;	α2			
	7.Treatment principles of haemophilias, thrombopenias and thrombopathias in children;	α2			
	8. First aid in case of acute haemorrhage or haemorrhagic shock in children;	α2			
	9. Prophylaxis of	α2			

	haemorrhagic diaeses in children; 10. Rehabilitation of children with haemorrhagic syndrome.	α2			
2	**Basic stage of professional skills and abilities forming:** 1.To conduct the patient management with haemorrhagic diseases, to take complaints and anamnesis.	α3	Practical professional training	Algorythmes for forming practical skills. Patients. Case history.	115 min.
	2.To conduct the pateint examination, to detect main symptoms and syndromes of haemorrhagic disease.	α3	Practical professional training	A reference chart for forming of professional abilities. Case history.	
	3.To formulate and substantiate the preliminary diagnosis	α3	Practical professional training		
	4.To compose the plan of patients laboratory and instrumental investigation.	α3	Practical professional training	A reference chart for forming of professional abilities.Situational typical tasks of third level.The third level tests. Prescribing chart.	
	5.To interpret the results of laboratory and instru-mental investigation.	α3	Practical professional training.		
	6.To conduct differential diagnosis among clinical conditions accompanied by blood systems changes.	α3	Tests and the third level control. The third level test control.		
	7.To give the recom-mendations for regimen and diet of patient.	α3	The practical pro-fessional training is in solving of non standard clinical situations.	The third level Non-typical situational tasks. Treatment algo-rythm for the haemorrhagic diseases patients. The third level non-typical situational tasks. The first aid algorythm in case of haemorrhage or haemorrhagic shock.	
	8.To compose the plan of treatment of patient with haemorrhagic dise-ase according to the sta-ge of disease and the presence of complications.	α3	The third level test control. Practical profess-sional training.		
	9.To be able to render the first aid in extreme situations	α3	The third level test control. Practical profess-sional training. The practical professional training in solving of non typical clinical situations.		

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			The third level test control. Practical professional training in solving of non typical clinical situations.		
3	**Concluding stage.** Control and correction of professional abilities and skills. Working out the totals of class. Home work (basic and additional literature on the topic)		Analysis of clinical work performances Solving of non typical tasks and the third level tests. Estimation of clinical work.	Clinical work performances The third level Non-typical situational tasks. A reference chart for independent work with literature	30 min.

Questions for elementary level of knowledges control.

1. To determine the concept of haemorrhagic syndrome in children.
2. Modern scheme of clotting, anticoagulative system, thrombocyte haemostasis.
3. What are haemophilia's, thrombopenia's and thrombopathia's etiology and pathogenesis?
4. What are the clinical manifestations of haemophilia, thrombopenia and thrombopathia in children?
5. What are the main diagnostic principles of haemophilia, thrombopenia and thrombopathia in children? To conduct differential diagnostic of haemorrhagic syndrome in children.
6. What is the first aid in case of acute bleeding or haemorrhagic shock?
7. To prescribe treatment, prophylactic and rehabilitations measures in children with haemophilia, thrombopenia and thrombopathia.

Examples of tests and tasks:

1. What is the transferring type of genetic defect in hemophiliaA?
A Dominant - autosomal.
B Recessive - autosomal.
C Recessive bonded to the X-chromosome.
D Recessive bonded to the Y-chromosome
E Dominant bonded to the Y-chromosome

2. What joints are the most frequently injured in hemophilia A acute hemarthrosises?
A. Humeral.
B Ulnar.
C Knee.
D Talocrural.
E-Radiocarpal.

3. What joints are the most frequently injured in hemophilia A secondary rheumatoid syndrome?

A. Ulnar.

B. Fine joints of a foot.

C. Knee.

D. Talocrural.

E. Fine joints of palm.

4. What causes the reniform bleedings in hemophiliaA patients?

A Spontaneously

B After a trauma of lumbar area

C. As a consequence of a pyelonephritis

D. As a consequence of a nephrolithiasis

E. Owing to the increased excretion of calcium.

5. What is the transferring type of genetic defect in hemophilia B?

A Dominant autosomal.

B Recessive - autosomal.

C Recessive bonded to the X-chromosome.

D Recessive bonded to the Y-chromosome

E .Dominant bonded to the Y-chromosome

6. What parameters of unified coagulogramme can be used for the diagnostics of hemophilia?

A. Determination of blood coagulation factors.

B. Prothrombine time.

C. Time of coagulation.

D. Thrombine time.

E. All listed above

7. What are the basic methods of transfusion therapy in Cristmas disease?

A Direct hemotransfusion.

B Using of the frozen donor plasma

C Indirect transfusion of donor plasma.

D Transfusion of the scarce factor of blood coagulation.

E Using of PPSB preparation.

8. What type of an immune thrombocytopenia is the most frequent in clinical practice?

A. Transimmune.

B. Heteroimmune.

C. Autoimmune.

D. Alloimmune.

E. Isoimmune

9.What is the basic diagnostic principle for idiopathic (autoimmune) thrombocytopenic purpura?:

A Revealing of autoantibodies in a blood serum.

B- Identification of autoantibodies on the surface of thrombocytes in blood.

C- Identification of antigenes on the surface of thrombocytes in blood.

D- Revealing of antigenes in blood serum.

E. Coombs test

10. What are the clinical forms of a hemorrhagic syndrome manifestation in idiopathic Werlhof's disease?

A Hemorrhage in knee joints.

B. Dermal hemorrhage.

C The hemorrhage in ulnar joints.

D Gingival bleedings.

E- Nasal bleedings.

11. What are the dimensions of spleen in idiopathic Werlhof's disease?

A Enlarged.

B. Unchanged.

C Diminished.

D. Diminished but dense in consistence

E .Unchanged and also dense in consistence

12. What is the amount of megacaryocytes of bone marrow in the immune type of an idiopathic Werlhof's disease?

A. Diminished.

B. Is not changed.

C. Enlarged.

D. Depending on a a thrombocytopenia level

E. Unchanged independently on a thrombocytopenia level.

13. What are the basic methods of pathogenetic therapy in heteroimmune type of an idiopathic Werlhof's disease?

A. Preparations of the thyroid gland.

B. Spleenectomy

C. Corticosteroids .

D. Immunodepressants.

E. .Immunostimulators

14. What are the basic methods of pathogenetic therapy in transimmune type of an idiopathic Werlhof's disease?

A Corticosteroids

B Artificial delivery.

C-Preparations of thyroid gland.

D Operative erasion of a lien.

E-Immunostimulators.

15. What are the basic methods of pathogenetic therapy in autoimmune type of idiopathic Werlhof's disease?

A Sandoglobulin
B. Artificial delivery.
C. Corticosteroids
D. Splenectomy.
E. Interferon.

16. What are the basic methods of pathogenetic therapy in alloimmune type of idiopathic Werlhof's disease?
A-Preparations of the thyroid gland
B Spleenectomy.
C-Plasmaferesis
D Stimulators of T-lymphopoiesis.
E Suppressors of T-lymphopoiesis.

17. What type of genetic defect transferring is in thrombasthenia of Hlantzman?
A Dominant autosomal
B Recessive autosomal.
C Dominant with a complete penetration.
D Dominant with incomplete penetration.
E Recessive bonded to the X-chromosome.

18. What is the basic hereditary pathogenetic defect in Hlantzman disease?
A. Infringement in structure of megacaryocytes.
B. Decrease in amount of megacaryocytes.
C. Infringement in structure of thrombocytes.
E. Decrease in amount of thrombocytes.

19.What are the clinical forms of hemorragic syndrome in disease of Hlantzman?
A Hemorrhage in knee-joints.
B Skinning hemorrhage.
C Bleeding in elbow joints.
D Sanguifluousness of mucous of nose.
E Sanguifluousness of sinovial coatings

20. What are the laboratory changes in patients with Hlantzman disease?
A Thrombocytopenia.
B Thrombocytosis.
C Infringement of thrombocytes adhesion.
D Infringement of thrombocytes aggregation.
E Presence of antibodies on a thrombocytes surface.

Tasks:
1. Two weeks after a viral syndrome, a 2-year-old child develops bruising and generalized petechiae, more prominent over the legs. No hepatosplenomegaly or lymph node enlargement is noted. The examination is otherwise unremarkable. Laboratory testing shows the patient to have a normal hemoglobin, hematocrit, and

white blood count and differential. The platelet count is 15,000/L.

To conduct the most likely diagnosis.

To conduct differential diagnosis.

In children, idiopathic or immune thrombocytopenic purpura (ITP) is the most common form of thrombocytopenic purpura. In most cases a preceding viral infection can be noted. No diagnostic test exists for this disease; exclusion of the other diseases listed in the question is necessary. In this disease, the platelet count is frequently less than 20,000/L, but other laboratory tests yield essentially normal results, including the bone marrow aspiration (if done). For ITP, platelets are sequestered and destroyed at the spleen by the reticuloendothelial system (RES) that binds self-immunoglobulins attached to the platelet. Exogenous IV gamma globulin can work to saturate the RES binding sites for platelet-bound self-immunoglobulin. Thus, there is less platelet uptake and destruction by the spleen. Aplastic anemia is unlikely if the other cell lines are normal. Von Willebrand disease might be expected to present with bleeding and not just bruising. It is unlikely that acute leukemia would present with thrombocytopenia only. Thrombotic thrombocytopenic purpura is rare in children.

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To conduct the most likely diagnosis.

Appropriate treatment of this child include…

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Treatment for ITP consists of observation and/or gamma globulin and steroids. Splenectomy is reserved for the most severe and chronic forms.

3. A 3-year-old child presents with a petechial rash but is otherwise well and without physical findings. Platelet count is 20,000/L; hemoglobin and WBC count are normal.

The most likely diagnosis is…

To conduct differential diagnosis.

The mean age of presentation of ITP is 6 years. Patients look well except for petechial rash. Patients with acute lymphoblastic leukemia frequently have symptoms of pallor and fever in addition to bleeding. Nearly 50% of them have hepatomegaly and splenomegaly. CBC reveals anemia, leukocytosis or leukopenia, and thrombocytopenia. Disseminated intravascular coagulopathy (DIC) is secondary to a severe underlying disease, such as fulminant bacterial sepsis with hypotension or profound hypoxia. Patients invariably appear ill and have leukocytosis, thrombocytopenia, and abnormal coagulation studies (e.g., prolonged PT and PTT, decreased fibrinogen concentration, and elevated fibrin split products). Patients with Henoch-Schonlein purpura have symptoms of skin rash and abdominal or joint pain. The rash is usually urticarial and purpuric and present over the buttocks or lower extremities. The platelet count is normal or elevated. Systemic lupus erythematosus (SLE) is very rare in a 3-year-old child. Findings include fever, joint pain, and skin rash. CBC can reveal anemia, leukopenia, and thrombocytopenia.

4. A 2-year-old child in shock has multiple nonblanching purple lesions of various sizes scattered about on the trunk and extremities; petechiae are noted, and oozing from the puncture site has been observed. The child's peripheral blood smear is presented.
Clotting studies are likely to show which of the following?
Prescribe the treatment to this patient.

The clinical history and blood-smear findings (fragmented cells and few platelets) presented in the question are typical of disseminated intravascular coagulation. The disorder, which can be triggered by endotoxin shock, results ultimately in the initiation of the intrinsic clotting mechanism and the generation of thrombin (prolonged PT and PTT, decreased fibrinogen concentration, and an increase in fibrin split products). Fibrin deposited in the microcirculatory system can lead to tissue ischemia and necrosis, further capillary damage, release of thromboplastic substances, and increased thrombin generation. Simultaneous activation of the fibrinolytic system produces increased amounts of fibrin split products, which inhibit thrombin activity. Of utmost importance in the treatment of children who have disseminated intravascular coagulation is the management of the condition that precipitated the disorder.

5. A 10-year-old boy is admitted to the hospital because of bleeding. Pertinent laboratory findings include a platelet count of 50,000/L, prothrombin time (PT) of 15 s (control 11.5 s), activated partial thromboplastin time (aPTT) of 51 s (control 36 s), thrombin time (TT) of 13.7 s (control 10.5 s), and factor VIII level of 14% (normal 38 to 178%).
The most likely cause of his bleeding is…
To conduct differential diagnosis.

The prolongation of PT, aPTT, and TT excludes the diagnosis of ITP. PT tests principally for factors I, II, V, VII, and X and is not prolonged in hemophilia A

(factor VIII deficiency) or hemophilia B (factor IX deficiency). In vitamin K deficiency, there is a decrease in the production of factors II, VII, IX, and X, and PT and aPTT are prolonged. The thrombin time, which tests for conversion of fibrinogen to fibrin, however, should be normal and the platelet count should also be normal. In DIC, there is consumption of fibrinogen; factors II, V, and VIII; and platelets. Therefore, there is prolongation of PT, aPTT, and TT and a decrease in factor VIII level and platelet count. In addition, the titer of fibrin split production is usually increased.

6. An 8-year-old child being treated with a combination of chemotherapy agents develops very red, inflamed sores in the mouth and esophagus. He has difficulty in eating and drinking food and liquids.
What cause is the most likely?

The description is that of a child with mucositis. The toxicity of methotrexate is dependent on the dose, schedule, and route of administration. The major toxicities include gastrointestinal mucositis, bone marrow suppression, skin erythema, and hepatic dysfunction. The main toxicities of vincristine include peripheral neuropathy, constipation, jaw pain, and inappropriate antidiuretic hormone secretion. The major side effects of prednisone include Cushingoid facies, truncal obesity, salt and water retention, hypertension, increased susceptibility to infection, gastric irritation, and osteoporosis. 6-Mercaptopurine can cause nausea, vomiting, marrow suppression, and hepatic dysfunction. Doxorubicin (Adriamycin) can lead to alopecia, nausea, vomiting, stomatitis, tissue necrosis (if drug extravasates), and bone marrow suppression. The doselimiting factor is cardiotoxicity, and the risk of cardiotoxicity increases at cumulative doses of doxorubicin above 550 mg/m2. In the latter two cases (6-mercaptopurine and doxorubicin), mucositis is possible but is seen less commonly than with methotrexate.

7. A few weeks after a viral syndrome, a 6-year-old child develops bruising and generalized petechiae, more prominent over the trunk. No hepatosplenomegaly or lymph node enlargement is noted. The examination is otherwise unremarkable. Laboratory testing shows the patient to have a normal hemoglobin, hematocrit, and white blood count and differential. The platelet count is 16,000/L.
To conduct the most likely diagnosis.
To conduct differential diagnosis and prescribe the treatment.

In children, idiopathic or immune thrombocytopenic purpura (ITP) is the most common form of thrombocytopenic purpura. In most cases a preceding viral infection can be noted. No diagnostic test exists for this disease; exclusion of the other diseases listed in the question is necessary. In this disease, the platelet count is frequently less than 20,000/L, but other laboratory tests yield essentially normal results, including the bone marrow aspiration (if done). For ITP, platelets are sequestered and destroyed at the spleen by the reticuloendothelial system (RES) that binds self-immunoglobulins attached to the platelet. Exogenous IV gamma globulin can work to saturate the RES binding sites for platelet-bound self-immunoglobulin. Thus, there is

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Treatment for ITP consists of observation and/or gamma globulin and steroids. Splenectomy is reserved for the most severe and chronic forms.

8. 4-yeard-old boy was admitted to the hospital with complaints at painful right knee, he was injured while the playing soccer. Right knee is enlarged, palpation is quite painful, other systems are without any changes.

To conduct the most likely diagnosis.

Prescribe the treatment to this patient.

Primary diagnosis is haemophilia. Prevention of trauma is an important aspect of care for the hemophilic child. During early life the crib and playpen should be padded, and the child should be carefully supervised while learning to walk. As he or she becomes older, physical activities that do not entail the risk of trauma should be encouraged. It is important that a course between overprotection and permissiveness be followed. Aspirin and other drugs that affect platelet function may provoke hemorrhage and must be avoided by hemophilic patients. As children with severe hemophilia are exposed to blood products throughout life, they should be immunized against hepatitis B virus. The vaccine may be given in the newborn period.

Replacement Therapy. When bleeding episodes occur, replacement therapy is essential to prevent pain, disability, or life-threatening hemorrhage. The aim of the therapy is to increase factor VIII activity in the plasma to a level that secures hemostasis. Currently, this can be done only by the intravenous infusion of fresh frozen plasma or of plasma concentrates.

Therapy of the hemophilic patient has been considerably facilitated by the development of factor VIII concentrates; these permit fairly precise estimation of the dosage necessary to attain hemostatic levels. By definition, 1 mL of normal plasma contains 1 unit of factor VIII. As the plasma volume is about 45 mL/kg, it is necessary to infuse 45 units/kg of factor VIII to increase its level in the hemophilic recipient from 0–100% (0–100 units/dL). A dose of 25–50 units/kg of factor VIII is usually given to raise the recipient's level to 50–100% (50–100 units/dL) of normal. Since the half-life of factor VIII in the plasma is about 8–12 hr, repeated infusions can be given, as necessary, to maintain the desired level of activity.

Several factor VIII concentrates are available. The most inexpensive of these is cryoprecipitate, which can be prepared in the blood bank from fresh plasma. The yield from 250 mL of fresh plasma is one bag of cryoprecipitate, which usually contains 75–125 units of factor VIII; there may, however, be marked variability in the content of bags. One bag of cryoprecipitate/5 kg of body weight raises the recipient's level to about 50% (50 units/dL) of normal. Because cryoprecipitate is produced from single units of whole blood, the risk of blood-borne diseases such as hepatitis B and AIDS is lower than with concentrates prepared from large plasma pools. Factor VIII concentrates that are produced by recombinant technology and those that are prepared by monoclonal antibody techniques are more expensive than cryoprecipitate but are

safer with regard to the transmission of infectious organisms. These concentrates are dispensed as lyophilized powders in bottles of 250–500 units that can be reconstituted just prior to use; they are tremendously useful and convenient. Their potency and relatively low protein content permit rapid restoration of normal hemostatic levels with very small volumes. Commercial factor VIII concentrates also contain anti-A and anti-B isohemagglutinins; when massive amounts are given to persons of blood group A or B, hemolysis may occur.

9. 4-yeard-old boy was admitted to the hospital with complaints at painful right knee, he was injured while the playing soccer. Right knee is enlarged, palpation is quite painful, other systems are without any changes.
To conduct the most likely diagnosis.
Laboratory changes are…

Primary diagnosis is haemophilia. The only significant laboratory abnormalities occur in coagulation tests and reflect a serious deficiency of factor VIII. The partial thromboplastin time (PTT) is greatly prolonged. The platelet count, bleeding time, and prothrombin time are normal. Mixing studies using normal plasma show the correction of the PTT. A specific assay for factor VIII activity confirms the diagnosis.

10. A newborn boy was admitted to the hospital because of bleeding. Pertinent laboratory findings include a platelet count of 250,000/L, prothrombin time (PT) of 15 s (control 11.5 s), activated partial thromboplastin time (aPTT) of 31 s (control 36 s), thrombin time (TT) of 10.7 s (control 10.5 s). Apt-test is positive.
What is the most likely cause of his bleeding.
The laboratory manifestations of illness are…

In newborn vitamin K deficiency takes place. The laboratory manifestations of vitamin K deficiency are prolonged prothrombin and partial thromboplastin times. The platelet count, bleeding time, and plasma fibrinogen level are normal. If needed, specific assays for factors II, VII, IX, and X or for detecting the noncarboxylated protein precursors of the vitamin K-dependent coagulation factors can be performed.

Metohodical materials to support basic stage class.

Professional algorythm of patient's management for practical skills and abilities forming.

№	Task	Sequence of implementation	Remarks and warnings related to self-control
1	To conduct examination of patient with haemorrhagic disease.	1.To conduct gathering of complaints and disease anamnesis.	Pay attention to features of disease course, underlying factors, concomitant diseases etc.
		2.To gather thoroughly the patient's life	To establish the availabili-ty of risk factors which

		anamnesis.	facilitate disease occurrence.
		3.To conduct patient's examination.	To assess patient's general condtion, position in bed, color and humidity of skin and mucose, presence of petechias, bruises, haemathomas on it, presence of neck veins and extremities swelling.
		4.To investigate cardiovascular system of the patient (palpation, percussion).	To pay regard for rhythm of pulse, it's tension on both hands, apex shove, it's properties, margins of absolute and relative car-diac dullness, it's changes, HR(tachi-or bradicardia, extrasystole),BP, presence of bleedings from mocoses, nasal bleedings, melena, hemarthrones, hematomas, bronchial hemorrhage, and so on.
		5.To conduct ausculta-tion of the heart and the main vessels. 6.To investigate the pulmonary system (percussion, bronchophony). 7.To conduct lungs auscultation. 8.To investigate the system of digestion.	To pay regard for heart tones weakening or amplifying, appearance of murmurs and additional III, IV tones. To focus attention on features of percussion and auscultation of different age children.
2	To formulate the preliminary diagnosis.	1.To formulate the preliminary diagnosis 2.To substantiate all components of prelimi-nary diagnosis based on complaints,anamnesis, and examinations.	To formulate preliminary diagnosis of haemorrhgic disease and subtantiate each component of it, based on modern classification
3	To evaluate the parameters of additional laboratory tests.	1.To evaluate the blood count data. 2. To evaluate the biochemistry data.	To pay attention to platelet count, bleeding time, prothrombin time, and activated partial

		3.To evaluate the platelet count, bleeding time, prothrombin time, and activated partial thromboplastin time (APTT), tourniquet test, whole blood clotting time, prothrombin consumption time, and thromboplastin generation test. 4.To evaluate the data of instrumental investigation.	thromboplastin time (APTT), tourniquet test, whole blood clotting time, prothrombin consumption time, and thromboplastin generation test, cholesterol, lipids and glucouse levels. To pay attention to US of internal organs, radiography of chest organs, joints.
4.	To conduct differential diagnosis.	1.To find out common signs in complaints, life and disease anamnesis, the data of examination, the data of laboratory and instrumental tests in patients with similar status. 2.To find differences among complaints, information of life and disease anamnesis, examination data, information about the laboratory and instrumental methods in similar nosology. 3. To find out the differences for excluding similar diseases from the list of probable diagnoses, being based on this algorithm. 4. To conduct different-tial diagnostic among all of nosologies which ha-ve the similar signs, among other blood dise-ases, using this algorithm 5.Taking into account	Special attention must be paid to differential diagnosis among the DIC-syndrome, hypo- and aplasic anaemias, leucosis, haemorrhagic vasculitis.

		the impossibility of excluding the diagnosis of haemorrhagic disease from the list of probable diagnoses to draw conclusion about the probability of such diagnosis.	
6	To formulate the final clininical diagnosis.	1. To formulate the final clininical diagnosis. 2. Based on primary diagnosis, additional investigations datas, conducted differential diagnosis to substantiate all elements of concluding clininical diagnosis.	Based on modern classification of haemorrhagic diseases to formulate diagnosis, complications of disease and concomitant diseases.
7	To prescribe treatment for patients.	1.To prescribe non-medicinal treatment 2.To prescribe medicinal treatment.	To specify regimen and detalized diet according to the disease. To prescribe modern medicinal treatment in accordance with the standards of haemorrhagic diseases therapy, taking into account age, severity of patient state, stage of disease, presence of complications and concomitant pathology,

Materials of control for conclusive classes stage:

1. What are the clinical manifestations of hemorrhagic syndrome in heparin overdosage?

A. Hemorrhage in joints

B Hematencephalon.

C Uterine bleedings.

D Bleedings from a gastrointestinal tract

E Sanguifluousness of mucosas.

2. What parameters from unified coagulogramme can be used for diagnostics of Heparin overdosage?

A. Prothrombin time.

B. Prothrombin ratio.

C. Thrombin time.

D. Time of coagulation.

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E. Concentration of Fibrinogen.

3. What deficient factor of blood coagulation predetermines a hemorrhagic syndrome in therapy with anticoagulants?
A. F 1.
B. F11.
C. F111.
D. F V.
E. F V11.

4. What are the basic methods of pathogenetic therapy in hemorrhagic syndrome caused by indirect anticoagulants?
A. Vicasolum in small doses (5-10 mg / kg).
B. Vicasolum in big doses (20-30 mg / kg).
C. Chilled plasma.
D. Dry plasma.
E. Preparations of PPSB.

5. What pathological states does the syndrome of disseminated intravascular coagulation develops more often in?
A. Infection
B. Sepsis.
C. Traumatic shock.
D. Peptic ulcer.
E. Burn shock.

6. What preparations are used as desaggregants in syndrome of disseminated intravascular coagulation?
A. Polyglucinum.
B. Rheopolyglucinum.
C. Acidum acetylsalicylicum.
D. Sulfanilic acid
E. Curantylum.

7. What are the basic pathogenetic factors in hemorrhagic vasculitis?
A. Activation of coagulative system.
B. Activation of anticoagulative system
C. Damaging action of circulating antibodies.
D. Damaging action of circulating immune complexes.
E. Activation of a kalicrein – kinin system.

8. What localization of skin eruption is more frequent in hemorrhagic vasculitis?
A. Trunk
B. Upper extremities
C Back
D. Lower extremities
E. Face

9. What features of hemorrhagic dermal eruption in hemorrhagic vasculitis?
 A. Dissymmetric
 B. Partially symmetric
 C. Spotty
 D. Symmetric
 E. Confluent

10. What preparations are used for treatment of hemorrhagic vasculitis?
 A. antibiotics
 B. antihistamine
 C. glucocorticoids
 D. mineralocorticoids
 E. Heparin

11. Two weeks after a viral syndrome, a 2-year-old child develops bruising and generalized petechiae, more prominent over the legs. No hepatosplenomegaly or lymph node enlargement is noted. The examination is otherwise unremarkable. Laboratory testing shows the patient to have a normal hemoglobin, hematocrit, and white blood count and differential. The platelet count is 15 x10 9/l. Appropriate treatment of this child includes
 A. Intravenous gamma globulin
 B. Platelet transfusion
 C. Aspirin therapy
 D. Factor VIII infusion
 E. Prednisone, vincristine, and asparaginase induction followed by methotrexate and 6-mercaptopurine

12. Girl of 13 years old complains of a long-term and abundant menses and general delicacy. On examination her general state is serious, lengthways the body there are hemorrhagic rashes which vary from spots up to ecchymomas and petechias were detected and on mucos. There are hemorrhages. Two weeks ago she had respiratory infection and took Sulfanilamides. What is the most probable cause of this state?
 A. Hemorrhagic vasculitis
 B. Werlhof's disease
 C. Disseminated intravascular coagulation syndrome
 D. Meningococcemy
 E. Cristmas disease

13. 5-yeared boy, 2 weeks ago was ill with respiratory infectoin and after that the abundant nasal bleeding, ecchymomas has appeared. In the hemogramme anemia (Нв-85 g/l) and thrombocytopenia are revealed. What is the most expedient remedy for this child to take for bleeding diminishing?
 A. ε- Acidum aminocapronicum
 B. Platelet concentrate
 C. Chilled plasma
 D. Crioprcipitate

E. the Packed red cells

14. 7-yeared boy, ill with hemophilia A, has bruised the knee and after expressed edema and hematoma appeared in the site of trauma. What preparation will be the most effective in this case?
A. Vitamin K
B. Acidum aminocapronicum
C. Chilled plasma
D. Dicynonum
E. Crioprecipitate

15. Boy G., 12 years old suffering from hemophilia A has been delivered in the hospital with the renal bleeding. What preparation is necessary to give to the child for controlling this state?
A. Crioprecipitate of VIII factor
B. Chilled plasma
C.Vicasolum
D. ε Acidum aminocapronicum
E. Dicynonum

16. A 7 y.o boy suddenly felt pain in his right knee, it became edematic. The day before he had taken part in a cross-country race. Family anamnesis has no data about hemophilia and bleeding sickness. Objectively: body temperature is $37,5^0$C. The knee is painful, hot to the touch, edematic with local tissue tension over it. Blood count: Hb- 123 g/L, leukocytes - $5,6*10^9$/L, thrombocytes - $354*10^9$/L, prothrombin time - 12 seconds (normally 10-15 seconds), partly activated thromboplastin time - 72 seconds (normally 35-45 seconds). Hemorrhage time is normal, VIII factor is 5% of norm. What is the most probable diagnosis?
A. Hemophilia B
B. Hemophilia A
C. Vitamin K deficiency
D. Schoenlein-Henoch disease
E. Thrombocytopenia

17. An 18 y.o girl complains of weakness, dizziness, loss of appetite, menorrhagia. There are many-coloured petechiae on the skin of the upper extremities. Blood test: Hb- 105 g/l; RBC- $3,2*10^{12}$/L; C.I.- 0,95; thromb.- $20*10^9$/L. The sedimentation time according to Lee White is 5'; hemorrhagia duration according to Duke is 8', "pinch and tourniquet" test is positive. What is the most probable diagnosis?
A. Hemorrhagic diathesis
B. Hemophilia
C. Iron deficiency anemia
D. Marchiafava-Micheli's disease
E. Idiopathic thrombocytopenic purpura

18. The child, aged 8 months, was taken with complaints to a flaccidity,

adynamia, petechial hemorrhagic rashes scattered through the body. From anamnesis it was known that the child eats cutruses on a regular basis. Blood count RBC 3,5 x 10 12/l, Hb: 110 g/l, reticulocytes: $_{20/000}$: thrombocytes 90 x 10 9/l WBC.:8,5 x 10 9/l, eosinophiles.:2 %,relating to stab neutrophiles :3 %, segmented neutrophiles :40 %, lymphocytes.:53%, monocytes : 7%, ESR 12 mm / h. What ivestigations are necessary for establishing the final diagnosis?

A. Determination of erythrocytes osmotic resistance

B. Blood coagulation time by White

C. Determination of a bilirubin.

D. Determination of VII coagulation factor.

E. Bloody clot retraction.

19. A newborn at the age of 3 days, was born from the mother that was sick of lupus. Blood count reveals the thrombocytopenia. Objectively: ecchymomas on the trunk and extremities. What is the initial diagnosis?

A. Transimmune thrompocytopenic purpura

B. DIC syndrome

C. Isoimmune Werlhof's disease of newborns

D. Hemorrhagic idisease of newborns

E. Idiopathic Werlhof's disease

20. The girl of 13 years old complains of a long-term and abundant menses and general delicacy. On examination her general state was serious, across the body and on the mucous there were hemorrhagic rashes varied from spots up to ecchymomas and petechias were detected. There are hemorrhages. Two weeks ago survived respiratory infection, she was taking Sulfanilamides. What is the most probable cause of this state?

A. Hemorrhagic vasculitis

B. Werlhof's disease

C. Disseminated intravascular coagulation syndrome

D. Meningococcemy

E. Cristmas disease

Materials of the medical support for students' self-prepapation: a reference chart for organization of students' independent work with educational literature.

Tasks	Instructions
To study etilogy of haemorrhagic diseases in children.	To enumerate basic ethiologic factors, to select the key links of haemorrhagic disease.
To study pathogenesis of haemorrhagic diseases in children.	To separate out the main links of haemorrhagic diseases' pathogenesis.
To study clinical manifestations of haemorrhagic diseases in children.	To establish the symptoms and to gather it into the clinical syndromes which enable to establish the

	probable diagnosis of haemorrhagic disease.
To study diagnostic criteria of haemorrhagic diseases	To make the flow diagram of disease
To study additional methods of research (laboratory, instrumental)	To work out a plan of patient's investigation.
To study changes in additional investigational methods which are pathognomonic for haemorrhagic diseases.	To enumerate the basic diagnostic criteria of haemorrhagic diseases according to the data of additional investigational methods.
To establish concluding diagnosis	To substantiate the basic components of diagnosis in accordance to modern classification, and to conduct a differential diagnosis.
To prescribe individual holiatry to patient with haemorrhagic disease. To be able to render the first aid in child with bleeding.	To prescribe specific regimen, diet, medicinal treatment, taking into account the age, severity of patient state, the stage of disease, the presence of complications and concomitant diseases.

THE RECOMMENDED LITERATURE

Basic:

1.Nelson textbook of pediatrics, 15th ed. / edited by Richard E. Behrman, Robert M. Kliegman, Ann M. Arvin; senior editor, Waldo E. Nelson, 1996, part XXII, chapter 441, 444-451.

2. Медицина дитинства / За ред. П.С. Мощича. - К.: Здоров'я, 1994.

3. Педиатрия : Учебник для студентов высших медицинских учебных заведений III – IV уровней аккредитации. – 3-е изд./ В.Г.Майданник;– Харьков: Фолио, 2006.-с.805-854.

Theme: Diabetes mellitus in children.

 Study time: 4 hours

Classification of diabetes mellitus in children Etiology, pathogenesis, clinical presentation, diagnostics, differential diagnostics, treatment, prophylaxis, prognosis. Insulin therapy. Hypoglycemic, hyperglycemic coma and ketoacidosis: etiology, pathogenesis, classification, clinical presentation, diagnostics, differential diagnostics. Emergency and prophilaxis in comas. Prognosis.

I**. Actuality of the theme.**

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia. Each year, approximately 600,000 people are diagnosed with diabetes. The disease is classified into several categories. Type 1 diabetes mellitus, formerly known as insulin-dependent diabetes mellitus or juvenile-onset diabetes mellitus, is caused by autoimmune destruction of the b-cells of the pancreas, rendering the pancreas unable to synthesize and secrete insulin. Type 2 diabetes mellitus, formerly known as non-insulin-dependent diabetes mellitus or adult-onset diabetes, results from a combination of insulin resistance and inadequate insulin secretion. Other types of diabetes are rare. Type 2 is the most common form, accounting for 90–95% of diabetes in developed countries.

In 1992, the costs of diabetes in the US were estimated to be $98 billion. The mean annual per capita healthcare costs for an individual with diabetes are approximately fourfold higher than those for individuals who do not have diabetes. Similarly, in the United Kingdom, diabetes accounts for roughly 10% of the National Health Service budget (49 billion).

The high costs of diabetes are attributable to care for both acute conditions (such as hypoglycemia and ketoacidosis) and debilitating complications. The latter include both microvascular complications—predominantly retinopathy, nephropathy, and neuropathy; and macrovascular complications, particularly stroke and coronary artery disease. Together these make diabetes the seventh most common cause of death in the developed world.

Concrete purposes:
1. To determine the etiological and pathogenic factors in diabetes mellitus.
2. To classify and analyze the typical clinical manifestation of diabetes mellitus.
3. To make a plan of investigation and analyze the information about laboratory and instrumental data in the classic course of diabetes mellitus in children.
4. To demonstrate skills of treatment, rehabilitation and prophylaxis of diabetes mellitus in children.

5. To diagnose and render urgent help in hyperglycemic, hypoglycemic, hyperosmolar , hyperlactacidemic and ketoacidosis coma patients.

6. To conduct differential diagnostics of diabetes mellitus in child, different kinds of comas and make a preliminary diagnosis.

7. To determine the prognosis for life in diabetes mellitus.

8. To demonstrate both the skills of medical specialists moral and deontological principles and the principles of professional subordination in pediatrics.

II. Classes (pointing of planned mastering level)

1. A student must know (to familiarize): α1

-about the place of diabetes mellitus in the structure of the endocrine system, and diseases in children which are widespread in different age-dependent and ethnic groups;

- about statistical information in relation to morbidity, frequencies of complications, lethality, and the nearest and remote prognosis in patients with diabetes mellitus;

-about the history of scientific study and payment of domestic scientists;

2. A student must know (master): α2

-the etiology of diabetes mellitus type 1 in children

-key links of diabetes mellitus pathogenesis type 1 ;

-clinical classification of diabetes mellitus type 1;

-the classic clinical manifestation of diabetes mellitus type 1;

-laboratory and instrumental diagnosis of diabetes mellitus type 1;

-the long-term complications of diabetes mellitus type 1;

-the acute complications of diabetes mellitus type 1;

-the treatment principles of diabetes mellitus type 1 in children and long-term complications of diabetes mellitus type 1.

3. A student must seize the skills of: α3

-collection of complaints and anamnesis of disease;

-examination of patients with diabetes mellitus and revealing the main symptoms and syndromes.

-formulating and substantiating the preliminary diagnosis;

-determining a laboratory and instrumental examination plan of patient's investigation (with obedience of diagnostics standards);

By the abilities:

- interpreting the results of laboratory and instrumental investigations;

- conducting a differential diagnosis among diabetes insipidus, kidney glucosuria, short-lived glucosuria and hyperglycemia ;

- conducting a differential diagnosis among different kind of comas;

- giving recommendations in relation to the patient regimen and diet with the diseases of diabetes mellitus - taking into account the stage of disease, severity of state and concomitant pathology;

- completing the treatment plan for diabetes mellitus according to the standards taking into account the stage of disease, complications and concomitant pathology.

- rendering first aid in extreme situations such as hyperglycemia, hypoglycemia, hyperosmolar , hyperlactacidemic, and ketoacidosis coma.

III. Aims of personality development (educative aims):

-A student must learn to adhere to the rules of behaviour and principles of medical etiquette and deontology near a bed ridden patient with diabetes mellitus;

-to try hand on ability to set a psychological contact with a patient and his family;

-to master a sense of professional responsibility for timely, adequate and skilled medicare.

IV. Interdisciplinary integration:

Subject	To know	Be able
1. Previous (providing)		
Anatomy	Structure of human endocrine system, of the pancreas , its circulation	
Histology	Structure of island of Langerhans	
Physiology	Normal physiology of the pancreas, normative indices of laboratory and instrumental investigation methods and their assesment.	To asses laboratory data and instrumental investigation methods.
Pathologic physiology	Key links of the pathogenesis of diabetes mellitus type 1	To asses laboratory data and instrumental investigation methods.
Pathologic anatomy	Morphological features of the pancreas, blood vessels, kidneys, organs of sight, and the nervous system - (depending on disease stage.)	To analyze and interpret the information of a clinical examination and additional methods of investigation
Pharmacology	Pharmacokinetics and pharmacodynamics; the side effects of prescriptions (short-acting , intermediate-acting , and long-acting insulin), and angiotensins (type 1	To prescribe: age dependent and individual patient characteristics treatment to identify the stage of disease and establish an individual prescription to take with the

	blockers,etc.)	correct dosage. To be able to make a prescription.
Propedeutical pediatrics.	The basic stages and methods for the clinical examination of patients.	To collect complaints and anamnesis vitae et morbid - to find out the basic risk factors of diabetes mellitus; to be able to conduct a patient examination to reveal the clinical signs of thyroid gland diseases; *and* to be able to interpret data for additional methods of investigation.
2.Followings(provided)		
Hospital pediatrics.	Clinical signs of diabetes mellitus and its complications and treatment tactics.	To reveal the clinical signs of diabetes mellitus and complications and be able to prescribe treatment.
3. Interdiscipline integration		
Diabetes insipidus in children	The clinical manifestation of diabetes insipidus	To identify specific clinical signs of diabetes insipidus and conduct a differential diagnosis for diabetes mellitus in children.
Renal glucosuria	The clinical manifestation of renal glucosuria	To identify specific clinical signs of glucosuria and conduct a differential diagnosis for diabetes mellitus in children.
Transient glucosuria and hyperglycemia	The clinical manifestation of transient glucosuria and hyperglycemia	To identify specific clinical signs of transient glucosuria and hyperglycemia and conduct a differential diagnosis for diabetes mellitus in children.
Renal glucosuria	The clinical manifestation of Renal glucosuria	To identify the specific clinical signs of renal glucosuria and hyperglycemia and conduct a differential diagnosis for diabetes mellitus in children.

V. Contents of the theme

Background

Diabetes mellitus (DM) is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin, an anabolic hormone. Insulin is produced by the beta cells of the islets of Langerhans located in the pancreas, and the absence, destruction, or other loss of these cells results in type 1 diabetes (insulin-dependent diabetes mellitus [IDDM]). Most children with diabetes have IDDM and a lifetime dependence on exogenous insulin.

Type 2 diabetes (non–insulin-dependent diabetes mellitus [NIDDM]) is a heterogeneous disorder. Most patients with NIDDM have insulin resistance, and their beta cells lack the ability to overcome this resistance. Although this form of diabetes was previously uncommon in children, in some, countries 20% or more of new patients with diabetes in childhood and adolescence have NIDDM, a change associated with increased rates of obesity. Other patients may have inherited disorders of insulin release leading to maturity onset diabetes of the young (MODY).

This chapter addresses only IDDM.

Pathophysiology

Insulin is essential to process carbohydrates, fat, and protein. Insulin reduces blood glucose levels by allowing glucose to enter muscle cells and by stimulating the conversion of glucose to glycogen (glycogenesis) as a carbohydrate store. Insulin also inhibits the release of stored glucose from liver glycogen (glycogenolysis) and slows the breakdown of fat to triglycerides, free fatty acids, and ketones. It also stimulates fat storage. Additionally, insulin inhibits the breakdown of protein and fat for glucose production (gluconeogenesis) in both liver and kidneys.

Hyperglycemia (ie, random blood glucose concentration more than 200 mg/dL or 11 mmol/L) results when insulin deficiency leads to uninhibited gluconeogenesis and prevents the use and storage of circulating glucose. The kidneys cannot reabsorb the excess glucose load, causing glycosuria, osmotic diuresis, thirst, and dehydration. Increased fat and protein breakdown leads to ketone production and weight loss. Without insulin, a child with IDDM wastes away and eventually dies from diabetic ketoacidosis (DKA).

An excess of insulin prevents the release of glucose into the circulation and results in hypoglycemia (blood glucose concentrations of <60 mg/dL or 3.5 mmol/L). Glucose is the sole energy source for erythrocytes, kidney medulla, and the brain.

Mortality/Morbidity

Information on mortality rates is difficult to ascertain without complete national registers of childhood diabetes, although age-specific mortality is probably double that of the general population. Particularly at risk are children aged 1-4 years who may die with DKA at the time of diagnosis. Adolescents are also a high-risk group.

Most deaths result from delayed diagnosis or neglected treatment and subsequent cerebral edema during treatment for DKA, although untreated hypoglycemia also causes some deaths. Unexplained death during sleep may also occur.

IDDM complications are comprised of 3 major categories: acute complications, long-term complications, and complications caused by associated autoimmune diseases.

- Acute complications reflect the difficulties of maintaining a balance between insulin therapy, dietary intake, and exercise. Acute complications include hypoglycemia, hyperglycemia, and DKA.
- Long-term complications arise from the damaging effects of prolonged hyperglycemia and other metabolic consequences of insulin deficiency on various tissues. While long-term complications are rare in childhood, maintaining good control of diabetes is important to prevent complications from developing in later life. The likelihood of developing complications appears to depend on the interaction of factors such as metabolic control, genetic susceptibility, lifestyle (eg, smoking, diet, exercise), pubertal status, and gender.Long-term complications include the following:
  - o Retinopathy
  - o Cataracts
  - o Hypertension
  - o Progressive renal failure
  - o Early coronary artery disease
  - o Peripheral vascular disease
  - o Neuropathy, both peripheral and autonomic
  - o Increased risk of infection
- Associated autoimmune diseases are common with IDDM, particularly in children who have the human leukocyte antigen DR3 (HLA-DR3). Some conditions may precede development of diabetes; others may develop later. As many as 20% of children with diabetes have thyroid autoantibodies.

Race

- Different environmental effects on IDDM development complicate the influence of race, but racial differences clearly exist.
- Whites have the highest reported incidence of IDDM; Chinese have the lowest.
- IDDM is 1.5 times more likely to develop in American whites than in American blacks or Hispanics.
- Current evidence suggests that when immigrants from an area with low incidence move to an area with higher incidence, their IDDM rates tend to increase toward the higher level.

Sex

- The influence of sex varies with the overall incidence rates.
- Males are at greater risk in regions of high incidence, particularly older males, whose incidence rates often show seasonal variation.
- Females appear to be at a greater risk in low-incidence regions.

Age

- Generally, incidence rates increase with age until mid-puberty then decline after puberty, but IDDM can occur at any age. Onset in the first year of life, though unusual, can occur and must be considered in any infant or toddler, because these children have the greatest risk for mortality if diagnosis is delayed. Their symptoms may include the following:
    - Severe monilial diaper/napkin rash
    - Unexplained malaise
    - Poor weight gain or weight loss
    - Increased thirst
    - Vomiting and dehydration, with a constantly wet napkin/diaper
- Where prevalence rates are high, a bimodal variation of incidence has been reported that shows a definite peak in early childhood (ie, 4-6 y) and a second, much greater peak of incidence during early puberty (ie, 10-14 y).

History

- The most easily recognized symptoms are secondary to hyperglycemia, glycosuria, and ketoacidosis (KA).
- Hyperglycemia: Hyperglycemia alone may not cause obvious symptoms, although some children report general malaise, headache, and weakness. They may also appear irritable and become ill-tempered. The main symptoms of hyperglycemia are secondary to osmotic diuresis and glycosuria.
- Glycosuria: This condition leads to increased urinary frequency and volume (eg, polyuria), which is particularly troublesome at night (eg, nocturia) and often leads to enuresis in a previously continent child. These symptoms are easy to overlook in infants because of their naturally high fluid intake and diaper/napkin use.
- Polydipsia: Increased thirst, which may be insatiable, is secondary to the osmotic diuresis causing dehydration.
- Weight loss: Insulin deficiency leads to uninhibited gluconeogenesis, causing breakdown of protein and fat. Weight loss may be dramatic, even though the child's appetite usually remains good. Failure to thrive and wasting may be the first symptoms noted in an infant or toddler and may precede frank hyperglycemia.

- Nonspecific malaise: While this condition may be present before symptoms of hyperglycemia, or as a separate symptom of hyperglycemia, it is often recognized only retrospectively.
- Symptoms of ketoacidosis
  - Severe dehydration
  - Smell of ketones
  - Acidotic breathing (ie, Kussmaul respiration), masquerading as respiratory distress
  - Abdominal pain
  - Vomiting
  - Drowsiness and coma
- Other nonspecific findings
  - Hyperglycemia impairs immunity and renders a child more susceptible to recurrent infection, particularly of the urinary tract, skin, and respiratory tract.
  - Candidiasis may develop, especially in groin and flexural areas.

Physical

- Apart from wasting and mild dehydration, children with early diabetes have no specific clinical findings.
- Physical examination may reveal findings associated with other autoimmune endocrinopathies, which have a higher incidence in children with IDDM (eg, thyroid disease with symptoms of overactivity or underactivity and possibly a palpable goiter).
- Cataract is a rare presenting problem, typically occurring in girls with a long prodrome of mild hyperglycemia.
- Necrobiosis lipoidica usually, but not exclusively, occurs in people with diabetes. Necrobiosis most often develops on the front of the lower leg as a well-demarcated, red, atrophic area. The condition is associated with injury to dermal collagen, granulomatous inflammation, and ulceration. The cause of necrobiosis is unknown, and the condition is difficult to manage.

Causes

Most cases (95%) of IDDM are the result of environmental factors interacting with a genetically susceptible person. This interaction leads to the development of autoimmune disease directed at the insulin-producing cells of the pancreatic islets of Langerhans. These cells are progressively destroyed, with insulin deficiency usually developing after the destruction of 90% of islet cells.

- Genetic issues
  - Clear evidence exists for a genetic component to IDDM.

- o Monozygotic twins have a 60% lifetime concordance for developing IDDM, although only 30% do so within 10 years after the first twin is diagnosed. In contrast, dizygotic twins have only an 8% risk of concordance, which is similar to the risk among other siblings.
- o The frequency of diabetes developing in children with a diabetic mother is 2-3% and 5-6% if the father has IDDM. The risk to children rises to almost 30% if both parents are diabetic.
- o HLA class II molecules DR3 and DR4 are associated strongly with IDDM. More than 90% of whites with IDDM express 1 or both of these molecules, compared to 50-60% in the general population.
- o Patients expressing DR3 also risk developing other autoimmune endocrinopathies and celiac disease. These patients are more likely to develop diabetes at a later age, to have positive islet cell antibodies, and to appear to have a longer period of residual islet cell function.
- o Patients expressing DR4 are usually younger at diagnosis and more likely to have positive insulin antibodies, yet they are unlikely to have other autoimmune endocrinopathies.
- o The expression of both DR3 and DR4 carries the greatest risk of IDDM; these patients have characteristics of both the DR3 and DR4 groups.
- Environmental factors
  - o Environmental factors are important because even identical twins have only a 30-60% concordance for IDDM, and because incidence rates vary in genetically similar populations under different living conditions.
  - o No single factor has been identified, but infections and diet are considered the 2 most likely environmental candidates.
  - o Viral infections may be the most important environmental factor in the development of IDDM, probably by initiating or modifying an autoimmune process. Instances have been reported of a direct toxic effect of infection in congenital rubella. A recent survey suggests enteroviral infection during pregnancy carries an increased risk of IDDM in the offspring. Paradoxically, IDDM's incidence is higher in areas where the overall burden of infectious disease is lower.
  - o Dietary factors are also relevant. Breastfed infants have a lower risk for IDDM, and a direct relationship exists between per capita cow milk consumption and incidence of diabetes. Some cow's milk proteins (eg, bovine serum albumin) have antigenic similarities to an islet cell antigen. Nitrosamines, chemicals found in smoked foods and some water supplies, are known to cause IDDM in animal models; however, no definite link has been made with humans.

- Chemical causes: Streptozotocin and RH-787, a rat poison, selectively damage islet cells and can cause IDDM.
- Other causes
  - Congenital absence of the pancreas or islet cells
  - Pancreatectomy
  - IDDM secondary to pancreatic damage (ie, cystic fibrosis, chronic pancreatitis, thalassemia major, hemochromatosis, hemolytic uremic syndrome)
  - Wolfram syndrome (diabetes insipidus, DM, optic atrophy, deafness [DIDMOAD])
  - Chromosomal disorders such as Down syndrome, Turner syndrome, Klinefelter syndrome, or Prader-Willi syndrome (The risk is said to be around 1% in Down and Turner syndromes.)

Lab Studies
- The need for and extent of laboratory studies vary, depending upon the general state of the child's health. For most children, only urine testing for glucose and blood glucose measurement are required for a diagnosis of diabetes. Other conditions associated with diabetes require several tests at diagnosis and at later review. (See Diabetic Ketoacidosis for information on laboratory studies needed to manage cases of DKA.)
- Urine glucose
  - A positive urine glucose test suggests but is not diagnostic for IDDM. Diagnosis must be confirmed by test results showing elevated blood glucose levels.
  - Test urine of ambulatory patients for ketones at the time of diagnosis.
- Urine ketones
  - Ketones in the urine confirm lipolysis and gluconeogenesis, which are normal during periods of starvation.
  - With hyperglycemia and heavy glycosuria, ketonuria is a marker of insulin deficiency and potential DKA.
- Blood glucose
  - Apart from transient illness- or stress-induced hyperglycemia, a random whole-blood glucose concentration more than 200 mg/dL (11 mmol/L) is diagnostic for diabetes, as is a fasting whole-blood glucose concentration exceeding 120 mg/dL (7 mmol/L). In the absence of symptoms, the physician must confirm these results on a different day. Most children with diabetes detected because of symptoms have a blood glucose level of at least 250 mg/dL (14 mmol/L).

- Blood glucose tests using capillary blood samples, reagent sticks, and blood glucose meters are the usual methods for monitoring day-to-day diabetes control.
- Glycated hemoglobin
  - Glycosylated hemoglobin derivatives (HbA1a, HbA1b, HbA1c) are the result of a nonenzymatic reaction between glucose and hemoglobin. A strong correlation exists between average blood-glucose concentrations over an 8- to 10-week period and the proportion of glycated hemoglobin. The percentage of HbA1c is more commonly measured. Normal values vary according to the laboratory method used, but nondiabetic children generally have values in the low-normal range. At diagnosis, diabetic children unmistakably have results above the upper limit of the reference range.
  - Measurement of HbA1c levels is the best method for medium- to long-term diabetic control monitoring. The Diabetes Control and Complications Trial (DCCT) has demonstrated that patients with HbA1c levels around 7% had the best outcomes relative to long-term complications. Check HbA1c levels every 3 months. Most clinicians aim for HbA1c values of 7-9%. Values less than 7% are associated with an increased risk of severe hypoglycemia; values more than 9% carry an increased risk of long-term complications.
- Renal function tests: If the child is otherwise healthy, renal function tests are typically not required.
- Islet cell antibodies
  - Islet cell antibodies may be present at diagnosis but are not needed to diagnose IDDM.
  - Islet cell antibodies are nonspecific markers of autoimmune disease of the pancreas and have been found in as many as 5% of unaffected children. Other autoantibody markers of type 1 diabetes are known, including insulin antibodies. More antibodies against islet cells are known (eg, those against glutamate decarboxylase [GAD antibodies]), but these are generally unavailable for routine testing.
- Thyroid function tests
  - Because early hypothyroidism has few easily identifiable clinical signs in children, children with IDDM may have undiagnosed thyroid disease.
  - Untreated thyroid disease may interfere with diabetes management. Check thyroid function regularly (every 2-5 years or annually if thyroid antibodies are present).

- Antithyroid antibodies: This test indicates risk of present or potential thyroid disease.
- Antigliadin antibodies
  - Some children with IDDM may have or develop celiac disease. Positive antigliadin antibodies, especially specific antibodies (eg, antiendomysial, antitransglutaminase) are important risk markers.
  - If antibody tests are positive, a jejunal biopsy is required to confirm or refute a diagnosis of celiac disease.

Imaging Studies

- No routine imaging studies are required.

Other Tests

- Oral glucose tolerance test (OGTT)
  - While unnecessary to diagnose IDDM, an OGTT can exclude the diagnosis of diabetes when hyperglycemia or glycosuria are recognized in the absence of typical causes (eg, intercurrent illness, steroid therapy) or when the patient's condition includes renal glucosuria.
  - Obtain a fasting blood sugar level, then administer a PO glucose load (2 g/kg for children aged <3 y, 1.75 g/kg for children aged 3-10 y [max 50 g], or 75 g for children aged >10 y). Check the blood glucose concentration again after 2 hours. A fasting whole-blood glucose level higher than 120 mg/dL (6.7 mmol/L) or a 2-hour value higher than 200 mg/dL (11 mmol/L) indicates diabetes. Mild elevations, however, may not indicate diabetes when the patient has no symptoms and no diabetes-related antibodies.
  - A modified OGTT can also be used to identify cases of MODY that often present as type 1 diabetes, if, in addition to blood glucose levels, insulin or c-peptide (insulin precursor) levels are measured at fasting, 30 minutes, and 2 hours. Type 1 diabetics cannot produce more than tiny amounts of insulin. People with MODY or type 2 diabetes show variable and substantial insulin production in the presence of hyperglycemia.
- Lipid profile
  - Lipid profiles are usually abnormal at diagnosis because of increased circulating triglycerides caused by gluconeogenesis.
  - Apart from hypertriglyceridemia, primary lipid disorders rarely result in diabetes.
  - Hyperlipidemia with poor metabolic control is common.
- Urinary albumin: Beginning at age 12 years, perform an annual urinalysis to test for a slightly increased albumin excretion rate (AER), referred to as microalbuminuria, which is an indicator of risk for diabetic nephropathy.

Medical Care

- All children with IDDM require insulin therapy.
- Only children with significant dehydration, persistent vomiting, or metabolic derangement, or with serious intercurrent illness, require inpatient management and intravenous rehydration.
- A well-organized diabetes care team can provide all necessary instruction and support in an outpatient setting. The only immediate requirement is to train the child or family to check blood glucose levels, to administer insulin injections, and to recognize and treat hypoglycemia. The patient and/or family should have 24-hour access to advice and know how to contact the team.

Consultations

- Always involve an experienced dietitian in the patient's care, typically as a regular member of the diabetes care team.
- Ophthalmology review may be needed at diagnosis if a cataract is suspected. All children with diabetes aged 12 years and older need a careful annual eye examination, either by direct ophthalmoscopy or high-quality retinal photography to identify and, if necessary, treat diabetes-related eye complications.
- Access to psychological counseling and support is desirable, preferably from a member of the diabetes care team.

Diet

Dietary management is an essential component of diabetes care. Diabetes is an energy metabolism disorder, and before insulin was discovered, children with diabetes could be kept alive by a diet severely restricted in carbohydrate and energy intake. These measures led to a long tradition of strict carbohydrate control and unbalanced diets. More recent dietary management of diabetes emphasizes a healthy, balanced diet, high in carbohydrates and fiber and low in fat.

- The following are universal recommendations:
    - Carbohydrates should provide 50-60% of daily energy intake. (No more than 10% of carbohydrates should be from sucrose or other refined carbohydrates.)
    - Fat should provide less than 30%.
    - Protein should provide 10-20%.
    - View these recommendations in the patient's cultural context.
- The aim of dietary management is to balance the child's food intake with insulin dose and activity and to keep blood glucose concentrations as close as possible to reference ranges, avoiding extremes of hyperglycemia and hypoglycemia.

- The ability to estimate the carbohydrate content of food (carb counting) is particularly useful for those children who give fast-acting insulin at meal times either by injection or insulin pump, as it allows for a more precise matching of food and insulin.
  - Adequate intake of complex carbohydrates (eg, cereals) is important before bedtime to avoid nocturnal hypoglycemia, especially for children having twice-daily injections of mixed insulin.
  - The dietitian should develop a diet plan for each child to suit individual needs and circumstances. Regularly review and adjust the plan to accommodate the patient's growth and lifestyle changes.
  - Low-carbohydrate diets as a management option for diabetes control have regained popularity in recent years. Logic dictates that the lower the carbohydrate intake, the less insulin is required. No trials of low-carbohydrate diets in children with type 1 diabetes have been reported, and such diets cannot be recommended at the present.

Activity

- IDDM requires no restrictions on activity; exercise has real benefits for a child with diabetes.
- Most children can adjust their insulin dosage and diet to cope with all forms of exercise.
- Children and their caretakers must be able to recognize and treat symptoms of hypoglycemia.
  - Hypoglycemia following exercise is most likely after prolonged exercise involving the legs, such as walking, running or cycling. It may occur many hours after exercise has finished and even affect insulin requirements the following day.
  - A large presleep snack is advisable following intensive exercise.

MEDICATION

Insulin is always required to treat IDDM. Attempts are being made to develop alternative routes to subcutaneous administration. In January 2006, a human insulin (rDNA origin) inhalant powder (Exubera) was been approved by the FDA for use in adults. Although insulin was originally derived from animal sources, recombinant human insulin and the newer 'designer' insulin analogues are now most commonly used. On October 18, 2007, Pfizer Inc announced that it is no longer making inhaled insulin (Exubera). The decision is not based on any safety concerns but is due to economic feasibility resulting from too few patients taking the inhaled insulin. Pfizer will work with physicians to transition patients from inhaled insulin to other treatment options over the next several months.

Insulin has 3 basic formulations: short-acting (eg, regular, soluble, lispro, aspart, glulisine), medium- or intermediate-acting (eg, isophane, lente, detemir), and long-acting (eg, ultralente, glargine).

Regular or soluble insulin is bound to either protamine (eg, isophane) or zinc (eg, lente, ultralente) in order to prolong the duration of action. Combinations of isophane and regular, lispro or aspart insulins are also available in a variety of concentrations that vary around the world, ranging from 10/90 mixtures (ie, 10% regular, 90% isophane) to 50/50 mixtures.

The recent development of insulin analogues have attempted to address some of the shortcomings of traditional insulin. Insulins lispro and aspart have a more rapid onset of action and shorter duration, making them more suitable for bolusing at mealtimes and for short-term correction of hyperglycemia. An intermediate-acting insulin, detemir, has a similar profile of action to isophane but is more pharmacologically predictable, while glargine has a relatively flat profile of action, lasting some 18-26 hours and seems especially suitable as a once-daily basal injection. Despite their apparent advantages over traditional insulins, no evidence suggests a long-term advantage of the analogue insulins in terms of metabolic control or complication rates.

With so many various insulins and mixtures available, a wide range of possible injection regimens exist. These can be broadly categorized into 4 types, as follows:

- Twice-daily combinations of short- and intermediate-acting insulin.
- Multiple injection regimens, using once- or twice-daily injections of long- or intermediate-acting insulin and short-acting insulins given at each meal
- A combination of the above 2 regimens, with a morning injection of mixed insulin, an afternoon premeal injection of short-acting insulin and an evening injection of intermediate- or long-acting insulin
- Continuous subcutaneous insulin infusion (CSII) using an insulin pump

While controlled clinical trials suggest improved short-term metabolic control in children using multiple injections or CSII, international comparisons do not support any particular insulin regimen, and all have their advantages and disadvantages.

A wide variety of insulin-injection devices exist, including a simple syringe and needle, semiautomatic pen injector devices, and needle-free jet injectors. Increasing numbers of young people use insulin pumps to deliver continuous SC insulin, with bolus doses at meal times.

Tailor the insulin dose to the individual child's needs. For instance, if using a twice-daily regimen, then, as a rule of thumb, prepubertal children require between 0.5 and 1 U/kg/d, with between 60-70% administered in the morning and 30-40% in the evening. Insulin resistance is a feature of puberty, and some adolescents may require up to 2 U/kg/d. About one third of the administered insulin is a short-acting

formulation and the remainder is a medium- to long-acting formulation. Basal bolus regimens have a higher proportion of short-acting insulin. Typically, 50% of the total daily dose is given as long- or intermediate-acting insulin. CSII uses only short-acting insulins, most often the analogues lispro or aspart.

Drug Category: Antidiabetic agents

These agents are used for treatment of insulin-dependent DM and also for NIDDM unresponsive to treatment with diet and/or PO hypoglycemics.

Drug Name	Insulin lispro (Humalog)
Description	Onset of action is 10-30 min, peak activity is 1-2 h, and duration of action is 2-4 h.
Adult Dose	0.5-1 U/kg/d SC initially; adjust doses to achieve premeal and bedtime blood glucose levels of 80-140 mg/dL (4-7.5 mMol/L)
Pediatric Dose	0.5-1 U/kg/d SC initially Adjust doses to achieve premeal and bedtime blood glucose levels of: <5 years: 100-200 mg/dL (5.5-10 mMol/L) >5 years: 80-140 mg/dL (4-7.5 mMol/L)
Contraindications	Documented hypersensitivity; hypoglycemia
Interactions	Medications that may decrease hypoglycemic effects of insulin include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine phenothiazines, cyclo-phosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin; medications that may increase hypoglycemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, beta blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAOIs, mebendazole, sulfona-mides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Due to prompt onset of action, administer within 15 min before or immediately after a meal; monitor glucose carefully; dose adjustments may be necessary in renal and hepatic dysfunction

Drug Name	Regular insulin (Humulin R, Novolin R)
Description	Onset of action is 0.25-1 h, peak activity is 1.5-4 h, and duration of action is 5-9 h.
Adult Dose	Adjust to needs
Pediatric Dose	Adjust to needs
Contraindications	Documented hypersensitivity; hypoglycemia
Interactions	Medications that may decrease hypoglycemic effects of insulin

	include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine phenothiazines, cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin; medications that may increase hypoglycemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, beta blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAOIs, mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Dose adjustments may be necessary in renal and hepatic dysfunction

Drug Name	Insulin NPH (Humulin N, Novolin N)
Description	Onset of action is 3-4 h, peak effect is in 8-14 h, and usual duration of action is 16-24 h.
Adult Dose	Adjust to needs
Pediatric Dose	Adjust to needs
Contraindications	Documented hypersensitivity; hypoglycemia
Interactions	Medications that may decrease hypoglycemic effects of insulin include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine phenothiazines, cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin; medications that may increase hypoglycemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, beta blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAOIs, mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Dose adjustments may be necessary in renal and hepatic dysfunction

Drug Name	Protamine zinc (Ultralente)
Description	Onset of action is 2-3 h, peak activity is 4-8 h, and duration of action is 8-16 h.

Adult Dose	Adjust to needs
Pediatric Dose	Adjust to needs
Contraindications	Documented hypersensitivity; hypoglycemia
Interactions	Medications that may decrease hypoglycemic effects of insulin include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine phenothiazines, cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin; medications that may increase hypoglycemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, beta blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAOIs, mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Dose adjustments may be necessary in renal and hepatic dysfunction

Drug Name	Insulin aspart (NovoLog)
Description	Onset of action is 10-30 min, peak activity is 1-2 h, and duration of action is 3-6 h. Homologous with regular human insulin, with the exception of single substitution of amino acid proline by aspartic acid in position B28. Produced by recombinant DNA technology. Insulin lowers blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Inhibits lipolysis in the adipocyte. Inhibits proteolysis. Enhances protein synthesis. Insulin is the principal hormone required for proper glucose use in normal metabolic processes.
Adult Dose	0.5-1 U/kg/d SC initially; adjust doses to achieve premeal and bedtime blood glucose levels of 80-140 mg/dL (4-7.5 mMol/L)
Pediatric Dose	0.5-1 U/kg/d SC initially Adjust doses to achieve premeal and bedtime blood glucose levels of: <5 years: 100-200 mg/dL (5.5-10 mMol/L)>5 years: 80-140 mg/dL (4-7.5 mMol/L)
Contraindications	Documented hypersensitivity; hypoglycemia
Interactions	Medications that may decrease hypoglycemic effects of insulin include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine, isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid hormone, estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine, phenothiazines,

	cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin Medications that may increase hypoglycemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, beta blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAO inhibitors, mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Hyperthyroidism may increase renal clearance of insulin and may need more insulin to treat hyperkalemia; hypothyroidism may delay insulin turnover, requiring less insulin to treat hyperkalemia; due to prompt onset of action, administer within 15 min before or immediately after a meal; monitor glucose carefully; dose adjustments may be necessary in renal and hepatic dysfunction

Drug Name	Insulin glargine (Lantus)
Description	Long-acting insulin analogue. Typical onset of action from 1-2 h, duration 20-26 h
Adult Dose	Usually 50% of total daily dose of insulin (0.25-0.5 U/kg); adjust to needs
Pediatric Dose	Licensed age varies between nations (2-6 y); adjust dose as indicated but similar to adult
Contraindications	Documented hypersensitivity; hypoglycemia
Interactions	Medications that may decrease hypoglycemic effects of insulin include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine, isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid hormone, estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine, phenothiazines, cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin Medications that may increase hypoglycemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, beta blockers, lithium carbonate, anabolic steroids, pyridoxine, salicylates, MAO inhibitors, mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Administer at the same time each day; use only if solution is clear and colorless; administer SC only; do not mix with any

	other insulin or solution; hyperthyroidism may increase renal clearance of insulin and may need more insulin to treat hyperkalemia; hypothyroidism may delay insulin turnover, requiring less insulin; monitor glucose carefully; dose adjustments of insulin may be necessary in patients diagnosed with renal and hepatic dysfunction

Drug Name	Insulin glulisine (Apidra)
Description	Human insulin analog produced by rDNA technology using a nonpathogenic laboratory strain of E coli (K12). Differs from human insulin by replacement of asparagine at B3 position with lysine, and the lysine at the B29 position is replaced by glutamic acid. Insulin regulates glucose metabolism by stimulating peripheral glucose uptake by skeletal muscle and fat, and inhibits hepatic glucose production. Glucose lowering is equipotent to regular human insulin when administered IV. After SC administration, insulin glulisine has more rapid onset and shorter duration of action compared to regular human insulin. Useful to regulate mealtime blood glucose elevation.
Adult Dose	Individualize dose; intended for intermittent SC injection with meals or use by external infusion pump
Pediatric Dose	0.5-1 U/kg/d SC initially; Adjust doses to achieve premeal and bedtime blood glucose levels of: <5 years: 100-200 mg/dL (5.5-10 mMol/L) >5 years: 80-140 mg/dL (4-7.5 mMol/L)
Contraindications	Documented hypersensitivity; hypoglycemia
Interactions	Corticosteroids, danazol, diazoxide, diuretics, sympathomimetic agents (eg, epinephrine, albuterol, terbutaline), glucagon, isonia-zid, phenothiazines, growth hormone, thyroid hormone, estro-gen, progestogens, protease inhibitors, and atypical antipsycho-tics (eg, olanzapine, clozapine) may increase blood glucose and reduce glucose lowering effect of insulin; oral antidiabetic agents, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAOIs, pentoxifylline, propoxyphene, salicylates, and sulfona-mides may decrease blood glucose and cause additive effects to insulin
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Hyperthyroidism may increase renal clearance of insulin and may need more insulin to treat hyperkalemia; hypothyroidism

	may delay insulin turnover, requiring less insulin to treat hyperkalemia; due to prompt onset of action, administer within 15 min before or immediately after a meal; monitor glucose carefully; dose adjustments may be necessary in renal and hepatic dysfunction				

VI. Plan and organizational structure of classes.

№ п/п	Basic stages of classes, their function and maintenance	Educational aims are in the levels of mastering	Methods of control and studies	Educational materials	Distribution of time in minutes
1 2 3	Preparatory stage Organizational measures of educational aims and motivation Control of basic knowledge and skill levels: 1. Keylinks of pathogenesis of diabetes mellitus type 1 in children 2. Classification of diabetes mellitus type 1 3. Classification of complications of diabetes mellitus type 1: long-term and acute 4. Laboratory and instrumental diagnosis of diabetes mellitus and complications 5 Treatment principles of diabetes mellitus and its complications 6.Complications of insulin-therapy	α2 α2 α2 α2 α2 α2 α2 α2 α2	Individual questioning Test control of the second level Individual (oral) questioning Typical situational task of 2 level Typical situational task of 2 level Typical situational situational task of 2 level Test control of 2 level Typical situational task of 2 level	П. II «Educational aims» П. I «Actuality of theme» Second level tests the table «Pathogenesis of diabetes mellitus type 1 » Tests of 2 level the table «Classification of diabetes mellitus type 1 » Structurally logical chart: long-term and acute complications Typical situational task of 2 level Tests of 2 level Typical situational tasks of 2 level Kit of medicines.	3 min. 12 min. 20 min.
4	Basic stages of professional skills and abilities forming: 1.To conduct the patient's management with diabetes mellitus, to take complaints and anamnesis.	α3 α3	Practical professional training Practical	Patient Patient	115 min.

	2.To conduct the patient's examination and detect the main symptoms and complications with diabetes mellitus.	α3	professional training	Case history
	3. To formulate and substantiate the preliminary diagnosis		Practical professional training	A reference chart for the forming of professional abilities. Case history.
	4.To compose the plan of patient's laboratory and instrumental investigation.	α3	Practical professional training	A reference chart for the forming of professional abilities. Situational typical tasks of the third level.The third level tests.
	5. To interpret the results of laboratory and instrumental investigation.	α3	Practical professional training. Tests and the third level control. The third level test control.	
	6.To conduct differential diagnosis for clinical conditions accompanied by hyperglycemia, polydipsia, glycosuria, polyuria.	α3	The practical professional training is in the solution of non standard clinical situations.	Prescribing chart
	7.To give recommendations for the regimen and diet of a patient.	α3	The third level test control.Practical professional training. The third level test control.	The third level non typical situational tasks. Treatment algorythm for the diabetes mellitus patients.
	8.To compose the treatment plan of diabetes mellitus patient's treatment taking into account the stage of disease and the presence of complications.	α3	Practical professional training .	The third level non typical situational tasks. First aid algorithm in diabetes mellitus.
	9. To be able to render the first aid in extreme situations: hyperglycemic, hypoglycemic, hyperosmolar , hyperlactacidemic, ketoacidosis coma.	α3	The practical professional training on solving of non typical clinical situations. The third level test control. Practical professsional training on solving of non typical clinical situations.	
5 6 7	Concluding stage. Control and correction of professional abilities and skills. Working out the totals of class. Home work (basic and additional literature on the topic)		Analysis of clinical work Solution of non typical tasks and the third level tests. Estimation of clinical work.	Clinical work The third level non typical situational tasks. A reference chart for independent work with literature	30 min.

Methodical materials for the class basic stage supporting

The questions for the control of primary knowledge level of abilities and skills:

1. What is the role of genetics in the development of diabetes mellitus type 1?

2. What is the main mechanism in the development of glycosuria in children with diabetes mellitus, type 1 ?

3. What leads to the occurrence of hyperglycemia in children with diabetes mellitus, type 1?

4. How can you estimate the level of glucose with the help of an oral glucose tolerance test (OGTT)?

5. What is the role of glycosylated hemoglobin derivatives (HbA1a, HbA1b, HbA1c) for the diagnosis of diabetes and its complications?

6. What is the role of hyperglycemia in the development of long-term complications (retinopathy, cataracts ,hypertension, progressive renal failure ,early coronary artery disease,peripheral vascular disease ,Neuropathy, both peripheral and autonomic)?

7. Describe the pathogenesis of microalbuminuria in children with diabetes mellitus, type 1.

Make the table " Classification of nephropathy"

Stage	Laboratory investigations
I	increased GFR increased RP hypertrophy of kidneys normal albumin excretion(< 30 μg/mg)
II	Thickening of membrane vessels of glomerulus increased GFR normal albumin excretion(< 30 μg/mg)
III	microalbuminuria (30–299) normal or increased GFR unstable blood pressure
IV	Sclerosis of 50-75% glomerulus Macro (clinical)-albuminuria mildly decreased GFR stable high blood pressure
V	Total sclerosis Severely decreased GFR stable high blood pressure increased level of creatinine Symptoms of intoxication

GFR – glomerular filtration rate

RP – renal perfusion

8. To render the first aid in the case of diabetic ketoacidosis.

9. How many various insulins and mixtures are available for children with diabetes mellitus?

10. Dietary management of diabetes care.

11. To render the first aid in the case of hypoglycemic coma.

12. To conduct a differential diagnosis for hyperglycemic, hypoglycemic, hyperosmolar , hyperlactacidemic, and ketoacidosis coma patients .

Primary tests

1. A boy of 7 years old, was hospitalized with complaints of thirst intensifying and poliuria . During 5 years he has been suffering from diabetes, in anamnesis a diabetic comma three times developed. The level of sugar in the blood is 15,54 mmol/l, in urine it is 5%. By the oculist Retinoangipathy was found. What dose of insulin will be administered to the child?

A. 1,5 U/kg

B.0,25 U/rg

C.0,5 U/kg

D.1,0 U/kg

E.2,0 U/kg

2. A diabetic boy was delivered to the induction centre of child's hospital in severe condition. On examination there was the absence of consciousness . His skin was dry and pale, skin turgor was diminished. Hypotonus of muscles and eyeballs. Lips mucus was dry and in bright red color. Heart tones were hyposthenic, tachycardia, decreased blood pressure, threadlike pulse. Koussmaul type of breathing . Strong smell of acetone midair. Specify the day's dose of insulin for the acute management.

A. 1,5 U/kg

B. 2,5 U/kg

C.2,0 U/kg

D.1,0 U/kg

E.3,0 U/kg

3. Patient O, 13 years old, has been suffering from diabetes for 6 years. Hospitalized to the department in comma. Consciousness was absent, reflexes were low-speed. Skin and mucuses were pale, dry. Breathing was loud. The smell of acetone. Anuria. Laboratory data: blood glucose –is 35 mmol / l, serum potassium is 2,5 mmol / l, sodium is 120 mmol/ l. Blood urea is 9,5 mmol/ l, ketonic bodies in the serum were 7,5 mmol /l. In the urine is ++++, glucose of urine –is 120 mmol /l. What is it necessary for the taking the patient out of comma?

A. to conduct blood transfusion

B. to conduct neuroleprtanalgesia

C. to conduct dehydration

D. to carry out the correction of acid - alkaline equilibrium

E. to administer hydrocortisonum

4. A child of 5 years old was firstl hospitalized in the department with a diagnosis of I type diabetes, decompensation (ketoacidosis). What is the main mechanism in the development of the disease?

A. Surplus of glucagon

B. Insulin insufficiency**.**

C. Surplus of somatostatin.

D. Disturbance of insulin complexing with receptors.

E.Disturbance of postreceptor mechanism of insulin action.

5. A child of 10 years old was hospitalized with complaints of thirst, intensifying emiction, weght loosing, weakness, languor   after the clinical and –laboratory examination. The diagnosis of I type diabetes was made, decompensation. How is it possible to explain the symptom of poliuria in the patient ?

A. Diminished production of thyroid hormone.

B. Diminished production of antidiuretic hormone.

C. Increased vasopressin production.

D. Glucose is selected with urine acts as osmotic diuretic.

E Elevated thyroid hormone production.

6. A girl of 12 years old. Since 2-years-old age she has been suffering from   diabetes. On examination there was considerably enlarged stomach, liver palpated 6 cm below costal arc, some what painful and, dense; Cushing –like type of obesity, nanism. The signs of the sexual maturation are not present. Blood glucose is 17 mmol/l, of urine is 4 mmol\l. In the blood elevated cholesterol, ketonic bodies. What is the preliminary diagnosis?

A. I type Diabetes, precoma

B. I type diabetes, Nobecur syndrome

C. I type diabetes, Mauriac syndrome

D. Cushing disease Illness

E. Cushing syndrome

7. A girl of 12 years old, was delivered to the hospital in the unconscious state. During the last month she has been loosing weight, although the appetite is preserved. Stomach-aches, vomiting, appeared. Weakness grew, became put on the brakes. On examination: without consciousness, sharply exhausted, the skin is pale-grey, dry, hyperemia of cheeks. Breathing is deep, noisy. The smell of aceton. Hearts tones are muffled and rhythmic. Pulse 90 b. per minute, blood pressure is 90/50 mmHg Stomach is falling back. Liver +3,0 cm. What disease can be supposed?

A. Acetonemic condition.

B . Coliform infection with neurotoxicosis

C. Hepatic coma

D. Diabetic coma

E. Suprarenal failure

8. A child of 7 years old was hospitalized with complaints on weight loss, thirst, frequent emiction. During the examination in the blood tests the level of sugar on an empty stomach was 14 mmol/l, the level of sugar in urine was 5 g/l. What caused hyperglycemia in the child?

A. Intensifying of lipolysis .

B. Intensifying of proteins cvatabolism.

C Decreasing of glyconeogenesis.

D. Intensifying of glycolysis

E. Decreasing of glycolysis and intensifying of glyconeogenesis.

9. A child of 7 years old was hospitalized with complaints on thirst, frequent emiction, weght loss (3 kg per month). On examination the level of glucose in the blood on an empty stomach was 19,2 mmol/l. A diagnosis of 1 type diabetes was made. How is it possible to explain the weght loss in the child? .

A. Intensifying of proteins catabolism and inhibiting of it synthesis.

B Decreasing of lipolysis..

C. Intensifyiong of gluconeogenesis.

D. Decreasing of lypolisis. .

E. Disturbancies of basic exchange.

10. A boy of 10 years old, sharp languor, somnolence, thirst, frequent emiction. On examination the smell of acetone from the mouth was marked, on the cheeks bright blush, noisy unrhythmic breathing, enlarged liver. In the blood tests the level of sugar was 20,5 mmol/l, sugar of urine is 20 g/l, acetone in urine is +++. How is it possible to explain the appearance of acetone midair and urine ?

A. By the increased disintegration of ketogenic amino acids and lipids.

B. By the disturbance of water - electrolyte balance.

C. By the disturbance of acid - alkaline balance.

D. By the disturbance of glucose phosphorylating processes.

E. Bt the decreasing of glycolys.

11.A patient of 8 years old, was taken to the hospital   without consciousness. A week ago she had a flu, whereupon a girl became sickly, ate badly, mainly milk, tea, grumbled about headache (mother reported). Stomach-aches appeared the day before, repeated vomiting,the girl was sleepy, and lost consciousness to the evening. Consciousness was absent. The skin was dry. The tongue was dry, red. Breathing was deep, noisy, 32/ min., the smell of acetone. Pulse 128 / min., small. Blood pressure - 75/40 mmHg. On palpation the stomach was soft, without pains. Liver + 4 cm, is soft. Body temperature   is 36,7 C. Kehr and other symptoms are negative. What is the preliminary diagnosis?

A. Acute adrenal insufficiency.

B. Meningitis.

C. Septic shock.

D. 1 type diabetes is revealed for the first time, ketoacidic comma.

E. Hepatitis.

12 .Patient K., has been suffering from diabetes for 8 years. Objectively: skin is dry, breathing is noisy, the smell of acetone. What type of comma is it possible to suspect?

À. ketoacidic

B hyperosmotic

D. lactatacidic

E. cerebral

13. A boy of 14 years old, complains on thirst, loss of weight, weakness, increased emiction (4 l per day), pain in the legs , itch of the skin. What diagnosis is the most probable?

   A neurogenic polydesum
   B. diabetes
   C. diabetes insipidus
   D. acute nephrite
   E. kidney diabetes

14. A boy of 14 years old, complains on thirst, loss of weight, weakness, increased emiction (4 l per day), pain in the legs , itch of the skin. What is it necessary to prescribe for clarification of the diagnosis?

   A test with xerophagia
   B to determine the level of sugar in the blood
   C. roentgenography of skull
   D. Zimnitski test
   E. to determine the protein loss with urine per day

15. Patient K., was delivered without consciousness. He has been suffering from diabetes for 10 years. During the last week he had gastroenteritis. Objectively: the skin is dry, eyeballs are soft. Breathing is superficial; the smell of acetone is not felt. Blood. pressure is 80/40 mm.Hg   What kind of coma is the most probable?

   À hyperosmotic
   B.hyperlactatacidemic
   C. ketoacidic
   D. glucopenia
   E. alcoholic

16. Patient K., was delivered without consciousness. He has been suffering from diabetes during 10 years. During the last week he had gastroenteritis. Objectively: the skin is dry, eyeballs are soft. Breathing is superficial; the smell of acetone is not felt. Blood. pressure is 80/40 mm.Hg   What do you expect to get from the results of analyses?

   A.. glycemia is more than 20 mmol/l, acetone in urine is «++»
   B glycemia is 2,0 mmol/l, acetone in urine is absent
   C. glycemia is than more than 40 mmol/l, acetone in urine is absent
   D. glycemia is up to 10 mmol/l, pH of blood is less than 7,2
   E. glycemia is 5,0 mmol/l, the high level of alcohol in the blood

17. Patient K., 8 years old. He has been suffering from diabetes for 6 years, got insulin 46 U/day. During the last 5 months for compensation of glycemia the dose of insulin was multiplied to 108 U. Glucopenia was not present.
How do you consider such a state?

   A. syndrome of chronic overdose of insulin
   B . resistance to insulin

C. lability of diabetes course

D. Kimmelstill –Wilson syndrome

 E. allergy to insulin

18. Patient K., 8 years old. He has been suffering from diabetes for 6 years, got insulin 46 U/day. During the last 5 months for compensation of glycemia the dose of insulin was multiplied to 108 U. Glucopenia was not present.

What is the further tactics of treatment for this patient?

A, to multiply the dose of insulin

B. to cancell insulin and to prescribe biguanids.

C. hyposensibilisation by the small doses of insulin

D. to increase the amount of carbonhydrates in the diet

E. to prescribe simple insulin + prednisolon

19. Patient M, without consciousness. The skin is moistured, on the shoulders and thighs there are signs of injections. Breathing is superficial. Blood pressure is 110/170 mmHg. Muscles tones and tendon reflexes are incraesed,there are cramps in the extremities. What disease is it possible to think about?

A.Hyperglycemic comma

B Glycopenic comma

C. Hyperosmotic comma

D. Hyperlactatacid comma

E. cerebral comma (stroke)

20. Patient K., has been suffering from diabetes for 8 years. During the last year the dose of insulin was diminished to 14 U. In the urine analysis of protein is 1,7 %, sugar 0,8 %, a lot of red corpuscles and cylinders.

 The indicated signs are the manifestation of:

A.resistance to insulin

B. nephrosclerosis

C. decompensations of diabetes

D. pyelitis

E. syndrome of chronic overdose of insulin

Answers : 1-A, 2-D, 3-D, 4-B, 5-D, 6-B, C, 7-D, 8-D, 9-A, 10-A, 11-D, 12-A, 13-B, 14-B, 15-A,16-C,17-B,E, 18-E,C, 19-C,20-B

Typical situational tasks of 2 level

1.A boy of 14 years old, from the 12-years-old age has been suffering from diabetes. In the anamnesis hypoglycemic diabetic comma developed, on the eyeground the microaneurysm of vessels, hemorrhages in the retina, pain in the legs, decrease of amplitude on a rheography, level of glucose in the blood is 13,1 mmol/l.

Task Taking modern classificationas as a basis formulate the diagnosis

2. A boy of 7 years old, was hospitalized with complaints of rashes, weakness, weight loss, he had flu 6 months ago. The level of glucose in the blood is 6,6 mmol/l, oral glucose tolerance test- fasting blood sugar level is 6,16 mmol/l, blood glucose

concentration again after 30 min(after glucose) is 7,7 mmol/l, blood glucose concentration again after 60 min is 12,1 mmol/l, blood glucose concentration again after 90 min is 10,54 mmol/l, blood glucose concentration again after 120 min is 11,7 mmol/l.

Task
- To evaluate the oral glucose tolerance test (OGTT)
- What is the initial diagnosis?
- To prescribe treatment

3. A girl of 11 years old, from the 9-years-old age has been suffering from diabetes, got insulin 18 U/day. She had a pneumonia 2 weeks ago. The girl was hospitalized with complaints of thirst, stomach-ache, vomiting, loss of consciousness. The smell of aceton. Pulse 120 b. per minute, Blood pressure is 80/45 mmHg . Breathing is deep, noisy.

Task
- What is the preliminary diagnosis?
- To work out a plan of patient investigation.
- To Prescribe treatment

4. A girl of 6 years old from 1-year-old age has been suffering from diabetes, was delivered to the hospital in the unconscious state. On examination the skin is pale-grey, lips mucus is dry and in a bright red color, constriction of pupils, heart tones are hyposthenic, tachycardia, decreased blood pressure, the smell of acetone. Blood glucose is 22,4 mmol/l.

Task
- What is the preliminary diagnosis?
- To render the first aid
- What kind of insulin will most probably be prescribed to the child?

5.A boy of 16 years old. Since 2-years-old age has been suffering from diabetes, got alcohol, hospitalized with complaints of weakness, consciousness,
    On examination : the skin is pale and cyanotic , consciousness, sweating.
    Breathing is superficial , the smell of alcohol, tachycardia, cramps.

Task
- What is the preliminary diagnosis?
- To render the first aid

6. A patient 8 years old, was taken to the hospital . A week ago had flu. Complains on thirst, loss of weight, weakness, polyuria. On examination: vomiting, the skin is dry, hyperemia of the cheeks. Breathing is deep, noisy. Smell of aceton. Hearts tones are muffled and rhythmic. Stomach is falling back.

Task
- What is the preliminary diagnosis?
- To work out a plan of patient investigation.
-To prescribe treatment

7. A patient K., 8 years old. Has been suffering from diabetes during 6 years. On

examination his stomach was considerably enlarged, liver palpated 6 cm below the costal arc, somewhat painful , dense; Cushing –like type of obesity, nanism. The signs of the sexual maturation are not present. Blood glucose is 17 mmol/l, urine is 4 mmol\l. In the blood increased cholesterol, ketonic bodies.

Task
-What is the preliminary diagnosis?
- To prescribe treatment

8. A patient M, 12 years old, has been suffering from diabetes during 6 years. Takes insulin of «Aktrapid» 13 U + «Protophan» 14 U. In anamnesis the comatose states relapsed. She is disturbed by the decreasing of sight acuity, weakness and pain in the legs. At ophtalmoscopy on the eyeground the microaneurysm of vessels, hemorrhages in the retina, neovascularisation. Glucose on an empty stomach is 9,7 mmol/l, glucosuria is 2 % (2,5 l), acetone in urine was not discovered.

Task
-What is the preliminary diagnosis?
-What correction of diabetes therapy will you conduct?

9. A child of 10 years old .Has been suffering from diabetes for 10 years. During the last 2 years she had albuminuria, high blood pressure. During the last week had gastroenteritis. Objectively: cramps, the skin is dry, hallucination ,eyeballs are soft. Breathing is superficial; the smell of acetone is not felt. Blood. pressure is 80/40 mm.Hg. On palpation the stomach is soft, without pains. Hypertonus of muscles.

Task
- What is the preliminary diagnosis?
- What are the laboratory findings
- Prescribe treatment

10. A girl of 12 years old, was delivered to the hospital. During the last month she was losing weight , although the appetite preserved. Stomach-aches, vomiting, appeared. The weakness grew, became put on the brakes. On examination: drowse, sharply exhausted, the skin pale-grey, dry, hyperemia of cheeks. Breathing is deep, noisy. The smell of aceton. Hearts tones are muffled and rhythmic. Pulse 90 b. per minute, Blood pressure is 90/50 mmHg Stomach is falling back. Liver +3,0 cm.

Task
-What disease can be supposed first of all?
- To render the first aid

Standard of answer
1. Type 1 diabetes, severe stage, decompensation, diabetec retinopathy 1, peripheral vascular disease.

2. Fasting hyperglycemia and after 120 min. Type 1 diabetes, first diagnosed, decompensation. Injections of short-acting insulin.

3. Ketoacidosis, coma. Blood glucose and urine ketones.
Infusion therapy and multiple injections of short-acting insulin (intravenous infusion of insulin 0.1 U/kg).

4.Ketoacidosis, coma. Infusion therapy and multiple injections of short-acting insulin (intravenous infusion of insulin 0.1 U/kg)

5. Hypoglycemic coma. Manage mild hypoglycemia by giving rapidly absorbed PO carbohydrate or glucose; for a comatose patient, administer an intramuscular injection of the hormone glucagon, which stimulates the release of liver glycogen and releases glucose into the circulation. Where appropriate, an alternative therapy is intravenous glucose (preferably not more than a 10% glucose solution). All treatments for hypoglycemia provide recovery in approximately 10 minutes.
6. Ketoacidosis, coma. Infusion therapy and multiple injections of short-acting insulin (intravenous infusion of insulin 0.1 U/kg).

7.I type diabetes, Mauriac syndrome . Insulin 0.8-1,0 u/kg.

8.Type 1 diabetes, severe stage, decompensation, diabetec retinopathy 111, peripheral vascular disease. Laser coagulation.

9.Hyperosmolar coma.
  Hypoglycemia, high level of natrium, high level of chlorine, high level of urea, glucosuria. . Infusion therapy and multiple injections of short-acting insulin
 (intravenous infusion of insulin 0.1 U/kg).

10. Diabetic precoma. Infusion therapy and multiple injections of short-acting insulin (intravenous infusion of insulin 0.1 U/kg).

Methodical materials for the class
     A professional algorythm of patients management implementation (reference chart) for the practical skills and abilities forming .

№	Task	Sequence of implementation	Remarks and warnings related to self-control
1	To conduct patient examination for diabetes mellitus type 1	1.To conduct complaints and disease's anamnesis taking. 2.To take thoroughly the patient's life anamnesis. 3.To conduct examination of the patient.	To pay attention to the features of disease course , underlying factors, concomitant diseases etc. To establish the risk factors which can cause the development of disease. To assess patient's general condition, position in bed, color and humidity of skin and mocouse, presence of neck veins and extermities swelling. To pay regard to pulse

		4.To investigate cardiovascular system of the patient (palpation, percussion).	rhythm , it tension and size on both hands, apex shove, its properties, margins of absolute and relative cardiac dullness, its changes, HR(tachi-or bradicardia, extrasystole), BP.
		5.To conduct heart and main vessels auscultation. 6.To investigate the pulmonary system (percussion, bronchophony). 7.To conduct lungs auscultation. 8.To investigate the system of digestion.	To pay regard to heart tones weakening or amplifying, appearance of murmurs and additional III, IV tones. To pay attention to features of percussion and auscultation in children of different age and stage of compensation. To pay attention to the changes in the case of decompensation and diabetic hepatosis.
2	To formulate the preliminary diagnosis.	1.To formulate the preliminary diagnosis 2.To substantiate all the components of preliminary diagnosis taking as a basis complaints, anamnesis, and examinations.	To formulate the preliminary diagnosis of diabetes mellitus and substantiate each component of it.
3	To evaluate the parameters of additional laboratory investigations.	1.To evaluate the blood and urine count data. 2. To evaluate the level of glycemia and glycosuria, oral glucose tolerance test (OGTT) . 3. To evaluate the biochemistry data of blood and urine, renal function tests. 4.To evaluate the blood hormonal profile	To pay attenttion to the signs of anemia, leucocytosis, changing of formula, elevation of sedimentation rate, glycosuria, urine ketones. To pay attention to urine glucose and blood glucouse levels. To pay attention to data of OGTT. To pay attention to cholesterol, lipids, creatinine, glomerular filtration rate , glycated hemoglobin, microalbuminuria. To pay attention to C-peptide changing.

4	To undersrtand the data of additional and laboratory investigation.	To undersrtand the data of thermography, ophthalmoscopy, rheography , vibration sensation	To pay special attention to long-term complications of diabetes mellitus.
5.	To conduct differential diagnosis.	1.Consistently to find the common signs in complaints, life and disease anamnesis, data of examination, data of laboratory and instrumental investiagtions in patient and in similar states. 2.To find differences between complaints, information of life and disease anamnesis, examination data, information about the laboratory and instrumental methods of research and in similar nosology. 3.On the basis of found the differences to exclude similar diseases from the list of possible diagnoses. 4. To conduct differenttial diagnostics according to the above mentioned algorithm among all the nosologies having the similar signs, among other diseases of thyroid gland 5.Taking into account the impossibility to exclude the diagnosis of diabetes mellitus from the list of credible diagnoses to draw a conclusion about the probability of such a diagnosis.	Special attention must be paid to differential diagnosis among the Diabetes Insipidus, renal glycosuria, transient glucosuria and hyperglycemia, renal glucosuria.
6	To formulate the clinical diagnosis.	1.To formulate the final clinical diagnosis. 2.Taking the preliminary diagnosis as a basis, additional investigations	Basing on modern classification of diabetes mellitus, formulate the diagnosis, complications of disease and the presence of

		data, conducted differential diagnosis, substantiate all the elements of the final clinical diagnosis.	concomitant diseases.
7	To prescribe treatment for patients.	1.To prescribe no medicinal treatment 2.To prescribe t medicinal treatment.	To specify the regimen and detalized diet according to a disease. Taking into account the age, severity of patient's state, the stage of disease, the presence of compli-cations and concomitant pathology, to prescribe modern medicinal treatment in accordance to the standards of diabetes mellitus therapy.

The material for the control of the secondary level of abilities and skills:

The secondary tests
1.Patient K., has been suffering from diabetes for 8 years. During the last year the dose of insulin diminished on 14 U. In the analysis of urine protein is 1,7 %, sugar 0,8 %, a lot of red corpuscles, cylinders. The diagnosis of nephrosclerosis was made. What is the reason of diminishing in insulin necessity?
    A) diminishing of contrainsular hormones activity
    B)diminishing of insulin binding to the proteins
    C)diminishing of insulin disintegration in the kidneys
    D) all indicated reasons
    E) none of the indicated reasons

2. Patient M, 12 years old, has been suffering from diabetes for 6 years. Takes insulin of «Aktrapid» 13 U + «Protophan» 14 U. In anamnesis the comatose states relapsed. He is disturbed by decrease of sight acuity, weakness and pain in the legs. On ophtalmoscopy on the eyeground the microaneurysm of vessels, hemorrhages in the retina, neovascularisation. Glucose on an empty a stomach is 9,7 mmol/l, glucosuria is 2 % (2,5 l), acetone in urine is not discovered.
 Specify the severity and the compensation of diabetes:
    A) mild form, subcompensated
    B) average severity, compensated
    C) severe, subcompensated
    D) mild form, decompensated
    E) severe form, compensated

    3. Patient M, 12 years old, has been suffering from diabetes for 6 years. He takes

insulin of «Aktrapid» 13 U + «Protophan» 14 U. In anamnesis the comatose states are relapsed. He is disturbed the decrease of sight acuty, weakness and pain in the legs. On ophtalmoscopy on the eyeground the microaneurysm of vessels, hemorrhages in the retina, neovascularisation. Glucose on an empty a stomach is 9,7 mmol/l, glucosuria is 2 % (2,5 l), acetone in urine is not discovered.
What correction of diabetes therapy will you conduct?

   A) to decrease the amount of proteins in day's ration
   B) to include biguanids in the complex of treatment
   C) to the therapy carried out to add äèöèííí
   D) to include the preparations of 1- generation sulphonurea
   E) to include the preparations of 2- generation sulphonurea

4. A child of 7 years old was hospitalized with complaints of thirst, frequent emiction, weight loss (3 kg for a month). On examination the level of glucose in the blood on an empty a stomach is 19,2 mmol/l. The diagnosis of I type diabetes was made. How is it possible to explain the decreasing of child's bodyweight ?
À) Intensifying of proteins catabolism and inhibition of its synthesis.
 B) Decreasing of lypolysis
 C) Intensifying of gluconeogenesis.
 D) Decreasing of lypolysis.
 E) Decreasing of basic exchange.

5. A girl of 12 years old, since the 2-years-old age has been suffering from diabetes. On examination: considerably enlarged stomach, liver is 6 cm below the costal arc, somewhat painful and dense; Cushing - like type of obesity, nanism. The signs of the sexual maturation are not present.Glucose in the blood is 17 mmol/l, in the urine it is 4 %. In the blood increased content of cholesterol and ketonic bodies. What is the preliminary diagnosis?

   A) 1n type diabetes, Mauriac syndrome
   B) 1 type diabetes And type, Nobecur
   C) 1 type diabetes, precomma
   D) Cushing disease
   E) Cushing syndrome

6. In the child of 9 years old diabetes was firstly found . How will skin injuries be manifested?

   A) By predilection to the purulent diseases
   B) By depigmentation
   C) By hyperpigmentattion.
   D) By development of elephantiasis
   E) By petechias

7. A child of 5 years old was first hospitalized in the depatment with a diagnosis of I type diabetes, decompensation (ketoacidosis). What is the main mechanism in the development of the disease?

   A) Insulin insufficiency.

B) Surplus of glucagon.
C) Surplus of somatostatinum.
D) Disturbancies of insulin binding to the receptors.
E) Disturbancies of postreceptor mechanisms of insulin action.

8. A child of 10 years old was hospitalized with complaints of thirst, increased emiction weight loss, weakness, languor. After clinical and laboratory investigation there was the diagnosis of 1 type diabetes in the phase of decompensation . How is it possible to explain the symptoms of poliuria in this patient ?
   A) Glucose selected with urine, operates as osmotic diuretic.
   B) Decreased production of antidiuretic hormone.
   C) Increased vasopressin production
   D) Decreased TTH production.
   E) Increased TTH production

9. A boy ill with diabetes was admitted to the induction centre of child's hospital in the severe condition. On examination the absence of consciousness was revealed.The skin is dry, pale, the turgor of skin is decreased. Hypotonus of muscles and decreased tonus of eyeballs. Mucus of lips is dry, in bright red color. Tones of heart are hyposthenic, tachycardia, low blood pressure, threadlike pulse. Breathing of Cousmaul. Strong smell of acetone midair. Specify day's dose of insulin for the acute management.
   A) 2,5 U/kg
   B) 1,5 U/kg
   C) 2,0 U/kg
   D) 1,0 U/kg
   E) 3,0 U/kg

10. A boy, 7 years old, was hospitalized with complaints on intensifying of thirst, poliuria. During the last 5 years he was ill with diabetes, in anamnesis a diabetic comma developed three times. The level of glucose in the blood is 15,54 mmol/l, in the urine is 5 %. Retinopathy was found by an oculist. What dose of insulin will most probably be prescribed to the child?
   A) 1,5 U/kg
   B) 0,25 U/kg
   C) 0,5 U/kg
   D) 1,0 U/kg
   E) 2,0 U/kg

11. What dose of insulin will most probably be prescribed to the child who has been suffering from diabetes during the last 5 years?
   A) 0,5-0,6 U/kg
   B) 0,7-0,8 U/kg
   C) 0,25 U/kg
   D) 1,0-2,0 U/kg
   E) 2,-3,0 U/kg

12.The level of albumin in urine in the case of microalbuminuria
   A) 1-10 mg/l
   B) 10-30 mg/l
   C) 30-300mg/l
   D)> 300 mg/l
   E) 0-10 mg/l

13. A child of 5 years old has been suffering from diabetes during 2 years. What is the number of BU that you will recommend?
   A) 12-13 BU
   B) 15-16 BU
   C) 16-17 BU
   D) 17-18 BU
   E) 19-21 BU

14. Which kind of insulin is short-acting?
   A) glulisine
   B) detemir
   C) isophane
   D) glargine
   E) ultralente

15. What is the dose of glucagons in the case of hypoglycemic coma for a ten-year old child ?
   A) 0,5 mg
   B) 1 mg
   C) 2 mg
   D) 5 mg
   E) 15 mg

16. What is the normal level of glycosylated hemoglobin ?
   A) 5-7 %
   B) 10%
   C) 10-15%
   D) 20%
   E) 20-25%

17. Refined carbohydrates in dietary management for children with diabetes mellitus should provide less than …..
   A) 10%
   B) 20%
   C) 30%
   D) 40%
   E) 50%

18. How is it possible to explain the appearance of acetone midair and urine ?
    A) By the increased disintegration of ketogenic amino acids and lipids.
    B) By the disturbance of water - electrolyte balance.

C) By the disturbance of acid - alkaline balance.
D) By the disturbance of glucose phosphorylating processes.
E) By the decreasing of glycolys.

19.The peak activity of Protamine zinc (Ultralente) insulin is…
   A) 1-2 h
   B) 3-4 h
   C) 4-8 h
   D) 10 h
   E) 24 h

20.Treatment of diabetic nephropathy and hypertension includes
   A) angiotensin-converting enzyme inhibitors
   B) blood pressure control.
   C) diabetes control
   D) Angiotensin type 1 blockers
   E) All listed above

Answers: 1-D, 2-C, 3-B, 4-A, 5-A,B, 6-A, 7-A, 8-A, 9-D,10-A,11-B, 12-C, 13-A, 14-A, 15-B, 16-A, 17-A, 18-A, 19-C, 20-E.

Materials of the medical support for the students independent training: a reference chart for organization of students independent work with educational literature.

Tasks	Instructions
To study the pathogenesis of diabetes mellitus in children.	Select the key links of diabetes mellitus pathogenesis type 1
To study the clinical manifestations of diabetes mellitus in children.	To establish the symptoms and gather it to clinical syndromes which enable to make the credible diagnosis of diabetes mellitus.
To study the clinical manifestations of complications of diabetes mellitus in children.	To establish the symptoms and gather it to the clinical syndromes which enable to make the credible diagnosis of complications of diabetes mellitus
To study diagnostic criteria of diabetes mellitus	To make a structural plan of disease
To study the additional methods of research (laboratory, instrumental)	To work out a plan of patient's examination.
To study the changes in additional investigational methods which are pathognomonic for diabetes mellitus and its complications.	To enumerate the basic diagnostic criteria of diabetes mellitus according to the data of additional investigational methods.
To conduct differential diagnostics, to establish a final diagnosis	To substantiate the basic components of diagnosis in accordance with modern classification, and to conduct a

	differential diagnosis.
To prescribe the individual treatment to patient with the diabetes mellitus type 1. To render the first aid in extreme situations: hyperglycemic, hypoglycemic, hyperosmolar, hyperlactacidemic, ketoacidosis coma.	To make the prescribing chart specifying the regimen, diet, medicinal treatment, taking into account the age, severity of patient's state, stage of disease, presence of complications and concomitant diseases.

Basic literature:

1.Nelson Textbook of Pediatrics, ed 16.2000.

2.Bode BW (Ed.): Medical Management of Type 1 Diabetes. 4th ed. Alexandria, VA, American Diabetes Association, 2004

3.Сахарный диабет и его осложнения у детей и подростков : Монография/ Н.В. Филиппова Е.А. и др.-Харьков: Основа 2005-300с.

4.Касаткина Э.Н. Сахарный диабет у детей.-М.:Медицина, 1990-272с.

Additional literature:

1.Klingensmith GJ (Ed.): Intensive Diabetes Management. 3rd ed. Alexandria, VA, American Diabetes Association, 2003

2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 26:3160–3167, 2003

Theme 5. Thyroid gland diseases in children.

Classification of thyroid diseases in children. Etiology, pathogenesis, clinical presentation, diagnostics, differential diagnostics, treatment, prophylaxis of diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, endemic goiter, acute and subacute thyroiditis, diffuse untoxic goiter, thyroid cancer in children. Degrees of goiter. Emergency in thyroid crisis. Prognosis.

I. Actuality of the theme.

Thyroid functions disturbances is the common state among children. Thyroid diseases is quite various in children age. Thyroid diseases problems are the main relating to Chernobyl disaster because of morbidity increasing among children in autoimmune thyroiditis, hypothyroidism, good-quality and malignant tumors of thyroid. One of major places occupies congenital hypothyroidism that meets in frequency of 1 case to 5000 newborns. Congenital hypothyroidism in 85 – 90% of cases is primary and related to the iodine deficit or thyroid dysgenesis. Thus, the aplasia, hypogenesis or dystopia of thyroid are the more frequent states. Primary hypothyroidism in 5 – 10% of cases unconditioned by dyshormonose (autosomal – recessive inheritance). Congenital hypothyroidism is the second or tertiary (pathology of hypophysis or hypothalamus) and meets no more than in 3 – 4% of cases. Congenital hypothyroidism leads to the mental and physical development retardation and psychical inability of children, that is why the early diagnosis is very important.

Concrete purposes:

1. To determine the etiologic and pathogenetic factors in diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, endemic goiter, acute and subacute thyroiditis, diffuse untoxic goiter, thyroid cancer in children

2. To classify and analyse the typical clinical manifestation of diffuse toxic goiter, thyroiditis, autoimmune thyroiditis, endemic goiter, acute and subacute thyroiditis, diffuse untoxic goiter, thyroid cancer in children. To determine the features of congenital hypothyroidism for newborns and children and put a preliminary clinical diagnosis.

3. To make the plan of examination and to analyse the information about laboratory and instrumental data in the classic course of diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, and endemic goiter in children.

4. To demonstrate skills of treatment, rehabilitation and prophylaxis in diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, endemic goiter in children.

5. To diagnose and render an urgent help in thyrotoxic crisis and hypothyroid coma in children.

6. To conduct differential diagnostics of diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, endemic goiter, acute and subacute thyroiditis, diffuse untoxic goiter, thyroid cancer in children and put a preliminary diagnosis.

7. To determine the prognosis for life in diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis and endemic goiter in children.

8. To demonstrate the skills of medical specialist's moral and deontological principles and principles of professional subordination in pediatrics.

II. Classes (pointing of planned mastering level)

1. A student must have a conception (familiarize): α1

- The place of thyroid diseases in the structure of endocrine system diseases in children, widespread in different age-dependent and ethnic groups;

- Statistical information in relation to morbidity, frequency of complications, lethality, the nearest and remote prognosis in patients with the diseases of thyroid gland;

- The history of scientific studying and the contribution of domestic scientists;

2. A student must know (master): α2

- etiology of diffuse toxic goiter, thyroiditis, autoimmune thyroiditis, endemic goiter, acute and subacute thyroiditis, diffuse untoxic goiter, thyroid cancer in children.

- key links of thyroid diseases pathogenesis ;

- clinical classification of thyroid diseases;

- degrees of goiter;

- classical clinical manifestation of hypothyroidism;

- classical clinical manifestation of diffuse toxic goiter;

- classical clinical manifestation of autoimmune thyroiditis;

- classical clinical manifestation of endemic goiter;

- classical clinical manifestation of diffuse untoxic goiter;

- laboratory diagnosis of hypothyreodism and hyperthyroidism;

- laboratory and instrumental diagnosis of thyroid diseases;

- complications of diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, endemic goiter in children.

- treatment principles of diffuse toxic goiter, congenital hypothyroidism, autoimmune thyroiditis, diffuse untoxic goiter in children.

3. A student must master: α3

Skills:

- Collection of complaints and anamnesis of disease;

- Examination of patient with thyroid diseases and revealing the main symptoms and syndromes.

- To formulate and substantiate the preliminary diagnosis;

-Determination of laboratory and instrumental inspection plan of patient's examination (according to diagnostics' standards);

Abilities:

- To interpret the results of laboratory and instrumental tests.

- To conduct differential diagnosis among acute and subacute thyroiditis, thyroid cancer, to diagnose thyrotoxic crisis and hypothyroid coma are required for emergencies.

- To conduct differential diagnosis with thyroid cancer.

- To give recommendations in relation to the patient's regimen and diet with diseases of thyroid gland, taking into account the stage of the disease, severity of the state and concomitant pathology;

- To complete the treatment plan in thyroid diseases according to the standards taking into account the stage of the disease, complications and concomitant pathology.

- To render the first aid in extreme situations and exigent states.

III. Aims of personality development (educative aims):

- A student must learn to adhere rules of behaviour and principles of medical etiquette and deontology, to develop bedside manner;

- Be able to set a psychological contact with a patient and his family;

- To master the sense of professional responsibility for a timely and adequate medicare.

IV. Interdisciplinary integration:

Subject	To know	To be able
1. Basic		
Human anatomy	Structure of human endocrine system, of thyroid gland , their circulation and innervation.	To determine the location of thyroid projection and palpation, of local lymphatic nodes.
Histology	Structure of thyroid gland vessel system.	
Physiology	Normal physiology of human endocrine system, normative indices of laboratory and instrumental investigational methods and their assessment.	To assess the data of laboratory and instrumental investigational methods and thyroid gland function.
Physiopathology	Key links of pathogenesis of thyroid gland diseases, of hypothyroidism and hyperthyroidism	To estimate the function of thyroid gland and other organs of the endocrine system
Pathologic anatomy	Morphological features of thyroid gland diseases development depending of the stage of the disease .	To analyse and interpret the information about clinical examination and about additional methods of investigation
Pharmacology	Pharmacokinetics and	To prescribe age- dependent

	pharmacodynamics, the side effects of preparations (thyroid hormones preparations, thyroidostatics, antibiotics, antiinflammatory drugs etc.)	treatment of patient, taking into account individual features and period of disease, to establish the individual regimen of preparations taking and dosage. To be able to make a prescription.
Propedeutics of pediatrics.	Basic stages and methods of patient clinical examination	To collect complaints, anamnesis vitae et morbi, to find out the basic risk factors of thyroid diseases, to be able to conduct patient's examination, to reveal the clinical signs of thyroid gland diseases, to interpret the data of additional methods of investigation.
Radiology	Normal parameters of ultrasound and radionuclide diagnostics in thyroid gland diseases.	To interpret the data of ultrasound and radionuclide diagnostics
2. Followings (provided)		
Hospital pediatrics.	Clinical signs of thyroid gland diseases, differential diagnosis and treatment tactics.	To reveal the clinical signs of thyroid gland disease and complications, to conduct differential diagnosis, to be able to prescribe treatment.
3. Interdisciplinary integration		
Acute and subacute thyreoiditis	Clinical manifestation of acute and subacute thyroiditis.	To establish specific clinical signs of acute and subacute thyroiditis and to conduct differential diagnosis to other thyroid diseases and acute lymphadenitis.
Thyroid cancer	Clinical manifestation of thyroid cancer	To establish specific clinical signs of thyroid cancer and to conduct differential diagnosis among other manifestattions of thyroid diseases

V. Contents of the theme

THYROID PHYSIOLOGY. The main function of the thyroid gland is to synthesize thyroxine (T4) and 3,5,3ŕ{prime}-triiodothyronine (T3). The only known physiologic role of iodine is in the synthesis of these hormones; the recommended dietary allowance of iodine is 40–50 m{mu}g/24 hr for infants, 70–120 m{mu}g/24 hr for children, and 150 m{mu}g/24 hr for adolescents and adults. The daily intake in North America varies from 240 to more than 700 m{mu}g. Whatever the chemical form ingested, iodine eventually reaches the thyroid gland as iodide. Thyroid tissue

has an avidity for iodine and is able to trap (with a gradient of 100:1), transport, and concentrate it in the follicular lumen for synthesis of thyroid hormone.

Before trapped iodide can react with tyrosine, it must be oxidized; this reaction is catalyzed by thyroidal peroxidase. The thyroid cells also elaborate a specific thyroprotein, a globulin with approximately 120 tyrosine units. Iodination of tyrosine forms monoiodotyrosine and diiodotyrosine; two molecules of diiodotyrosine then couple to form one molecule of T4, or one molecule of diiodotyrosine and one of monoiodotyrosine to form T3. Once formed, hormones are stored as thyroglobulin in the lumen of the follicle (colloid) until ready to be delivered to the body cells. Thyroglobulin is a large globular glycoprotein with a molecular weight of about 660,000 and under normal conditions is detectable in the blood of most individuals at nanogram levels. T4 and T3 are liberated from thyroglobulin by activation of proteases and peptidases.

The metabolic potency of T3 is 3–4 times that of T4. In adults, the thyroid produces approximately 100 m{mu}g of T4 and 20 m{mu}g of T3 daily. Only 20% of circulating T3 is secreted by the thyroid; the remainder is produced by deiodination of T4 in the liver, kidney, and other peripheral tissues by type I 5г{prime}-deiodinase. In the pituitary and brain, approximately 80% of required T3 is produced in situ from T4 by a different enzyme, type II 5г{prime}-deiodinase. In the fetal rat, although plasma levels of T3 are very low, cerebral concentrations increase to almost adult levels. T3 carries out most of the physiologic actions of the thyroid hormones. T4 is more abundant, but it binds weakly to nuclear receptors, and most of its physiologic effects occur by conversion to T3. The level of T3 in blood is 1/50 that of T4.

The thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate, lipid, and vitamin metabolism. The free hormones enter cells, where T4 may be converted to T3 by deiodination. Intracellular T3 then enters the nucleus, where it binds to thyroid hormone receptors. Thyroid hormone receptors are members of the steroid hormone receptor superfamily that includes glucocorticoids, estrogen, progesterone, vitamin D, and retinoids. Four different isoforms of the thyroid hormone receptor (α1 and 2, β 1 and 2) are expressed in different tissues; the protein product of the formerly designated c-erb A proto-oncogene (now called THRA2) has been identified as the a2 thyroid hormone receptor in the brain and hypothalamus. Thyroid hormone receptors consist of a ligand-binding domain (binds T3), hinge region, and DNA-binding domain (zinc finger). Binding of T3 activates the thyroid hormone receptor response element, resulting in production of an encoded mRNA and protein synthesis and of secretion specific for the target cell. In this manner, a single hormone, T4, acting through tissue-specific thyroid hormone receptor isoforms and gene-specific thyroid

response elements, can produce multiple effects in various tissues.

About 70% of the circulating T4 is firmly bound to thyroxine-binding globulin (TBG). Less important carriers are thyroxine-binding prealbumin, now named transthyretin (TTR), and albumin. Only 0.03% of T4 in serum is not bound and comprises free thyroxine (FT4). Approximately 50% of circulating T3 is bound to TBG, and 50% is bound to albumin; 0.30% of T3 is unbound or free T3. Because the concentration of TBG is altered in many clinical circumstances, its status must be considered when interpreting T4 or T3 levels.

The thyroid is regulated by thyroid-stimulating hormone (TSH), a glycoprotein produced and secreted by the anterior pituitary. This hormone activates adenylate cyclase in the thyroid gland to effect release of thyroid hormones. TSH is composed of two noncovalently bound subunits (chains): a and b (hTSH-b). The a subunit is common to luteinizing hormone, follicle-stimulating hormone, and chorionic gonadotropin; the specificity of each hormone is conferred by the b subunit. TSH synthesis and release are stimulated by TSH-releasing hormone (TRH), which is synthesized in the hypothalamus and secreted into the pituitary. TRH is found in other parts of the brain besides the hypothalamus and in many other organs; aside from its endocrine function, it seems to serve as a neurotransmitter. TRH, a simple tripeptide, was the first neuropeptide to be identified, synthesized, and used in clinical medicine. In states of decreased production of thyroid hormone, TSH and TRH are increased. An excess of TRH or of TSH results in hypertrophy and hyperplasia of thyroid cells, increased trapping of iodine, and increased synthesis of thyroid hormones. Exogenous thyroid hormone or increased thyroid hormone synthesis inhibits TSH and TRH production. Except in the neonate, levels of TRH in serum are very low.

Further control of the level of circulating thyroid hormones occurs in the periphery. In many nonthyroidal illnesses extrathyroidal production of T3 decreases; factors that inhibit thyroxine-5ŕ{prime}-deiodinase include fasting, chronic malnutrition, acute illness, and certain drugs. Levels of T3 may be significantly decreased while levels of T4 and TSH remain normal. Presumably, the decreased levels of T3 result in decreased rates of oxygen production, of substrate use, and of other catabolic processes.

THYROID HORMONE STUDIES

SERUM THYROID HORMONES. Methods are available to measure all of the thyroid hormones in sera: thyroxine (T4), free T4, triiodothyronine (T3), free T3, and the diiodothyronines. A metabolically inert T3 (3,5ŕ{prime},3ŕ{prime}-triiodothyronine), called reverse T3, is also present in sera. Age must be considered in interpreting results, particularly in the neonate.

Thyroglobulin (Tg) is a glycoprotein dimer that is secreted through the apical

surface of the thyrocyte into the colloid. Small amounts escape into the circulation and are measurable in serum. Levels increase with thyroid-stimulating hormone (TSH, also called thyrotropin) stimulation and decrease with TSH suppression. Levels are increased in the neonate, in patients with Graves disease, and in those with endemic goiter. The most marked elevations of Tg occur in patients with differentiated carcinoma of the thyroid. Athyreotic infants may have markedly reduced levels of Tg in serum.

TSH levels in serum are an extremely sensitive indicator of primary hypothyroidism. Radioimmunoassay methods for the measurement of serum levels of TSH have been replaced by immunometric assay methods, which are capable of quantitating the lower limits of normal as well as elevated levels. A 3rd generation of assays (chemiluminescent assays) that can measure complete suppression of TSH is now standard. These sensitive TSH assays obviate the need for thyrotropin-releasing hormone (TRH) stimulation in the diagnosis of most patients with thyroid disorders.

After the neonatal period, normal levels of TSH are below 6 m{mu}U/mL. TSH secretion can be stimulated by intravenous administration (7 m{mu}g/kg) of TRH. In normal subjects, TRH administration increases baseline levels of TSH within 30 min. In hyperthyroidism, there is no rise in serum levels of TSH in response to TRH because the elevated levels of thyroid hormones block the effect of TRH on the pituitary. In patients with even very mild degrees of thyroid failure, administration of TRH results in an exaggerated TSH response. Patients with pituitary or hypothalamic failure have low basal levels of TSH, although it may not be below the lower range of normal; a normal response to TRH localizes the defect in the hypothalamus.

FETAL AND NEWBORN THYROID. The fetal hypothalamic-pituitary-thyroid system develops independently of maternal influence. By 10–12 wk of gestation, the fetal thyroid is able to concentrate iodine and to synthesize iodothyronines. By the same time, the fetal pituitary contains TSH. Fetal serum T4 increases progressively from midgestation to approximately 11.5 m{mu}g/dL at term. Fetal levels of T3 are low before 20 wk and then gradually rise to about 60 ng/dL at term. Reverse T3 levels, however, are very high in the fetus (250 ng/dL at 30 wk) and fall to 150 ng/dL at term. Serum levels of TSH gradually rise to 10 m{mu}U/mL at term. Approximately one third of maternal T4 crosses the placenta to the fetus. Maternal T4 may play a role in fetal development, especially that of the brain, before the synthesis of fetal thyroid hormones begins. The fetus of a hypothyroid mother may be at risk for neurologic damage, and a hypothyroid fetus may be partially protected by maternal T4 until delivery.

At birth, there is an acute release of TSH; peak serum concentrations reach 70 m{mu}U/mL in 30 min in full-term infants. A rapid decline occurs in the ensuing 24 hr and a more gradual decline within the next 2 days to below 10 m{mu}U/mL. The

acute increase in TSH produces a dramatic rise in levels of T4 to approximately 16 m{mu}g/dL and of T3 to approximately 300 ng/dL in about 4 hr. This T3 seems largely derived from increased peripheral conversion of T4 to T3. T4 levels gradually fall during the first 2 wk of life to 12 m{mu}g/dL. T3 levels then decline during the 1st wk of life to levels under 200 ng/mL. Reverse T3 levels are maintained for 2 wk (200 ng/dL) and fall by 4 wk to around 50 ng/dL. Small amounts of T4 cross the placenta but are not sufficient to interfere with a diagnosis of congenital hypothyroidism in the neonate.

SERUM THYROXINE-BINDING GLOBULIN. The thyroid hormones are transported in plasma bound to thyroxine-binding globulin (TBG), a glycoprotein synthesized in the liver. Estimation of TBG levels is occasionally necessary because TBG is increased or decreased in a variety of clinical situations, with effects on the level of thyroxine. TBG binds about 70% of T4 and 50% of T3. TBG levels increase in pregnancy and in the newborn period, and with administration of estrogens (oral contraceptives), perphenazine, and heroin and decrease with androgens, anabolic steroids, glucocorticoids, and L-asparaginase. These effects are the results of modulation of hepatic synthesis of TBG. Phenytoin (diphenylhydantoin) is another cause of drug-induced abnormality of thyroid function tests. Phenytoin, an inducer of hepatic enzymes, stimulates hepatic degradation of T4 and accelerates transport of T4 into tissues. Phenobarbital has a similar effect. Some drugs, particularly phenytoin, also inhibit binding of T4 and T3 to TBG. Decreased or increased levels of TBG also occur as genetic traits (see later). TBG levels may be markedly decreased owing to loss in the urine, as in infants with congenital nephrotic syndrome.

The most commonly used measures of TBG or TBG-binding capacity are variations of the resin triiodothyronine uptake test (RT3U), a test that allows interpretation of T4 results, which vary depending on TBG levels; it should never be used as an autonomous test of thyroid function. The product of the serum T4 concentration and T3 uptake (thyroxine-resin T3 index or T4-RT3U index) correlates closely with free T4 concentration in serum. This index increases in hyperthyroidism, decreases in hypothyroidism, and is normal in euthyroid patients with mild abnormalities in the concentration of TBG. Normal values for the index vary among laboratories because T4 levels and T3 uptakes are often determined by a variety of kit methods and calculations and expressions of the index vary among laboratories. A radioimmunoassay method for TBG is available.

IN VIVO RADIONUCLIDE STUDIES. Markedly improved direct tests of thyroid function have made radioiodine uptake studies less useful. The iodine-trapping or concentrating mechanism of the thyroid can be evaluated by the radioactive isotope 123I (half-life of 13 hr). The technology allows doses of radioiodine (0.1–0.5 m{mu}Ci) that are only a fraction of those formerly used.

Technetium (99mTc) is a particularly useful radioisotope for children, because in contrast to iodine, it is trapped but not organified by the thyroid and has a half-life of only 6 hr. Thyroid scanning may be indicated to detect ectopic thyroid tissue, to evaluate thyroid nodules, or to assess the presence of thyroid tissue in questions of thyroid agenesis. These studies should be performed with 99mTc as pertechnetate because it has the advantages of lower radiation exposure and high-quality scintigrams. Use of 131I in children should be limited to those known to have thyroid cancer.

DEFECTS OF THYROXINE-BINDING GLOBULIN

Angelo M. DiGeorge and Stephen LaFranchi

Abnormalities in levels of thyroxine-binding globulin (TBG) are not associated with clinical disease and do not require treatment. They are usually uncovered by a chance finding of abnormally low or high levels of thyroxine (T4) and may be sources of confusion in the diagnosis of hypo- or hyperthyroidism.

TBG deficiency occurs as an X-linked dominant disorder. Congenital TBG deficiency is most often discovered through screening programs for neonatal hypothyroidism that use levels of T4 as the primary screen. Affected patients have low levels of T4 and elevated resin triiodothyronine uptake (RT3U), but levels of free T4 and thyroid-stimulating hormone (TSH) are normal. The diagnosis is confirmed by the finding of absent or low levels of TBG by radioimmunoassay. The disorder is more readily recognized in males because it is caused by a gene on the short arm of the X chromosome. TBG deficiency occurs in 1 in 2,400 newborn males, of whom 36% have TBG levels below 1 mg/L. Milder forms of TBG deficiency occur in approximately 1 of 42,000 heterozygous females. Complete TBG deficiency (<5 m{mu}g/L) occurs much less frequently. Three of eight families with complete TBG deficiency have been found to have a codon mutation (leucine to proline); other patients with reduced affinity of TBG for T4 have had other point mutations that affect the tertiary structure of the protein.

Elevated TBG is also a harmless X-linked dominant anomaly, occurring in about 1 of 2,500 persons. It has been recognized primarily in adults, but neonatal screening programs are uncovering the condition in the neonate. The level of T4 is elevated, T3 is variably elevated, TSH and free T4 are normal, and RT3U is decreased. The elevated levels of TBG and normal levels of free T4 confirm the diagnosis. In neonates, levels of T4 as high as 95 m{mu}g/dL have been found, which decrease to 20–30 m{mu}g/dL after 2–3 wk. Such high levels of T4 are thought to be related in part to the normally elevated levels of TBG in neonates during the 1st mo of life, presumably as an effect of maternal estrogens. Affected patients are euthyroid. Family studies may be indicated to alert other affected individuals. Acquired elevations of TBG occur with pregnancy, estrogen treatment, and hepatitis.

Familial dysalbuminemic hyperthyroxinemia is an autosomal dominant disorder that may be confused with hyperthyroidism. Markedly increased binding of T4 to an abnormal albumin variant leads to increased serum concentrations of T4. However, the levels of free T4, free T3, and TSH are normal. Levels of T3 are normal or only slightly elevated. Affected patients are euthyroid.

HYPOTHYROIDISM

Hypothyroidism results from deficient production of thyroid hormone or a defect in its receptor. The disorder may be manifest from birth. When symptoms appear after a period of apparently normal thyroid function, the disorder may be truly "acquired" or may only appear so as a result of one of a variety of congenital defects in which the manifestation of the deficiency is delayed. The term cretinism is often used synonymously with congenital hypothyroidism but should be avoided.

CONGENITAL HYPOTHYROIDISM

Congenital causes of hypothyroidism may be sporadic or familial, goitrous or nongoitrous. In many cases, the deficiency of thyroid hormone is severe, and symptoms develop in the early weeks of life. In others, lesser degrees of deficiency occur, and manifestations may be delayed for months or years.

ETIOLOGY. Thyroid Dysgenesis. Since the establishment of nationwide programs for neonatal screening for congenital hypothyroidism, many millions of neonates have been screened. The prevalence of congenital hypothyroidism has been found to be 1 in 4,000 infants worldwide, lower in black Americans (1 of 20,000) and higher in Hispanics and Native Americans (1 of 2,000). Developmental defects (thyroid dysgenesis) account for 90% of infants in whom hypothyroidism is detected; in about one third, even sensitive radionuclide scans can find no remnants of thyroid tissue (aplasia). In the other two thirds of infants, rudiments of thyroid tissue are found in an ectopic location, anywhere from the base of the tongue (lingual thyroid) to the normal position in the neck. Most infants with congenital hypothyroidism are asymptomatic at birth even if there is complete agenesis of the thyroid gland. This situation is attributed to the transplacental passage of moderate amounts of maternal thyroxine (T4), which provides fetal levels that are 25–50% of normal at birth. These low serum levels of T4 and concomitantly elevated levels of thyroid-stimulating hormone (TSH) make it possible to screen and detect most hypothyroid neonates.

Little is known about the factors that interfere with the normal migration and development of the thyroid gland. Thyroid dysgenesis occurs sporadically, but familial cases have occasionally been reported. Twice as many females as males are affected. The frequent finding of thyroid dysgenesis confined to only one of a pair of monozygotic twins suggests the operation of a deleterious factor during intrauterine life. For years, it had been proposed that maternal antithyroid antibodies might be that

factor, especially because antibodies in patients with autoimmune thyroid disease belong predominantly to the IgG class and can cross the placenta. Although thyroid antimicrosomal antibodies have been detected in some mother-infant pairs, there is little evidence of their pathogenicity. The demonstration of thyroid growth-blocking and cytotoxic antibodies in some infants with thyroid dysgenesis and in their mothers suggests a more likely pathogenetic mechanism. Maternal TSH-binding antibodies as a cause of transient congenital hypothyroidism and of neonatal Graves disease are well established.

Ectopic thyroid tissue (lingual, sublingual, subhyoid) may provide adequate amounts of thyroid hormone for many years or may fail in early childhood. Affected children come to clinical attention because of a growing mass at the base of the tongue or in the midline of the neck, usually at the level of the hyoid. Occasionally, ectopia is associated with thyroglossal duct cysts. It may occur in siblings. Surgical removal of ectopic thyroid tissue from a euthyroid individual usually results in hypothyroidism, because most such patients have no other thyroid tissue. Newborn screening programs may detect these patients and obviate delayed diagnosis.

Thyrotropin Receptor–Blocking Antibody (TRBAb). TRBAb was formerly called thyroid-binding inhibitor immunoglobulin (TBII). An unusual cause of transitory congenital hypothyroidism is the transplacental passage of maternal antibodies that inhibit binding of TSH to its receptor in the neonate. The frequency is approximately 1 of 50,000–100,000 infants. It should be suspected whenever there is a history of maternal autoimmune thyroid disease, including Hashimoto thyroiditis, Graves disease, hypothyroidism on replacement therapy, or recurrent congenital hypothyroidism of a transient nature in subsequent siblings. In these situations, maternal levels of TRBAb should be measured during pregnancy. Affected infants and their mothers often also have thyrotropin receptor–stimulating antibodies (TRSAb) and antiperoxidase (formerly antimicrosomal) antibodies. Technetium pertechnetate and 125I scans may fail to detect any thyroid tissue, mimicking thyroid agenesis, but after the condition remits, a normal thyroid gland is demonstrable after discontinuation of replacement treatment. The half-life of the antibody is 7.5 days, and remission of the hypothyroidism occurs in about 3 mo. Correct diagnosis of this cause of congenital hypothyroidism prevents protracted unnecessary treatment, alerts the clinician to possible recurrences in future pregnancies, and allows the offering of a favorable prognosis to the parents.

Defective Synthesis of Thyroxine. A variety of defects in the biosynthesis of thyroid hormone may result in congenital hypothyroidism; when the defect is incomplete, compensation occurs, and onset of hypothyroidism may be delayed for years. A goiter is almost always present, and the defect is detected in 1 in 30,000–50,000 live births in neonatal screening programs. These defects are genetically

determined and are transmitted in an autosomal recessive manner.

DEFECT OF IODIDE TRANSPORT. This rare defect has been reported in nine related infants of the Hutterite sect, and about half the cases are from Japan. Consanguinity has occurred in about one third of the families. In the past, clinical hypothyroidism with or without a goiter often developed in the first few months of life, but in recent years, the condition has been detected in neonatal screening programs. In Japan, however, untreated patients develop goiter and hypothyroidism after 10 yr of age, perhaps because of the very high iodine content (often 19 mg/24 hr) of the Japanese diet.

The energy-dependent mechanisms for concentrating iodide are defective in the thyroid and in the salivary glands. In contrast to other defects of thyroid hormone synthesis, uptake of radioiodine and pertechnetate is low; a saliva:serum ratio of 123I may be required to establish the diagnosis. This condition responds to treatment with large doses of potassium iodide, but treatment with thyroxine is preferable.

THYROID PEROXIDASE DEFECTS OF ORGANIFICATION AND COUPLING. This is the most common of the thyroxine synthetic defects. After iodide is trapped by the thyroid, it is rapidly oxidized to reactive iodine, which is then incorporated into tyrosine units. This process requires generation of H_2O_2, thyroid peroxidase, and hematin (an enzyme cofactor); defects can involve each of these components, and there is considerable clinical and biochemical heterogeneity. In the Dutch neonatal screening program 23 infants have been found with a complete organification defect (1 of 60,000), but its prevalence in other areas is unknown. A characteristic finding in all patients with this defect is a marked decrease in thyroid radioactivity when perchlorate or thiocyanate is administered 2 hr after administration of a test dose of radioiodine. In these patients, perchlorate discharges 40–90% of radioiodine compared with less than 10% in normal individuals. Several mutations in the TPO gene have been reported in children with congenital hypothyroidism. Patients with Pendred syndrome, a disorder comprising sensorineural deafness and goiter, also have a positive perchlorate discharge, but the precise biochemical defect in these people is unknown.

DEFECTS OF THYROGLOBULIN SYNTHESIS. This heterogeneous group of disorders, characterized by goiter, elevated TSH, low T4 levels, and absent or low levels of thyroglobulin (Tg), has been reported in 89 patients. Studies in animal models with congenital goiter have disclosed point mutations of the gene for Tg in Afrikander cattle and in Dutch goitrous goats. Analogous molecular defects have been described in a few patients.

DEFECTS IN DEIODINATION. Monoiodotyrosine and diiodotyrosine released from thyroglobulin are normally deiodinated within the thyroid or in peripheral tissues by a deiodinase. The liberated iodine is reused in the synthesis of Tg. Patients

with a deficiency of this enzyme develop severe iodine loss from the constant urinary excretion of nondeiodinated tyrosines, leading to hormonal deficiency and goiter. The deiodination defect may be limited to thyroid tissue only or to peripheral tissue only, or it may be universal.

Radioiodine. Hypothyroidism has been reported as a result of inadvertent administration of radioiodine during pregnancy for treatment of cancer of the thyroid or of hyperthyroidism. Although only a few affected infants have been reported, a 1976 mail survey of endocrinologists uncovered 237 women who had inadvertently received therapeutic doses of 131I during the 1st trimester of pregnancy. The fetal thyroid is capable of trapping iodide by 70–75 days. Whenever radioiodine is administered to a woman of child-bearing age, a pregnancy test must be performed before a therapeutic dose of 131I is given, regardless of the menstrual history or putative history of contraception. Administration of radioactive iodine to lactating women is also contraindicated because it is readily excreted in milk.

Thyrotropin Deficiency. Deficiency of TSH and hypothyroidism may occur in any of the conditions associated with developmental defects of the pituitary or hypothalamus (see Chapter 512). More often in these conditions, the deficiency of TSH is secondary to a deficiency of thyrotropin-releasing hormone (TRH). TSH-deficient hypothyroidism is found in 1 of 30,000–50,000 infants, but only 30–40% of these are detected by neonatal thyroid screening. The majority of affected infants have multiple pituitary deficiencies and present with hypoglycemia, persistent jaundice, and micropenis in association with septo-optic dysplasia, midline cleft lip, midface hypoplasia, and other midline facial anomalies.

Pit-1 mutations are a recessive cause of hypothyroidism secondary to TSH deficiency. Affected children also have deficiency of growth hormone and prolactin. Pit-1, a tissue transcription factor, is essential to differentiation, maintenance, and proliferation of somatotrophs, lactotrophs, and thyrotrophs. Examination of prolactin and TSH responses to TRH stimulation can detect these patients. Failure of the prolactin response to TRH should prompt examination of the Pit-1 gene.

A mutation in the TSH-receptor (TSHR) gene has been reported in three siblings with elevated levels of TSH and normal levels of T4; two of them had been detected during neonatal screening. Despite persistent resistance to TSH through childhood, they remained euthyroid without treatment. Patients in three other reports of presumed TSHR mutations had severe hypothyroidism which required treatment. The disorder is inherited in an autosomal recessive fashion.

Isolated deficiency of TSH is a rare autosomal recessive disorder that has been reported in five sibships. DNA studies in two Japanese children and in three children in two related Greek families have revealed different point mutations in the TSH b{beta}-subunit gene.

Thyrotropin Hormone Unresponsiveness. Mild congenital hypothyroidism has been detected in newborn infants who subsequently proved to have type Ia pseudohypoparathyroidism. The molecular cause of resistance to TSH in these patients is the generalized impairment of cAMP activation caused by genetic deficiency of the α subunit of the guanine nucleotide regulatory protein, Gsa α/

Only five instances of isolated TSH unresponsiveness have been detected. Serum levels of T4 were low, those of TSH by radioimmunoassay and bioassay were elevated, and there was no response to exogenous TSH administration.

Thyroid Hormone Unresponsiveness. An increasing number of patients are being found who have resistance to the actions of endogenous and exogenous T4 and T3. Most patients have a goiter, and levels of T4, T3, free T4, and free T3 are elevated. These findings have often led to the erroneous diagnosis of Graves disease, although most affected patients are clinically euthyroid. The unresponsiveness may vary among tissues. There may be subtle clinical features of hypothyroidism, including mild mental retardation, growth retardation, and delayed skeletal maturation. One neurologic manifestation is an increased association of attention-deficit hyperactivity disorder (ADHD); the converse is not true, however, because individuals with ADHD do not have an increased risk of thyroid hormone resistance. It is presumed that these patients have incomplete resistance to thyroid hormone. TSH levels are diagnostic in that they are not suppressed as in Graves disease but instead are moderately elevated or normal but inappropriate for the levels of T4 and T3 when measured by a sensitive TSH assay. A TSH response to TRH occurs in these patients, unlike the situation in Graves disease. The failure of TSH suppression indicates that the resistance is generalized and affects the pituitary gland as well as peripheral tissues. The disorder is most often inherited in an autosomal dominant fashion. More than 40 distinct point mutations in the hormone-binding domain of the b-thyroid receptor have been identified. Different phenotypes do not correlate with genotypes. The same mutation has been observed in individuals with generalized or pituitary resistance, even in different individuals of the same family. Individuals heterozygous for a complete deletion of one hTRb β allele are normal; a child homozygous for the receptor mutation showed unusually severe resistance. These cases support the dominant negative effect of mutant receptors, in which the mutant receptor protein inhibits normal receptor action in heterozygotes. Elevated levels of T4 on neonatal thyroid screening should suggest the possibility of this diagnosis. No treatment is usually required unless growth and skeletal retardation are present.

Two infants of consanguineous matings are known to have an autosomal recessive form of thyroid resistance. These infants had manifestations of hypothyroidism early in life, and DNA studies revealed a major deletion of the β-thyroid receptor in one individual. The resistance appears to be more severe in this

form of the entity.

On rare occasions, resistance to thyroid hormone may selectively affect the pituitary gland. Because the peripheral tissues are not resistant to thyroid hormones, the patient presents with a goiter and manifestations of hyperthyroidism. The laboratory findings are the same as those seen with generalized thyroid hormone resistance. This condition must be differentiated from a pituitary TSH-secreting tumor. At least one young child has been successfully treated with D-thyroxine therapy.

Other Causes of Hypothyroidism. Congenital hypothyroidism may result from fetal exposure to excessive iodides or antithyroid drugs. This condition is transitory and must not be mistaken for the other forms of hypothyroidism described. In the neonate, topical iodine-containing antiseptics used in nurseries and by surgeons can also cause transient congenital hypothyroidism, especially in low-birthweight infants, and can lead to abnormal results on neonatal screening tests. In older children, the usual sources of iodides are proprietary preparations used to treat asthma. In a few instances, the cause of hypothyroidism was amiodarone, an antiarrhythmic drug with a high iodine content. In most of these instances a goiter is present .

CLINICAL MANIFESTATIONS. The clinician is becoming increasingly dependent on neonatal screening tests for diagnosis of congenital hypothyroidism. Laboratory errors occur, however, and awareness of early symptoms and signs must be maintained. Congenital hypothyroidism is twice as common in girls as in boys. Before neonatal screening programs, congenital hypothyroidism was rarely recognized in the newborn since the signs and symptoms are usually not sufficiently developed. It can be suspected and the diagnosis established during the early weeks of life if the initial but less characteristic manifestations are recognized. Birthweight and length are normal, but head size may be slightly increased because of myxedema of the brain. Prolongation of physiologic icterus, caused by delayed maturation of glucuronide conjugation, may be the earliest sign. Feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking spells during nursing, are often present during the 1st mo of life. Respiratory difficulties, due in part to the large tongue, include apneic episodes, noisy respirations, and nasal obstruction. Typical respiratory distress syndrome may also occur. Affected infants cry little, sleep much, have poor appetites, and are generally sluggish. There may be constipation that does not usually respond to treatment. The abdomen is large, and an umbilical hernia is usually present. The temperature is subnormal, often below 35ϵ{degree} C (95ϵ{degree} F), and the skin, particularly of the extremities, may be cold and mottled. Edema of the genitals and extremities may be present. The pulse is slow; heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common. Anemia is often present and is refractory to treatment with hematinics. Since

symptoms appear gradually, the diagnosis is often delayed.

These manifestations progress; retardation of physical and mental development becomes greater during the following months, and by 3–6 mo of age, the clinical picture is fully developed. When there is only a partial deficiency of thyroid hormone, the symptoms may be milder, the syndrome incomplete, and the onset delayed. Although breast milk contains significant amounts of thyroid hormones, particularly T3, it is inadequate to protect the breast-fed infant with congenital hypothyroidism, and it has no effect on neonatal thyroid screening tests.

The child's growth is stunted, the extremities are short, and the head size is normal or even increased. The anterior and posterior fontanels are widely open; observation of this sign at birth may serve as an initial clue to the early recognition of congenital hypothyroidism. Only 3% of normal newborn infants have a posterior fontanel larger than 0.5 cm. The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids swollen. The mouth is kept open, and the thick and broad tongue protrudes from it. Dentition is delayed. The neck is short and thick, and there may be deposits of fat above the clavicles and between the neck and shoulders. The hands are broad and the fingers short. The skin is dry and scaly, and there is little perspiration. Myxedema is manifest, particularly in the skin of the eyelids, of the back of the hands, and of the external genitalia. Carotenemia may cause a yellow discoloration of the skin, but the scleras remain white. The scalp is thickened, and the hair is coarse, brittle, and scanty. The hairline reaches far down on the forehead, which usually appears wrinkled, especially when the infant cries.

Development is usually retarded. Hypothyroid infants appear lethargic and are late in learning to sit and stand. The voice is hoarse, and they do not learn to talk. The degree of physical and mental retardation increases with age. Sexual maturation may be delayed or may not take place at all.

The muscles are usually hypotonic, but in rare instances generalized muscular hypertrophy occurs (Kocher-Debrй{acute-e}-Sй{acute-e}мй{acute-e}laigne syndrome). Affected children may have an athletic appearance due to pseudohypertrophy, particularly in the calf muscles. Its pathogenesis is unknown; nonspecific histochemical and ultrastructural changes seen on muscle biopsy return to normal with treatment. Boys are more prone to develop the syndrome, which has been observed in siblings born to a consanguineous mating. Affected patients have hypothyroidism of longer duration and severity.

LABORATORY DATA. Most newborn screening programs in North America measure levels of T4, supplemented by measurement of TSH when T4 is low. This approach identifies infants with primary hypothyroidism, those with low thyroxine-binding globulin (TBG) and some with hypothalamic or pituitary hypothyroidism,

and infants with hyperthyroxinemia. European and Japanese neonatal screening programs are based on a primary measurement of TSH; this approach misses infants with hyperthyroxinemia, low TBG, and hypothalamic or pituitary hypothyroidism but may detect infants with compensated hypothyroidism (normal T4, elevated TSH). With any of these assays, special care should be given to the normal range of values for age of the patient, particularly in the first weeks of life. Regardless of the approach used for screening, some infants escape detection because of technical or human errors; clinicians must maintain their vigilance for clinical manifestations of hypothyroidism.

Serum levels of T4 are low; serum levels of T3 may be normal and are not helpful in the diagnosis. If the defect is primarily in the thyroid, levels of TSH are elevated, often to above 100 m{mu}U/mL. Serum levels of prolactin are elevated, correlating with those of TSH. Serum levels of Tg are usually low in infants with thyroid dysgenesis or defects of Tg synthesis or secretion. Undetectable levels of Tg usually indicate thyroid aplasia.

Special attention should be paid to monoamniotic twins, because in at least four cases neonatal screening failed to detect the discordant twin with hypothyroidism, and the diagnosis was not made until the infants were 4–5 mo of age. Apparently, transfusion of euthyroid blood from the unaffected twin normalized the serum level of T4 and TSH in the affected twin at the initial screening.

Retardation of osseous development can be shown roentgenographically at birth in about 60% of congenitally hypothyroid infants and indicates some deprivation of thyroid hormone during intrauterine life. For example, the distal femoral epiphysis, normally present at birth, is often absent (Fig. 520–2 Fig. 520–2A). In untreated patients, the discrepancy between chronological age and osseous development increases. The epiphyses often have multiple foci of ossification (epiphyseal dysgenesis, Fig. 520–2 Fig. 520–2B); deformity ("breaking") of the 12th thoracic or 1st or 2nd lumbar vertebra is common. Roentgenograms of the skull show large fontanels and wide sutures; intersutural (wormian) bones are common. The sella turcica is often enlarged and round; in rare instances there may be erosion and thinning. Delays in formation and eruption of teeth may occur. Cardiac enlargement or pericardial effusion may be present.

Scintigraphy can help to pinpoint the underlying cause in infants with congenital hypothyroidism, but treatment should not be unduly delayed for this study. 125I-sodium iodide is superior to 99mTc-sodium pertechnetate for this purpose. Neither thyroid ultrasound examination nor serum levels of Tg are reliable alternatives to radionuclide scanning. Demonstration of ectopic thyroid tissue is diagnostic of thyroid dysgenesis and establishes the need for lifelong treatment with T4. Failure to demonstrate any thyroid tissue suggests thyroid aplasia but also occurs in neonates

with TRBAb and in infants with the iodide-trapping defect. A normally situated thyroid gland with a normal or avid uptake of radionuclide indicates a defect in thyroid hormone biosynthesis. Patients with goitrous hypothyroidism may require extensive evaluation, including radioiodine studies, perchlorate discharge tests, kinetic studies, chromatography, and studies of thyroid tissue, if the biochemical nature of the defect is to be determined.

The electrocardiogram may show low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion. The electroencephalogram frequently shows low voltage. In children older than 2 yr of age, the serum cholesterol level is usually elevated.

PROGNOSIS. With the advent of neonatal screening programs for detection of congenital hypothyroidism, the prognosis for affected infants has improved dramatically. Early diagnosis and adequate treatment from the first weeks of life result in normal linear growth and intelligence comparable with that of unaffected siblings. Some screening programs report that the most severely affected infants, as judged by the lowest T4 levels and retarded skeletal maturation, have slightly reduced IQs and other neuropsychologic sequelae. Without treatment, affected infants become mentally deficient dwarfs. Thyroid hormone is critical for normal cerebral development in the early postnatal months; biochemical diagnosis must be made soon after birth, and effective treatment must be initiated promptly to prevent irreversible brain damage. Delay in diagnosis, inadequate treatment, and poor compliance result in variable degrees of brain damage. When onset of hypothyroidism occurs after 2 yr of age, the outlook for normal development is much better even if diagnosis and treatment have been delayed, indicating how much more important thyroid hormone is to the rapidly growing brain of the infant.

TREATMENT. Sodium-L-thyroxine given orally is the treatment of choice. Because 80% of circulating T3 is formed by monodeiodination of T4, serum levels of T4 and T3 in treated infants return to normal. This is also true in the brain, where 80% of required T3 is produced locally from T4. In neonates, the dose is 10–15 m{mu}g/kg (37.5 or 50 m{mu}g/24 hr). Levels of T4 and TSH should be monitored and maintained in the normal range. Children with hypothyroidism require about 4 m{mu}g/kg/24 hr, and adults require only 2 m{mu}g/kg/24 hr.

Later, confirmation of the diagnosis may be necessary for some infants to rule out the possibility of transient hypothyroidism. This is unnecessary in infants with proven thyroid ectopia or in those who manifest elevated levels of TSH after 6–12 mo of therapy owing to poor compliance or an inadequate dose of T4. Discontinuation of therapy at about 3 yr of age for 3–4 wk results in a marked increase in TSH levels in children with permanent hypothyroidism.

The only untoward effects of sodium-L-thyroxine are related to its dose. An

occasional older child (8–13 yr) with acquired hypothyroidism may develop pseudotumor cerebri within the first 4 mo of treatment. In older children, after catch-up growth is complete, the growth rate provides an excellent index of the adequacy of therapy. Parents should be forewarned about changes in behavior and activity expected with therapy, and special attention must be given to any developmental or neurologic deficits.

ACQUIRED HYPOTHYROIDISM

ETIOLOGY. The most common cause of acquired hypothyroidism is lymphocytic thyroiditis (see Chapter 521). Although typically seen in adolescence, it occurs as early as in the first 2 yr of life. Some patients with congenital thyroid dysgenesis or with incomplete genetic defects in thyroid hormone synthesis may not develop clinical manifestations until childhood and appear to have acquired hypothyroidism; most patients with these conditions are now detected in newborn screening programs. Subtotal thyroidectomy for thyrotoxicosis or cancer may result in hypothyroidism, as may removal of ectopic thyroid tissue. For example, lingual thyroid, subhyoid median thyroid, or thyroid tissue in a thyroglossal duct cyst usually constitutes the only source of thyroid hormone, and excision results in hypothyroidism. Because subhyoid glands usually mimic thyroglossal duct cysts, a radionuclide scan before surgery is indicated in these patients.

Children with nephropathic cystinosis, a disorder characterized by intralysosomal storage of cystine in body tissues, develop impaired thyroid function. Hypothyroidism may be overt, but compensated forms are more common, and periodic assessment of TSH levels is indicated. By 13 yr of age, two thirds of these patients require thyroxine replacement.

Histiocytic infiltration of the thyroid in children with Langerhans cell histiocytoses may result in hypothyroidism.

Irradiation to the area of the thyroid that is incidental to the treatment of Hodgkin disease or other malignancies or that is given before bone marrow transplantation often results in thyroid damage. About one third of such children develop elevated TSH levels within a year after therapy, and 15–20% progress to hypothyroidism within 5–7 yr. Some clinicians recommend periodic TSH measurements, but others recommend treatment of all exposed patients with doses of T4 to suppress TSH .

Protracted ingestion of medications containing iodides can cause hypothyroidism, usually accompanied by a goiter (see Chapter 522). Amiodarone, a drug used for cardiac arrhythmias, consisting of 37% by weight of iodine, causes hypothyroidism in about 20% of treated children. It affects thyroid function directly by its high iodine content as well as by inhibition of 5r{prime}-deiodinase, which

converts T4 to T3. Children treated with this drug should have serial measurements of T4, T3, and TSH.

CLINICAL MANIFESTATIONS. Deceleration of growth is usually the first clinical manifestation, but this sign often goes unrecognized . Myxedematous changes of the skin, constipation, cold intolerance, decreased energy, and increased need for sleep develop insidiously. Surprisingly, school work and grades usually do not suffer, even in severely hypothyroid children. Osseous maturation is delayed, often strikingly, which is an indication of the duration of the hypothyroidism.

Some children present with headaches, visual problems, precocious puberty, or galactorrhea. These children usually have hyperplastic enlargement of the pituitary gland, often with suprasellar extension, after longstanding hypothyroidism; this condition may be mistaken for a pituitary tumor .

All of these changes return to normal with adequate replacement of T4, but in children with longstanding hypothyroidism, catch-up growth may be incomplete. During the first 18 mo of treatment, skeletal maturation often exceeds expected linear growth, resulting in a loss of about 7 cm of predicted adult height. The cause for this is unknown.

Diagnostic studies and treatment are the same as those described for congenital hypothyroidism. Measurement of antithyroglobulin and antiperoxidase (formerly antimicrosomal) antibodies may pinpoint autoimmune thyroiditis as the cause. During the 1st yr of treatment, deterioration of school work, poor sleeping habits, restlessness, short attention span, and behavioral problems may ensue, but these are transient; forewarning families about these manifestations enhances appropriate management.

Case histories

1. Congenital hypothyroidism in an infant 6 mo of age. The infant fed poorly in the neonatal period and was constipated. She had a persistent nasal discharge and a large tongue; she was very lethargic; and she had no social smile and no head control. A, Notice the puffy face, dull expression, and hirsute forehead. Tests revealed a negligible uptake of radioiodine. Osseous development was that of a newborn. B, Four mo after treatment, notice the decreased puffiness of the face, the decreased hirsutism of the forehead, and the alert appearance.

2. Congenital hypothyroidism. A, Absence of distal femoral epiphysis in a 3-mo-old infant who was born at term. This is evidence for the onset of the hypothyroid state during fetal life. B, Epiphyseal dysgenesis in the head of the humerus in a 9-yr-old girl who had been inadequately treated with thyroid hormone.

3. Acquired hypothyroidism in a girl 6 yr of age. She was treated with a wide variety of hematinics for refractory anemia for 3 yr. She had almost complete cessation of growth, constipation, and sluggishness for 3 yr. The height age was 3 yr;

the bone age was 4 yr. She had a sallow complexion and immature facies with a poorly developed nasal bridge. Serum cholesterol, 501 mg/dL; radioiodine uptake, 7% at 24 hr; PBI, 2.8 m{mu}g/dL. B, After therapy for 18 mo, notice the nasal development, the increased luster and decreased pigmentation of hair, and the maturation of face. The height age was 5.5 yr; the bone age was 7 yr. There was a decided improvement in her general condition. Menarche occurred at 14 yr. The ultimate height was 155 cm (61 in). She graduated from high school. The disorder was well controlled with sodium-L-thyroxine daily.

Etiologic Classification of Hypothyroidism---

Pit-1 (homeobox protein) mutations
  Deficiency of thyrotropin, growth hormone, and prolactin
Thyrotropin–releasing hormone (TRH) deficiency
  Isolated?
  Multiple hypothalamic deficiencies (e.g., craniopharyngioma)
Thyrotropin (TSH) deficiency
  Mutations in a chain
  Multiple pituitary deficiencies
Thyrotropin unresponsiveness
  Gsa mutation (e.g., type IA pseudohypoparathyroidism)
  Mutation in TSH receptor
    Mouse (autosomal recessive)
    Man?
Defect of fetal thyroid development
  Aplasia, ectopia (dysgenesis)
Defect in thyroid hormone synthesis (e.g., goitrous hypothyroidism)
  Iodide transport defect
  Thyroid peroxidase defect
  Thyroglobulin synthesis defect
  Deiodination defect
Iodine deficiency (endemic goiter)
  Neurologic type
  Myxedematous type
Maternal antibodies
  Thyrotropin receptor–blocking antibody (TRBAb)
Maternal medications
  Radioiodine, iodides
  Propylthiouracil, methimazole
  Amiodarone
Autoimmune (acquired hypothyroidism)

Hashimoto thyroiditis

Polyglandular autoimmune syndrome, types I, II, and III

Iatrogenic

Propylthiouracil, methimazole, iodides, lithium, amiodarone

Irradiation

Radioiodine

X–rays (neck or whole body)

Thyroidectomy

Systemic disease

Cystinosis

Histiocytic infiltration

Resistance to thyroid hormone (only occasional clinical manifestations of hypothyroidism)

THYROIDITIS

LYMPHOCYTIC THYROIDITIS

(Hashimoto Thyroiditis; Autoimmune Thyroiditis)

Lymphocytic thyroiditis is the most common cause of thyroid disease in children and adolescents and accounts for many of the enlarged thyroids formerly designated "adolescent" or "simple" goiter. It is also the most common cause of acquired hypothyroidism, with or without goiter. Its incidence may be as high as 1% among school children.

ETIOLOGY. This is a typical organ-specific autoimmune disease. The condition is characterized histologically by lymphocytic infiltration of the thyroid. Early in the course of the disease, there may be only hyperplasia; this is followed by infiltration of lymphocytes and plasma cells between the follicles and by atrophy of the follicles. Lymphoid follicle formation with germinal centers is almost always present; the degree of atrophy and of fibrosis of the follicles varies from mild to moderate.

Intrathyroidal lymphocyte subsets differ from those in blood. About 60% of infiltrating lymphoid cells are T cells, and about 30% express B-cell markers; the T-cell population is represented by helper (CD4+) and cytotoxic (CD8+) cells. Participation of cellular events in the pathogenesis is clear. Certain HLA haplotypes (HLA-DR4, HLA-DR5) are associated with an increased risk of goiter and thyroiditis, and others (HLA-DR3) are associated with the atrophic variant of thyroiditis. Much remains to be discovered about the disturbance in immunoregulation and how it interacts with genetic predisposition and environmental factors in the pathogenesis of autoimmune thyroid disease.

A variety of different thyroid antigen autoantibodies are also involved in the process. Thyroid antiperoxidase antibodies (TPOAb), formerly called antimicrosomal antibodies, are demonstrable in the sera of 90% of children with lymphocytic

thyroiditis and in many patients with Graves disease. For many years TPOAb has been considered nonpathogenic, but evidence now shows that TPOAb inhibit enzyme activity and stimulate natural killer cell cytotoxicity. With the molecular cloning of the TPO gene, a new generation of ultrasensitive tests for the measurement of these antibodies is under development.

Antithyroglobulin antibodies occur in a smaller percentage of affected children but are much more common in adults. Thyrotropin receptor–blocking antibodies (TRBAb) are frequently present, especially in patients with hypothyroidism, and it is now believed they are related to the development of hypothyroidism and thyroid atrophy in patients with autoimmune thyroiditis.

CLINICAL MANIFESTATIONS. The disorder is 4–7 times more frequent in girls than in boys. It may occur during the first 3 yr of life but becomes sharply more common after 6 yr of age and reaches a peak incidence during adolescence. The most common clinical manifestations are growth retardation and goiter. The goiter may appear insidiously and may be small or large. In most patients, the thyroid is diffusely enlarged, firm, and nontender. In about one third of the patients, the gland is lobular and may seem to be nodular. Most of the affected children are clinically euthyroid and asymptomatic; some may have symptoms of pressure in the neck. Some children have clinical signs of hypothyroidism, but others who appear clinically euthyroid have laboratory evidence of hypothyroidism. A few children have manifestations suggestive of hyperthyroidism, such as nervousness, irritability, increased sweating, or hyperactivity, but results of laboratory studies are not necessarily those of hyperthyroidism. Occasionally, the disorder may coexist with Graves disease. Ophthalmopathy may occur in lymphocytic thyroiditis in the absence of Graves disease.

The clinical course is variable. The goiter may become smaller or may disappear spontaneously, or it may persist unchanged for years while the patient remains euthyroid. A significant percentage of patients who are euthyroid initially exhibit hypothyroidism gradually within months or years; thyroiditis is the cause of most cases of nongoitrous (atrophic) hypothyroidism.

Familial clusters of lymphocytic thyroiditis are common; the incidence in siblings or parents of affected children may be as high as 25%. Autoantibodies to thyroglobulin (Tg) and human thyroid peroxidase (hTPO) in these families appear to be inherited in an autosomal dominant fashion, with reduced penetrance in males. The concurrence within families of patients with lymphocytic thyroiditis, "idiopathic" hypothyroidism, and Graves disease provides cogent evidence for a basic relationship among these three conditions. The disorder has been associated with many of the other autoimmune disorders more often than would be expected by chance alone. Autoimmune thyroiditis occurs in 10% of patients with type I polyglandular

autoimmune syndrome, which consists of hypoparathyroidism, Addison disease, and mucocutaneous candidiasis. The association of Addison disease with insulin-dependent diabetes mellitus or autoimmune thyroid disease or both is known as Schmidt syndrome or type II polyglandular autoimmune disease. Autoimmune thyroid disease also tends to be associated with pernicious anemia, vitiligo, or alopecia. TPOAb are found in approximately 20% of white and 4% of black children with diabetes mellitus. Autoimmune thyroid disease has an increased incidence in children with congenital rubella. Lymphocytic thyroiditis is also associated with certain chromosomal aberrations, particularly Turner syndrome and Down syndrome. The pathogenetic mechanisms for these associations are not known.

LABORATORY DATA. The definitive diagnosis can be established by biopsy of the thyroid, but this procedure is rarely indicated for clinical purposes alone. Thyroid function tests are often normal, although the level of thyroid-stimulating hormone (TSH) may be slightly or even moderately elevated in some euthyroid individuals. With progressive thyroid failure, a decrease in the levels of thyroxine (T4) is followed by a decrease in levels of triiodothyronine (T3) and progressive increases in levels of TSH. The fact that many patients with lymphocytic thyroiditis do not have elevated levels of TSH indicates that the goiter may be caused by the lymphocytic infiltrations or by thyroid growth–stimulating immunoglobulins. In 50% of patients, thyroid scans reveal irregular and patchy distribution of the radioisotope, and in about 60% or more, the administration of perchlorate results in a greater than 10% discharge of iodide from the thyroid gland. Thyroid ultrasonography shows scattered hypoechogenicity in most patients. Most patients with lymphocytic thyroiditis have serum antibody titers to thyroid peroxidase, but the antithyroglobulin test for thyroid antibodies is positive in fewer than 50%. When both tests are used, approximately 95% of patients with thyroid autoimmunity are detected. In general, levels in children and adolescents are lower than those in adults with lymphocytic thyroiditis, and repeated measurements are indicated in questionable instances because titers may increase later in the course of the disease.

Antithyroid antibodies may be found also in almost one half the siblings of affected patients and in a significant percentage of the mothers of children with Down syndrome or Turner syndrome without demonstrable thyroid disease. They are also found in 20% of children with diabetes mellitus and in 23% of children with the congenital rubella syndrome.

TREATMENT. If there is evidence of hypothyroidism, replacement treatment with sodium-L-thyroxine (50–150 m{mu}g daily) is indicated. The goiter usually shows some decrease in size but may persist for years. Antibody levels fluctuate in both treated and untreated patients and persist for years. Because the disease may be self-limited in some instances, the need for continued therapy requires periodic re-

evaluation. Untreated patients should also be periodically checked. Prominent nodules that persist despite suppressive therapy should be examined histologically because thyroid cancer has occurred in patients with lymphocytic thyroiditis.

OTHER CAUSES OF THYROIDITIS

Specific conditions such as tuberculosis, sarcoidosis, mumps, and cat-scratch disease are rare causes of thyroiditis.

Acute suppurative thyroiditis is uncommon; it is usually preceded by a respiratory infection. The left lower lobe is affected predominantly. Abscess formation may occur. Anaerobic organisms, with or without aerobes, are the most common organisms; Eikenella corrodens has been reported. Recurrent episodes or the detection of a mixed bacterial flora suggests that the infection arises from a thyroglossal duct remnant or, more often, from a piriform sinus fistula. Exquisite tenderness of the gland, swelling, erythema, dysphagia, and limitation of head motion are characteristic findings. Systemic manifestations are often absent, and leukocytosis is present. Scintigrams of the thyroid often reveal decreased uptake in the affected areas, and ultrasonography may show a complex echogenic mass. Thyroid function is usually normal, but thyrotoxicosis due to escape of thyroid hormone has been encountered in a child with suppurative thyroiditis resulting from Aspergillus. When suppuration occurs, incision and drainage and administration of antibiotics are indicated. After the infection subsides, a barium esophagram is indicated to search for a fistula tract; if one is found, exteriorization is indicated.

Subacute nonsuppurative thyroiditis (deQuervain disease) is rare in children. It is thought to have a viral cause and remits spontaneously. The disorder becomes manifest by a vague tenderness over the thyroid and low-grade fever or by severe pain in the region of the thyroid and systemic manifestations with chills and high fever. Inflammation results in leakage of preformed thyroid hormone from the gland into the circulation. Serum levels of T4 and T3 are elevated, and mild symptoms of hyperthyroidism may be present, but radioiodine uptake is depressed. The erythrocyte sedimentation rate is increased. The course is variable, usually passing through a euthyroid to a hypothyroid phase; remission usually occurs in several months. Occasionally, this condition is superimposed on lymphocytic thyroiditis.

GOITER

A goiter is an enlargement of the thyroid gland. Persons with enlarged thyroids may have normal function of the gland (euthyroidism), thyroid deficiency (hypothyroidism), or overproduction of the hormones (hyperthyroidism). Goiter may be congenital or acquired, endemic or sporadic.

The goiter often results from increased pituitary secretion of thyrotropic hormone in response to decreased circulating levels of thyroid hormones. Thyroid

enlargement may also result from infiltrative processes that may be inflammatory or neoplastic. Goiter in patients with thyrotoxicosis is caused by thyrotropin receptor–stimulating antibodies (TRSAb).

Congenital Goiter

Congenital goiter is usually sporadic and may result from the administration of antithyroid drugs or iodides during pregnancy for the treatment of thyrotoxicosis. Goitrogenic drugs and iodides cross the placenta and at high doses may interfere with synthesis of thyroid hormone, resulting in goiter and hypothyroidism in the fetus. The concomitant administration of thyroid hormone with the goitrogen does not prevent this effect, because insufficient amounts of thyroxine (T4) cross the placenta. Iodides are included in many proprietary preparations used to treat asthma; these preparations must be avoided during pregnancy, because they have often been a cause of unexpected congenital goiter. Amiodarone, an antiarrhythmic drug with a 37% iodine content, has also caused congenital goiter with hypothyroidism. Even when the infant is clinically euthyroid, there may be retardation of osseous maturation, low levels of T4, and elevated levels of thyroid-stimulating hormone (TSH). Because these effects can occur when the mother takes only 100–200 mg of propylthiouracil/24 hr, all such infants should undergo thyroid studies at birth. Administration of thyroid hormone to affected infants may be indicated to treat clinical hypothyroidism, to hasten the disappearance of the goiter, and to prevent brain damage. Because the condition is rarely permanent, thyroid hormone may be safely discontinued after several months.

Enlargement of the thyroid at birth may occasionally be sufficient to cause respiratory distress that interferes with nursing and may even cause death. The head may be maintained in extreme hyperextension. When respiratory obstruction is severe, partial thyroidectomy rather than tracheostomy is indicated

Goiter is almost always present in the congenitally hyperthyroid infant. These goiters are usually not large; the infant manifests clinical symptoms of hyperthyroidism, and the mother often has a history of Graves disease .

When no causative factor is identifiable, a defect in synthesis of thyroid hormone should be suspected. One of 30,000–50,000 live births is found in neonatal screening programs to have such a defect. Study of this group of infants is complex. If the infant is hypothyroid, it is advisable to treat immediately with thyroid hormone and to postpone more detailed studies for later in life. Because these defects are transmitted by recessive genes, a precise diagnosis is important for genetic counseling. Monitoring subsequent pregnancies with ultrasound can be useful in detecting fetal goiters .

Iodine deficiency as a cause of congenital goiters has become rare but persists in isolated endemic areas. More important is the recent recognition that severe iodine

deficiency early in pregnancy may cause neurologic damage during fetal development even in the absence of goiter. The iodine deficiency may result in maternal and fetal hypothyroidism, preventing the partially protective transfer of maternal thyroid hormones.

When the "goiter" is lobulated, asymmetric, firm, or large to an unusual degree, a teratoma within or in the vicinity of the thyroid must be considered in the differential diagnosis (.

Endemic Goiter and Cretinism

The association between dietary deficiency of iodine and the prevalence of goiter or cretinism has been recognized for over half a century. A moderate deficiency of iodine can be overcome by increased efficiency in the synthesis of thyroid hormone. Iodine liberated in the tissues is returned rapidly to the gland, which resynthesizes the hormone at a higher rate than normal. This increased activity is achieved by compensatory hypertrophy and hyperplasia, which satisfy the demands of the tissues for thyroid hormone. In geographic areas where deficiency of iodine is severe, decompensation and hypothyroidism may result. It is estimated that 800 million people in developing countries live in areas of iodine deficiency.

Sea water is rich in iodine, and the iodine content of fish and shellfish is also high. Endemic goiter is rare therefore in populations living along the sea. Iodine is deficient in the water and native foods in the Pacific West and the Great Lakes areas of the United States. Deficiency of dietary iodine is even greater in certain Alpine valleys, the Himalayas, the Andes, the Congo, and the highlands of Papua New Guinea. In areas such as the United States, where iodine is provided in foods from other areas and in iodized salt, endemic goiter has disappeared. Iodized salt in the United States contains potassium iodide (100 m{mu}g/g) and provides excellent prophylaxis. Further iodine intake in the United States is contributed by iodates used in baking, iodine-containing coloring agents, and iodine-containing disinfectants used in the dairy industry. The recommended daily allowance of iodine for infants is 40–50 m{mu}g/24 hr; this amount is exceeded 4-fold in breast-fed infants and 10-fold in infants fed cow's milk in the United States.

CLINICAL MANIFESTATIONS. If the deficiency of iodine is mild, thyroid enlargement does not become noticeable except when there is increased demand for the hormone during periods of rapid growth, as in adolescence and during pregnancy. In regions of moderate iodine deficiency, goiter observed in school children may disappear with maturity and reappear during pregnancy or lactation. Iodine-deficient goiters are more common in girls than in boys. Where iodine deficiency is severe, as in the hyperendemic highlands of Papua New Guinea, nearly half the population has large goiters, and endemic cretinism is common.

Serum T4 levels are often low in people with endemic goiter, although clinical

hypothyroidism is rare. This is true in New Guinea, the Congo, the Himalayas, and South America. Despite low serum levels of thyroid hormone, serum TSH concentrations are often only moderately increased. In such patients circulating levels of triiodothyronine (T3) are elevated. Moreover, T3 levels are also elevated in those patients with normal T4 levels, indicating a preferential secretion of T3 by the thyroid in this disease.

Endemic cretinism, the most serious consequence of iodine deficiency, has been recognized for centuries; it occurs only in geographic association with endemic goiter. The term endemic cretinism includes two different but overlapping syndromes, a neurologic type and a myxedematous type. The frequency of the two types varies among different populations; in Papua New Guinea, the neurologic type occurs almost exclusively, but in Zaire, the myxedematous type predominates. Both types are found in all endemic areas, and some individuals have intermediate or mixed features.

The neurologic syndrome is characterized by mental retardation, deaf-mutism, disturbances in standing and gait, and pyramidal signs such as clonus of the foot, Babinski sign, and patellar hyperreflexia. Affected individuals are goitrous but euthyroid, have normal pubertal development and adult stature, and have little or no impaired thyroid function. Individuals with the myxedematous syndrome also are mentally retarded and deaf and have neurologic symptoms, delayed sexual development and growth, myxedema, and absence of goiter; serum T4 levels are low, and TSH levels are markedly elevated. Delayed skeletal maturation may extend into the 3rd decade or later. Ultrasound examination shows thyroid atrophy.

The pathogenesis of the neurologic syndrome has been attributed to iodine deficiency and hypothyroxinemia during pregnancy leading to fetal and postnatal hypothyroidism. Although some investigators have attributed brain damage to a direct effect of elemental iodine deficiency in the fetus, others believe the neurologic symptoms are caused by fetal and maternal hypothyroxinemia. There is evidence that the human fetal brain has receptors for thyroid hormone before development of the fetal thyroid, and there is also evidence of some transplacental passage of maternal thyroid hormone into the fetus, which normally might ameliorate the effects of fetal hypothyroidism on the developing nervous system. The pathogenesis of the myxedematous syndrome leading to thyroid atrophy is more bewildering. Searches for additional environmental factors that may provoke continuing postnatal hypothyroidism have led to incrimination of selenium deficiency, goitrogenic foods, thiocyanates, and Yersinia. Studies from Western China suggest that thyroid autoimmunity may play a role. Myxedematous cretins with thyroid atrophy, but not euthyroid cretins, were found to have thyroid growth–blocking immunoglobulins (TGBI) of the kind found in infants with sporadic congenital hypothyroidism. Others

are skeptical about any role of TGBI in goitrogenesis and in endemic goiter.

In many developing countries, administration of a single intramuscular injection of iodinated poppy seed oil to women prevents iodine deficiency during future pregnancies for about 5 yr. This form of therapy given to children under 4 yr of age with myxedematous cretinism results in a euthyroid state in 5 mo. However, older children respond poorly and adults not at all to iodized oil injections, indicating an inability of the thyroid gland to synthesize hormone; these patients require treatment with T4. In the Xinjiang province of China, where the usual methods of iodine supplementation had failed, iodination of irrigation water has increased iodine in soil, animals, and human beings.

Sporadic Goiter

The term sporadic goiter encompasses goiters developing from a variety of causes; patients are usually euthyroid but may be hypothyroid. The most common cause of sporadic goiter is lymphocytic thyroiditis (see Chapter 523). Intrinsic biochemical defects in the synthesis of thyroid hormone are almost always associated with goiter. The occurrence of the disorder in siblings, onset in early life, and possible association with hypothyroidism (goitrous hypothyroidism) are important clues to the diagnosis.

IODIDE GOITER. A small percentage of patients treated with iodide preparations for prolonged periods develop goiters. Iodides are commonly included for their expectorant effect in cough medicines and in proprietary mixtures for asthma. Goiters resulting from iodine administration are firm and diffusely enlarged, and in some instances hypothyroidism may develop. In normal subjects acute administration of large doses of iodine inhibits the organification of iodine and the synthesis of thyroid hormone (Wolff-Chaikoff effect). This effect is short-lived and does not lead to hypothyroidism. When iodide administration continues, an autoregulatory mechanism in normal persons limits iodine trapping and permits the level of iodide in the thyroid to fall and organification to proceed normally. In patients with iodide-induced goiter, this escape does not occur because of an underlying abnormality of biosynthesis of thyroid hormone. Persons most susceptible to the development of iodide goiter are those with lymphocytic thyroiditis or with a subclinical inborn error in thyroid hormone synthesis and those who have had partial thyroidectomy.

Lithium carbonate also causes goiters; it is currently widely used as a psychotropic drug. Lithium competes with iodide; the mechanism producing the goiter or hypothyroidism is similar to that described earlier for iodide goiter. Lithium and iodide also act synergistically to produce goiter; their combined use should be avoided.

Amiodarone, a drug used to treat cardiac arrhythmias, can cause thyroid

dysfunction with goiter because it is rich in iodine. It is also a potent inhibitor of 5r{prime}-deiodinase, preventing conversion of T4 to T3. It can cause hypothyroidism, particularly in patients with underlying autoimmune disease; in other patients, it may cause hyperthyroidism.

SIMPLE GOITER (COLLOID GOITER). A few children with euthyroid nontoxic goiters have simple goiters, a condition of unknown etiology not associated with hypothyroidism or hyperthyroidism and not caused by inflammation or neoplasia. The condition predominates in girls and has a peak incidence before and during the pubertal years. Histologic examination of the thyroid either is normal or reveals variable follicular size, dense colloid, and flattened epithelium. The goiter may be small or large. It is firm in consistency in half the patients and is occasionally asymmetric or nodular. Levels of TSH are normal or low; scintiscans are normal; thyroid antibodies are absent. Differentiation from lymphocytic thyroiditis may not be possible without a biopsy, but biopsy is ordinarily not indicated. Therapy with thyroid hormone may help to avoid progression to a large multinodular goiter, although it is difficult to separate any treatment effects from the natural history, which is for the goiter to decrease in size. Untreated patients should be re-evaluated periodically. This condition must be differentiated from lymphocytic thyroiditis **MULTINODULAR GOITER**. Rarely, a firm goiter with a lobulated surface and single or multiple palpable nodules is encountered. Areas of cystic change, hemorrhage, and fibrosis may be present. The incidence of this condition has decreased markedly with the use of iodine-enriched salt. A mild goitrogenic stimulus, acting over a long time, is thought to be the cause. Ultrasound examination may reveal multiple echo-free and echogenic lesions that are nonfunctioning on scintiscans. Thyroid studies are usually normal, but TSH may be elevated and thyroid antibodies may be present. The condition occurs in children with McCune-Albright syndrome and has been described in three children (including two siblings) with digital anomalies and cystic renal disease. If the nodules are not suppressed by replacement therapy with T4, surgery is indicated, because malignancy cannot readily be ruled out.

Intratracheal Goiter

One of the many ectopic locations of thyroid tissue is within the trachea. The intraluminal thyroid lies beneath the tracheal mucosa and is frequently continuous with the normally situated extratracheal thyroid. The thyroid tissue is susceptible to goitrous enlargement, which involves the normally situated and the ectopic thyroid. When there is obstruction of the airway associated with a goiter, it must be ascertained whether the obstruction is extratracheal or endotracheal. If obstructive manifestations are mild, administration of sodium-L-thyroxine usually causes the goiter to decrease in size. When symptoms are severe, surgical removal of the

endotracheal goiter is indicated.

GOITROUS CRETINISM

Congenital goiter in infancy. A, Large congenital goiter in an infant born to a mother with thyrotoxicosis who had been treated with iodides and methimazole during pregnancy. B, A 6-wk-old infant with increasing respiratory distress and cervical mass since birth. The operation revealed a large goiter that almost completely encircled the trachea. Notice the anterior deviation and posterior compression of the trachea. Partial thyroidectomy completely relieved the symptoms. It is apparent why a tracheostomy is not adequate treatment for these infants. The cause for the goiter was not found.

HYPERTHYROIDISM

Hyperthyroidism results from excessive secretion of thyroid hormone and, with few exceptions, is due to diffuse toxic goiter (Graves disease) during childhood. Two large pedigrees have been reported of nonautoimmune autosomal dominant hyperthyroidism. These patients have thyroid hyperplasia with goiters and suppressed levels of thyroid-stimulating hormone (TSH). Both families have germline mutations of the TSH receptor resulting in constitutively activating (i.e., gain of function) mutations. Different activating mutations have been identified in some cases of thyroid adenomas. Other rare causes of hyperthyroidism that have been observed in children include toxic uninodular goiter (Plummer disease), hyperfunctioning thyroid carcinoma, thyrotoxicosis factitia, subacute thyroiditis, and acute suppurative thyroiditis. Hyperthyroidism occurs in some patients with McCune-Albright syndrome, which is associated with autonomous thyroid adenomas. Suppression of plasma TSH indicates that the hyperthyroidism is not pituitary in origin. Hyperthyroidism due to excess thyrotropin secretion is rare and, in most cases, is caused by pituitary unresponsiveness to thyroid hormone. TSH-secreting pituitary tumors have been reported only in adults. In infants born to mothers with Graves disease, hyperthyroidism may occur as a transitory phenomenon or as classic Graves disease during the neonatal period. Choriocarcinoma, hydatidiform mole, and struma ovarii have caused hyperthyroidism in adults but have not been recognized as causes in children.

Graves Disease

ETIOLOGY. Enlargement of the thymus, splenomegaly, lymphadenopathy, infiltration of the thyroid gland and of retro-orbital tissues with lymphocytes and plasma cells, and peripheral lymphocytosis are well-established findings in Graves disease. In the thyroid gland, T helper cells (CD4+) tend to predominate in dense lymphoid aggregates; in areas of lower cell density, cytotoxic T cells (CD8+) predominate. The percentage of activated B lymphocytes infiltrating the thyroid is

higher than in peripheral blood. A postulated failure of T suppressor cells allows expression of T helper cells, sensitized to the TSH antigen, which interact with β-cells. These cells differentiate into plasma cells, which produce thyrotropin receptor–stimulating antibody (TRSAb). TRSAb binds to the receptor for TSH and stimulates cAMP, analogous to TSH itself. In addition to TRSAb, thyrotropin receptor–blocking antibody (TRBAb) may also be produced, and the clinical course of the disease usually correlates with the ratio between the two antibodies.

The ophthalmopathy occurring in Graves disease is caused by antibodies against antigens shared by the thyroid and eye muscle. The antibodies that bind to the extraocular muscles and orbital fibroblasts stimulate the synthesis of glycol-saminoglycans by orbital fibroblasts and produce cytotoxic effects on muscle cells.

In whites, Graves disease is associated with HLA-B8 and HLA-DR3; the latter carries a 7-fold relative risk for Graves disease. Therefore, it is not surprising that Graves disease is also associated with other HLA-D3–related disorders such as Addison disease, insulin-dependent diabetes mellitus, myasthenia gravis, and celiac disease. Systemic lupus erythematosus, rheumatoid arthritis, vitilago, idiopathic thrombocytopenic purpura, and pernicious anemia have been described in children with Graves disease. In family clusters, the most frequent association with Graves disease is lymphocytic thyroiditis, autoimmune hypothyroidism, and neonatal hyperthyroidism.

CLINICAL MANIFESTATIONS. About 5% of all patients with hyperthyroidism are under 15 yr of age; the peak incidence occurs during adolescence. Graves disease has begun between 6 wk and 2 yr of age in children born to mothers without a history of hyperthyroidism. The incidence is about five times higher in girls than in boys.

The clinical course in children is highly variable but usually is not so fulminant as in many adults. Symptoms develop gradually; the usual interval between onset and diagnosis is 6–12 mo. The earliest signs in children may be emotional disturbances accompanied by motor hyperactivity. The children become irritable, excitable, and cry easily owing to emotional lability. Their school work suffers as a result of a short attention span. Tremor of the fingers can be noticed if the arm is extended. There may be a voracious appetite combined with loss of or no increase in weight. The size of the thyroid is variable. It may be so little enlarged that it escapes detection initially, but with careful examination, a goiter is found in almost all patients. Exophthalmos is noticeable in most patients but is usually mild. Lagging of the upper eyelid as the eye looks downward, impairment of convergence, and retraction of the upper eyelid and infrequent blinking may be present. The skin is smooth and flushed, with excessive sweating. Muscular weakness is uncommon but may be severe enough to result in falling spells. Tachycardia, palpitations, dyspnea, and cardiac enlargement and

insufficiency cause discomfort but rarely endanger the patient's life. Atrial fibrillation is a rare complication. Mitral regurgitation, probably resulting from papillary muscle dysfunction, is the cause of the apical systolic murmur present in some patients. The systolic blood pressure and the pulse pressure are increased. Many of the findings in Graves disease result from hyperactivity of the sympathetic nervous system.

Thyroid "crisis" or "storm" is a form of hyperthyroidism manifested by an acute onset, hyperthermia, and severe tachycardia and restlessness. There may be rapid progression to delirium, coma, and death. "Apathetic" or "masked" hyperthyroidism is another variety of hyperthyroidism characterized by extreme listlessness, apathy, and cachexia. A combination of both forms may also occur. These symptom complexes are rare in children.

LABORATORY DATA. Serum levels of thyroxine (T4), triiodothyronine (T3), free T4, and free T3 are elevated. In some patients, levels of T3 may be more elevated than those of T4. Levels of TSH measured by a sensitive assay are suppressed below normal levels. Thyroid peroxidase antibodies are often present. Most patients with newly diagnosed Graves disease have measurable TSH receptor–stimulating antibodies, and their disappearance predicts remission of the disease. Assays of TSH-receptor antibodies are rarely necessary for diagnosis or management of Graves disease. Radioiodine is rapidly and diffusely concentrated in the thyroid, but this study is rarely necessary. Very young children with Graves disease often have advanced skeletal maturation and craniostenosis.

DIFFERENTIAL DIAGNOSIS. Diagnosis is rarely difficult once it has been considered. Elevated levels of T4 and free T4 in association with suppressed levels of TSH are usually diagnostic. The presence of TRSAb establishes the cause as Graves disease.

Most other causes of hyperthyroxinemia are rare but may result in erroneous diagnosis. Patients with elevated thyroxine-binding globulin (TBG) levels or familial dysalbuminemic hyperthyroxinemia have normal levels of free T4 and TSH. If a thyroid nodule is palpable, or if T3 is preferentially elevated, a functional thyroid nodule must be considered; radionuclide study is diagnostic. If precocious puberty, polyostotic fibrous dysplasia, or cafй{acute-e}-au-lait pigmentation is present, the autonomous thyroid disorder of McCune-Albright syndrome is likely. Patients with generalized thyroid hormone unresponsiveness have elevated or normal levels of free T4, but levels of TSH are inappropriately elevated. Patients with pituitary unresponsiveness to thyroid hormone also have clinical hyperthyroidism, but their levels of TSH are elevated or normal, and they must be differentiated from patients with TSH-secreting pituitary tumors, who have elevated serum levels of the TSH α chain.

When hyperthyroxinemia is caused by exogenous thyroid hormone, levels of free T4 and TSH are the same as those seen in Graves disease, but the level of

thyroglobulin is very low, although in patients with Graves disease, it is elevated.

TREATMENT. Most pediatric endocrinologists recommend medical therapy rather than subtotal thyroidectomy or radioiodine. The two thionamide drugs in widest use are propylthiouracil (PTU) and methimazole (Tapazole). Both compounds inhibit incorporation of trapped inorganic iodide into organic compounds, and they may also suppress levels of TRSAb by directly affecting intrathyroidal autoimmunity. But there are important differences between the two drugs. Methimazole is at least 10 times more potent than PTU on a weight basis and has a much longer serum half-life (6–8 hr vs 0.5 hr); PTU must be administered three times daily, but methimazole can be given once daily. Unlike methimazole, PTU is heavily protein bound and has a lesser ability to cross the placenta and to pass into breast milk; theoretically, PTU is the preferred drug during pregnancy and for nursing mothers. PTU, more than methimazole, inhibits extrathyroidal conversion of T4 to T3; this may be advantageous in the treatment of neonatal thyrotoxicosis.

Toxic reactions occur with both drugs; most are mild, but some are life threatening. They are unpredictable and can occur after therapy of any duration. There is increasing evidence that these reactions may be fewer in patients treated with methimazole. Transient leukopenia (<4,000/mm3) is common; it is asymptomatic and not a harbinger of agranulocytosis, and it usually is not a reason to discontinue treatment. Transient urticarial rashes are common. These can be managed by a short period off therapy and restarting the alternate antithyroid drug. The most severe reactions are hypersensitive in nature and include agranulocytosis, hepatitis, hepatic failure, a lupus-like syndrome, glomerulonephritis, and a vasculitis involving the skin and other organs. Although rare, these reactions have been reported with both drugs, and it is probably best to treat unusually hypersensitive patients with radioiodine or thyroidectomy. Cases of congenital skin defects (aplasia cutis) have been seen in infants exposed in fetal life to methimazole, but this association does not appear to be a strong one.

The initial dose of PTU is 5–10 mg/kg/24 hr given three times daily, and that of methimazole is 0.5–1.0 mg/kg/24 hr given once or twice daily. Smaller initial doses should be used in early childhood. Careful surveillance is required after treatment is initiated. Raising serum levels of TSH above normal indicates overtreatment and leads to increased size of the goiter. Clinical response becomes apparent in 2–3 wk, and adequate control is evident in 1–3 mo. The dose is decreased to the minimal level required to maintain a euthyroid state.

Drug therapy may be necessary for 6 yr or longer because there appears to be a remission rate of about 25% every 2 yr. If a relapse occurs, it will usually appear within 3 mo and almost always within 6 mo after therapy has been discontinued. Therapy may be resumed in case of a relapse. Patients over 13 yr of age, boys, and

those with small goiters and modestly elevated T3 levels appear to have earlier remissions.

A b{beta}-adrenergic blocking agent such as propranolol (0.5–2.0 mg/kg/24 hr, given three times daily) is a useful supplement in management of severely toxic patients. Thyroid hormones potentiate the actions of catecholamines, which include tachycardia, tremor, excessive sweating, lid lag, and stare. These symptoms abate with use of propranolol, which does not, however, alter thyroid function or exophthalmos.

Operation or radioiodine treatment is indicated when adequate cooperation for medical management is not possible or when adequate trial of medical management has failed to result in permanent remission. Subtotal thyroidectomy, a rather safe procedure, is performed only after the patient has been brought to a euthyroid state. This may be accomplished with PTU or methimazole over 2–3 mo. After a euthyroid state has been attained, 5 drops of a saturated solution of potassium iodide/24 hr are added to the regimen for 2 wk before operation to decrease the vascularity of the gland. Complications of surgical treatment are rare and include hypoparathyroidism (transient or permanent) and paralysis of the vocal cords. The incidence of residual or recurrent hyperthyroidism or of hypothyroidism depends on the extent of the surgery. Some recommend near-total thyroidectomy. The incidence of recurrence will be low, but that of hypothyroidism may exceed 50%.

Radioiodine has proved to be an effective, relatively safe first or alternate therapy for Graves disease in children. Pretreatment with antithyroid drugs is unnecessary; if a patient is on them, they should be stopped 5 days before radioiodine administration. Most children become euthyroid after one dose (88% in one study), but a few may require a second or third treatment dose. Because the full effects of treatment may not be complete for 2–3 mo, adjunctive therapy with a β-adrenergic antagonist is recommended. Although there have been concerns about radiation oncogenesis and genetic damage, follow-up of treated children for as long as 40 yr has not shown this. The risk of benign adenoma may be increased (0.6–1.9% in one study). The major consequence of radioiodine is hypothyroidism, which occurs in 10–20% of patients after the first year and in about 3% per year thereafter.

The ophthalmopathy remits gradually and usually independently of the hyperthyroidism. Severe ophthalmopathy may require treatment with prednisone.

Congenital Hyperthyroidism

Onset of neonatal hyperthyroidism usually begins prenatally and is present at birth, although it may not be noticed until a few days after birth; occasionally, onset may be delayed for several weeks or more. The mothers of these infants have active Graves disease, Graves disease in remission, or rarely, hypothyroidism and a history

of lymphocytic thyroiditis. The condition is caused by transplacental passage of TRSAb, but the clinical onset, severity, and course may be modified by

the concurrent presence of TRBAb and by the transplacental passage of antithyroid drugs taken by the mother. Very high levels of TRSAb usually result in classic neonatal hyperthyroidism, but if the infant has been exposed to the antithyroid drugs, onset of symptoms is delayed 3–4 days to allow degradation of the maternally derived antithyroid drug. If TRBAb is also present, onset of hyperthyroid symptoms may be delayed for several weeks.

Neonatal hyperthyroidism occurs in only about 2% of infants born to mothers with a history of Graves disease. The finding of very high levels of TRSAb in these mothers usually predicts the occurrence of an affected infant. Fetal tachycardia and goiter may allow prenatal diagnosis. Unlike Graves disease at all other ages, neonatal hyperthyroidism affects males as often as females. The disorder usually remits spontaneously within 6–12 wk but may persist longer, depending on the levels of TRSAb. Mild asymptomatic hyperthyroxinemia also occurs. Occasionally, classic neonatal Graves disease does not remit but persists for several years or longer. These patients have impressive family histories of Graves disease. In these infants TRSAb transfer from the mother apparently blends with the infantile onset of autonomous Graves disease.

Many of the infants are premature and appear intrauterine growth retarded. Most have goiters. The infant is extremely restless, irritable, and hyperactive and appears anxious and unusually alert. Microcephaly and ventricular enlargement may be present. The eyes are widely opened and appear exophthalmic. There may be extreme tachycardia and tachypnea, and the temperature is elevated. In severely affected infants, there is a progression of symptoms; weight loss occurs despite a ravenous appetite, hepatosplenomegaly increases, and jaundice may become manifest. Cardiac decompensation is common, and severe hypertension may occur. The infant may die if therapy is not instituted promptly. The serum level of T4 is markedly elevated and TSH is suppressed. Advanced bone age, frontal bossing with triangular facies, and cranial synostosis are common, especially in those infants with persistent clinical manifestations of hyperthyroidism. Prognosis for intellectual development is guarded for infants with cranial synostosis.

Treatment consists of oral administration of Lugol solution (1 drop every 8 hr) and PTU (5–10 mg/kg/24 hr given every 8 hr). If the thyrotoxic state is severe, parenteral fluid therapy, propranolol (2 mg/kg/24 hr, orally in three divided doses), and corticosteroids may be indicated. When propranolol is used during pregnancy to treat thyrotoxicosis, it crosses the placenta and may cause respiratory depression in the newborn infant. If heart failure occurs, digitalization is indicated. After a euthyroid state is reached, only PTU treatment is necessary. The dose should be

gradually tapered to keep the infant euthyroid. Most remit by 3–4 mo of age.

Occasionally, neonatal hyperthyroidism does not remit but persists into childhood. These patients may have an impressive family history of hyperthyroidism, but TSH-stimulating antibodies are absent. Advanced osseous maturation, microcephaly, and mental retardation occur when treatment is delayed. It has been recently established that a child with this disorder has a mutation of the TSH-receptor (TSHR) gene. A gene-line mutation in the TSHR gene resulted in constitutive activation of the receptor. Persistent and adequate treatment is necessary to prevent irreversible consequences.

Disorders of the Parathyroid Glands
Angelo M. DiGeorge • Stephen LaFranchi

Parathyroid hormone (PTH) and vitamin D are the principal regulators of calcium homeostasis. Calcitonin and PTH-related peptide (PTHrP) appear to be important primarily in the fetus.

PARATHYROID HORMONE. PTH is an 84-amino acid chain (9,500 dalton), but its biologic activity resides in the first 34 residues. In the parathyroid gland, a pre-proPTH (115–amino acid chain) and a proparathyroid hormone (90 amino acids) are synthesized. Pre-pro-PTH is converted to pro-PTH and pro-PTH to PTH. PTH (1–84) is the major secretory product of the gland, but it is rapidly cleaved in the liver and kidney into smaller COOH-terminal, midregion, and NH2-terminal fragments.

The occurrence of these fragments has complicated the reliable measurement of PTH in serum and has led to the development of a variety of assays. The 1–34 amino-terminal (N-terminal) fragments possess biologic activity but are present in very low amounts in the circulation; assay of these fragments is most useful for detecting acute secretory changes. The carboxy–terminal (C-terminal) and midregion fragments, although biologically inert, are cleared more slowly from the circulation and represent 80% of plasma immunoreactive PTH; values of the Cterminal fragment are 50–500 times the level of the active hormone. The C-terminal assays are effective in detecting patients with hyperparathyroidism, but because C-terminal fragments are removed from the circulation by glomerular filtration, these assays are less useful for evaluating the secondary hyperparathyroidism characteristic of renal disease. Only certain sensitive radioimmunoassays for PTH can differentiate the subnormal concentrations that occur in hypoparathyroidism from normal levels. A sensitive 15-min immunochemiluminometric assay, developed for intraoperative use, can provide the surgeon with useful information.

When serum levels of calcium fall, secretion of PTH increases. PTH stimulates activity of 1a{alpha}-hydroxylase in the kidney, enhancing production of 1,25-dihydroxycholecalciferol (1,25[OH]2D3). The increased level of 1,25[OH]2D3

induces synthesis of a calcium-binding protein (calbindin-D) in the intestinal mucosa with resultant absorption of calcium. PTH also mobilizes calcium by directly enhancing bone resorption, an effect that requires 1,25[OH]2D3. The effects of PTH on bone and kidney are mediated through binding to specific receptors on the membranes of target cells and through activation of a transduction pathway involving a G protein coupled to the adenylate cyclase system.

PTH-RELATED PEPTIDE. PTHrP is homologous to PTH only in the first 13 amino acids of its amino terminus, 8 of which are identical to PTH. Its gene is on the short arm of chromosome 12, and that of PTH is on the short arm of chromosome 11.

PTHrP, like PTH, activates PTH receptors in kidney and bone cells and increases urinary cAMP and renal production of 1,25[OH]2D3. It is produced in almost every type of cell of the body, including every tissue of the embryo at some stage of development. PTHrP is critical for normal fetal development, and deletion of the gene in mice results in neonatal death and skeletal defects. It appears to have a paracrine or autocrine role, because serum levels are quite low except in a few clinical situations. Cord blood contains levels of PTHrP that are three-fold higher than in serum from adults; it is produced by the fetal parathyroids and appears to be the main agent stimulating maternal-fetal calcium transfer. PTHrP appears to be essential for normal skeletal maturation of the fetus, which requires 30 g of calcium. During pregnancy, maternal absorption of calcium increases from about 150 mg daily to 400 mg during the second trimester.

As in cord blood, PTHrP levels are increased during lactation and in patients with benign breast hypertrophy. Breast milk and pastureized bovine milk have levels of PTHrP that are 10,000 times higher than those of normal plasma. Most instances of the hormonal hypercalcemia syndrome of malignancy are caused by elevated concentrations of PTHrP.

CALCITONIN (CT). CT is a 32–amino acid polypeptide. Its gene is on chromosome 11p and is tightly linked to that of PTH. The CT gene encodes three peptides: CT, a 21–amino acid carboxy-terminal flanking peptide (katacalcin), and a CT gene–related peptide. Katacalcin and CT are cosecreted in equimolar amounts by the parafollicular cells (C cells) of the thyroid gland. CT appears to be of little consequence in children and adults, because very high levels in patients with medullary carcinoma of the thyroid (a tumor arising from the C cells) does not cause hypercalcemia. In the fetus, however, circulating levels are high and appear to augment bone metabolism and skeletal growth; these high levels are probably stimulated by the normally high fetal calcium levels. Unlike the high levels in cord blood and circulating concentrations in young children, levels in older children and adults are quite low. Infants and children with congenital hypothyroidism (and presumed deficiency of C cells) have lower levels of CT than normal children.

Its action appears to be independent of PTH and of vitamin D. Its main biologic effect appears to be the inhibition of bone resorption by decreasing the number and activity of bone-resorbing osteoclasts. This action of CT is the rationale behind its use in treatment of Paget disease. CT is synthesized in other organs, such as the gastrointestinal tract, pancreas, brain, and pituitary. In these organs, CT is thought to behave as a neurotransmitter to impose a local inhibitory effect on cell function.

HYPOPARATHYROIDISM

ETIOLOGY. The normal level of parathyroid hormone (PTH) in cord blood is low; it doubles by the 6th day to reach a level nearly that of normal infants and children. Hypocalcemia is common from 12–72 hr of life, especially in premature infants, in infants with asphyxia at birth, and in infants of diabetic mothers (early neonatal hypocalcemia). After the 2nd–3rd day and during the 1st wk of life, the type of feeding is also a determinant of the level of serum calcium (late neonatal hypocalcemia). The role played by the parathyroids in these hypocalcemic infants remains to be clarified, although functional immaturity of the parathyroids has often been invoked as a pathogenetic factor. In a group of infants with transient idiopathic hypocalcemia (1–8 wk of age) serum levels of PTH were significantly lower than in normal infants. It is possible that the functional immaturity is a manifestation of a delay in development of the enzymes that convert glandular PTH to secreted PTH; other mechanisms are possible.

Hyperparathyroidism during pregnancy may result in transient hypocalcemia of the newborn infant. It appears that their hypocalcemia results from suppression of the fetal parathyroids by exposure to elevated levels of calcium in maternal serum. Tetany usually develops within 3 wk but may be delayed 1 mo or more if the infant is breast-fed. Hypocalcemia may persist for weeks or months. When the cause of hypocalcemia in young infants is unknown, their mothers should have measurements of calcium, phosphorus, and parathyroid hormone. Most affected mothers are asymptomatic, and the cause of their hyperparathyroidism is usually a parathyroid adenoma.

Aplasia or hypoplasia of the parathyroid glands is often associated with the DiGeorge syndrome and less often with the velocardiofacial (Shprintzen) syndrome. These two syndromes appear to be one and the same condition. Although the most common associations are conotruncal heart defects, thymic hypoplasia, abnormal facies, and cleft palate, the phenotype is variable, and the spectrum continues to widen. Most patients have a deletion within chromosome 22q11. Hypocalcemia usually occurs in the neonatal period and is often transient, but it may recur later or it may not have its onset until later in life. The syndrome and hypocalcemia also occur in some patients with the CHARGE and VATER syndromes, in infants of diabetic mothers, and in infants born to mothers treated with retinoic acid for acne early in

pregnancy.

Administration of 131I during pregnancy has resulted in hypoparathyroidism and in hypothyroidism.

Familial Congenital Hypoparathyroidism. Familial clusters of hypoparathyroidism with various patterns of transmission have been described. In two large North American pedigrees, this disorder appears to be transmitted by an X-linked recessive gene. In these families, the onset of afebrile seizures characteristically occurs in infants from 2 wk–6 mo of age. The absence of parathyroid tissue after detailed examination of a boy with this condition suggests it is a defect in embryogenesis.

An autosomal recessive syndrome of hypoparathyroidism with dysmorphic features has been described in Middle Eastern children. Parental consanguinity occurred for almost all of several dozen affected patients. Profound hypocalcemia occurs early in life, and dysmorphic features include microcephaly, deep-set eyes, beaked nose, micrognathia, and large floppy ears. Intrauterine and postnatal growth retardation are severe, and mental retardation is common. The cause is unknown. The autosomal recessive form of hypoparathyroidism that occurs with type I polyglandular autoimmune disease is described subsequently. In a few patients with autosomal recessive inheritance of isolated hypoparathyroidism, mutations of the PTH gene have been found.

Most often, hypoparathyroidism occurs as an autosomal dominant disorder. The gene has been localized to chromosome 3q13, the location of the Ca2+-sensing receptor. Inactivating mutations of this receptor result in familial hypocalciuric hypercalcemia and neonatal hyperparathyroidism. In patients with hypoparathyroidism, the mutation in the Ca2+-sensing receptor is an activating one, forcing the receptor to an "on" state and depression of PTH secretion. The hypocalcemia is usually mild and does not require treatment beyond childhood.

Another distinct form of autosomal dominant hypoparathyroidism is associated with sensorineural deafness and renal dysplasia.

Surgical Hypoparathyroidism. Removal or damage of the parathyroid glands may complicate thyroidectomy. Hypoparathyroidism has developed although the parathyroid glands have been identified and left undisturbed at the time of operation. This presumably is the result of interference with the blood supply or of postoperative edema and fibrosis. Symptoms of tetany may occur abruptly postoperatively and be temporary or permanent. In some instances, symptoms may develop insidiously and go undetected until months after thyroidectomy. Occasionally, the first evidence of surgical hypoparathyroidism may be the development of cataracts. The status of parathyroid function should be carefully monitored in all patients subjected to thyroidectomy.

Deposition in the parathyroid glands of iron pigment (e.g., thalassemia) or of copper (e.g., Wilson disease) may produce hypoparathyroidism.

Idiopathic Hypoparathyroidism. The term idiopathic should be reserved for the small residuum of children with hypoparathyroidism for when no etiologic mechanism can be defined. Most children in whom onset of hypoparathyroidism occurs after the first few years of life have an autoimmune condition. Some have incomplete forms of DiGeorge syndrome or the autosomal dominant type of familial hypoparathyroidism.

Autoimmune Hypoparathyroidism. An autoimmune mechanism for hypoparathyroidism is strongly suggested by the finding of parathyroid antibodies and by the frequent association with other autoimmune disorders or organ-specific antibodies. Autoimmune hypoparathyroidism is often associated with Addison disease and chronic mucocutaneous candidiasis. The association of at least two of these three conditions has been tentatively classified as polyglandular autoimmune disease, type I. One third of patients with this syndrome have all three components; two thirds have only two of three conditions. The candidiasis almost always precedes the other disorders (70% of cases occur in children younger than 5 yr of age); the hypoparathyroidism (90% after 3 yr of age) usually occurs before Addison disease (90% after 6 yr of age). A variety of other disorders occur at various times; these include alopecia areata or totalis, malabsorption disorder, pernicious anemia, gonadal failure, chronic active hepatitis, vitiligo, and insulin-dependent diabetes. Some of these associations may not appear until adult life. Autoimmune thyroid disease is a rare concomitant.

Affected siblings may have the same or different constellations of disorders (e.g., hypoparathyroidism and Addison disease). The disorder is thought to have an autosomal recessive mode of inheritance, and it occurs more frequently among Finns and Iranian Jews. Patients with Addison disease, whether isolated or part of polyendocrinopathy syndrome type I or type II, have demonstrated adrenal specific 21-hydroxylase autoantibody reactivity.

CLINICAL MANIFESTATIONS. There is a spectrum of parathyroid deficiencies with clinical manifestations, varying from no symptoms to those of complete and longstanding deficiency. Mild deficiency may be revealed only by appropriate laboratory studies. Muscular pain and cramps are early manifestations; they progress to numbness, stiffness, and tingling of the hands and feet. There may be only a positive Chvostek or Trousseau sign or laryngeal and carpopedal spasms. Convulsions with loss of consciousness may occur at intervals of days, weeks, or months. These may begin with abdominal pain, followed by tonic rigidity, retraction of the head, and cyanosis. Hypoparathyroidism is frequently mistaken for epilepsy. Headache, vomiting, increased intracranial pressure, and papilledema may be

associated with convulsions and may suggest a brain tumor.

The teeth erupt late and irregularly. Enamel formation is irregular, and the teeth may be unusually soft. The skin may be dry and scaly, and the nails of the fingers and toes may have horizontal lines. Manifestations of a wide variety of other disorders that are not direct consequences of PTH deficiency may also be seen. Mucocutaneous candidiasis, when present, antedates the development of hypoparathyroidism; the candidal infection most often involves the nails, the oral mucosa, the angles of the mouth, and less often, the skin.

Cataracts in patients with longstanding untreated disease are a direct consequence of hypoparathyroidism; other autoimmune ocular disorders such as keratoconjunctivitis may also occur. Manifestations of Addison disease, lymphocytic thyroiditis, pernicious anemia, alopecia areata or totalis, hepatitis, and primary gonadal insufficiency may also be associated with those of hypoparathyroidism.

Permanent physical and mental deterioration occur if initiation of treatment is long delayed.

LABORATORY DATA. The serum calcium level is low (5–7 mg/dL) and the phosphorus elevated (7–12 mg/dL). Blood levels of ionized calcium (approximately 45% of the total) more nearly reflect physiologic adequacy. The serum level of alkaline phosphatase is normal or low, and the level of 1,25[OH]2D3 is usually low, but high levels have been found in some children with severe hypocalcemia. The level of magnesium is normal but should always be checked in hypocalcemic patients. By immunometric assay serum levels of PTH are low. Administration of the synthetic 1–34 fragment of human PTH (teriparatide acetate) results in increased urinary levels of cAMP and phosphate. This response differentiates hypoparathyroidism from pseudohypoparathyroidism. With the advent of very sensitive PTH assays, this test may no longer be necessary. Roentgenograms of the bones occasionally reveal an increased density limited to the metaphyses, suggestive of heavy metal poisoning, or an increased density of the lamina dura. Roentgenograms or computed tomography of the skull may reveal calcifications in the basal ganglia. There is a prolongation of the QT interval on the electrocardiogram, which disappears when the hypocalcemia is corrected. The electroencephalogram usually reveals widespread slow activity; the tracing returns to normal after the serum calcium has been within the normal range for a few weeks unless irreversible brain damage has occurred or unless the parathyroid insufficiency is associated with epilepsy. When hypoparathyroidism occurs concurrently with Addison disease, the serum level of calcium may be normal, but hypocalcemia appears after effective treatment of the adrenal insufficiency.

TREATMENT. Emergency treatment for neonatal tetany consists of intravenous injections of 5–10 mL of a 10% solution of calcium gluconate at the rate of 0.5–1

mL/min. Additionally, 1,25-dihydroxycholecalciferol (calcitriol) should be given. The initial dose is 0.25 m{mu}g/24 hr; the maintenance dose ranges from 0.01–0.10 m{mu}g/kg/24 hr, to a maximum of 1–2 m{mu}g/24 hr. Calcitriol has a short half-life and should be given in two equal divided doses; it has the advantages of rapid onset of effect (1–4 days) and rapid reversal of hypercalcemia after discontinuation in the event of overdosage (i.e., calcium begins to fall in 3–4 days).

After normocalcemia has been achieved, one may wish to continue therapy with vitamin D2 because it is considerably less costly than calcitriol. The usual doses are 0.1–0.5 mg/24 hr in infants and young children. One milligram of vitamin D2 has a biologic activity of 40,000 IU. Older children require 1.25–2.50 mg (50,000–100,000 IU) once daily. Vitamin D2 has a slow onset of effect, and reversal of hypercalcemia after discontinuation of treatment is markedly delayed; its main advantage is its low cost.

An adequate intake of calcium should be ensured. Supplemental calcium can be given in the form of calcium gluconate or calcium glubionate (Neo-Calglucon) to provide 800 mg of elemental calcium daily, but it is rarely essential. Foods with a high phosphorus content such as milk, eggs, and cheese should be reduced in the diet.

Clinical evaluation of the patient and frequent determinations of the serum calcium levels are indicated in the early stages of treatment to determine the requirement for calcitriol or vitamin D2. If hypercalcemia occurs, therapy should be discontinued and resumed at a lower dose after the serum calcium level has returned to normal. In longstanding cases, repair of cerebral and dental changes is not likely. Pigmentation, lowering of the blood pressure, or weight loss may indicate adrenal insufficiency, which requires specific treatment.

DIFFERENTIAL DIAGNOSIS. Magnesium deficiency must be considered in patients with unexplained hypocalcemia. Concentrations of magnesium in serum below 1.5 mg/dL (1.2 mEq/L) are usually abnormal. Familial hypomagnesemia with secondary hypocalcemia has been reported in 37 patients, most of whom developed tetany and seizures from 2–6 wk of age. Administration of calcium is ineffective, but administration of magnesium promptly corrects both calcium and magnesium levels. Oral supplements of magnesium are necessary to maintain levels of magnesium in the normal range. The profoundly low levels of magnesium result from a specific defect in intestinal absorption. The disorder appears to be caused by an autosomal recessive gene.

Hypomagnesemia also occurs in malabsorption syndromes and has occurred in granulomatous colitis and cystic fibrosis. Therapy with aminoglycosides causes hypomagnesemia by increasing urinary losses. Patients with autoimmune hypoparathyroidism may have concurrent steatorrhea and low magnesium levels.

It is not clear how low levels of magnesium lead to hypocalcemia. Evidence

suggests that hypomagnesemia impairs release of PTH and induces resistance to the effects of the hormone, but other mechanisms also may be operative.

Poisoning with inorganic phosphate leads to hypocalcemia and tetany. Infants administered large doses of inorganic phosphates, either as laxatives or as sodium phosphate enemas, have had sudden onset of tetany, with serum calcium levels below 5 mg/dL and markedly elevated levels of phosphate. Symptoms are quickly relieved by intravenous administration of calcium. The mechanism of the hypocalcemia is not clear.

Hypocalcemia may occur early in the course of treatment of acute lymphoblastic leukemia. It is usually associated with hyperphosphatemia (resulting from destruction of lymphoblasts), which is probably the primary cause of hypocalcemia.

Episodic symptomatic hypocalcemia occurs in the Kenny-Caffey syndrome, which is characterized by medullary stenosis of the long bones, short stature, delayed closure of the fontanel, delayed bone age, and eye abnormalities. Idiopathic hypoparathyroidism and abnormal PTH levels have been found. Autosomal dominant and autosomal recessive modes of inheritance have been reported.

Etiologic Classification of Hypocalcemia

Etiologic Classification of Hypocalcemia

Parathyroid hormone (PTH) deficiency

  Aplasia or hypoplasia of parathyroids

    With 22q11 deletion

      DiGeorge syndrome

      Velocardiofacial syndrome

      Conotruncal–face syndrome

    With maternal diabetes mellitus or retinoic acid treatment

    With VATER, CHARGE syndromes

    With X–linked isolated hypoparathyroidism

  PTH gene mutations

    Autosomal recessive

  PTH receptor defects (pseudohypoparathyroidism)

    Type IA (inactivating mutation of Gsa)

      With gonadotropin–independent precocious puberty

    Type IB (normal Gsa)

    Type II (normal cAMP response)

  Ca2+-sensing receptor defects

    Activating mutation (autosomal dominant)

  Autoimmune parathyroiditis

    Isolated

    With Addison disease or mucocutaneous candidiasis (type 1

autoimmune polyendocrinopathy)

   Infiltrative lesions

     Hemosiderosis (treatment of thassemia)

     Copper deposition (Wilson disease)

   Unknown cause of hypoparathyroidism

     With dysmorphic features in Middle Eastern children

      Autosomal recessive

     With sensorineural deafness and renal dysplasia

      Autosomal dominant

     Kenny–Caffey syndrome

 Vitamin D deficiency (see Chapter 45.3)

 Magnesium deficiency

   Primary hypomagnesemia

   Renal tubular defect

   Aminoglycoside therapy

 Inorganic phosphate excess

   Laxatives

PSEUDOHYPOPARATHYROIDISM
(ALBRIGHT HEREDITARY OSTEODYSTROPHY)

In this syndrome, in contrast to the situation in idiopathic hypoparathyroidism, the parathyroid glands are normal or hyperplastic histologically, and they can synthesize and secrete parathyroid hormone (PTH). Serum levels of immunoreactive PTH are elevated when the patient is hypocalcemic. Neither endogenous nor administered PTH raises the serum levels of calcium or lowers the levels of phosphorus. The genetic defects in the hormone receptor–adenylate cyclase system are classified into various types depending on the phenotypic and biochemical findings.

TYPE IA. This type accounts for 50% of patients with pseudohypoparathyroidism (PHP). Affected patients have a genetic defect of the α subunit of the stimulatory guanine nucleotide–binding protein (Gsα). This coupling factor is required for PTH bound to cell-surface receptors to activate cAMP. Heterogeneous mutations of the Gsα gene have been documented. Deficiency of the G unit is a generalized cellular defect and accounts for the association of other endocrine disorders with type IA PHP. The defect is inherited as an autosomal dominant trait, and the paucity of father-to-son transmissions is thought to be due to decreased fertility in males.

Tetany is often the presenting sign. Affected children have a short, stocky build and a round face. Brachydactyly with dimpling of the dorsum of the hand is usually present. The 2nd metacarpal is the least often involved. As a result, the index finger

may occasionally be longer than the middle finger. Likewise, the 2nd metatarsal is only rarely affected. There may be other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of the calvaria. These patients frequently have calcium deposits and metaplastic bone formation subcutaneously. Moderate degrees of mental retardation, calcification of the basal ganglia, and lenticular cataracts are common in patients who are diagnosed late.

Some members of affected kindreds may have the usual anatomic stigmata of PHP, but serum levels of calcium and phosphorus are normal despite reduced Gsα activity and mutations in its gene. This variant of PHP type Ia is called pseudopseudohypoparathyroidism. Transition from the normocalcemic to the hypocalcemic form has been observed. These phenotypically similar but metabolically dissimilar patients also have mutations of Gsα protein. It is not known what other factors cause clinically overt hypocalcemia.

In addition to resistance to PTH, resistance to the metabolic effects of TSH, gonadotropins, and glucagon may be detected in patients with type IA PHP. Clinical hypothyroidism is uncommon, but basal levels of TSH are elevated, and TRH-stimulated TSH responses are exaggerated. Moderately decreased levels of thyroxine and increased levels of TSH have been detected in newborn thyroid screening programs, leading to the detection of type IA PHP in infancy. In adults, gonadal dysfunction is common, as manifested by sexual immaturity, amenorrhea, oligomenorrhea, and infertility. Each of these abnormalities can be related to deficient synthesis of cAMP secondary to a deficiency of Gsα, but it is not clear why resistance to other G-protein–dependent hormones (e.g., corticotropin, vasopressin) is much less affected.

Serum levels of calcium are low, and those of phosphorus and alkaline phosphatase are elevated. Levels of both immunoreactive and bioactive PTH are elevated. Definitive diagnosis rests on the demonstration of a markedly attenuated response in urinary phosphate and cAMP after intravenous infusion of the synthetic 1–34 fragment of human PTH (teriparatide acetate).

Type IA with Precocious Puberty. Two boys with type IA PHP were reported to have gonadotropin-independent precocious puberty (see Chapter 517.6). They have a single mutation of Gsα rendering the G protein temperature sensitive. At normal body temperature (37ϵ{degree} C), the Gsα is degraded, resulting in PHP, but in the cooler temperature of the testes (33ϵ{degree} C), the Gsα results in constitutive activation of the luteinizing hormone receptor and precocious puberty.

TYPE IB. Affected patients have normal levels of G-protein activity and a normal phenotypic appearance. These patients have resistance to PTH but not to other hormones. Serum levels of calcium, phosphorus, and immunoreactive PTH are the same as those in patients with type IA PHP; however, bioactive PTH is not increased.

The pathophysiology of the disorder in this group of patients is uncertain. Proposed explanations include production of a defective, biologically inactive hormone, presence of inhibitory PTH peptides, and a defect in the PTH receptor or in the catalytic subunit of adenyl cyclase. It is likely that the cause of the abnormality in this group is heterogeneous.

TYPE II. This type of pseudohypoparathyroidism has been detected in only a few patients and differs from type I in that the urinary excretion of cAMP is elevated both in the basal state and after stimulation with PTH, but phosphaturia does not increase. It appears that cAMP is normally activated, but the cell is unable to respond to the signal.

HYPERPARATHYROIDISM

Excessive production of parathyroid hormone (PTA) may result from a primary defect of the parathyroid glands such as an adenoma or hyperplasia (primary hyperparathyroidism).

More often, the increased production of PTH is compensatory, usually aimed at correcting hypocalcemic states of diverse origins (secondary hyperparathyroidism). In vitamin D–deficient rickets and in the malabsorption syndromes, intestinal absorption of calcium is deficient, but hypocalcemia and tetany may be averted by increased activity of the parathyroid glands. In pseudohypoparathyroidism, PTH levels are elevated because of mutation in the Gsa{alpha} protein interferes with PTH response. Early in chronic renal disease, hyperphosphatemia results in a reciprocal fall in the calcium concentration with a consequent increase in PTH, but in advanced stages of renal failure, production of 1,25[OH]2D3 is also decreased, leading to increased hypocalcemia and further stimulation of PTH. In some instances, if stimulation of the parathyroids has been sufficiently intense and protracted, the glands may continue to secrete increased levels of PTH for months or years after renal transplantation, with resulting hypercalcemia.

ETIOLOGY. Primary hyperparathyroidism is rare in children. When its onset occurs in the neonatal period, it is always caused by generalized hyperplasia of the parathyroid glands, but onset during childhood is usually the result of a single benign adenoma.

Neonatal primary hyperparathyroidism has been reported in fewer than 50 infants. Symptoms develop shortly after birth and consist of anorexia, irritability, lethargy, constipation, and failure to thrive. Roentgenograms reveal subperiosteal bone resorption, osteoporosis, and pathologic fractures. Symptoms may be mild, resolving without treatment, or may have a rapidly fatal course if diagnosis and treatment are delayed. Histologically, the parathyroid glands consist of diffuse hyperplasia. Affected siblings have been observed in three kindreds, and parental

consanguinity has been reported in four kindreds.

Many affected infants have been in kindreds with the clinical and biochemical features of familial hypocalciuric hypercalcemia (FHH). These infants are homozygous for the mutation in the Ca2+-sensing receptor gene; individuals with one copy of this mutation exhibit autosomally dominant familial hypocalciuric hypercalcemia.

Childhood hyperparathyroidism usually becomes manifest after 10 yr of age and is most frequently caused by a single adenoma. There have been many kindreds in which three or more members have hyperparathyroidism. In such cases of autosomal dominant hyperparathyroidism, most of the affected family members are adults, but children have been involved in about a third of the pedigrees. Some affected patients in these families are asymptomatic and are detected only by careful study. In some kindreds, hyperparathyroidism also occurs as part of the constellation known as the multiple endocrine neoplasia (MEN) syndromes.

MEN type I is an autosomal dominant disorder characterized by hyperplasia or neoplasia of the pancreatic islets (which secrete gastrin, insulin, pancreatic polypeptide, or occasionally glucagon), the anterior pituitary (which usually secretes prolactin), and the parathyroids. In most kindreds, hyperparathyroidism is usually the presenting manifestation, with a prevalence approaching 100% by 50 yr of age but occurring only rarely in children younger than 18 yr of age. In the past, after an affected family was identified, it was necessary to perform repeated metabolic screening for many years to detect other affected family members. With appropriate DNA probes, it is possible to detect carriers of the gene with 99% accuracy as early as birth, avoiding unnecessary biochemical screening programs.

The gene for MEN type I has been localized to 11q13. The gene appears to function as a tumor-suppressor gene and follows the two-hit hypothesis of tumor development. The 1st mutation (germinal) is inherited and is recessive to the dominant allele; this does not result in tumor formation. A 2nd mutation (somatic) is required to eliminate the normal allele, which leads to tumor formation.

MEN type II is also associated with hyperparathyroidism .

Transient neonatal hyperparathyroidism has occurred in a few infants born to mothers with hypoparathyroidism (idiopathic or surgical) or with pseudohypoparathyroidism. In each case, the maternal disorder had been undiagnosed or inadequately treated during pregnancy. The cause of the condition is chronic intrauterine exposure to hypocalcemia with resultant hyperplasia of the fetal parathyroid glands. In the newborn, manifestations involve the bones primarily, and healing occurs between 4 and 7 mo.

CLINICAL MANIFESTATIONS. At all ages, the clinical manifestations of hypercalcemia of any cause include muscular weakness, anorexia, nausea, vomiting,

constipation, polydipsia, polyuria, loss of weight, and fever. Calcium may be deposited in the renal parenchyma (nephrocalcinosis), with progressively diminished renal function. Renal calculi are common and may produce renal colic and hematuria. Osseous changes may produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors. Height may decrease from compression of vertebras; the patient may become bedridden. Completely asymptomatic patients are being detected with the use of automated serum calcium determinations.

Abdominal pain is occasionally prominent and may be associated with acute pancreatitis. Parathyroid crisis may occur, manifested by serum calcium levels greater than 15 mg/dL and progressive oliguria, azotemia, stupor, and coma. In infants, failure to thrive, poor feeding, and hypotonia are common. Mental retardation, convulsions, and blindness may occur as sequelae.

LABORATORY DATA. The serum calcium level is elevated; 39 of 45 children with adenomas had levels over 12 mg/dL. The hypercalcemia is more severe in infants with parathyroid hyperplasia; concentrations ranging from 15–20 mg/dL are common, and values as high as 30 mg/dL have been reported. Ionized (Ca2+) calcium levels are often elevated, even when total serum calcium is borderline or only slightly elevated. The serum phosphorus level is reduced to about 3 mg/dL or less, and the level of serum magnesium is low. The urine may have a low and fixed specific gravity, and serum levels of nonprotein nitrogen and uric acid may be elevated. In patients with adenomas who have skeletal involvement, serum phosphatase is elevated, but in infants with hyperplasia the levels of alkaline phosphatase may be normal even when there is extensive involvement of bone.

Serum levels of PTH measured by carboxy-terminal antisera are elevated, especially in relation to the level of calcium. Results may vary markedly from one laboratory to another, depending on the antibody used. Calcitonin levels are normal. Acute hypercalcemia can stimulate calcitonin release, but with prolonged hypercalcemia, hypercalcitoninemia does not occur.

The most consistent and characteristic roentgenographic findings are resorption of subperiosteal bone, best seen along the margins of the phalanges of the hands. In the skull, there may be gross trabeculation or a granular appearance resulting from focal rarefaction; the lamina dura may be absent. In more advanced disease, there may be generalized rarefaction, cysts, tumors, fractures, and deformities. About 10% of patients have roentgenographic signs of rickets. Roentgenograms of the abdomen may reveal renal calculi or nephrocalcinosis.

DIFFERENTIAL DIAGNOSIS. Hypercalcemia of any origin results in a similar clinical pattern; other causes must be differentiated from hyperparathyroidism (Table 527–1 Table 527–1). A low serum phosphorus level with hypercalcemia is characteristic of primary hyperparathyroidism; elevated levels of PTH are also

diagnostic. With hypercalcemia of any cause except hyperparathyroidism and familial hypocalciuric hypercalcemia, PTH levels are suppressed. Pharmacologic doses of corticosteroids lower the serum calcium level to normal in patients with hypercalcemia from other causes but generally do not affect the calcium level in patients with hyperparathyroidism.

TREATMENT. Surgical exploration is indicated in all instances. All glands should be carefully inspected; if an adenoma is discovered, it should be removed; very few instances of carcinoma are known in children. Most neonates with severe hypercalcemia require total parathyroidectomy; less severe hypercalcemia may remit spontaneously in others. A portion of a parathyroid gland may be autografted into the forearm; four infants treated in this fashion were able to maintain normocalcemia without supplementary treatment, but no long-term outcome has yet been reported. The patient should be carefully observed postoperatively for the development of hypocalcemia and tetany; intravenous administration of calcium gluconate may be required for a few days. The serum calcium level then gradually returns to normal, and under ordinary circumstances, a diet high in calcium and phosphorus needs to be maintained for only several months after operation.

Arteriography and selective venous sampling with radioimmunoassay of PTH for preoperative localization and for differentiation of a single adenoma from hyperplasia have been replaced by imaging methods. Computed tomography, real-time ultrasound, and subtraction scintigraphy using 99mTc pertechnetate and 201Tl have each proved effective in 50–90% of adults. These procedures are rarely required by the expert parathyroid surgeon but may be advisable before re-exploration in cases of persistent or recurrent hyperparathyroidism.

PROGNOSIS. The prognosis is good if the disease is recognized early and there is appropriate surgical treatment. When extensive osseous lesions are present, deformities may be permanent; with renal disease the prognosis is less hopeful. A search for other affected family members is indicated.

Other Causes of Hypercalcemia

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FAMILIAL BENIGN HYPERCALCEMIA). Patients with this disorder are usually asymptomatic, and the hypercalcemia comes to light by chance during routine investigation for other conditions. The parathyroid glands are normal, PTH levels are inappropriately normal, and subtotal parathyroidectomy does not correct the hypercalcemia. Serum levels of magnesium are high normal or mildly elevated. The rate of calcium to creatinine clearance is usually decreased despite hypercalcemia. The disorder is inherited in an autosomal dominant manner and is caused by a mutant gene on chromosome 3q2. Penetrance is near 100%, and affected individuals can be diagnosed early in childhood by serum and urinary calcium concentrations. Detection

of other affected family members is important to avoid inappropriate parathyroid surgery. The basic defect in this condition results from inactivating mutations in the CA2+-sensing receptor gene. This G-protein–coupled receptor senses the level of free CA2+ in the blood and triggers the pathway to increase intracellular CA2+. It appears that this receptor functions in the parathyroid and kidney to regulate calcium homeostasis; inactivating mutations lead to resistance to extracellular Ca2+ with mild to moderate hypercalcemia in heterozygotes.

GRANULOMATOUS DISEASES. Hypercalcemia occurs in 30–50% of children with sarcoidosis and less often in patients with other granulomatous diseases such as tuberculosis. Levels of PTH are suppressed, and levels of 1,25[OH]2D3 are elevated. The source of ectopic 1,25[OH]2D3 is the activated macrophage, through stimulation by interferon α from T lymphocytes, which are present in abundance in granulomatous lesions. Unlike renal tubular cells, the 1α-hydroxylase in macrohages is unresponsive to homeostatic regulation. Oral administration of prednisone (2 mg/kg/24 hr) lowers serum levels of 1,25[OH]2D3 to normal and corrects the hypercalcemia.

HYPERCALCEMIA OF MALIGNANCY. Hypercalcemia frequently occurs in adults with a wide variety of solid tumors but is identified much less often in children. It has been reported in infants with malignant rhabdoid tumors of the kidney or congenital mesoblastic nephroma and in children with neuroblastoma, medulloblastoma, leukemia, Burkitt lymphoma, and rhabdomyosarcoma. Serum levels of PTH are rarely elevated. In most patients, the hypercalcemia associated with malignancy is caused by elevated levels of PTHrP. Rarely, tumors produce 1,25[OH]2D3 or PTH ectopically.

MISCELLANEOUS CAUSES OF HYPERCALCEMIA. Hypercalcemia may occur in infants with subcutaneous fat necrosis. Levels of PTH are normal. In one infant, the level of 1,25[OH]2D was elevated, and biopsy of the skin lesion revealed granulomatous infiltration, suggesting that the mechanism of the hypercalcemia was akin to that seen in patients with other granulomatous disease. In another infant, although 1,25[OH]2D was normal, PTH was suppressed, suggesting the hypercalcemia was not PTH related. Treatment with prednisone is effective.

Hypophosphatasia, especially the severe infantile form, is usually associated with mild to moderate hypercalcemia. Serum levels of phosphorus are normal, and those of alkaline phosphatase are subnormal. The bones exhibit rachitic-like lesions on roentgenograms. Urinary levels of phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5ŕ{prime}-phosphate are elevated; each is a natural substrate to a tissue-nonspecific (liver, bone, kidney) alkaline phosphatase enzyme. Missense mutations of the gene result in an inactive enzyme in this autosomal recessive disorder.

Idiopathic hypercalcemia of infancy is manifested by failure to thrive and hypercalcemia during the 1st yr of life followed by spontaneous remission. Serum levels of phosphorus and PTH are normal. The hypercalcemia results from increased absorption of calcium. Vitamin D may be involved in the pathogenesis. Both normal and elevated levels of 1,25[OH]2D have been reported. An excessive rise in the level of 1,25[OH]2D in response to PTH administration years after the hypercalcemic phase suggests that vitamin D has a role in the pathogenesis. A blunted calcitonin response to intravenous calcium has also been reported.

Williams syndrome is frequently associated with infantile hypercalcemia. The phenotype consists of feeding difficulties, slow growth, an elfin facies, renovascular disorders, and a gregarious personality. The IQ scores of 50 to 70 is curiously accompanied by enhanced quantity and quality of vocabulary, auditory memory, and social use of language. A submicroscopic deletion at chromosome 7q11.23, which includes deletion of one elastin allele, occurs in 90% of patients and seems to account for the vascular problems. The hypercalcemia and central nervous system symptoms may be caused by deletion of adjacent genes. Hypercalcemia has been successfully controlled with either prednisone or calcitonin.

Hypervitaminosis D resulting in hypercalcemia from drinking milk incorrectly fortified with vitamin D has been reported. Serum levels of 25[OH]D is a better indicator of hypervitaminosis D than 1,25[OH]2D because of its longer half-life.

Prolonged immobilization may lead to hypercalcemia and occasionally to decreased renal function, hypertension, and encephalopathy.

Jansen-type metaphyseal chondrodysplasia is associated with asymptomatic hypercalcemia and hypophosphatemia; a constitutively active mutant PTH-PTHrP receptor appears to be the cause.

VI. Plan and organizational structure of classes.

№ п/п	Basic stages of classes, their function and maintenance	Educational aims are in the levels of mastering	Methods of control and studies	Educational materials	Distributing of time in minutes
1	**Preparatory stage** Organizational measures Raising of educational aims and motivation Control of basic knowledges and skills level: 1. Etiology of diffuse toxic goitre, hypo-thyroidism, autoim-	α2 α2	Individual oral questioning Test control of the second level Individual (oral) questioning	I «Actuality of theme» II «Educational aims» The second level tests The table «classification of thyroid gland diseases» Structurally logical chart of thyroid diseases Typical situational task of 2 level	3 min. 12 min. 20 min.

	mune thyroiditis, endemic goitre, acute and subacute thyroiditis, diffuse untoxic goitre, thyroid cancer in children		Typical situational task of the 2 level	Tests of 2 level Typical situational tasks of 2 level Kit of medicines.	
	2.Key links of thyroid diseases pathogenesis; classification of throid diseases;	α2	Typical situational task of 2 level Typical situational task of 2 level Test control of 2 level		
	3.Goitre degrees; 4.Typical manifesta-tion of diffuse toxic goitre, autoimmune thyroiditis, endemic goitre, acute and subacute thyroiditis, diffuse non toxic goitre in children.	α2 α2	Typical situational task of 2 level		
	5. Laboratory and instrumental diagno-sis of hypothyroidism and hypothyroidism:	α2			
	6.Complication of diffuse toxic goitre, autoimmune thyroiditis, endemic goitre, acute and subacute thyroiditis, diffuse non toxic goitre in children.;	α2			
	7.Treatment princip-les of diffuse toxic goitre, autoimmune thyroiditis, endemic goitre, acute and subacutethyroiditis, diffuse non toxic goitre in children;	α2			
2	**Basic stage of professional skills and abilities forming:** 1.To conduct the patient's management with thyroid diseases, to take complaints and anamnesis.	α3	Practical professional training	Patient	115 min.
	2.To conduct the pa-teint examination, to detect main sym-ptoms and syndromes	α3	Practical professional training	Patient	

			Practical professional training	Case history	
	3.To formulate and substantiate the preliminary diagnosis	α3			
	4.To compose the plan of patient's laboratory and instrumental investigation.	α3	Practical professional training	A reference chart for forming of professional abilities. Case history.	
	5.Interpret the results of laboratory and instrumental investigation.	α3	Tests and the third level control. The third level test control.	A reference chart for forming of professional abilities. Situational typical tasks of 3 level.	
	6.To conduct differrential diagnosis among clinical conditions accompanied by thyroid gland changes.	α3	The practical professional training in solving of non typical clinical situations.	The third level tests. Prescribing chart	
	7.To give the recommendations for regimen and diet of patient.	α3	The third level test control. Practical professional training.	The third level non typical situational tasks.	
	8.To compose the plan of thyroid disease patient treatment taking into account the stage of the disease and the presence of complications.	a3	The third level test control. The practical professional training on solving of non	Treatment algorithm for the thyroid diseases patients. The third level non typical situational tasks.	
	9.To be able to render the first aid in extreme situations	α3	typical clinical situations.	The first aid algorithm in thyroid diseases.	
3	**Concluding stage.** Control and correction of professional abilities and skills. Working out the totals of class. Home work (basic and additional literature on the topic)		Analysis of clinical work. Solving of non typical tasks and the third level tests. Estimation of the clinical work.	Clinical work. The third level non typical situational tasks. A reference chart for independent work with literature	30 min.

Questions for elementary level of knowledge control

1. The role of thyroid hormones, mechanism of action and regulation of secretion,

2. The degrees of thyroid gland enlargement.

3. Definition of struma. Different kinds of struma.

4. Laboratory methods for the diagnosis of thyroid glands disorders.

5. Factors promotes the development of diffuse toxiferous struma.

6 What is the classic clinical tirade in diffuse toxiferous struma.

7.The principles of conservative treatment in diffuse toxiferous struma and indications to the surgical treatment.

8. Causes and treatment of thyroid toxic crisis.

9. Laboratory and instrumental criterions of hypothyroidism in children.

10. The causes of development of asquired and congenital hypothyroidism. The principles of treatment. Specialties in early age children.

11. Clinical and laboratory criterions of thyroiditis. Treatment.

12. The criterions of compensation in thyroid gland disorders in children.

13. Methods of early diagnosis of thyroid gland cancer in children.

The primary control tests

1. Patient Г., 14 years old, complains of irritability, sweating, tremor of hands, palpitation, decreasing of body weight in normal appetite. The thyroid gland enlarged up to II degree, unpainful, elastic. The diagnosis of diffuse toxiferous struma clinically fixed. What from results of examination will confirm your diagnosis?
   A Hyperphosphatemia
   B. T3 and T4 is normal
   C. T3 and T4 is reduced
   D. Hypocalcaemia
   E. T3 and T4 is increased

2. Girl of 14 years old complains of sleeping disturbances, decreasing of body weight, palpitation, cardialgias, and fatigability. A thyroid gland hyperplasia of II degree and exophthalmia is marked.. What changes in hormones level are most typical for this disease?
   A. Decreasing of a thyroxin
   B. Increasing of Thyrotrophic hormone
   C. Increasing of the iodine level connected to protein
   D. Rising a thyroxin and triiodthyronin
   E. Increasing of triiodthyronin

3. In the girl of 12 years old after examination the diagnosis of mild diffuse toxic struma established. What dose of thyreostatic Mercazolilum is necessary to administrate for child in this case?
   A. 10-15 mg per day
   B.5-10 mg per day
   C. 20-30 mg per day
   D.1-5 mg per day
   E.40-50 mg per day

4. In the child of 4 years old the basic exchange is 28 %, a level of a cholesterol in a blood is 8,6 mmol/l, inclusion of a radioactive iodine in a thyroid gland after 6 hours is 2,1 %, after 24 hours is 3,0 %, after 48 hours is 3,5 %.
   For what disease such laboratory parameters are characteristic?

A. Diabetes

B. Hypothyroidism

C. Diseases of metabolism

D. Hyperthyroidism

E. Pituitary nanism

5.   In child clinical examination there are follow signs revealed - skin humidity, exaltation, irritability, decreasing of body weight, tachycardia, syndromes of Grefe, Stellwag, Moebius, palpitation. For what disease these signs are characteristic?

A. Acromegalia

B. Hypothyroidism

C. Diabetes

D. Down disease

E. Thyreotoxicosis

6. In examination of 14 years old girl the nodal struma of III degree is found out. On scenogramm the "hot" unit revealed. Levels of T3 and T4 in a blood are increased. What disease is it possible to think of?

A. Diffuse toxic struma

B Cancer of a thyroid gland

C Toxic adenoma of a thyroid gland

D Autoimmune thyroiditis

E. Fibrous struma of Riddell

7. In the patient. of 13 years old, relapse of a nephrolithiasis, ostealgia, weakness, fatigability, growing thin are observed.

What from the specified diseases can be suspected?

A. Sarcoma of bones

B Hypoparathyrosis

C. Hyperparathyroidism

D. Multiple myeloma

E. Any of the specified diseases

8. Patient G., complains of irritability, sweating, a tremor of hands, palpitation, body weight reduction in normal appetite. The thyroid gland is enlarged up to I – II degree, unpainful, elastic. The specified symptomatology most of all corresponds to:

A. to a diffuse toxiferous struma

B. to nervosisms

C. to a hypothyroidism

D. to a nodal toxic struma

E. to a hypoparathyrosis

9. In examination of 14 years old girl the nodal struma of III degree is found out. On scenogramm the "hot" unit revealed. Levels of T3 and T4 in a blood are increased.

What treatment will you recommend to the patient?

A. Thyrostatic preparations

B. Preparations of inorganic iodine

C. Radio-active iodine
D. Surgical treatment
E. Supervision

10. In boy of 15 years old the attacks of seizures in masseters and hands with prevalence of flexors tone are observed. Seizures are painful and symmetric. In examination there are positive signs of Hvostek and Trussot.
    What is your diagnosis?
    A. Epilepsy
    B Hypoparathyroidism
    C. Hyperparathyroidism
    D. Tetanus
    E. Spasmophilia

11. In the girl of 13 years old in examination there is I degree thyroid gland enlargement. Does not show any complaints. In palpation the thyroid gland is elastic, painless and of homogeneous consistence, . In investigation the disorders of thyroid gland functions are not revealed, a level of thyroid hormones are normal. What is the diagnosis?
    A. Juvenile struma.
    B. Autoimmune thyroiditis.
    C. Cancer of a thyroid gland.
    D. Diffuse toxic struma.
    E. Ridel fibrosal struma.

12. In the girl of 10 years old, complaints to irritability, sweating, pains in the area of heart, headache. Enlargement of a thyroid gland. In examination the III degrees nodal struma is found out. Skin is wet, hot by touch, tachycardia 104 b. per minute. On a scanning image the hot node reveals. Level of thyroid hormones is high. What is the diagnosis?
    A. Diffuse toxic struma.
    B. Autoimmune thyroiditis.
    C. A cancer of a thyroid gland.
    D. Toxic adenoma.
    E. Ridel fibrosal struma

13. Patient C., 14 years old, enlargement of a thyroid gland is marked during 3 months, gland is unpainful and mobile. On scenogramme there is some non-uniformity of structure admitted.
    What is it possible to suspect on the basis of resulted data?
    A. Diffuse toxiferous struma
    B. Cancer of a thyroid gland
    C. Autoimmune thyroiditis
    D. Subacute thyroiditis
    E. Fibrous thyroiditis

14. What is typical for the secondary hypothyroidism?

A. A low level of Adrenocorticotrophin.
B. A high level of thyroliberin.
C. A low level of thyroliberin.
D. A low level of thyrotropin.
E. A high level of thyrotropin.

15. In examination of 10 years old child the small body height, disproportionate of a body development, lag in mental development, constipations are fixed. What hormone's deficiency caused these signs?
A. Thyroxine
B. Parathormone
C. Thyrocalcitonin
D. Corticotropin
E. Oxytocinum

16. In 2 week old newborn there are constipations, icterus, flaccidity, sleepiness. In examination: moderate icterus, inflated abdomen, enlargement of liver and lien, puffing in respiration. What is the most probable diagnosis?
A. Hepatitis
B. Down syndrom
C. Rinitis.
D Hypothyroidism.
E. Rickets.

17. In the patient of 10 years old the delicacy, fatigability, decreasing of progress in school, dry and cold skin, fragility of hair and nails are marked. During the further investigation the hypothyroidism was diagnosed. What therapy is necessary to prescribe for this patient?
A. Mercazolilum.
B. Prednisolonum.
C.**Thyroxine.**
D. DOCSA.
E. Hidrocortisonum.

18. Child, in 9 months old for the first time the congenital hypothyroidism clinically and according to thyroid hormones tests was confirmed. Now the most expressive manifestation is the serious lag in psychophysical development. What in this case the most rational therapeutic tactics?
A. Mercazolilum
B. Thyreoidinum
C. Ttriiodthyroninum
D. L-thyroxine + Pyracetamum
E. L-thyroxine + Retabolilum

19. In the patient of 10 years old the delicacy, fatigability, decreasing of progress in school, dry and cold skin, fragility of hair and nails are marked. During the further investigation the hypothyroidism was diagnosed. What therapy is necessary to

prescribe for this patient?
- A. Mercazolilum.
- B. Prednisolonum.
- C. **Thyroxine.**
- D. DOCSA.
- E. Hidrocortisonum

20. In examination of 10 years old child the small body height, disproportionate of a body development, lag in mental development, constipations are fixed. What hormone's deficiency caused these signs?
- **A. Thyroxine**
- B. Parathormone
- C. Thyrocalcitonin
- D. Corticotropin
- E. Oxytocinum

Answers to the primary control tests
1-E, 2-D, 3-C, 4-B, 5-E, 6-C, 7-C, 8-A, 9-D, 10-B, 11-A, 12-D, 13-C, 14-D, 15-A, 16-D, 17-C,18-D, 19-C, 20-A.

Situational tasks
Situational Task 1
You are seeing a 2-week-old boy at a routine visit. The mother complains that he has been constipated, jaundiced, sluggish, and excessively sleepy. The physical examination is normal except for mild jaundice and a distended abdomen in a sleepy infant.

1. What assessment is the most appropriate course to pursue initially?
2. What diagnosis is most likely indicates?
3. What tests are confirmed the suspected diagnosis?

The answers are
1. The results of the neonatal metabolic screen
2. Congenital hypothyroidism
3. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), and thyroglobulin in the infant.
The main thrust is directed at the need for speed in the diagnosis and treatment of congenital hypothyroidism because the earlier treatment is started with thyroid hormone, the better the prognosis for intellectual function. Time should not be spent in exhaustive investigation. Regardless of the reason for the hypothyroidism, treatment with replacement thyroid hormone is indicated. If it turns out that the initial diagnosis was erroneous, little harm will be done by treating an infant with a physiologic dose of thyroid hormone for a few days. Waiting for laboratory tests or x-rays to be performed, interpreted, and probably repeated is inappropriate if this will delay treatment. Eventually, they should be done, along with an evaluation of the mother's immune status, her health history, and a complete family history

looking for one of the many known, although relatively rare, causes of congenital

hypothyroidism. Thyroid dysgenesis is found in 90% of the cases. Neonatal screening

for hypothyroidism has allowed for the much earlier diagnosis of hypothyroidism,

resulting in improvement of prognosis, so that frank cretinism is now quite rare. Most industrialized countries test for phenylketonuria and hypothyroidism; there is variability in testing for other metabolic and genetic diseases.

Situational Task 2

The boy of 3 months old was taken to the hospital because of delayed icterus and persistent constipations. He is sick from birthday. Mother's pregnancy has been complicated with a hestosis. In examination is poorly active, the hydropic face, macroglossy, icteric skin. Narrow palpebral fissures. Muscle tone is reduced. Bradycardia.

1. What is the most probable diagnosis?
2. What tests are confirmed the suspected diagnosis?
3. What is the most appropriate next step?

The answers are

1. Congenital hypothyroidism.
2. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), and thyroglobulin in the infant.
3. Begin on the baby oral sodium-L-thyroxine, 10 to 15 mg/(kg_d)

Situational Task 3

Blood samples of a 3-day-old full-term infant are sent for screening to identify diseases that would have serious, permanent consequences without prompt and appropriate treatment.

1. Match the disease with the treatment – Phenylketonuria, Hypothyroidism-
a. Special diet
b. Hormone therapy
2. What tests are confirmed the suspected congenital hypothyroidism ?
3. What is the most appropriate next step?

The answers are

1. Phenylketonuria-a, Hypothyroidism-b
2. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), and thyroglobulin in the infant.
3. The treatment of congenital hypothyroidism with oral levothyroxine sodium should begin as early as possible to prevent psychomotor retardation. Periodic measurement of T3, T4, and TSH is necessary to assess the response to therapy and the need for adjustment of the dose of thyroxine. Careful evaluation of somatic growth by plotting sequential measurements and monitoring bone age is essential

Situational Task 4

In the boy of 5 years old after viral syndrome the temperature up to 39,2 has raised suddenly, the headache, pain in the thyroid gland area is intensified in swallowing and head turning has appeared. The thyroid gland enlarged, painful in palpation, the hyperemia of the skin above it. In laboratory data the function of thyroid gland is unchanged. In the analysis of a blood the leukocytosis and accelerated BSR.

Questions

1. What is the diagnosis?
2. What examinations are necessary?
3. What changes in hormones level are most typical for this disease?

The answers are

1 Acute thyroiditis.

2. Levels of thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4).

3. Decrease of thyroid-stimulating hormone (TSH), increase of tri-iodothyronine (T3), reverse T3, levothyroxine (T4).

Situational Task 5

The girl of 11 years old. Complaints to the general delicacy, fatigability, enlargement of neck. Objectively: thyroid gland in palpation is dense, impure and enlarged up to II degree. In it structure investigation the hyperecho and hypoecho sites were marked. TTH level and of antibodies levels to the thyroid gland are raised.

1. What is the preliminary diagnosis?
2. What of examination will confirm your diagnosis?
3. Conduct differential diagnostics.

The answers are

1. Multinodal struma.
2. Puncture biopsy of thyroid gland
3. a. Autoimmune thyroiditis, the hypertrophic type b. Cancer of a thyroid gland c. Fibrose struma of Riedel d. Endemic struma.

Situational Task 6

Child of 12 years old, sick of autoimmune thyroiditis, there are changes in the blood count: RDC.: 2,1 x 10 12/l; Hb: 82 g/l; the CI: 0,9; thrombocytes: 310 x 10 9/l; reticulocytes.: 30 ‰; WBC.:4,2 x 10 9/L; eosinophiles.: relating to stab neutrophile 2 %; segmented neutrofiles.: 58 %; lymphocytes.: 28 %;monocytes.:6 %; ESR: 28 mm / h. total bilirubin: 115 mmol/l, direct.: 12,5 mmol/l, AST: 0,2 mmol/l, ALT: 0,3 mmol/l. Coombs test is positive.

1. What is the preliminary diagnosis?
2. What therapy is necessary to prescribe for this patient?

The answers are

1. Autoimmune hemolytic anemia.
2. Prednisolonum, Thyroxine.

Situational Task 7

The patient of 4 years old retards in mental development. Birth weight is 3900 g, body height is 52 sm. From the first months of life lags behind in development, a head started to hold in one year, to sit in 1, 8 years. Separate words started to speak from 3 years. Objectively: body height is 80 sm, weight is 11kg, face is bloat, amimic and pastose, palpebral fissures are narrow, lips are thick, mouth is slightly opened, tongue is fill out and extended from a mouth. Skin acyanotic, dry and shelled, hair dry and infrequent. The big fontanel is still open. There are only 4 teeth. A stomach is normal. Sexual development corresponds to 1 year. Ps is 84 per minute; blood pressure is 85/60 mm Hg. Cardiac tones is weakened. What is the preliminary diagnosis?.

1. What is the preliminary diagnosis?
2. What of examination will confirm your diagnosis?
3. What therapy is necessary to prescribe for this patient?

The answers are

1. Congenital hypothyroidism.
2. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), and thyroglobulin in the infant.
3. Begin on the baby oral sodium-L-thyroxine, 10 to 15 mg/(kg_d)

Situational Task 8

Patient G., 12 years old. Growing weight on 10 kg for 4 months, complains of constant irritability, palpitation, pain in eyes and lacrimation. In examination: skin is warm and wet, mild exophthalmia and hyperemia of conjunctiva, positive signs of Grefe, Koher and Moebius. The thyroid gland is unpainful and diffusively enlarged, that is seen in swallowing,. Pulse 108 per minute, blood pressure is 140 / 66 mm Hg. There is fine tremor in hands fingers.

1. What is the diagnosis?
2. What of examination will confirm your diagnosis?
3. What therapy is necessary to prescribe for this patient?

The answers are

1. Diffuse toxic struma of II degree with an average thyrotoxicosis
2. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), antibodies levels to the thyroid gland and thyroglobulin
3. Thyreostatic Mercazolilum is necessary to administrate for child in dose 20-30 mg per day, beta-blokers (anaprilin).

Situational Task 9

In the girl of 10 years old, complaints to irritability, sweating, pains in the area of heart, headache. Enlargement of a thyroid gland. In examination the III degrees nodal struma is found out. Skin is wet, hot by touch, tachycardia 104 b. per minute. On a scanning image the hot node reveals. Level of thyroid hormones is high.

1. What is the preliminary diagnosis?
2. What of examination will confirm your diagnosis?

3. What therapy is necessary to prescribe for this patient?

The answers are

1. Toxic adenoma.

2. Puncture biopsy of thyroid gland to differential diagnostics whis cancer of a thyroid gland.

3. Surgical treatment

Situational Task 10

Girl, aged 14, about one year ago the irritability and tearfulness has appeared. Then, the diffusively enlarged thyroid gland of II degree was detected. This state was considered as pubertal age manifestation.. Treatment was not conducted. Irritability was gradually changed by complete apathy. Bradycardia, constipations, bloated face, pastose skin, have appeared, .The paleness of a skin with waxy shade, inspissations of thyroid gland were increased.

1. What is the preliminary diagnosis?

2. What of examination will confirm your diagnosis?

3. What therapy is necessary to prescribe for this patient?

The answers are

1. Autoimmune thyroiditis, struma of II degree with an average hypothyroidism.

2. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone

(TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), antibodies levels to the thyroid gland and to the thyroglobulin.

1.   The treatment with oral levothyroxine sodium.

VII. Methodical materials to support basic stage class.

Professional algorithm of patient's management (reference chart) for the practical skills and abilities forming .

№	Task	Sequence of implementation	Remarks and warnings related to self-control
1	To conduct examination of the patient with thyroid disease.	1.To conduct the complaints and disease anamnesis. 2.To take thoroughly the patient's life anamnesis. 3.To conduct examination of the patient. 4.To investigate cardiovascular system of the patient (palpation, percussion).	To pay attention to the features of disease course , underlying factors, concomitant diseases etc. To establish the risk factors which can cause the development of disease. To assess patient's general condition, position in bed, color and humidity of skin and mucose, presence of neck veins and extremities' swelling. To pay regard to rhythm of pulse, it tension and size on both hands, apex shove, it properties, margins of absolute and relative

			cardiac dullness, it changes, HR(tachi- or bradicardia, extrasystole), BP.
		5.To conduct auscultation of the heart and of the main vessels . 6.To investigate the pulmonary system (percussion, bronchophony). 7.To conduct lungs auscultation. 8.To investigate the system of digestion. 9. To conduct examination and palpation of thyroid gland and local lymphatic nodes.	To pay regard to heart tones weakening or amplifying, appearance of murmurs and additional III, IV tones. To pay attention to features of percussion and auscultation in children of different age. To pay attention to changes in hyper- and hypothyroidism. To determine the degree of thyroid gland enlargement.
2	To formulate the preliminary diagnosis.	1.To formulate the preliminary diagnosis 2.To substantiate all com-ponents of preliminary diagnosis taking as a basis complaints,anamnesis, and examinations.	To formulate the based on modern classification preliminary diagnosis of thyroid disease and to substantiate each component of it.
3	To evaluate the parameters of additional laboratory tests.	1.To evaluate the blood count data. 2. To evaluate the biochemistry data. 3.To evaluate the blood hormonal profile.	To pay attention to signs of anemia, leucocytosis, changing of formula, elevation of sedimentation rate. To pay attention to cholesterol, lipids and glucose levels. To pay attention to TSH and thyroid hormones changing.
4	To evaluate the data of additional examination.	To understand the data of thyroid ultrasound.	To pay special attention to the thyroid volume depending of age, tissue characteristics, presence of nodes.
5.	To conduct differential diagnosis.	1.Consistently to find the common signs in com-plaints, life and disease anamnesis, the data of examination, the data of laboratory and instrument-tal examination in patients with similar status.	Special attention must be paid to differential diagnosis among the acute and subacute thyroiditis, thyroid cancer, tuberculosis of lymphatic nodes, systemic diseases of connective tissue, systemic blood diseases, in congenital hypothyroidism –

		2.To find the differences among complaints, infor-mation of life and disease anamnesis, examination data, information about the laboratory and instru-mental methods in similar nosology. 3. To find out the differ-rentces for excluding simi-lar diseases from the list of probable diagnoses, being based on this algorithm. 4. To conduct differential diagnostics according to the algorithm among all of nosologies are having the similar signs, among other diseases of thyroid gland. 5.Taking into account the impossibility to exclude the diagnosis of thyroid disease from the list of probable diagnoses to draw a conclusion about most probability of such diagnosis	among physical and mental retardation of child.
6	To formulate the concluding clinical diagnosis.	1.To formulate the concluding clinical diagnosis. 2. Basing on preliminary diagnosis, additional investigations data, conducted differential diagnosis to substantiate all elements of concluding clinical diagnosis.	Being based on modern classification of thyroid diseases to formulate the diagnosis, complications of disease and presence of concomitant diseases.
7	To prescribe treatment for patients.	1.To prescribe non medicinal treatment 2.To prescribe the medicinal treatment.	To specify the regimen and detailed diet according to the disease. Taking into account age, severity of patient state, the stage of disease, the presence of complications and concomitant

			pathology, to prescribe modern medicinal treatment in accordance with the standards of thyroid diseases therapy.

Materials of control for conclusive classes stage:
   The secondary control tests

1. The girl of 11 years old. Complaints to the general delicacy, fatigability, enlargement of neck. Objectively: thyroid gland in palpation is dense, impure and enlarged up to I degree. In it structure investigation the hyperecho and hypoecho sites were marked. TTH level and of antibodies levels to the thyroid gland are raised. What is the preliminary diagnosis?
   A. Autoimmune thyroiditis, the atrophic type.
   B. Autoimmune thyroiditis, the hypertrophic type.
   C. A diffuse nontoxical strumaof I degree.
   D. Subclinical hypothyroidism.
   E. Multinodal struma

2. In child clinical examination there are follow signs revealed - skin humidity, exaltation, irritability, decreasing of body weight, tachycardia, syndromes of Grefe, Stellwag, Moebius, palpitation. For what disease these signs are characteristic?
   A. Acromegalia
   B. Hypothyroidism
   C. Diabetes
   D. Down disease
   E. Thyrotoxicosis

3. In the child of 1, 5 years old the activity is reduced, does not walk, does not talk. Objectively: skin acyanotic, dry and hydropic, the tongue is big, saddle-like nose, a voice is low and rasping and hair is thick and rasping. The large fontanel is 3, 0x3, 0 sm. Teeth are not present. What diagnosis is it possible to think of?
   A. Down disease
   B. Hypothyroidism
   C. Rachitis
   D.Pituitary nanism
   E. Diabetes

4. In examination of 14 years old girl the nodal struma of III degree is found out. On scenogramm the "hot" unit revealed. Levels of T3 and T4 in a blood are increased. What disease is it possible to think of?
   A. Diffuse toxic struma
   B Cancer of a thyroid gland
   C Toxic adenoma of a thyroid gland
   D Autoimmune thyroiditis
   E. Fibrous struma of Riddell

5. In the patient. of 13 years old, relapse of a nephrolithiasis, ostealgia, weakness,

fatigability, growing thin are observed.
What from the specified diseases can be suspected?
  A. Sarcoma of bones
  B Hypoparathyrosis
  C. Hyperparathyroidism
  D. Multiple myeloma
  E. Any of the specified diseases

6. Patient G., complains of irritability, sweating, a tremor of hands, palpitation, body weight reduction in normal appetite. The thyroid gland is enlarged up to I – II degree, unpainful, elastic. The specified symptomatology most of all corresponds to:
  A. to a diffuse toxiferous struma
  B. to nervosisms
  C. to a hypothyroidism
  D. to a nodal toxic struma
  E. to a hypoparathyrosis

7. The girl of 13 years old complains of a xeroderma and decreasing of memory. In examination: tongue enlarged and reflexes are time-lapsed.
 For what disease these signs are characteristic?
  A. A diffuse toxic struma
  B. A hypothyroidism
  C. A subacute thyroiditis
  D. An adenoma of a thyroid gland
  E. Endemial Struma with euthyroidism

8. In patient G. of 15 years old in examination the enlargement of thyroid gland seen in a swallowing and infringement of eyes convergence are revealed.
  What from eye signs is found out in the patient?
  A. Moebius
  B Schtelwag
  C Koher
  D Krause
  E Grefe

9. Patient G., complains of irritability, a sweating, a tremor of hands, palpitation, body weight reduction in a normal appetite. The thyroid gland is enlarged up to II degree, unpainful and elastic.
    To what disease most there corresponds the specified symptomatology?
  A. To a diffuse toxiferous struma
  B. Nervosisms
  C. A hypothyroidism
  D. To a nodal toxiferous struma
  E. To a hypoparathyrosis

10. How long antithyroid therapy of a diffuse toxic struma in children in condition of achievement   and preservation of euthyroidism can be conducted?

A. during 3 months.
B. during 6 months.
C. during 1-1,5 years.
D. during 1 month
E. during 2 months

11. A 13-year-old asymptomatic girl with enlarged thyroid gland up to 3 degree from non endemic region. She states that the findings demonstrated began more than a year ago. Treatment for the patient in the previous question includes
a. Iodine
b. Synthroid (L-Thyroxin)
c. PTU (propylthiouracil)
d. Psychiatry consult
e. Surgical removal of thyroid

12. A 12-year-old girl has a mass in her neck. Physical examination reveals a thyroid nodule, but the rest of the gland is not palpable. A technetium scan reveals a "cold" nodule. The child appears to be euthyroid. Which of the following diagnoses is the *least* likely?
a. Simple adenoma
b. Follicular carcinoma
c. Papillary carcinoma
d. Cyst
e. Dysgenetic thyroid gland

13. You are seeing a 2-week-old boy at a routine visit. The mother complains that he has been constipated, jaundiced, sluggish, and excessively sleepy. The physical examination is normal except for mild jaundice and a distended abdomen in a sleepy infant. The most appropriate course to pursue
initially is assessment of
a. The mother's serum for autoantibodies to thyroid gland
b. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), and thyroglobulin in the mother
c. The results of the neonatal metabolic screen
d. Levels of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), tri-iodothyronine (T3), reverse T3, levothyroxine (T4), and thyroglobulin in the infant
e. The effects on growth and symptoms with increasing feeds by 20% per day

14. You are seeing a 2-week-old boy at a routine visit. The mother complains that he has been constipated, jaundiced, sluggish, and excessively sleepy. The physical examination is normal except for mild jaundice and a distended abdomen in a sleepy infant. The most appropriate next step is to
a. Repeat all the baby's abnormal laboratory results (if any)
b. Obtain x-rays of the baby's skull, wrists, and knees

c. Begin on the baby oral sodium-L-thyroxine, 10 to 15 mg/(kg_d)

d. Evaluate the neonate in 2 weeks for the results of symptomatic treatment

e. Obtain a pediatric endocrinology consultation within 2 weeks

15. A 4-year-old child has mental retardation, shortness of stature, brachydactyly (especially of the fourth and fifth digits), and obesity with round facies and short neck. The child is followed by an ophthalmologist for subcapsular cataracts, and has previously been noted to have cutaneous, subcutaneous, and perivascular calcifications of the basal ganglia. This patient is likely to have which of the following features?

a. Hypercalcemia

b. Hypophosphatemia

c. Elevated concentrations of parathyroid hormone

d. Advanced height age

e. Decreased bone density, particularly in the skull

16. Patient Г., 14 years old, complains of irritability, sweating, tremor of hands, palpitation, decreasing of body weight in normal appetite. The thyroid gland enlarged up to II degree, unpainful, elastic. The diagnosis of diffuse toxiferous struma clinically fixed. What from results of examination will confirm your diagnosis?

A Hyperphosphatemia

B. T3 and T4 is normal

C. T3 and T4 is reduced

D. Hypocalcaemia

E. T3 and T4 is increased

17. Girl of 14 years old complains of sleeping disturbances, decreasing of body weight, palpitation, cardialgias, and fatigability. A thyroid gland hyperplasia of II degree and exophthalmia is marked.. What changes in hormones level are most typical for this disease?

A. Decreasing of a thyroxin

B. Increasing of Thyrotrophic hormone

C. Increasing of the iodine level connected to protein

D. Rising a thyroxin and triiodthyronin

E. Increasing of triiodthyronin

18. In the girl of 12 years old after examination the diagnosis of mild diffuse toxic struma established. What dose of thyreostatic Mercazolilum is necessary to administrate for child in this case?

A. 10-15 mg per day

B.5-10 mg per day

C. 20-30 mg per day

D.1-5 mg per day

E.40-50 mg per day

19. In the child of 4 years old the basic exchange is 28 %, a level of a cholesterol in a blood is 8,6 mmol/l, inclusion of a radioactive iodine in a thyroid gland after 6 hours

is 2,1 %, after 24 hours is 3,0 %, after 48 hours is 3,5 %.
 For what disease such laboratory parameters are characteristic?
    A. Diabetes
    B. Hypothyroidism
    C. Diseases of metabolism
    D. Hyperthyroidism
    E. Pituitary nanism

20. A 13-year-old asymptomatic girl with enlarged thyroid gland up to 3 degree from non endemic region. She states that the findings demonstrated began more than a year ago. The most likely diagnosis is
    a. Iodine deficiency
    b. Congenital hypothyroidism
    c. Graves disease
    d. Exogenous ingestion of synthroid
    e. Lymphocytic (Hashimoto) thyroiditis

21. A 4-year-old child has mental retardation, shortness of stature, brachydactyly (especially of the fourth and fifth digits), and obesity with round facies and short neck. The child is followed by an ophthalmologist for subcapsular cataracts, and has previously been noted to have cutaneous, subcutaneous, and perivascular calcifications of the basal ganglia. This patient is likely to have which of the following features?
    a. Hypercalcemia
    b. Hypophosphatemia
    c. Elevated concentrations of parathyroid hormone
    d. Advanced height age
    e. Decreased bone density, particularly in the skull

22. What is typical for the secondary hypothyroidism?
    A. A low level of Adrenocorticotrophin.
    B. A high level of thyroliberin.
    C. A low level of thyroliberin.
    D. A low level of thyrotropin.
    E. A high level of thyrotropinum

23. Child of 7 months old with complaints on retardation in physical and psychomotor development. In examination the rasping face, dry skin, get hoarsen voice, enlarged tongue with the impresses of gingives, bradycardia, enlarged stomach, umbilical hernia are marked. For what disease these signs are characteristic?
    A. Rachitis.
    B. Down disease.
    C. Congenital hypothyroidism.
    D. Endemic struma.
    E. Sporadic struma.

24. Child, in 9 months old for the first time the congenital hypothyroidism clinically

and according to thyroid hormones tests was confirmed. Now the most expressive manifestation is the serious lag in psychophysical development. What in this case the most rational therapeutic tactics?

A. Mercazolilum
B. Thyreoidinum
C. Ttriiodthyroninum
D. L-thyroxine + Pyracetamum
E. L-thyroxine + Retabolilum

25. You are seeing a 2-week-old boy at a routine visit. The mother complains that he has been constipated, jaundiced, sluggish, and excessively sleepy. The physical examination is normal except for mild jaundice and a distended abdomen in a sleepy infant. The most appropriate next step is to

a. Repeat all the baby's abnormal laboratory results (if any)
b. Obtain x-rays of the baby's skull, wrists, and knees
c. Begin on the baby oral sodium-L-thyroxine, 10 to 15 mg/(kg_d)
d. Evaluate the neonate in 2 weeks for the results of symptomatic treatment
e. Obtain a pediatric endocrinology consultation within 2 weeks

26. In the child of 4 years old the basic exchange is 48 %, a level of a cholesterol in a blood is 2,6 mmol/l, inclusion of a radioactive iodine in a thyroid gland after 6 hours is 78 %, after 24 hours is 62 %, after 48 hours is 50 %.
For what disease such laboratory parameters are characteristic?

A. Diabetes
B. Hypothyroidism
C. Disease of Cushing
D. Acromegalia
E. Diffuse toxic struma

27. In boy of 15 years old the attacks of seizures in masseters and hands with prevalence of flexors tone are observed. Seizures are painful and symmetric. In examination there are positive signs of Hvostek and Trussot.
What is your diagnosis?

A. Epilepsy
B Hypoparathyroidism
C. Hyperparathyroidism
D. Tetanus
E. Spasmophilia

28. Patient C., 14 years old, enlargement of a thyroid gland is marked during 3 months, gland is unpainful and mobile. On scenogramme there is some non-uniformity of structure admitted.
What is it possible to suspect on the basis of resulted data?

A. Diffuse toxiferous struma
B. Cancer of a thyroid gland
C. Autoimmune thyroiditis

D. Subacute thyroiditis

E. Fibrous thyroiditis

29. Patient, 13 y.o., the strumectomy one year ago has been made, was taken with complaints on delicacy and flaccidity. Decreasing in studying progress , memory impairment were admitted. In examination the dryness of skin, fragile and dim hair, bradycardia, predilection to constipations are marked. For what disease these signs are characteristic?

A. Hypothyroidism.

B.Adenoma of thyroid gland.

C.Diffuse toxic struma.

D.Subacute thyroiditis.

E.Fibrose struma of Riedel

30. In the girl of 10 years old, complaints to irritability, sweating, pains in the area of heart, headache..Enlargement of a thyroid gland. In examination the III degrees nodal struma is found out. Skin is wet, hot by touch, tachycardia 104 b. per minute. On a scanning image the hot node reveals. Level of thyroid hormones is high.

A. Diffuse toxic struma.

B. Autoimmune thyroiditis.

C. A cancer of a thyroid gland.

D. Toxic adenoma.

E. Ridel fibrosal struma

Answers to the secondary control tests

1-E, 2-E, 3-B, 4-C, 5-C, 6-A, 7-B, 8-A, 9-A, 10-C, 11-B, 12-E, 13-C, 14-C, 15-C, 16-E, 17-D, 18-C, 19-B, 20-E, 21-C, 22-D, 23-C, 24-D, 25-C, 26-E, 27-B, 28-C, 29-A, 30-D.

Materials of the medical support for the students' self training:
a reference chart for organization of students' independent work with educational literature.

Tasks	Instructions
To study the etiology and pathogennesis of diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, endemic goiter, acute and subacute thyroiditis, diffuse untoxic goiter, thyroid cancer in children. Be able to detect the degrees of goiter.	To enumerate basic etiologic factors, to select the key links of thyroid gland disease pathogenesis.
To study clinical manifestations of of diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, endemic goiter, acute and subacute thyroiditis, diffuse untoxic goiter, thyroid cancer in children.	To establish the symptoms and to gather it in the clinical syndromes to put the probable diagnosis of thyroid gland disease.

To study diagnostic criteria of thyroid gland diseases	To make the flow diagram of disease
To study the additional methods of examination (laboratory, instrumental)	To work out a plan of patient examination.
To study the changes in additional investigational methods which are pathognomonic for thyroid diseases.	To enumerate the basic diagnostic criteria of thyroid gland diseases according to the data of additional investigational methods.
To conduct differential diagnostics, to establish concluding diagnosis	To substantiate the basic components of diagnosis in accordance with the modern classification, and to conduct a differential diagnosis.
To prescribe the individual treatment to patient with the thyroid gland disease. To be able to render the first aid in thyroidotoxic crisis for children.	To make the prescribing chart specifying the regimen, diet, medicinal treatment, taking into account the age, severity of patient's state, the stage of disease, the presence of complications and concomitant diseases.

THE RECOMMENDED LITERATURE

Basic:

1. Nelson Essentials of Pediatrics, fifth edition, Copyright © 2007
   / edited by Richard E. Behrman, Robert M. Kliegman, Ann M. Arvin; senior editor, Waldo E.
2. Rudolph's Pediatrics, 21st Edition.

Additional:

1.Майданник В.Г. Педиатрия. Учебник (2-е издание, испр. и доп.)- Харьков: Фолио, 2002. - 1125 с.

2. Волосовец А.П., Кривопустов СП., Криворук І.М., Черній О.Ф. Навчальний посібник з дитячої ендокринології. - Тернопіль: Укрмедкнига, 2004. -495 с

3. ЖуковскийМ.Н.Детская эндокринология.-М.: Медицина, 1996.

4. Наказ МОЗ України від 27.04.2006 № 254 Про затвердження протоколів надання медичної допомоги дітям за спеціальністю "Дитяча ендокринологія"

THE DISEASES OF HYPOTHALAMIC PITUITARY SYSTEM AND SEXUAL GLANDS IN CHILDREN.

Etiology, pathogenesis, classification, clinic, diagnostics, differential diagnostics, treatment, prophylaxis of different clinical forms of growth disorders (exogenous constitutional, pituitary, somatogenic); obesity (exogenous constitutional, subthalamic), pubertal dispituitarism, in children, different forms of sexual glands, disorders, pathology of sexual glands for children (disturbances of boys and girls sexual development). Prognosis.

I. **Actuality of the theme.**

Hypothalamic – pituitary system is one of the major links in adjusting and control of endocrine glands. The disorders hypothalamic – pituitary glands are the cause of pathological processes origin in organism and the development of many endocrine diseases. It predetermines the necessity of studying and improvement of knowledge of these problems for precise diagnostics and institution of adequate therapy.

II. **Classes (studies pointing with mastering level planned)**

1. 1. An of student must know (to familiarize with):α1
- About the diseases of hypothalamic – pituitary system in the structure of endocrine diseases in children, prevalence in different age groups;
 - About statistical information in relation to morbidity, frequency of complications origin, nearest and remote prognosis of patients.
- About history of problem scientific studying and contribution of domestic scientists;
2. A student must know (master): α2
- Anatomic physiological features endocrine system of healthy children endocrine system; the features of metabolism;
- Structure and functions to the hypothalamus and hypophysis; hormones, mechanism of their action; regulation of hemadens functions.
- To familiarize with the modern state of problems for diagnostics and treatment of the hypothalamic – pituitary system and obesity.
 - Etiology, pathogenesis and clinical displays of hypothalamic – pituitary system diseases and different forms of obesity in children.
- Methods of treatment of different clinical forms of obesity, growth disorders, diabetes insipidus, pubertal dispituitarism, disorders of sexual development.
- Urgent condition in pathology of hypothalamic – pituitary system and different forms of obesity in children. Pathogenesis clinic and treatment methods of prophylaxis in hypothalamic – pituitary system and obesity; organization of outpatient clinical observation..

- Differential diagnosis.
3. A student must master: α3
   Skills:
- Collection of complaints and anamnesis of disease;
- Examination of patients with the diseases of hypothalamic – pituitary systems and revealing of basic symptoms and syndromes;
- Formulate and substantiate the preliminary diagnosis.
 - Determination of laboratory and instrumental plan of patient examination (according to diagnostics standards);
 Abilities:
- to interpret the result of laboratory and instrumental tests.
- To conduct differential diagnosis
- Using the sygmal and centile tables to detect the indexes of physical development, the degree of delaying and acceleration, weight excess and deficiency in children.
- To detect the bone age of children.
- To give recommendations in relation to the patient regimen and diet in diseases of hypothalamic – pituitary systems
- taking into account the stage of disease to specify the severity of the state and concomitant pathology;
- to complete the treatment plan in leukemias and lymphoadenomas according to standards taking into account the stage of disease, complications and concomitant pathology.
- To render first aid in extreme situations and exigent states.

III. Aims of personality development (educative aims):
- A student must learn to adhere to the rules of behavior and principles of medical etiquette and deontology to develop bedside manner in patients with leukemias and lymphoadenomas ;
- to lay hands on ability to set a psychological contact with a patient and his family;
- to master the sense of professional responsibility for a timely and adequate medicare.

IV. Interdisciplinary integration:

Subject	To know	To be able
1. Previous (providing)		
anatomy	Anatomic-physiologic features of hypothalamic – pituitary system of healthy children.	
Histology	Structure and functions of hypothalamus and	

	hypophysis.	
Physiology	Hormonal regulations of of hemadens functions	To asses the data of laboratory and instrumental investigational methods
Pathologic physiology	Pathogenesis of of hypothalamic – pitutary system diseases.	
Pathologic anatomy	Morphological features of development of diseases of the hypothalamic – pitutary system are depending on the stage of process	To analyse and interpret the information about clinical examination and about additional methods of investigation
Pharmacology	Pharmacocinetics and pharmacodynamics, the side effects of preparations (hormonal drugs, metabolic preparations, etc.), are using in treatment of patients with the hypothalamic – pituitary system diseases.	To prescribe age dependent and patient individual features treatment, period of disease, to establish the individual regimen of preparations taking and dosage. To prescribe recipes.
Internal diseases propedeutics.	Basic stages and methods of patient clinical examination	To collect complaints, anamnesis vitae et morbi, to find out the basic risk factors, to coduct patient examination, to reveal the clinical signs of pituitary hypothalamic diseases, to interpret the data about additional methods of investigation.
To detect the hormones of hypo-talamic –pituitary-suprarenal axes.	Normal ranges of hormones of hypothalamic – pituitary –suprarenal axes.	To interpret the data of hormonal investigations.
3. Introdiscipline integration		
Primary obesity (exogenous – constitutional).	Clinical manifestation of exogenous – constitutional obesity.	To establish the specific signs of exogenous – constitutional obesity, to conduct differential diagnosis among hypothalamic syndrome of pubertal age.
Terner syndrome.	Clinical signs of Terner syndrome.	To establish the clinical signs of Terner syndrome and conduct the differential

		diagnosis with dwarfism.
Hypohonadism,	The clinical signs of hyponadism.	To determine the clinical signs of hypohonadism and conduct the differential diagnostics among different forms of sexual development delaying.

VI. Contents of theme:

The anterior pituitary gland originates from the Rathke pouch as an invagination of the oral endoderm. It then detaches from the oral epithelium and becomes an individual structure of rapidly proliferating cells. Persistent remnants of the original connection between the Rathke pouch and the oral cavity can develop into craniopharyngiomas, which are the most common type of tumor in this area. Five cell types in the anterior pituitary produce six peptide hormones. Somatotropes produce growth hormone (GH), lactotropes produce prolactin, and thyrotropes make thyrotropin or thyroid-stimulating hormone (TSH). A single transcriptional activation protein, Pit-1, contributes to the embryologic development and differentiated function of these three cell types. Developing under the influence of unidentified differentiation factors, gonadotropes make lutropin or luteinizing hormone (LH) and follitropin or follicle-stimulating hormone (FSH), and corticotropes produce corticotropin (ACTH) and other peptides from the pro-opiomelanocorticotropic (POMC) precursor protein.

ANTERIOR LOBE HORMONES. The protein hormones produced by the anterior pituitary act on other endocrine glands and on certain body cells to affect almost every organ. Anterior pituitary cells are themselves controlled by neuropeptide-releasing and release-inhibiting hormones that are produced by hypothalamic neurons, secreted into the capillaries of the median eminence, and carried by portal veins to the anterior pituitary. Many conditions formerly classified as pituitary in origin are caused by hypothalamic defects. The identification and availability of hypothalamic hormones permits more precise delineation of these conditions.

Human GH is a protein with 191 amino acids. Its gene (GH1) is the first in a cluster of five closely related genes on the long arm of chromosome 17 (q22–24). The four other genes have greater than 90% sequence identity with the GH1 gene. They consist of the CS1 and CS2 genes, which encode the same human chorionic somatomammotropin (hCS) protein; a placental growth hormone gene (GH2); and a partly disabled pseudogene (CSP). Syncytiotrophoblastic cells of the fetal placenta produce large quantities of hCS, and placental GH replaces pituitary GH in the maternal circulation after 20 wk of gestation. When the fetal genome lacks the CS1, CS2, GH2, and CSP genes, hCS and placental GH are absent, but fetal growth and

postpartum lactation are normal.

The GH1 gene is expressed in pituitary somatotropes under the control of two hypothalamic hormones. Growth hormone–releasing hormone (GHRH) stimulates, and somatostatin inhibits, GH release. Alternating secretion of GHRH and somatostatin accounts for the rhythmic secretion of GH. Peaks of GH occur when peaks of GHRH coincide with troughs of somatostatin. When plasma levels of GH are measured by standard radioimmunoassay (RIA), its secretion appears to be pulsatile, but when measured by an ultrasensitive immunoradiometric assay (IRMA), which can measure GH in a previously undetectable range, it is observed to be secreted in a rhythmic fashion with a dominant 2-hr periodicity. The highest levels of GH are achieved during sleep when measured by RIA or IRMA.

The three molecular species of GHRH contain 37, 40, or 44 amino acids. A fully active 29–amino acid synthetic GHRH is available for diagnostic use. Somatostatin exists in 14–and 28–amino acid forms. Somatostatin production is not limited to the hypothalamus. It also acts through autocrine and paracrine mechanisms in the islets of Langerhans and in the gastrointestinal tract. Somatostatin inhibits secretion of insulin, glucagon, secretin, gastrin, vasoactive intestinal peptide (VIP), GH, and thyrotropin. In the pancreatic islets, it is localized to the D cells. Somatostatin-secreting pancreatic tumors (i.e., somatostatinomas) have been reported in adults. A potent, long-acting somatostatin analog, octreotide, which inhibits GH preferentially over insulin, is available to treat patients with GH-secreting tumors. It is also useful in managing patients with gastrinomas, insulinomas, glucagonomas, VIPomas, and carcinoids. 123I-labeled octreotide appears to be useful in localizing somatostatin receptor–positive tumors and their metastases.

GH acts through binding to receptor molecules on the surface of target cells. The GH receptor is a single-chain molecule of 620 amino acids. It has an extracellular domain, a single membrane-spanning domain, and a cytoplasmic domain. Proteolytically cleaved fragments of the extracellular domain circulate in plasma and act as a GH-binding protein. In common with other members of the cytokine receptor family, the cytoplasmic domain of the GH receptor lacks intrinsic kinase activity; instead, GH binding induces receptor dimerization and activation of a receptor-associated Janus kinase (Jak2). Phosphorylation of the kinase and other protein substrates initiates a series of events that leads to alterations in nuclear gene transcription.

The mitogenic actions of GH are mediated through increases in the synthesis of insulin-like growth factor-I (IGF-I), formerly named somatomedin C, a single-chain peptide with 70 amino acids coded for by a gene on the long arm of chromosome 12. IGF-I has considerable homology to insulin. Circulating IGF-I is synthesized primarily in the liver and formed locally in mesodermal and ectodermal cells,

particularly in the growth plate of children, where its effect is exerted by paracrine or autocrine mechanisms. Circulating levels of IGF-I are related to blood levels of GH to a large extent, except in the fetus and during the neonatal period. IGF-I circulates bound to several different binding proteins; the major one is a 150-dalton complex (IGF-BP3), which is decreased in GH-deficient children but is in the normal range in children who are short for other reasons. Human recombinant IGF-I is being used experimentally to determine its therapeutic potential. IGF-II is a single-chain protein with 67 amino acids that is coded for by a gene on the short arm of chromosome 11. It has homology to IGF-I, but much less is known about its physiologic roles, although it appears to be an important mitogen in bone cells, where it occurs in a concentration many times higher than that of IGF-I.

Several disorders of growth are caused by abnormalities of the genes that code for the GHRH receptor, Pit-1, GH1, and the GH receptor. No growth disorders have been localized to the genes that code for GHRH, IGF-I, IGF-I receptor, or IGF-II.

Prolactin is composed of 199 amino acids, and its gene is located on chromosome 6. The identity of the prolactin-releasing factor (PRF) is unknown, but evidence suggests that it is localized almost exclusively in the intermediate lobe of the pituitary rather than in the hypothalamus. The major prolactin-inhibiting factor (PIF) is dopamine, and medications that disrupt hypothalamic dopaminergic pathways result in increased serum levels of prolactin. Serum levels of prolactin are increased after administration of thyrotropin-releasing hormone (TRH), in states of primary hypothyroidism, and after disruption of the pituitary stalk, as may occur in children with craniopharyngioma.

The main established role for prolactin is the initiation and maintenance of lactation. Concentrations in amniotic fluid are 10–100 times the levels in maternal or fetal serum. The major source of amniotic prolactin appears to be the decidua. Mean serum levels in children and in fasting adults of both sexes are about 5–20 m{mu}g/L, but levels in the fetus and in neonates during the 1st wk of life are usually higher than 200 m{mu}g/L.

TSH consists of two glycoprotein chains linked by hydrogen bonding. The a{alpha} chain is identical to that found in FSH, LH, and chorionic gonadotropin (hCG). The b{beta} chain is unique in each of these hormones and confers specificity. The gene for the a{alpha} chain has been mapped on chromosome 6, that for the b{beta} chain of TSH on chromosome 1, and those for the b{beta} chains for LH and hCG on chromosome 19. TSH increases iodine uptake, iodide clearance from the plasma, iodotyrosine and iodothyronine formation, thyroglobulin proteolysis, and release of thyroxine (T4) and triiodothyronine (T3) from the thyroid. Most of the effects of TSH are mediated by cyclic adenosine monophosphate. Deficiency of TSH results in inactivity and atrophy of the thyroid, and excess results in hypertrophy and

hyperplasia.

TRH was the first hypothalamic hormone to be isolated, characterized, and synthesized; it is a tripeptide ([pyro] Glu-His-Pro-NH2). T4 and T3 inhibit TSH secretion by blocking the action of TRH on the pituitary cell. TRH also stimulates the release of prolactin in both sexes. Synthetic TRH is useful for testing pituitary reserves of TSH and prolactin.

ACTH is derived by proteolytic cleavage from a large precursor glycoprotein product of the pituitary gland called POMC. Cleavage of POMC yields ACTH, a single, unbranched glycoprotein chain of 39 amino acids, and b-lipotropin (b-LPH), a 91–amino acid glycoprotein. Further cleavage of ACTH and b-LPH in the pituitary yields yet other hormonal products. The a-melanocyte-stimulating hormone is identical to the first 13 amino acids of ACTH but has no corticotropin activity; cleavage of b-LPH results in neurotropic peptides with morphinomimetic activity (fragment 61–91 is b-endorphin), and b-melanocyte-stimulating hormone consists of a 17–amino acid fragment of b-LPH.

ACTH acts primarily on the adrenal cortex. It produces changes in structure, chemical composition, enzymatic activity, and release of corticosteroid hormones. ACTH release has a diurnal rhythm. The level is lowest between 10 P.M. and 2 A.M., with peak levels reached about 8 A.M.. Levels of b-LPH and of b-endorphin are elevated in patients with increased levels of ACTH. It appears that ACTH rather than FSH is the principal pigmentary hormone in humans.

POMC peptides are also produced in nonpituitary tissues. In the testis, some peptides act as autocrine regulators of androgen-secreting Leydig cells, and others may potentiate or oppose the action of FSH on Sertoli cells.

Secretion of ACTH, b{beta}-endorphin, and other POMC-related peptides is regulated by corticotropin-releasing hormone (CRH). CRH is a 41–amino acid peptide found predominantly in the median eminence but also in other areas of the brain and in tissues outside the brain, particularly the placenta. During pregnancy, levels of CRH rise several hundred-fold, increase further during labor and delivery, and then fall to nonpregnant levels within 24 hr. Its source is probably the placenta, which contains the peptide and its mRNA. Synthetic ovine (oCRH) and human CRH (hCRH) have been used clinically. The oCRH is the clinical agent of choice, because responses to it are greater and longer lasting than with hCRH. It is particularly useful in differentiating the different forms of Cushing syndrome.

Gonadotropic hormones include two glycoproteins: LH and FSH. Each has an a subunit and a b subunit. The a subunits of these two hormones and of TSH are identical; specificity of hormone action resides in the b subunit, which is different for each of the three. Receptors for FSH on the ovarian granulosa cells and on testicular Sertoli cells mediate FSH stimulation of follicular development in the ovary and of

gametogenesis in the testis. On binding to specific receptors on ovarian theca cells and testicular Leydig cells, LH promotes luteinization of the ovary and Leydig cell function of the testis. The receptors for LH and FSH belong to a class of receptors with seven membrane-spanning protein domains. Receptor occupancy activates adenylyl cyclase through mediation of G proteins.

Hypothalamic control of gonadotropic hormones has long been known, and separate releasing hormones for FSH and LH were once anticipated. Luteinizing hormone–releasing hormone (LHRH), a decapeptide, has been isolated, synthesized, and widely used in clinical studies. Because it leads to the release of LH and FSH from the same gonadotropic cells, it appears that there is only one gonadotropin-releasing hormone.

Secretion of LH is inhibited by androgens and estrogens, and secretion of FSH is suppressed by gonadal production of inhibin, a 31-kD glycoprotein produced by the Sertoli cells. Inhibin consists of a and b subunits joined by disulfide bonds. The b dimer (activin) also occurs, but its biologic effect is to stimulate FSH secretion. The biology of these newer hormones is being delineated. In addition to its endocrine effect, activin has paracrine effects in the testis. It facilitates LH-induced testosterone production, indicating a direct effect of Sertoli cells on Leydig cells analogous to the interaction of these cells through the paracrine effects of POMC.

POSTERIOR LOBE HORMONES. The posterior lobe of the pituitary is part of a functional unit, the neurohypophysis, that consists of the neurons of the supraoptic and paraventricular nuclei of the hypothalamus; neuronal axons, which form the pituitary stalk; and neuronal terminals in the median eminence or in the posterior lobe.

The neurohypophysis is the source of arginine vasopressin (AVP, the antidiuretic hormone) and of oxytocin. Both are octapeptides, differing in only two amino acids. These hormones are produced by neurosecretion in the hypothalamic nuclei. Vasopressin derives its name from early observations of its pressor and antidiuretic activities; however, the latter is its physiologically important function. At levels 50–1,000 times those found in blood, it affects blood pressure, intestinal contractility, hepatic glycogenolysis, platelet aggregation, and release of factor VIII. AVP and oxytocin are secreted by separate cells of the supraoptic and paraventricular nuclei. Secreted concurrently in equimolar amounts with these hormones are vasopressin neurophysin (neurophysin II) and oxytocin neurophysin (neurophysin I). Each hormone binds to its respective neurophysin and is transported to the nerve terminals in the posterior pituitary, where it is secreted in the free form. RIAs of the neuronphysins provide a direct index of AVP and oxytocin levels in plasma. The concentration of AVP in umbilical cord plasma appears to be a sensitive indicator of fetal stress.

AVP has a short half-life and responds quickly to changes in hydration. The stimuli for AVP release are increased plasma osmolality, perceived by osmoreceptors

in the hypothalamus, and decreased blood volume, perceived by baroreceptors in the carotid sinus of the aortic arch. AVP changes the permeability of the renal tubular cell membrane through cAMP. A synthetic analog, desmopressin, combines high potency, selectivity for antidiuretic hormone receptors, and resistance to degradation by proteases. Small amounts administered intranasally are effective therapy for patients with diabetes insipidus.

HYPOPITUITARISM

This chapter discusses the hypopituitary states associated with a deficiency of growth hormone (GH), with or without a deficiency of other pituitary hormones . Isolated deficiencies of thyrotropin, corticotropin (ACTH), and gonadotropin are also addressed. Affected children have in common a phenotype of growth impairment that is specifically corrected by replacement of GH.

ETIOLOGY. Congenital Defects. Pituitary hypoplasia can occur as an isolated phenomenon or in association with more extensive developmental abnormalities, such as anencephaly, holoprosencephaly (i.e., cyclopia, cebocephaly, orbital hypotelorism), and septo-optic dysplasia (de Morsier syndrome). In Hall-Pallister syndrome, absence of the pituitary gland is associated with hypothalamic hamartoblastoma, postaxial polydactyly, nail dysplasia, bifid epiglottis, imperforate anus, and anomalies of the heart, lungs, and kidneys. In the neonate, symptoms of hypopituitarism with postaxial polydactyly and bifid epiglottis suggest this diagnosis. Hypoplasia of the pituitary with anencephaly has long been known, but recent observations reveal a large residuum of normal pituitary function and suggest that hypoplasia may be secondary to the hypothalamic defect. With hypothalamic-releasing hormones, it is possible to determine whether defects in pituitary function reside in the pituitary or hypothalamus. Deficiency of GH occurs in 4% of all patients with cleft lip or cleft palate and in 32% of those who also have short stature. Midfacial anomalies or the finding of a solitary maxillary central incisor indicate a high likelihood of GH deficiency.

Bilateral or unilateral optic nerve hypoplasia is often associated with hypopituitarism. When it is also associated with absence of the septum pellucidum, the condition is known as septo-optic dysplasia. The fundus exhibits hypoplastic discs with typical double rims and sparse retinal vessels. Endocrine abnormalities are extremely variable. Hormonal deficiency most often involves GH alone, but multiple pituitary deficiencies, including diabetes insipidus, may occur. The defect resides primarily in the hypothalamus. Delay in linear growth may begin as early as 3 mo of age or may not be observed before 3–4 yr of age. Affected newborns often have apnea, hypotonia and seizures, prolonged jaundice, hypoglycemia without hyperinsulinism, and (in males) microphallus. The condition is usually sporadic but has been reported in first cousins. The cause is unknown, but young maternal age and

nulliparity are strongly associated factors.

Aplasia of the pituitary without abnormalities of the brain or skull is rare, but affected infants are being increasingly recognized because hypoglycemia occurs early and, in males, there is microphallus. Some infants have shown evidence of the neonatal hepatitis syndrome, but the relationship with hypopituitarism is obscure. The condition has been reported in siblings of both sexes, and consanguinity has been observed in two families; autosomal recessive inheritance is suggested. Studies of some children have placed the defect in the hypothalamus. This may be a heterogeneous group of disorders.

In empty-sella syndrome, a deficient sellar diaphragm leads to herniation of the suprasellar subarachnoid space into the sella turcica, with remodeling of the sella and flattening of the pituitary gland. It may develop after surgery or radiation therapy, or it may be idiopathic. Of 17 pediatric cases, significant hypopituitarism was found in 5. Empty-sella syndrome with an enlarged sella and hypopituitarism has been observed in siblings.

Other syndromes in which short stature is a prominent feature may be associated with deficiency of GH. For example, some patients with Turner, Fanconi, Russell-Silver, Rieger, Williams, or the CHARGE syndrome have hypopituitarism.

Destructive Lesions. Any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary may cause pituitary hormone deficiency. Because such lesions are not selective, multiple hormonal deficiencies are usually observed. The most common lesion is the craniopharyngioma. Central nervous system germinoma, eosinophilic granuloma, tuberculosis, sarcoidosis, toxoplasmosis, and aneurysms may also cause hypothalamic-hypophyseal destruction. These lesions are frequently associated with roentgenographic changes in the skull. Besides diabetes insipidus, a deficiency of GH and other pituitary hormones may occur in children with histiocytosis, especially if treated with cranial irradiation. Enlargement of the sella or deformation or destruction of the clinoid processes usually indicates a tumor. Intrasellar or suprasellar calcifications usually indicate a craniopharyngioma. Trauma, including child abuse, traction at delivery, anoxia, and hemorrhagic infarction, may also damage the pituitary, its stalk, or the hypothalamus.

Improved survival of children who receive radiotherapy for malignancies of the central nervous system or other cranial structures has resulted in a substantial group of patients with GH deficiency. Children with acute lymphocytic leukemia who have received prophylactic cranial irradiation also belong in this group. Growth typically slows during radiation therapy or chemotherapy, improves for a year or two, and then declines with the development of hypopituitarism. Spinal irradiation contributes to disproportionately poor growth of the trunk. The dose of irradiation and the fractionation schedule used are important determinants of the incidence of

hypopituitarism. GH deficiency is almost universal 5 yr after therapy with a total dose of 35–45 Gy. Subtler defects are seen with doses around 20 Gy. Deficiency of GH is the most common defect, but deficiencies of thyroid-stimulating hormone (TSH) and ACTH may also occur. Unlike in other forms of hypopituitarism, puberty is not delayed. A pubertal growth spurt at a normal to early age may lessen clinical suspicion of GH deficiency.

Idiopathic Hypopituitarism. Most patients with hypopituitarism have no demonstrable lesion of the pituitary or hypothalamus. In most, the functional defect is hypothalamic rather than pituitary. The deficiency may be of GH only or of multiple hormones. The condition is most often sporadic. Association with breech birth, forceps delivery, and intrapartum and maternal bleeding suggests that birth trauma and anoxia may be pathogenic factors in some instances.

Genetic Forms of Hypopituitarism. Well-recognized genetic forms of hypopituitarism account for at least 5% of cases. As in idiopathic hypopituitarism, the defect may be limited to GH, or it can involve deficiencies of several other anterior pituitary hormones. Roman numerals are used to denote the mode of inheritance. In the McKusick classification of isolated GH deficiency (IGHD), type I is autosomal recessive, type II is autosomal dominant, and type III is X linked. Similarly, autosomal recessive multiple pituitary hormone deficiency is type I, and the X-linked form is type III.

Among families with autosomal recessive IGHD, some have complete deletions of the GH1 gene and are considered to have IGHD type IA. Early reports of this disorder stressed the tendency of these children to form antibodies to human GH during treatment and to experience a lessening of growth response. With more widespread application of Southern blotting and polymerase chain reaction techniques for detecting GH1 gene deletions and with the availability of less antigenic biosynthetic GH preparations, it appears that a minority develop such antibodies. There are several different sizes of deletions, reflecting nonhomologous crossing over at different sites in the GH and CS gene cluster. The smallest and most common deletions are 6.7 kb long. Other deletion sizes are 7.0, 7.6, and greater than 45 kb. All cases show extreme postnatal growth failure and fail to release GH after stimulation with growth hormone–releasing hormone (GHRH) or more conventional stimuli to GH release.

Autosomal recessive IGHD type IB is heterogeneous with respect to severity and the sites of mutations. Some children have 1- or 2-bp deletions in the GH1 gene that introduce a frameshift, followed by an early translational stop signal. Homozygosity for this type of GH1 allele or compound heterozygosity for a small and a large GH1 deletion results in total absence of GH and a clinical picture equally as severe as that of IGHD type IA. Other families have mutations within the fourth and last intron of

the GH1 gene. These mutations compromise the efficiency of normal pre-mRNA splicing at the usual exon 3 to exon 4 splice boundary. In some IGHD IB families, tracking the restriction fragment length polymorphisms shows that transmission of the disease is not linked to transmission of GH1 alleles. Attempts to link IGHD IB to defects in the GHRH gene have been uniformly unsuccessful. The little mouse model of IGHD IB is caused by a mutation in the gene for the GHRH receptor. It seems likely that some human forms of IGHD result from mutations in the same gene.

Some cases of autosomal dominant IGHD III are caused by mutations in the GH1 gene. They involve single-base substitutions in intron 3 that result in omission of exon 3 from the spliced mRNA. The predicted protein has a molecular weight of 17,000, lacks amino acids 32 to 71, and lacks one of the cysteine residues involved in formation of intramolecular disulfide bonds. It has been speculated that this mutant protein forms intermolecular bonds with the product of the normal GH1 allele and interferes with secretion of GH from secretory granules.

The gene responsible for X-linked IGHD III has not been identified. In several families, GH deficiency has been transmitted along with immunoglobulin deficiency. The disorder in these families may involve deletion of several contiguous genes.

Most cases of autosomal recessive and X-linked multiple pituitary hormone deficiency involve underproduction of GH, TSH, ACTH, luteinizing hormone, and follicle-stimulating hormone. Prolactin (PRL) values tend to be normal or high. Other hormones are often released in response to administration of releasing factors. These observations suggest a hypothalamic rather than a pituitary defect, and no candidate genes have been implicated. A subset of familial cases lack GH, TSH, and PRL but have normal secretion of ACTH and gonadotropins. Affected children in several families have been shown to have defects in the gene for the Pit-1 pituitary transcript-tional activation protein. Gene deletions and nonsense and missense mutations have been described. Most eliminate binding of Pit-1 to target sequences in the GH, PRL, and b{beta}-TSH promoters. At least one mutant protein retains binding activity although it lacks the ability to activate transcription. It may retain some role in pituitary development, because children with this mutation have normal anterior pituitary size on magnetic resonance imaging (MRI). Another mutation, substituting tryptophan for arginine at position 271, exerts a dominant negative effect in vivo and in vitro. It provides an example of multiple pituitary hormone deficiency type II.

Growth Hormone–Receptor Defects. Children with Laron syndrome have all the clinical findings of those with hypopituitarism, but they have elevated levels of circulating GH. Levels of insulin-like growth factor-I (IGF-I) are very low and fail to respond to exogenous hGH. Absence of GH-binding activity confirms the diagnosis and points to an abnormality of the GH receptor. A variety of gene defects have been discovered in different families, ranging from the deletion of several exons of the

gene, through nonsense mutations, to missense mutations, and to mutations that alter splicing of pre-mRNA. More than 40 affected individuals in two large Ecuadorian kindreds are homozygous for a base substitution that creates a new splice site and results in a protein that lacks 12 of the amino acids normally found in the extracellular domain. A second kindred living in the Bahamas expresses a different mutation that also introduces a new splice site and results in a nonfunctional protein. Most of the mutations responsible for Laron syndrome produce a loss of GH-binding activity in the membrane receptor and the circulating GH-binding protein representting the extracellular domain of the receptor. The mutant protein in at least one family retains normal affinity for GH binding but lacks the ability to form dimers of GH receptor around a single bound GH molecule. Most parents of children with Laron syndrome are within the normal range for adult stature. With the availability of techniques for screening the GH-receptor gene sequence, it will be interesting to see whether some mutations act in a dominant fashion to cause milder forms of short stature.

CLINICAL MANIFESTATIONS. Patients Without Demonstrable Lesions of the Pituitary. The child with hypopituitarism is usually of normal size and weight at birth. Retrospective studies of children with multiple pituitary hormone deficiencies and those with genetic defects of the GH1 or GHR gene indicate that birth length averages 1 SD below the mean. Children with severe defects in GH production or action fall more than 4 SD below the mean by 1 yr of age. Others with less severe deficiencies may have regular but slow growth in height, with the increments always below the normal percentiles, or periods of lack of growth may alternate with short spurts of growth. Delayed closure of the epiphyses permits growth beyond the age when normal persons cease to grow. Without treatment, adult heights are 4–12 SD below the mean.

Infants with congenital defects of the pituitary or hypothalamus usually present neonatal emergencies such as apnea, cyanosis, or severe hypoglycemia. Microphallus in the male provides an additional diagnostic clue. Deficiency of GH may be accompanied by hypoadrenalism and hypothyroidism, and clinical manifestations of hypopituitarism evolve more rapidly than in the usual hypopituitary child. Prolonged neonatal jaundice is common. It involves elevation of conjugated and unconjugated bilirubin and may be mistaken for neonatal hepatitis.

The head is round, and the face is short and broad. The frontal bone is prominent, and the bridge of the nose is depressed and saddle shaped. The nose is small, and the nasolabial folds are well developed. The eyes are somewhat bulging. The mandible and the chin are underdeveloped and infantile, and the teeth, which erupt late, are frequently crowded. The neck is short and the larynx small. The voice is high pitched and remains high after puberty. The extremities are well proportioned, with small hands and feet. The genitalia are usually underdeveloped for the child's

age, and sexual maturation may be delayed or absent. Facial, axillary, and pubic hair usually is lacking, and the scalp hair is fine. Symptomatic hypoglycemia, usually after fasting, occurs in 10–15% of children with panhypopituitarism and those with an IGHD. Intelligence is usually normal. Affected children may become shy and retiring.

Patients with Demonstrable Lesions of the Pituitary. The child is normal initially, and manifestations similar to those seen in idiopathic pituitary growth failure gradually appear and progress. When complete or almost complete destruction of the pituitary gland occurs, signs of pituitary insufficiency are present. Atrophy of the adrenal cortex, thyroid, and gonads results in loss of weight, asthenia, sensitivity to cold, mental torpor, and absence of sweating. Sexual maturation fails to take place or regresses if already present; there may be atrophy of the gonads and genital tract with amenorrhea and loss of pubic and axillary hair. There is a tendency to hypoglycemia and coma. Growth ceases. Diabetes insipidus may be present early but tends to improve spontaneously as the anterior pituitary is progressively destroyed.

If the lesion is an expanding tumor, symptoms such as headache, vomiting, visual disturbances, pathologic sleep, decreased school performance, seizures, polyuria, and growth failure may occur. Growth failure frequently antedates the neurologic signs and symptoms, especially with craniopharyngiomas, but symptoms of hormonal deficit account for only 10% of presenting complaints. In other patients, the neurologic manifestations may precede the endocrinologic, or evidence of pituitary insufficiency may first appear after surgical intervention. In children with craniopharyngiomas, visual field defects, optic atrophy, papilledema, and cranial nerve palsy are common.

LABORATORY DATA. The diagnosis of classic GH deficiency is suspected in cases of profound postnatal growth failure, with heights more than 3 SD below the mean for age and gender. Acquired GH deficiency can occur at any age. There is dramatic slowing of growth, but when the disorder is of short duration, height may still be within the normal range. A strong clinical suspicion is important in establishing the diagnosis, because laboratory measures of GH sufficiency lack specificity. Observation of low serum levels of IGF-I and the GH-dependent IGF-BP3 can be helpful. Values that are in the upper part of the normal range for age effectively exclude GH deficiency. Values for normally growing and hypopituitary children overlap, particularly during infancy and early childhood.

Definitive diagnosis rests on demonstration of absent or low levels of GH in response to stimulation. A variety of provocative tests have been devised that rapidly increase the level of GH in normal children. These include a 20-min period of strenuous exercise or administration of L-dopa, insulin, arginine, clonidine, or glucagon. Peak levels of GH below 7 m{mu}g/L are compatible with GH deficiency.

The frequency of false-negative responses in normally growing children with any single test is considered to be approximately 20%. If this were true, about 4% of normal children would fail both tests. One study suggests that a majority of normal prepubertal children fail to achieve GH values above 7 m{mu}g/L with two pharmacologic tests. The researchers suggest that 3 days of estrogen priming should be used before GH testing to achieve greater diagnostic specificity.

During the 3 decades when hGH was obtained by extraction from human pituitary glands culled at autopsy, its supply was sharply limited, and only patients with classic GH deficiency were treated. With the advent of an unlimited supply of recombinant GH, there has been a marked interest in redefining the criteria for GH deficiency to include children with lesser degrees of deficiency. It has become popular to evaluate the spontaneous secretion of GH by measuring its level every 20 min during a 24- or 12-hr (8 P.M.–8 A.M.) period. Some short children with normal levels of GH when studied by provocative tests show very little spontaneous GH secretion. Such children are considered to have GH neurosecretory dysfunction. With the collection of more normative data, it is clear that frequent GH sampling also lacks diagnostic specificity. There is a wide range of spontaneous GH secretion in normally growing prepubertal children and considerable overlap with the values observed in children with classic GH deficiency. Although the clinical and laboratory criteria for GH deficiency in patients with severe (classic) hypopituitarism are well established, the diagnostic criteria are unsettled for short children with lesser degrees of GH deficiency.

In addition to establishing the diagnosis of GH deficiency, it is necessary to examine other pituitary functions. Levels of TSH, thyroxine (T4), ACTH, cortisol, dehydroepiandrosterone sulfate, gonadotropins, and gonadal steroids may provide evidence of other pituitary hormonal deficiencies. The defect can be localized to the hypothalamus if there is a normal response to the administration of hypothalamic-releasing hormones for GH, TSH, ACTH, or gonadotropins. When there is a deficiency of TSH, serum levels of T4 and TSH are low. A normal rise in TSH and PRL after stimulation with thyrotropin-releasing hormone places the defect in the hypothalamus, and absence of such a response localizes the defect to the pituitary. An elevated level of plasma PRL taken at random in the patient with hypopituitarism is also strong evidence that the defect is in the hypothalamus rather than in the pituitary. Some children with craniopharyngioma have elevated PRL levels before surgery, but after surgery, PRL deficiency occurs because of pituitary damage. Antidiuretic hormone deficiency may be established by appropriate studies.

ROENTGENOGRAPHIC EXAMINATION. Roentgenograms of the skull are most helpful when there is a destructive or space-occupying lesion causing hypopituitarism. In patients with nausea, vomiting, loss of vision, headache, or

increase in circumference of the head, evidence of increased intracranial pressure may be found. Enlargement of the sella, especially ballooning with erosion and calcifications within or above the sella, may be detected. MRI is indicated in all patients with hypopituitarism. In addition to providing detail about space-occupying lesions, it can define the size of the anterior and posterior pituitary lobes and the pituitary stalk. It is superior to computed tomography in differentiating a full from an empty sella turcica. The posterior pituitary is readily recognized as a bright spot. In many cases of idiopathic multiple pituitary hormone deficiency with prenatal or perinatal onset, the posterior pituitary bright spot it ectopic. It appears at the base of the hypothalamus rather than in the pituitary fossa. This diagnostic technique can provide timely confirmation of suspected hypopituitarism in a newborn with hypoglycemia and micropenis.

Skeletal maturation is markedly delayed in patients with longstanding GH deficiency. The bone age tends to be approximately 75% of chronological age. It may be even more delayed for patients with TSH and GH deficiency. The fontanels may remain open beyond the 2nd yr, and intersutural wormian bones may be found. Long bones are slender and osteopenic. Newer methods of assessing body composition, such as dual photon x-ray absorptiometry, show deficient bone mineralization, deficiencies in lean body mass, and a corresponding increase in adiposity.

DIFFERENTIAL DIAGNOSIS. The causes of growth disorders are legion; systemic conditions such as inflammatory bowel disease, occult renal disease, and Turner syndrome must always be considered. Many theoretical defects of molecular structure resulting in bioinactive GH are possible, but none has been documented at the genetic level. A few otherwise normal children are short (i.e., >3 SD below the mean for age) and grow 5 cm/yr or less but have normal levels of GH in response to provocative tests and normal spontaneous episodic secretion. Most of these children show increased rates of growth when treated with GH in doses comparable to those used to treat children with hypopituitarism. Plasma levels of IGF-I in these patients may be normal or low. Several groups of treated children have achieved final or near final adult heights. On average, they did not exceed the heights predicted from heights and bone ages at the start of treatment. There are no methods that can reliably predict which of these children will become taller as adults and which will have compromised adult height as a result of GH treatment. Such treatment of short children without proven hypopituitarism is undergoing experimental trials.

Constitutional growth delay is one of the variants of normal growth commonly encountered by the pediatrician. Length and weight measurements of affected children are normal at birth, and growth is normal for the first 4–12 mo of life. Growth then decelerates to near or below the 3rd percentile for height and weight. By 2–3 yr of age, growth resumes at a normal rate of 5 cm/yr or more. Studies of GH

secretion and other studies are within normal limits. Bone age is closer to height age than to chronological age. Detailed questioning often reveals other family members (frequently one or both parents) with histories of short stature in childhood, delayed puberty, and eventual normal stature. The prognosis for these children to achieve normal adult height is good. Boys with unusual degrees of delayed puberty may benefit from a short course of testosterone therapy to hasten puberty after 14 yr of age. The cause of this variant of normal growth is thought to be persistence of the relatively hypogonadotropic state of childhood (see Chapter 535). Constitutional growth delay can be differentiated from genetic short stature by the level of skeletal maturation, which is consistent with chronological age in the latter condition. Genetic short stature is usually found in other family members. Results of studies of hormones related to growth, however, are normal.

Primary hypothyroidism is usually easily diagnosed on clinical grounds. Responses to GH provocative tests may be subnormal, and enlargement of the sella may be present. Low T4 and elevated TSH levels clearly establish the diagnosis. Pituitary hyperplasia recedes during treatment with thyroid hormone. Because thyroid hormone is a necessary prerequisite for normal GH synthesis, its levels must always be assessed before GH studies.

Emotional deprivation is an important cause of retardation of growth and mimics hypopituitarism. The condition is known as psychosocial dwarfism, deprivation dwarfism, or reversible hyposomatotropism. The mechanisms by which sensory and emotional deprivation interfere with growth are not fully understood. Functional hypopituitarism is indicated by low levels of IGF-I, by inadequate responses of GH to provocative stimuli, and perhaps by delayed puberty. Appropriate history and careful observations reveal disturbed mother-child or family relations and provide clues to the diagnosis. Proof may be difficult to establish, because the adults responsible often hide from professionals the true situation in the family, and the children rarely divulge their plight. Emotionally deprived children frequently have perverted or voracious appetites, enuresis, encopresis, insomnia, crying spasms, and sudden tantrums. They may be excessively passive or aggressive and are borderline or dull-normal in intelligence. When child-rearing practices are altered or when the child is removed from the domicile of abuse, the rate of growth improves significantly. During this period of catch-up growth, separation of the cranial sutures and other evidence of pseudotumor cerebri may occur; these should not be mistaken for signs of a mass lesion.

The Silver-Russell syndrome is characterized by short stature, frontal bossing, small triangular facies, sparse subcutaneous tissue, shortened and incurved 5th fingers, and in many cases, asymmetry (i.e., hemihypertrophy). Affected children have low birthweights for gestational age. Studies have revealed some degree of GH

secretory deficiency in very short children with intrauterine growth retardation, whether or not they have Silver-Russell syndrome. Short-term treatment with GH often results in increased rates of growth, but its long-term benefits are unknown.

TREATMENT. In patients with demonstrable organic lesions, treatment should be directed to the underlying disease process. Evaluation of pituitary function is indicated after surgery or irradiation.

Treatment of children with classic GH deficiency should begin as early as possible. Younger children respond better than older ones, and long-term expectations are better. The recommended dose of hGH is 0.18–0.3 mg/kg/wk. It is administered subcutaneously in six or seven divided doses. Therapy should be continuous until there is no further response, a point usually concomitant with closure of the epiphyses. If the effect of therapy wanes, compliance should be evaluated before the dose is increased. Some patients treated with GH have subsequently developed leukemia. The risk of leukemia in treated patients may be double that in the general population, but this is still under investigation. Other reported side effects include pseudotumor cerebri, slipped capital femoral epiphysis, and worsening of scoliosis. There is an increase in total body water during the first 1–2 wk of treatment. Fasting and postprandial insulin levels are characteristically low before treatment, and they normalize during GH replacement. Development of diabetes mellitus is rare. Older GH-deficient patients treated with cadaver pituitary extracts are at risk for Creutzfeldt-Jakob disease for at least 10–15 yr after therapy. Recombinant GH has eliminated this risk.

Maximal response to GH occurs in the 1st yr of treatment. With each successive year of treatment, the response tends to decrease. Some patients receiving GH develop reversible hypothyroidism because of enhanced conversion of T4 to T3 and decreased levels of TSH. Periodic evaluation of thyroid function is indicated for all patients treated with GH. GHRH is just as effective as GH in the treatment of children with hypopituitarism with a deficiency of GHRH, but multiple daily subcutaneous injections are required. When a depot form becomes available, it may provide a practical form of treatment for this group of children. Recombinant IGF-I may prove useful in the treatment of children with Laron syndrome and possibly those with GH1 gene deletions and high titers of antibodies.

The doses of GH used to treat children with classic GH deficiency usually enhance growth of many non–GH-deficient children as well. Intensive investigation is in progress to determine the full spectrum of short children who may benefit from treatment with GH. Children with intrauterine growth retardation, chronic renal failure, Noonan syndrome, Turner syndrome, and others experience increases in growth velocity when treated with GH. Girls with Turner syndrome treated with GH appear to have a final height several centimeters greater than that of untreated girls.

For children with all other causes of short stature, it is unknown whether GH treatment increases their final height, and treatment of such patients should be confined to prospective clinical trials until further data establish the validity of this expensive, long-term form of therapy.

Replacement should also be directed at other hormonal deficiencies. In TSH-deficient subjects, thyroid hormone is given in full replacement doses. In ACTH-deficient patients, the optimum dose of hydrocortisone should not exceed 10 mg/m2/24 hr. Increases are made during illness or in anticipation of surgical procedures. Therapy can often be deferred until growth has been completed if the deficiency is partial. In patients with a deficiency of gonadotropins, gonadal steroids are given when the bone age reaches the age when puberty usually takes place. For infants with microphallus, one or two 3-mo courses of monthly intramuscular injections of 25 mg of testosterone enanthate may bring the penis to normal size without an inordinate effect on osseous maturation.

DIABETES INSIPIDUS
(ARGININE VASOPRESSIN DEFICIENCY)

Diabetes insipidus (DI), characterized by polyuria and polydipsia, results from lack of the antidiuretic hormone, arginine vasopressin (AVP). Destruction of the supraoptic and paraventricular nuclei or division of the supraoptic-hypophyseal tract above the median eminence results in permanent DI. Transection of the tract below the median eminence or removal of just the posterior lobe may result in transitory polyuria, but in this case, AVP released into the median eminence prevents occurrence of DI. AVP acts directly on the distal tubules and collecting ducts of the kidney by binding to V2 receptors, which are G protein coupled before triggering cAMP. The V2 receptor is also responsible for vasodilator effects of the hormone, for increasing factor VIII activity, and for increasing the concentration of von Willebrand factor in plasma. AVP deficiency may be total or partial, with varying degrees of polydipsia and polyuria.

ETIOLOGY. Any lesion that damages the neurohypophyseal unit may result in DI. Tumors of the suprasellar and chiasmatic regions, particularly craniopharyngiomas, optic gliomas, and germinomas, are common causes; the symptoms of increased intracranial pressure may accompany those of DI or may follow years later. Approximately 25% of patients with Langerhans cell histiocytosis develop DI as a consequence of histiocytic infiltration of the hypothalamus and pituitary. DI is seldom present when histiocytosis is diagnosed but almost always occurs within 4–5 yr. It occurs most often in children with multisystem disease and in those with proptosis. About half of these patients have cytoplasmic antibodies to AVP-producing cells, suggesting an autoimmune response to histiocytic cell invasion

of the hypothalamus. Encephalitis, sarcoidosis, tuberculosis, actinomycosis, and leukemia are occasional causes. Injuries to the head, especially basal skull fractures, may produce DI immediately or after a delay of several months. Operative procedures near the pituitary or hypothalamus may result in transitory or permanent DI.

In a few cases, DI is hereditary. An autosomal dominant form is characterized by variable onset, from birth to several years of age, and variable severity within a family and in individuals over time. Symptoms decrease in the 3rd–5th decades. Levels of AVP may be absent (<0.5 pg/mL) or variably decreased. The gene is on chromosome 20, and the preprotein it encodes contains AVP and neurophysin II (NP II), the hormone's carrier protein. This single polypeptide chain is cleaved within secretory granules and then reassembled into an AVP–NP II complex before secretion. Mutations causing autosomal dominant DI have been localized to the NP II moiety. Although the mutation involves only one allele, the mutant AVP–NP II complex disrupts the functioning of the normal allele, resulting in autosomal dominant inheritance. The mutated gene product is thought to be the cause of selective death of the magnocellular neurons in patients with longstanding familial DI.

Wolfram syndrome, also known by the acronym DIDMOD, consists of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. It has an autosomal recessive inheritance pattern, and the gene is located on chromosome 4p. Pathologic studies suggest a degenerative process involving b{beta} cells, supraoptic and paraventricular nuclei, the optic nerve, and cranial nerve VIII.

Absence of islet cell antibodies and of the usual HLA haplotypes associated with classic insulin-dependent diabetes mellitus differentiates the cause of this condition from that of the usual type 1 autoimmune diabetes mellitus.

DI occasionally accompanies septo-optic dysplasia.

DI has been reported in the newborn infant following asphyxia, intraventricular hemorrhage, intravascular coagulopathy, Listeria monocytogenes sepsis, and group B b{beta}-hemolytic streptococcal meningitis.

In many instances, the cause of DI cannot be found initially, but disease in only about 20% of affected patients eventually is classified as idiopathic. In more than one half of all patients with intracranial tumors, clinical or neuroradiologic signs (or both) are not manifested until 1 yr after DI has been diagnosed, and in 25%, the delay is as long as 4 yr. Periodic re-evaluation is required for at least 4 yr before the entity can be called idiopathic. About one third of patients with idiopathic DI have antibodies to AVP-producing cells, suggesting an autoimmune basis for the condition. This idea is further supported by the frequent occurrence in this subgroup of patients of other autoimmune endocrine disorders, especially autoimmune thyroid disease. These

autoimmune disorders are particularly evident in adults. DI is increasingly recognized as a terminal event in brain-dead individuals.

CLINICAL MANIFESTATIONS. Polydipsia and polyuria are the outstanding symptoms of DI. In families with the hereditary disorder, the polyuria is often noticed in early infancy. The infant cries excessively and is not satisfied with additional milk but is quieted with water. Hyperthermia, rapid loss of weight, and collapse are common in infancy. Vomiting, constipation, and growth failure may be observed. Dehydration in early infancy may result in brain damage and mental impairment. In children with AVP deficiency, there is wide variation in the manifestations. Severity tends to increase with age, and some affected children are asymptomatic until adolescence. Many affected families accept polydipsia and polyuria as a family habit and do not seek medical attention or may even prefer the symptoms to therapy.

In a child who has acquired bladder control, enuresis may be the first symptom. The excessive thirst is disturbing and interferes with play, learning, and sleep. Children with DI do not perspire; their skin is dry and pale. Anorexia is common; there is a preference for carbohydrates.

Other signs and symptoms depend on the primary lesion; for example, patients with tumors in the region of the hypothalamus may have disturbance of growth, progressive cachexia or obesity, hyperpyrexia, sleep disturbance, sexual precocity, or emotional disorders. Lesions initially causing DI may eventually destroy the anterior pituitary; in such instances, the DI tends to become milder or disappear completely.

LABORATORY DATA. The daily volume of urine may be 4–10 L or more. The urine is pale or colorless; the specific gravity varies from 1.001 to 1.005, with a corresponding osmolality of 50–200 mOsm/kg water. During periods of severe dehydration, the specific gravity may rise to 1.010 and the osmolality to 300. Other renal function studies are normal. Serum osmolality is normal with adequate hydration. During water deprivation tests, patients must be closely observed to prevent surreptitious intake of water and to avoid severe and rapid development of dehydration. In patients with severe deficiency, a 3-hr period of dehydration leads to elevation of plasma osmolality while urine osmolality characteristically remains below plasma levels. Administration of desmopressin or AVP quickly raises urine osmolality. When polyuria is mild and the deficiency is incomplete, urine osmolality may exceed that of plasma, and the response to AVP is attenuated.

Radioimmunoassay for vasopressin is available; plasma levels consistently below 0.5 pg/mL indicate severe neurogenic DI. AVP levels that are subnormal for the concomitant hyperosmolality indicate partial neurogenic DI. The assay is particularly useful in differentiating partial DI from primary polydipsia.

Roentgenograms of the skull may reveal evidence of an intracranial tumor such as calcifications, enlargement of the sella turcica, erosion of the clinoid processes, or

increased width of the suture lines. Magnetic resonance imaging (MRI) is indicated for all patients suspected of having DI. T1-weighted MRI images can differentiate the posterior pituitary from the anterior pituitary by the hyperintense signal, also referred to as a bright signal or bright spot. The bright spot is present on scans of most normal patients, but it usually is absent for patients with hypothalamic-neurohypophyseal tract lesions. For patients with autosomal dominant DI, the bright spot is usually present, presumably caused by accumulation of mutant AVP–NP II complex. Thickening of the pituitary stalk may be seen by MRI in patients with DI and Langerhans cell histiocytosis (LCH) or lymphocytic infiltration; in some patients this MRI abnormality may be detected even before other clinical evidence of LCH.

DIFFERENTIAL DIAGNOSIS. Polydipsia, polyuria, and impaired concentration are common in patients with hypercalcemia or potassium deficiency. In the male infant, nephrogenic DI must be differentiated from inherited or acquired AVP deficiency; failure of response to exogenous AVP or desmopressin is a critical differential.

Defects in urinary concentrations also occur in a variety of chronic renal disorders. Familial nephronophthisis, in particular, can mimic DI. Elevated plasma levels of urea and creatinine, anemia, and isotonic rather than hypotonic urine are characteristics of primary renal disease.

Compulsive water drinking (i.e., psychogenic polydipsia) is rare but may easily be confused with DI. Affected persons are usually able to produce a concentrated urine when fluids are withheld. Occasionally, however, diagnosis is difficult, because prolonged polydipsia lowers the maximal urinary concentrations achievable after dehydration or even after infusion of hypertonic saline solution. As a rule, a urine osmolality greater after dehydration than after administration of AVP alone indicates the ability to secrete vasopressin. If administration of AVP produces a urinary osmolality that is substantially higher than that with dehydration alone, AVP secretion is deficient. This rule seems to apply no matter how low or how high the urinary concentration may be.

Adipsia or hypodipsia, as an isolated defect of the thirst center, is extremely rare. Because the osmoreceptors for thirst and AVP occupy contiguous areas of the anterior hypothalamus, hypodipsic hypernatremia is usually associated with defects in antidiuretic function. This most often occurs in patients with hypothalamic tumors, especially germinomas, gliomas, histiocytosis, congenital malformations, and microcephaly. Adipsia seriously complicates the management of problems of water balance.

PROGNOSIS. When DI is diagnosed, the underlying process must be determined. DI itself rarely threatens life, but it may signify a serious underlying condition. It may be only transitory after trauma or surgical intervention in the region of

the hypothalamus or pituitary. In some patients with Langerhans cell reticul-oendothelioses, spontaneous remission occurs, but in others, DI may be the only residuum long after remission of the primary condition. Amelioration of clinical DI may herald development of anterior pituitary insufficiency. The prognosis of patients with brain tumors depends on the site of the lesion and the type of neoplastic cell.

TREATMENT. The causative factor deserves first consideration in the treatment. Patients with uncomplicated DI may live untreated for years with only the inconvenience of polyuria and polydipsia so long as they have an intact thirst mechanism and are allowed free access to water.

The drug of choice is desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP), a highly effective analog of AVP. This analog is more resistant to degradation by peptidases than native AVP. The antidiuretic activity of DDAVP is 2,000–3,000 times greater than its pressor activity, and 1 m{mu}g produces an antidiuresis that lasts 8–10 hr, compared with only 2–3 hr for native AVP. DDAVP is given by a nasal tube delivery system that delivers precise amounts to the nasal mucosa. The usual dose ranges from 5–15 m{mu}g, given as a single dose or divided into two doses. Children younger than 2 yr of age require smaller doses (0.15–0.5 m{mu}g/kg/24 hr). The dose must be individualized, and it is important that the dosage schedule be adjusted to allow patients to revert to mild polyuria before the next dose is given. For patients requiring over 10 m{mu}g/dose, a nasal spray preparation is also available. A parenteral preparation of DDAVP (0.03–0.15 m{mu}g/kg) is available and is useful postoperatively, particularly after transsphenoidal surgery, when nasal packing precludes nasal insufflation.

Great care must be taken in patients with DI who are comatose, undergoing surgery, or receiving intravenous fluids for any reason. Regardless of the form of therapy, any effective dose should be repeated only after its effect has worn off and polyuria recurs. Postoperative DI is often transient; daily reassessment of the need for antidiuretic hormone is necessary after it has been initiated.

DDAVP also has an effect on V2-like extrarenal receptors, resulting in release of factor VIII and von Willebrand factor. Selected patients with mild or moderate hemophilia A or von Willebrand disease can be successfully treated with doses of DDAVP 15 times higher than the dose used for antidiuresis. Desmopressin is being increasingly used in the management of children with enuresis. Some of these children have been said to have nocturnal deficiency of vasopressin secretion, but this is not established. The dose required is slightly higher (20–40 m{mu}g) than that used to treat neurogenic DI. It is given as a nasal spray before bedtime.

INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE
 (HYPERSECRETION OF VASOPRESSIN)

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is now recognized as one of the most common aberrations of arginine vasopressin (AVP) secretion. In this condition, plasma levels of AVP are inappropriately high for the concurrent osmolality of the blood and are not suppressed by further dilution of body fluids.

ETIOLOGY. The syndrome is recognized in an increasing number of clinical conditions, particularly those involving the central nervous system, including meningitis, encephalitis, brain tumor and abscesses, subarachnoid hemorrhage, GuillainBarrй{acute-e} syndrome, head trauma, and after transsphenoidal surgery for pituitary tumors. Pneumonia, tuberculosis, acute intermittent porphyria, cystic fibrosis, infant botulism, perinatal asphyxia, use of positive-pressure respirators, and certain drugs such as vincristine and vinblastine also produce the syndrome. The mechanism of the disturbed regulation of AVP in these conditions is not fully understood, but in many instances, there is direct involvement of the hypothalamus. The syndrome has been observed in patients with Ewing sarcoma; with malignant tumors of the pancreas, duodenum, or thymus; and particularly with oat cell carcinoma of the lung. In these instances, the tumor presumably synthesizes and secretes AVP, with the syndrome disappearing when the tumor is removed. In rare cases, no cause for the syndrome has been found.

The syndrome has occurred during chlorpropamide therapy for diabetes mellitus, presumably because this drug potentiates AVP. Patients with diabetes insipidus treated with various antidiuretic preparations readily develop the syndrome during periods of excessive ingestion of fluids or during intravenous fluid therapy.

CLINICAL MANIFESTATIONS. The syndrome is probably most often latent and asymptomatic and forms the basis for the observation that serum sodium levels may be unexpectedly low in conditions such as pneumonia, tuberculosis, and meningitis. Careful attention to fluid replacement in patients with conditions known to be associated with the syndrome may prevent the development of symptoms.

The clinical manifestations are attributable to hypotonicity of body fluids and are those of water intoxication. If the serum sodium level is not below 120 mEq/L, there may be no symptoms. Early, the loss of appetite is followed by nausea and sometimes by vomiting. Irritability and personality changes, including hostility and confusion, may occur. When the serum sodium level falls below 110 mEq/L, neurologic abnormalities or stupor is common, and convulsive seizures may occur. Skin turgor and blood pressure are normal, and there is no evidence of dehydration.

LABORATORY DATA. Serum sodium and chloride concentrations are low, but the serum bicarbonate level usually remains normal. Despite low serum sodium, there is continued renal excretion of sodium. The serum is hypo-osmolar, but the urine is less than maximally dilute, and its osmolality is greater than appropriate for the

tonicity of the serum. Hypouricemia is common, probably because of increased urate clearance secondary to volume expansion. Concurrence of hypouricemia with hyponatremia is a clue to the diagnosis of SIADH and is especially helpful in the neonate. Renal and adrenal functions are normal.

TREATMENT. Successful treatment of the underlying disorder (e.g., meningitis, pneumonia) is followed by spontaneous remission. Immediate management of the hyponatremia consists simply of restriction of fluids. Sodium should be made available to replace the sodium loss; hypertonic saline solution is usually of little benefit, because even large sodium loads are excreted in the urine. In cases of severe water intoxication, with convulsions or coma, administration of hypertonic saline solution increases osmolality and controls the central nervous system manifestations. In such emergencies, administration of furosemide with 300 mL/m2 of 1.5% sodium chloride causes a rise in sodium levels and diuresis. Demeclocycline interferes with the action of AVP on the renal tubule. Experience in adults with SIADH indicates that this agent may be useful, but its role in the treatment of children is not established. An 8-yr-old child with chronic SIADH has been successfully treated with single daily doses of furosemide.

514.1 Cerebral Salt Wasting

Children with acute or chronic central nervous system damage may develop a distinctive syndrome of salt wasting. The disorder has been associated with head trauma, central nervous system surgery, tumor, or meningitis. These children, unlike those with SIADH, have hypovolemia, excessive urine flow rate while receiving maintenance fluids, a large net loss of sodium, and a decreased plasma concentration of ADH. Levels of natriuretic hormone (ANH) are increased, but plasma renin and aldosterone levels are decreased; this suggests the syndrome is caused by inappropriate secretion of ANH. Therapy consists of volume-for-volume replacement of the urine loss with a 0.9% or 3% solution of sodium chloride. The condition usually remits but may recur and, in some instances, persists.

HYPERPITUITARISM

Hypersecretion of pituitary hormones is an expected finding in conditions in which deficiency of a target organ gives decreased hormonal feedback, as in primary hypogonadism or hypoadrenalism. In primary hypothyroidism, pituitary hyperfunction and hyperplasia can enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such changes should not be confused with primary pituitary tumors; they disappear when the underlying thyroid condition is treated. Pituitary hyperplasia also occurs in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome, secondary to corticotropin-releasing hormone excess, or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by

a variety of systemic tumors.

Primary hypersecretion of pituitary hormones by a suspected or proved adenoma is rare in childhood. The most commonly encountered pituitary tumors are those that secrete corticotropin, prolactin, or growth hormone (GH). With rare exceptions, pituitary adenomas that secrete gonadotropins or thyrotropin occur in adults. Hypothalamic hamartomas that secrete gonadotropin-releasing hormone are known to cause precocious puberty. It is suspected that some pituitary tumors may result from stimulation with hypothalamic-releasing hormones and in other instances, as in McCune-Albright syndrome, the tumor is caused by constitutive activating mutation of the Gsa{alpha} gene. Any pituitary tumor may also cause various hormonal deficiencies by compressing pituitary tissue.

PITUITARY GIGANTISM AND ACROMEGALY

In young persons with open epiphyses, overproduction of GH results in gigantism; in persons with closed epiphyses, the result is acromegaly. Often, some acromegalic features are seen with gigantism, even in children and adolescents; after closure of the epiphyses, the acromegalic features become more prominent.

ETIOLOGY. Pituitary gigantism is rare. The cause is most often a pituitary adenoma, but gigantism has been observed in a 2.5-yr-old boy with a hypothalamic tumor that presumably secreted GHRH. Other tumors, particularly in the pancreas, have produced acromegaly by secretion of large amounts of GHRH with resultant hyperplasia of the somatotrophs; GHRH was first isolated from two such pancreatic tumors. The GH-secreting adenomas associated with McCune-Albright syndrome are caused by an activating mutation of the Gsa{alpha} gene (see Chapter 517).

CLINICAL MANIFESTATIONS. The usual manifestations consist of rapid linear growth, coarse facial features, and enlarging hands and feet. In young children, rapid growth of the head may precede linear growth. Some patients have behavioral and visual problems. In most of the recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period in one child and at 21 mo of age in another. Giants may grow to a height of 8 ft or more. Acromegaly consists chiefly of enlargement of the distal parts of the body, but manifestations of abnormal growth involve all portions. The circumference of the skull increases, the nose becomes broad, and the tongue is often enlarged, with coarsening of the facial features. The mandible grows excessively, and the teeth become separated. The fingers and toes grow chiefly in thickness. There may be dorsal kyphosis. Fatigue and lassitude are early symptoms. Delayed sexual maturation or hypogonadism may occur. Signs of increased intracranial pressure appear later; visual loss may be demonstrable only on careful examination of visual fields.

LABORATORY DATA. GH levels are elevated and may occasionally reach

400 ng/mL. The episodic pattern of secretion and the nocturnal surge may be preserved in some patients. There is usually no suppression of GH levels by the hyperglycemia of a glucose tolerance test. There may be no response, normal responses, or paradoxical responses to various other stimuli. For example, L-dopa may paradoxically decrease GH levels. Administration of thyrotropin-releasing hormone results in increased GH levels in some acromegalics, and in a 5-yr-old giant, it resulted in a threefold increase in levels of GH. Insulin-like growth factor-I (IGF-I) levels are consistently elevated in acromegaly, in one study ranging from 2.6–21.7 U/mL; normal levels are 0.3–1.4 U/mL. Most patients also have marked hyperprolactinemia as a result of plurihormonal adenomas that secrete GH and prolactin.

Adenomas may compromise other anterior pituitary function through growth or cystic degeneration. Secretion of gonadotropins, thyrotropin, or corticotropin may be impaired.

Roentgenograms of the skull may reveal enlargement of the sella turcica and of the paranasal sinuses; computed tomography scans or magnetic resonance imaging (MRI) delineates the tumor. Tufting of the phalanges and increased heel pad thickness are common. Osseous maturation is normal.

DIFFERENTIAL DIAGNOSIS. In the differential diagnosis, hereditary tall stature must be considered; in this condition, there is usually abnormal height in one or both parents or in close relatives. Such tall persons are well proportioned and free of signs of increased intracranial pressure. Excessive growth during preadolescence in obese children is a temporary state; although such children may become tall, they do not attain the height of giants. Children with precocious puberty are often unusually tall but do not develop into giants, because their epiphyses close early and growth ceases prematurely. Patients with tall stature associated with hypogonadism or Marfan syndrome are easily differentiated clinically and have normal levels of GH. Gigantism and increased GH levels may occur in some patients with lipodystrophy, but absence of subcutaneous fat is a characteristic finding; there is increasing evidence of disordered hypothalamic function in this condition. Sotos syndrome, which is more common than pituitary gigantism, can usually be differentiated on clinical grounds.

TREATMENT. Modalities include surgery, irradiation, and medical therapy; there are advantages and disadvantages of each. Octreotide, a long-acting analog of somatostatin, is 45 times more active than the native peptide in suppressing GH secretion. Experience in adults with acromegaly indicates that octreotide persistently suppresses GH and IGF-I concentrations and reduces tumor size in a significant number of patients. This agent may be helpful in some patients as primary therapy or when surgery has not been successful.

SOTOS SYNDROME
(Cerebral Gigantism)

Although it is characterized by rapid growth, there is no evidence that Sotos syndrome is an endocrine disorder. A hypothalamic defect has been suggested as a cause, but none has been demonstrated functionally or at necropsy. Birthweight and length are above the 90th percentile in most affected infants, and macrocrania may be noted. Growth is rapid, and by 1 yr of age, affected infants are over the 97th percentile in height. Accelerated growth continues for the first 4–5 yr and then returns to a normal rate. Puberty usually occurs at the normal time but may occur slightly early. The hands and feet are large, with thickened subcutaneous tissue. The head is large and dolichocephalic, the jaw is prominent, there is hypertelorism, and the eyes have an antimongoloid slant. Clumsiness and awkward gait are characteristic, and affected children have great difficulty in sports, in learning to ride a bicycle, and in other tasks requiring coordination. Some degree of mental retardation affects most patients; in some children, perceptual deficiencies may predominate.Roentgenograms reveal a large skull, a high orbital roof, a sella of normal size but slightly posterior inclination, and an increased interorbital distance. Osseous maturation is compatible with the patient's height. GH levels and results of other endocrine studies are usually normal; there are no distinctive laboratory markers for the syndrome. Abnormal electroencephalograms are common; other studies frequently reveal a dilated ventricular system.

The cause of the disorder is unknown, nor is it clear whether all patients with this syndrome have the same defect. Most cases are sporadic. Familial cases are usually consistent with autosomal dominant inheritance, occasionally with autosomal recessive inheritance. Affected patients may be at increased risk for neoplasia; hepatic carcinoma and Wilms, ovarian, and parotid tumors have been reported.

PROLACTINOMA

Prolactin-secreting pituitary adenomas are the most common tumors of the pituitary in adolescents. With the advent of MRI, more of these tumors, particularly microadenomas (<1 cm), are being detected. The most common presenting manifestations are headache, amenorrhea, and galactorrhea. The disorder affects more than twice as many girls as boys; most have undergone normal puberty before becoming symptomatic. Only a few patients have delayed puberty. In some kindreds with type I multiple endocrine neoplasia, prolactinomas are the presenting features during adolescence.

Prolactin levels may be moderately (40–50 ng/mL) or markedly (10,000–15,000 ng/mL) elevated. Most prolactinomas in children have been large (macroadenomas), have caused the sella to enlarge, and in some cases, have caused visual field defects.

Approximately one third of patients with macroadenomas develop hypopituitarism, particularly GH deficiency.

Prolactinomas should not be confused with the hyperprolactinemia and pituitary hyperplasia that may occur in patients with primary hypothyroidism, which is readily treated with thyroid hormone. Moderate elevations (<200 ng/mL) of prolactin are also associated with a variety of medications, with pituitary stalk dysfunction such as may occur with craniopharyngioma, and with other benign conditions. Treatment for most children has been surgical resection by transfrontal or transsphenoidal approach. However, the management of prolactinoma is becoming increasingly conservative. Some patients can be effectively managed by treatment with bromocriptine, the standard drug for treating hyperprolactinemia. About 80% of adult patients respond with shrinkage of the tumor and marked decreases in serum prolactin levels.

VI. Plan and organizational structure of classes.

№ п/п	Basic stages of classes and their function and maintenance	Educational aims are in the levels of mastering	Methods of control and studies	Educational materials	Distri-buting of time in minutes
1 2 3	Preparatory stage Organizational measures Raising of education-nal aims and motiva-tion Control of basic knowledge and skills level: 1. Ethiology of hypothalamic-pituitary disease in children. 2. Key links of hypothalamic-pituitary diseases pathogenesis in children. Obesity in children. 3. Growth disorders in children 4. Sexual develop-ment disorders in children. 5. Laboratory diag-nosis of obesity, sexual deve-	α2 α2 α2 α2 α2 α2 α2 α2 α2	Individual oral questioning Test control of second level Individual oral questioning Typical situational tasks of 2 level Typical situational tasks of 2 level Second level tests Typical situational tasks of 2 level	II «Educational aims» I «Actuality of theme» II «Educational aims» П. I «Actuality of theme» Test control of second level Typical situational tasks of 2 level Typical situational tasks of 2 level Second level tests Typical situational tasks of 2 level Kit of medicines.	3 min. 12 min. 20 min..

	lopment disorders, diabetes insipidus, growth disorders in children. 6. Complications of of obesity, sexual development disorders, diabetes insipidus, growth disorders in children. 7. The principles of treatment of hypothalamus – pituitary diseases.				
4	1. Basic stage of professional skills and abilities forming 1. To conduct the patient management with obesity, sexual development diso-ders, diabetes insipi-dus, growth disor-ders' in children and, to take complaints and anamnesis.	α3 α3 α3	Practical professional training. Practical professional training.	Patient. Patient. Case history.	115 min.
	2.Conducting of patient examination to reveal the main symptoms and syn-dromes of obesity, sexual development disorders, diabetes insipidus, growth disorders in children.	α3 α3 α3	Practical professional training. Practical professional training. Practical professional training. The third level test control. The practical professional training is in the solving of non standard clinical situations. The third level	A reference chart for forming of professional abilities. Case history. A reference chart for forming of professional abilities. Case history. A reference chart for forming of professional abilities. Typical situational tasks of 3 level Third level tests. Prescribing chart	
	3.To formulate and substantiate the preliminary diagnosis				
	4. To compose the plan of patient la-boratory and instru-mental investigation:	α3			
	5.To interpret the data of laboratory and instrumental	α3		Non typical situational tasks and third level tests. Treatment	

№					
	investigation. To conduct differrential diagnosis among clinical conditions accompanied by obesity, sexual development disorders, diabetes insipidus and congenital conditions, accompanied by growth disorders in children. 6. To give the recommendations for regimen and diet of patent with hypothalamic-pituitary disorders. 7. To compose the plan patient treatment taking into account the stage of disease and presence of complications. 8. Able to render the first aid in extreme situations.	α3	tests. Practical professional training. The practical professional training is in the solving of non standard clinical situations. The third level tests. The practical professional training is in the solving of non standard clinical situations.	algorithm. Non typical situational tasks First aid algorithm.	
5 6 7	Concluding stage. Control and correction of professional abilities and skills. Working out the totals of class. Home work (basic and additional literature on the topic)		Analysis of clinical work performances Solving of non typical tasks and the third level tests. Estimation of clinical work performances.	Clinical work performances The third level non typical situational tasks. A reference chart for independent work with literature	30 min.

Methodical materials to support basic stage
professional algorithm of patients management implementation (reference chart) for the practical skills and abilities forming.

№	Task	Sequence of implementation	Remarks and warnings related to self-control
1	To conduct of patient examination with	1.To conduct the complaints and disease's anamnesis gathering.	To pay attention to features of disease course ,

	obesity, sexual development disorders, diabetes insipidus, growth disorders.	2.Carefully gathering the life anamnesis of patient. 3.To conduct examination of the patient. . . 4.To investigate the state of hypodermic fatty layer, estimate anthropometric information, sexual development of child.	underlying factors, concomitant diseases etc. Pay attention for features of disease course , underlying factors, concomitant diseases etc. to establish the availability of risk factors which facilitate the disease occurrence. To assess patient general condition, position in the bed, color and wetness of skin and mucous, presence of neck veins and extremities swelling. To pay a regard to rhythm of pulse, it tension and size on both hands, apex shove, it properties, margins of absolute and relative cardiac dullness, it changes, HR(tachi-or bradicardia, extrasystoly),BP.
		5.To conduct of heart and of main vessels auscultation. 6..To investigate the pulmonary system (percussion, bronchophony). 7.To conduct lungs auscultation. 8.To investigate the system of digestion.	To pay regard to heart tones weakening or amplifying, appearance of murmurs and additional III, IV tones. To pay attention to features of percussion and auscultation in children of different age.
2	To formulate the preliminary diagnosis.	1.To formulate the preliminary diagnosis. 2.To substantiate all components of preliminary diagnosis based on complaints, anamnesis, and examinations.	Based on modern classifi-cation to formulate the preli-minary diagnosis of hypo-thalamic-pulmonary system disease and to substantiate each component of it.
3	To evaluate the parameters of additional laboratory tests..	1.To evaluate the blood count data, to determ the bony age, the body mass index, indexes of masculinisation and feminization. 2.To interpret the additional investigations data. .	To pay attention to the presence of changes of anthropometric information, information of harmoniousness of physical and sexual development. To pay a regard to presence of delayed in sexual deve-lopment from the age from age-old ranges, information about lipidogrammes, to maintenance of cholesterol, biochemical indexes.

4	To understand the data of additional and laboratory investigation.	To understand the chest X-Ray data, the data of ECG, and of ultrasound.	To turn the special attention on the signs of changes in cella turcica configuration, information of X-ray of the skull and the long bones, the presence of additional formations in the area of cella turcica, information about specific gravity of urine, and others like that, changes of ECG
5.	To conduct differential diagnosis.	1.Consistently to find the common signs in complaints,life and disease anamnesis, data of examination, data of laboratory and instrumental tests in patient and in similar states. 2.To find differences among complaints, information of life and disease anamnesis, examination data, information about the laboratory and instrumental methods of research and in similar nosology. 3.On the basis of found out differences to exclude similar diseases from the list of probable diagnoses. 4.To conduct differential diagnostics according to the above mentioned algorithm with all of nosologies which have an alike clinical picture with a patient, including with the signs of hypothalamus-pituitary diseases. 5.Taking into account the impossibility to exclude the diagnosis of leukemia from the list of probable diagnoses to draw a conclusion about most probability of such diagnosis.	The special attention need to be spared to differential diagnostics with exogenous-constitutional obesity, diabetes, inherited syndromes are accompanied by the growth delaying.
6	To formulate the final clinical diagnosis.	1.To formulate the final clinical diagnosis. 2.Based on initial diagnosis, additional investigations data, conducted differential diagnosis to substantiate all elements of concluding clinical diagnosis.	Being based on modern classification of obesity, diabetes, growth disorders, disorders of sexual development, to formulate a previous diagnosis, complications of basic disease and presence of concomitant diseases.
7.	To prescribe treatment for patients.	1.To prescribe not medicinal treatment 2.To prescribe the medicinal treatment.	Expressly to specify the regimen and detailed diet according to a disease. Taking into account age, severity of patient state, the stage of disease, the presence of complications and

			concomitant pathology, to prescribe modern medicinal treatment in accordance with standards of obesity, diabetes, growth disoders, disoders of sexual developmen traetment.

tests – 1

1.The clinical signs of diabetes insipidus could be all listed below except for
   A) disuria;
   B) thirst;
   C) poliuria
   D) dryness of skin and mucoses;
   E) diminishing of apetite.

2.The most reliable sign of diabetes insipidus will be:
   A) hypotonic poliuria ;
   B) decreasing of blood plasma osmolarity.
   C) decreasing of cortisol level in a blood;
   D) increasing of aldosteron level in a blood;
   E) increasing of glucose level in the urine

3. The main signs of central diabetes or diabetes insipidus are all, except for:
   A) increasing of antidiuretic hormone level in a blood;
   B) decreasing of urine density;
   C) absence of kidneys disease;
   D) increasing of plasma osmolarity ;
   E) thirst, poliuria.

4.Glucosuria inherent by all diseases listed below, except for:
   A) Diabetes mellitus;
   B) Fanconi nephrophtysis;
   C) to the hepatin illness;
   D) idiopatic family renal glucosuria;
   E) protracted starvation.

10. The most reliable sign of diabetes insipidus will be all, except for:
   A) hypotonic poliuria ;
   B) decreasing of blood plasma osmolarity.
   C) decreasing of cortisol level in a blood;
   D) decreasing of aldosteron level in a blood;
   E) increasing of urea level in the blood.

11. The main signs of central diabetes or diabetes insipidus are all, except for:
   A) increasing of antidiuretic hormone level in a blood;
   B) decreasing of urine density;
   C) absence of kidneys disease;

D) increasing of plasma osmolarity ;

E) thirst, poliuria.

12. Glucosuria inherent by all diseases listed below, except for:

A) Diabetes insipidus;

B) Fanconi nephrophtysis;

C) to the hepatin illness;

D) idiopatic family renal glucosuria;

E) protracted starvation.

13. In the regiulation of ADH secretion the main factor will be:

A) osmolarity of plasma;

B) level of glucose in a blood;

C) level of electrolites in a blood;

D) level pH in ablood;

E) level of urea in a blood.

14. The inherited diabetes insipidus is more frequent diagnosed at children of:

A) first year;

B) pubertal age;

C) in a period of babyhood;

D) in prepubertal period;

E) in a period of senior age.

16. The causes of the acquired diabetes insipidus must be all,, except for:

A) mutations of ADH receptor gene;

B) primary pyelonephritis;

C) secondary pyelonephritis;

D) amyloidosis;

E) hypercalcemia, hypokaliemia.

17. For treatment of nephrogenic diabetes insipidus are uses:

A) tiaside preparations;

B) osmotic diuretics;

C) preparations of ADH;

D) preparations of potassium;

E) antiinflammatory preparations.

18. Nephrogenic diabetes insipidus is characterized by the all, except for:

A) hyperosmolarity of urine;

B) elevated or normal level of ADH in a blood;

C) hypostenury;

D) not effective treatment with adiurecrin

E) normal parameters of glomular filtration and tubular reabsorbtion

19. The causes of acquired central diabetes insipidus are the all, except for:

A) genetic defect of ADH transport synthesis;

B) craniocerebral trauma;
C) neuroinfection (encephalitis, meningitis);
D) operations in the area of hypophysis;
E) tumors (craniopharigeomas, meningeomas).

20. The basic factors of the poluria are:
    A) all reasons;
    B) central diabetes incipidus;
    C) nephrogenic diabetes insipidus;
    D) psychogenic polidesum;
    E) dipsogenic diabetes incipidus.

Answers: 1-a,2-a,3-a,4-a,5-a,6-a,7-a,8-a,9-a,10-a,11-a, 12-a, 13-a,14-a,15-a,16-a, 17-a, 18-a, 19-a,20-a.

VII.   The questions for the control of secondary knowledge level of abilities and skills:

VII.1 Materials of control for the preparatory stage of class.
A questions for control of initial level of knowledge of skills and abilities:
1.   Hormones of hypothalamus and hypophysis, mechanism of action.
2.   Syndromes of growth disorders (after the method of sygmal deviations).
3.   Diagnostics of growth acceleration signs.
4.   The definition of bony age and it detecting.
5.   The causes of origin and clinical signs of hypophisial dwarfism.
6.   Differential diagnosis of pituitary nanism.
7.   What functional tests uses for the detecting of pituitary somathotropin reserves?
8.   The principles of pituitary nanism treatment ?
9.   The causes of origin, clinical and laboratory criteria for the diagnosis of gigantism and acromegaly.
10.   Name the symptoms are characteristic for progress of hypophisis adenoma growth.
11.   Partial gigantism in children. The principles of treatment.
12.   The causes of origin and clinical signs of pubertal dispithuitarism.
13.   What clinical signs reveals in adiposogenital dystrophy?
14.   Classification of obesity. Degrees of obesity.
15.   Clinical signs of exogenous - constirtutional and subthalamic obesity.
16.   The principles of different clinical forms therapy in obesity in children.
17.   The causes and clinical signs of diabetes insipidus in children.
18.   Laboratory and instrumental criteria for diagnostics of diabetes insipidus. Functional tests in children.
19.   The treatment of diabetes insipidus in children.
20.   Hormones of sexual glands and the hypothalamic-pituitary system, mechanism of action, regulation of secretion, principles of feedback links.
21.   The definition of genetic and gonad sex. Passport sex.
22.   The definition of intersexualism.

23. Physiology of sexual maturation. (formation of gonads, of internal and external genitalia (formation of gonads, internal and external genitalia, secondary sexual signs.)
24. The criteria for girls sex maturation.
25. The criteria for boys sex maturation.
26. Factors are impaired the process of sex maturation.
27. The pathogenesis of sexual apparatus congenital anomalies
28. The classification of sexual anomalies congenital anomalies.
29. The diagnosis of sexual maturation disorders.
30. True agenesia and dysgenesia of gonads. Diagnosis and teatment.
31. Terner syndrome. Causes of origin, manifestation, diagnosis, treatment.
32. Dysgenesia of testicules and oavries. Causes of origin. Diagnosis, treatment.
33. The syndrome of incomplete masculinisation. Ethyology. Clinical forms. Treatment.
34. Syndrome of testicular feminization.Ethiology. Clinical signs, diagnosis, treatment.
35. Kleinfelter syndrome. Ethiology. Manifestation. Diagnosis. Treatment.
36. The main princioles of intersexualism treatment.
37. Organization of outpatient observation in children with sexual maturation disorders.

Test -2

1. What is not typical for exogenous - constitutional type of primary obesity?
A) Changes of a skin with a pigmentation, folliculitis, strias on hips and breeches;
B) Early terms of superfluous body mass occurrence;
C) The subcutaneously - fatty layer is distributed in regular intervals;
D) Slow, gradual progress of obesity;
E) Family predilection to obesity.

2. Attributes of an Itsenko-Cushing syndrome are all signs, except for:
A) Premature sexual development;
B) Lunar face;
C) Oteoporosis;
D) Pemature sexual pilosis;
E) Distribution of subcutaneously - fatty layer non-uniformly, in the top part of a body.

3. What percent of superfluous body mass is characteristic for III degree of obesity?
A) 50-100 %;
B) 5-10 %;
C) 10-15 %;
D) 25-50 %;
E) 15-30 %

4. Typical attributes of Lawrence -Moon-Barde-Bidl syndromt are everything, except for:

A) Cataract;
B) Pigmentary retinopathy;
C) Uniform obesity;
D) Oligophrenia;
E) Polysyndactylia, congenital anomalies of a skeleton.

5. The laboratory data in Itsenko – Cushing syndrome will have the following signs, except for:
A) Decreasing of hydrocortisone derivates in urine
B) Increasing of cortisone concentration in a blood
C) Rising in a blood of a cholesterol level;
D) Rising in a blood of sodium and chlorines levels
E) Rising in a blood of a glycemia.

6. What is not typical for a clinical signs of Itsenko - Cushing syndrome?
A) Premature ossification of bones;
B) Obesity;
C) Lunar face;
D) Osteoporosis;
E) Arterial hypertension.

7. In treatment of an initial obesity all is used, except for
A) Increased exercise stresses;
B) Balneotherapy;
C) Dieteticses;
D) Hydrotherapy;
E).Fangotherapy

8. What disease is characterized of obesity, retardation in mental and physical development, hypotonia since early years and cryptorchism?
A) Prader – Willy syndrome
B) Down.syndrome
C) Itsenko – Cushing syndrome.
D) Lawrence - Moon sendrome.
E) Pubertal subthalamic.syndrome

9. What disease is characterized of obesity, retardation in mental and sexual development, polydactylia and pigmentary retinitis?
A) Lawrence - Moon syndrome.
B) Down syndrome
C)) Itsenko – Cushing syndrome
D)) Prader – Willy syndrome
E) Pubertal subthalamic.syndrome

10. What are the relative contraindications for treatment of obesity?
A) Tuberculosis;
B) Chronic renal failure;

C) Psychoneuroses;
D) HIV-infection;
E) All listed above

11. What wide-spread disturbances of a metabolism could find in patients with obesity?
    A) Hyperinsulinemia, hypercholesterolemia.
    B) Hypoinsulinemia , hypocholesterolemia.
    C) Hyperinsulinemia, hypocholesterolemia
    D) A normal level of blood glucose and hypercholesterolemia.
    E) A normal level of cholesterol, β – lipoproteids and disproteinemia.

12. Name the preparations promotes of appetite diminishing
    A) Phepranonum;.
    B) Thyreoidinum;
    C) Furosemidum;
    D) ATP;
    E) Aloe.

13. What diseases are more wide-spread among the patients suffering of obesity?
    A) Hypertension.
    B) Diabetes.
    C) Osteoarthrosis.
    D) Coronary failure.
    E) All listed above

14. What malignant neoplasms more wide-spread among the patients suffering of obesity?
    A) Cancer of gold bladder and cholic ducts.
    B) Lungs cancer
    C) A cancer of prostate, direct and colonic intestines in men.
    D) A cancer of endometrium and mamma in women.
    E) All listed above

15. For 2 degree of obesity excess of weight makes
    A) 30-50 %;
    B) 50 %;
    C) 10-15 %;
    D) 15-20 %;
    E) 20-25 %.

16. Risk factors of paratrophy development are everything, except for:
    A) Nutritional;
    B) Constitutional;
    C) A hypokinesia;
    D) Endocrine diseases of mother;
    E) A long antibiotic therapy.

17. Calculation of nutrition in paratrophy is conducted on:
  A) Approximately - appropriate weight;
  B) Appropriate weight;
  C) Actual weight;
  D) Weight-height index.

18. For what endocrine disease the increasing of body weight is not typical ?
  A) Itsenko - Cushing syndrome
  B) Hypothyroidism.
  C) Hypogonadism.
  D) Hyperdysinsulinism.
  E) Typically for all listed,

19. For 1 degree of obesity excess of body weight makes:
  A) 14-25 %;
  B) 5-10 %;
  C) 15-30 %;
  D) 10-15 %;
  E) 10-23 %.

20. An otherwise healthy 7-year-old girl is brought to your office by her father because she has some acne, breast development, and fine pubic hair. The most likely etiology for her condition is
  a. A feminizing ovarian tumor
  b. A gonadotropin-producing tumor
  c. A lesion of the central nervous system
  d. Exogenous estrogens
  e. Early onset of "normal" puberty (constitutional)

Answers: 1-a,2-a,3-a,4-a,5-a,6-a,7-e,8-a, 9-a,10-b,11-a,12-a,13-e,14-a,15-a,16-e, 17 – a, 18-e, 19-c, 20-c.

Tasks:

1.The parents of a 14-year-old boy are concerned about his short stature and lack of sexual development. By history, you learn that his birth weight and length were 3 kg and 50 cm, respectively, and that he had a normal growth pattern, although he was always shorter than children his age. The physical examination is normal. His upper-to-lower segment ratio is 0.98. A small amount of fine axillary and pubic hair is present. There is no scrotal pigmentation; his testes measure 4.0 cm3 and his penis is 6 cm in length. What is the probable diagnosis.In this situation you should.

Answers: 1.Delaying in sexual development, constitutional type.
         2.Measure pituitary gonadotropin

2. The parents of a 14-year-old boy are concerned about his short stature and lack of sexual development. By history, you learn that his birth weight and length were 3

kg and 50 cm, respectively, and that he had a normal growth pattern, although he was always shorter than children his age. The physical examination is normal. His upper-to-lower segment ratio is 0.98. A small amount of fine axillary and pubic hair is present. There is no scrotal pigmentation; his testes measure 4.0 cm3 and his penis is 6 cm in length. Compose the plan of laboratory investigations. Compose the plan additional investigation.

1. Hormonal profile (FSH,GSH, testosteron), blood count, urine tests, biochemical tests.
2. ECG, cranial X-ray, ECHO-EG.

3. A 10-year-old obese boy has central fat distribution, arrested growth, hypertension, plethora, purple striae, and osteoporosis. Which of the following disorders is most likely to be responsible for the clinical picture that this boy presents? What tests are confirmed the diagnosis?
1. Craniopharyngioma
2. Cella turcica tomography, CT, ECHO-EG, cortisol, ACTH, testosteron levels, MRI of adrenals,

4. A 10-year-old obese boy has central fat distribution, arrested growth, hypertension, plethora, purple striae, and osteoporosis. What conditions must be include in differential diagnosis of disease.? What therapeutic approach must be applied in this case.
1. Adrenal glands hyperplasia, adrenal adenoma, adrenal carcinoma.
2. Neurosurgery.

5. An otherwise healthy 7-year-old child is brought to you to be evaluated because he is the shortest child in his class. Careful measurements of his upper and lower body segments demonstrate normal body proportions for his age. Which of the following disorders of growth is likely? What investigations must be prescribed for diagnosis confirming?
1. Pituitary nanism
2. Cranial X-ray, pituitary hormones tests.

6.A 4-year-old child has mental retardation, shortness of stature, brachydactyly (especially of the fourth and fifth digits), and obesity with round facies and short neck. The child is followed by an ophthalmologist for subcapsular cataracts, and has previously been noted to have cutaneous, subcutaneous, and perivascular calcifications of the basal ganglia. What diagnosis is more likely? This patient is likely to have which of the following features?
1. Lawrence-Moon syndrome.
2. Elevated concentrations of parathyroid hormone

7. Child, 14 years old, complaints of fast body weight increasing during the last 3 years accompanied with appetite increasing, thirst, fatigue. The diagnosis of II degree obesity with alimentary genesis established.
What are the main features of dietary treatment? What is the plan of investigation?
1. Restriction of culinary salt entering.

2. Blood count, cholesterol level, ECG, lipidogramme, cranial X-ray, ECHO-EG, fast glucose, glucose tolerance test.

8. In 13 year old child with III degree of obesity in the glucose tolerance test obtained follows data: glucose on empty stomach is 5,4 mmol/l, after 1 hours of carbohydrates loading is 10 mmol/l, after 2 hours of carbohydrates loading is 7,8 mmol/l. What condition being established? What measures are necessary for carbohydrates metabolism normalization?
1. Impaired tolerance to carbohydrates.
2. To administrate a diet, to encourage active movements aimed to normalize body weight

9. Patient C., 12 years old. The obesity, fatigue, sleepiness, headache disturbs.
Objectively: body height of 171 cm, weight of 106 kg, and the adiposity is mainly on arms and trunk.
A skin dry with a crimson - mottled shade. On arms, breast and hips there are crimson - cyanotic strips of a stretching. Pulse is 76 per min., blood. pressure is 160 / 102 mm Hg.
What is the more likely diagnosis?
What kind of excess is the main cause of hypertension in the patient?
1. Cushing disease
2. ACTH, epinephrine, hydrocortisone, aldosteronum, androstendion

10. In the girl of 15 years old the obesity, mainly on brachiums and trunk, and hirsutism, disturbances of a menses is observed. On brachiums, breast and on both sides of a stomach and on her hips there are crimson - cyanochroic strips of skin stretching
What diagnosis is the most authentic?
What investigations could confirm the diagnosis?
Cushing disease.
ACTH, cortisol, cranial X-ray.

VII. Materials of the medical support for the students independent prepapation: a reference chart for organization of students independent work with educational literature.

Tasks	Instructions
To study the ethiology and pathogenesis of hypothalamus- pituitary diseases.Be able to detect the risk group for the obesity, diabetes insipidus, growth disorders, sexual maturation disorders..	To enumerate basic ethiologic factors of hypothalamus- pituitary diseases, select the key links of hypothalamus- pituitary diseases pathogenesis.
To study clinical manifestations of hypothalamus- pituitary diseases pathogenesis in children.	To establish the symptoms and gather it to clinical syndromes are enable to put the credible diagnosis of diabetes insipidus, obesity,

	growth disorders and sexual maturation disorders.
To study diagnostic criteria of hypothalamus- pituitary diseases.	To make the flow diagram of disease
To study the additional methods of research (laboratory, instrumental)	To work out a plan of patient investigation.
To study the changes in additional investigational methods are pathognomonic for hypothalamus- pituitary diseases. .	To enumerate the basic diagnostic criteria of lhypothalamus-pituitary diseases. according to the data of additional investigational methods.
To conduct differential diagnostics, s to establish a concluding diagnosis	To substantiate the basic components of diagnosis in accordance to modern classification, and to conduct a differential diagnosis.
To prescribe the individual holiatry to patient with the diabetes insipidus, obesity, growth disorders and sexual maturation disoders. Able to render the first aid in hypothalamus-pituitary diseases.	To make the prescribing chart specifying the regimen, diet, medicinal treatment, taking into account the age, severity of patient state, stage of disease, presence of complications and concomitant diseases.
To study the ethiology and pathogenesis of diabetes insipidus, obesity, growth disorders and sexual maturation disorders.in children.	To enumerate basic ethiologic factors, select the key links of diabetes insipidus, obesity, growth disorders and sexual maturation disorders pathogenesis.

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