**STATE UNIVERSITY OF MEDICINE AND PHARMACY**

**„NICOLAE TESTEMITSANU” FROM REPUBLIC OF MOLDOVA**

CONGENITAL HEART DISEASES

**CHISINAU 2024**

* Congenital heart diseases (CHD) are the consequences of different external and internal noxious agents which affect in the embryonic stage of fetus from 2 – 8 weeks (up to 3 months) resulting in postnatal manifestations.

# Etiology

* Etiology in majority of CHD cases is unknown. Frequently CHDs appear in first 2 – 8 weeks up to 3 months of life. 6 – 10% of CHDs have genetic origin, 2% from the

environmental factors and 88 – 90% from the interaction of genetic factors with environmental factors.

* In primary genetic cause 5% occur due to chromosomal aberrations and 3 – 5% from isolated gene mutations. However, even the smallest chromosomal anomaly may affect many organs and systems.
* Primary etiologic factors represent: congenital rubella syndrome causing CHDs in children (VSD,PDA) in approximately 1% of cases.

# Etiology

Coxsakie B virus, mumps, cytomegalovirus, herpes, influenza, lithium, thalidomide, alcohol in pregnancy, smoking, diabetes in mother, systemic lupus erythematosus, phenothiazines, meprobamate, anticonvulsivants (hydantoin), vitamin D, radiation and hypoxia are the etiologic factors of CHD.

Interaction of environmental factors and multifactorial genetic factors is 90%.

* Individual should have genetic predisposition to CHDs;
* Individual should have a genetic predisposition for an unfavourable reaction for a teratogen. Exposure to noxious factors in the 2 – 3 months of pregnancy

Risk of CHDs during pregnancy in healthy parents is 1 – 5%. If the second order relative has CHD the risk factor triples. In hereditary autosomal recessive diseases the risk is 25%.

Hereditary autosomal dominant disease risk is 50%

# Clinical evolution of CHDs

after birth has 3 stages of development:

I stage: Primary adaptation. This stage may vary from some months to 2 – 3 years. At this stage the child adapts itself to the environmental and to the blood circulation irregularities. This stage is dependent on the type of abnormality, intensity of the defect and the blood circulation abnormality. In this period it requires a special attention from the doctor for early detection and treatment.

II stage: Relative compensatory stage. In this stage:

1. The general condition gets better;
2. The signs of cardiac failure and hypoxic shock decrease or disappear; 3.Hemodynamic index stabilizes;

4.The child gains weight; 5.Psychomotor development normalizes.

* The duration of this stage is variable and depends on many factors like strict regime, prolonged conservative treatment, increased immunity. The children require surgical treatment especially in this compensatory stage.
* III stage: Terminal stage.

The signs of cardiac failure and hypoxic attacks increase. This may lead to irreversible

degenerative processes which have a bad prognosis.

# Classification

* A.Abnormal communication between systemic and pulmonary circulation. 1.ASD.

1. VSD.
2. Atrio-ventricular septal defect. 4.PDA.

* B.Anomaly of the left ventricular outlet.
  1. Aortic valvular stenosis.
  2. Supravalvular aortic stenosis. 3.Coarctation of aorta.

4.Hypoplastic heart syndrome.

* C.Anomaly of the right ventricular outlet.
  1. Isolated pulmonary valve stenosis.
  2. Pulmonary artery branch stenosis. 3.Pulmonary atresia.

4.Tetralogy of Fallot.

* D.Atrioventricular valvular anomalies. 1.Congenital malformation of the mitral valve. a)congenital mitral stenosis.

1. Congenital malformation of the tricuspid valve. a)tricuspid atresia.
2. Ebstein’s anomaly.

* E.Anomalous great vessels and coronary arteries. 1.Transposition of great vessels (D-transposition).

1. Corrected type of transposition of great vessels (L-transposition).
2. Truncus arteriosus.
3. Anomalous origin of coronary arteries.

* F.Anomalous return of pulmonary veins.
  1. Partial Anomalous Pulmonary venous return.
  2. Total Anomalous Pulmonary venous return.
* G.Malposition of the heart and the viscera. 1.Dextrocardia.

1. Levocardia.
2. Mesocardia (medial).

* Confirmation of the diagnosis is based on the following criteria:
  1. Past history;
  2. Determination of anatomical changes in CHD;
  3. Determination of hemodynamic changes (general physical examination);
  4. CHD evolution:
  5. CHD complications;
  6. Peripheral blood circulation.

# Congenital heart defects with dominant left-to-right shunt:

* Atrial septal defect (ASD).
* Incidence is 10 – 20% of total CHDs. ASD with left-to-right shunt is predominant in females. ASD is a easely tolerated cardiac malformation and permits long life.

*Anatomic forms of ASD:*

* High to sinus venosus, situated next to superior venacaval orifice associated with pulmonary venous return.
* Middle ASD (50% of cases) of type ostium secundum situated in the center of fossa ovale.
* Low ASD (19 – 20% of total ASDs) situated next to inferior vena cava opening, usually known as persistent ostium primum. It is associated with mitral valve and/or tricuspidal valve defects.

*Clinical manifestations*

* In majority of the cases ASD may be asymptomatic and may be accidentally diagnosed. Rarely ASD may lead to dyspnea, recurrent pulmonary infections, short stature. Precordial region is rarely deformed. Apex beat is felt in many intercostals spaces and is more lateral.
* On auscultation: Moderate intensity of systolic murmur by II-III degree, heard vell in the third intercostals space, irradiating to apex or back. II heart sound – constant and split. Raised right ventricular systolic output.
* Radiologic findings: the heart is moderately enlarged, with right chambers predominance. Right inferior arch bulge. Pulmonary artery trunk is prominent and hyperpulsative. Pulmonary artery dilatation and pulmonary hypervascularization are observed.
* ECG: Diastolic overloading of the right ventricle – right axis deviation is seen. High R waves in the right precordial leads, incomplete or partial right bundle block, moderately prolonged PQ interval.
* Echocardiography: ASD can be seen in bidimensional ECHO.

Ventricular septal defect (VSD).

Left-to-right shunt, represents 20 – 40% of all the cardiac malformations. After 5 years of age VSD may go for spontaneous closure (Roger’s disease) or may have unfavourable complications.

*Clinical manifestations*

* Clinical manifestations depend on the diameter of the ventricular septal defect.
* Roger’s disease (small VSD) is a frequent anomaly constituting 40% of VSD cases. Occasionally holosystolic murmur is heard in grade III-IV. It is best heard in IV intercostals space in the left with irradiation all over cardiac fields. Chest X-ray, ECG and ECHO are

normal.

*Evolution, prognosis and treatment*

* In majority of the cases evolution is favourable. 50 – 60% of the cases close spontaneously and the rest reduces in the size of defect significantly. Stature is normal.

VSD with left-to-right shunt (diameter more than 1 cm) and pulmonary arterial hypertension have the following clinical manifestations:

* Signs appear from the first day or week of life;
* Dyspnea with tachypnea;
* Cough;
* Drawing of intercostals muscles;
* Profuse transpiration;
* Growth curve stationary or slow ascending;
* Recurrent bronchopulmonary infections, short stature, pallor of skin;
* Deformed thorax, bulge in the upper portion;
* Frequently noted hepatomegaly;
* Apex beat is down and pushed lateral
* Systolic thrill on palpating the precordial region. Systolic murmur is followed by accentuated second heart sound. VSD with pulmonary hypertension leads to low intensity systolic murmur and marked second heart sound.

*X-ray findings:*

* Cardiomegaly (cardio-thoracic index 0,6 – 0,65); moderate enlargement of both left atrium and ventricle.
* Hilar and perihilar pulmonary vessels are dilated and pulmonary fields are accentuated.

*ECG:*

Increased volume in the left cavities. Overloading of right ventricle may lead to pulmonary hypertension. Biventricular hypertrophy is found.

*ECHO cardiography:*

Right ventricular dilatation and pulmonary artery dilatation may be found. Ventricular septal defect can be seen.

*Treatment:* The treatment for VSD is medical and surgical.

* In moderate VSD medical treatment is given for correcting respiratory irregularities due to cardiac failure and powerful antibiotics, ionotropic agents and diuretics. Alimentation should support the weight gain. More number of intakes is supported with less salt diet.
* Surgical treatment: Small VSDs are closed by sutures. They are closed by Dacron for large VSD at the age of 3 – 5 years. Postoperative prognosis is good.

Atrio-ventricular septal defect

* It is a complex malformation due to the mal development of endocardium. This may be associated with interatrial communication, of ostium primum type, high interventricular communication and atrio-ventricular valve anomalies. Usually – dissected mitral and/or

tricuspid valve.

* Atrio-ventricular septal defect is relatively rare (2 – 6% of CHDs). It is more frequently seen in Down’s syndrome.

*Pathophysiologically*

Atrio-ventricular septal defect may lead to:

* Left-to-right shunt at the atrial level;
* Left-to-right shunt at the ventricular level;
* Left-to-right shunt from left ventricle to right atrium;
* Atrio-ventricular valvular insufficiency.

*Clinical signs*

Precordial bulge, normal or diminished pulse, cardiac failure signs, many times severe hepatomegaly. First heart sound is accentuated, split second heart sound, grade III-IV-VI systolic murmur in the sterna left margin. The appearance of pulmonary vascular obstruction may decrease or diminish the systolic murmur but may lead to rapid pulmonary hypertension.

*Chest X-ray*

The heart is enlarged. Cardiac silhouette is enlarged due to each and other cavities. Right atrial dilation is depicted by bulging of superior portion of the right inferior arch. Left atrial dilation is depicted by the bulging of the inferior portion of the left middle arch. Hypertrophy and dilation of the ventricules are depicted by rounded left inferior arch.

Pulmonary arteries are dialted and pulmonary vascularisation is increased. The increase in the peripheral transparency of the lung fields suggests pulmonary vascular obstruction.

*ECG*

* ECG examination shows left axis deviation (between 60° and 120°), prolongation of PR interval (grade I atrioventricular block), atrial hypertrophy and right ventricular or biventricular hypertrophy.

*ECHO-cardiography*

* Mitral valve is seen with anterior valve in right ventricle and posterior valve in left ventricle, interventricular communications and atrioventricular anomalies are seen.

# Another investigations

* *Catheterisation and angiocardiography*, which determine the pressures in the heart cavities, are necessary for confirming the diagnosis of atrio-ventricular septal defect.

*Treatment:*

* Medical (conservative) treatment aims to alleviating cardiac failure. Surgical treatment in the complete type of atrio-ventricular defect is to repair the mitral and tricuspid valve, closure of

atrial and ventricular septal defect. Surgical treatment is preferred between 2 and 5-6 years. Surgical treatment has a good prognosis in infants.

Patent ductus arteriosus(PDA).

PDA is an acyanotic congenital heart defect characterized by a persistent connection between pulmonary artery and aorta. This connection is necessary in intrauterine life. Isolated PDA constitutes 12-15% of CHDs and 25% of total associated cardiac anomalies. Females have more preponderance. Ratio male:female is 1:2.

*Clinical manifestations* Clinical manifestations are dependent on:

* Difference between aortic and pulmonary pressures;
* Systemic and pulmonary resistances;
* Adaptation capacity of themyocardium for this supplementary effort.

*Clinical manifestations in infants*

* Ductus Arteriosus with moderate shunt. Functionally the infant is normal. PDA may be an accidental finding in the routine investigations for the systolic murmur. Pulse is strong and ample. Anterior fontanella is hyperpulsative.
* Pathognomonic sign on auscultation is systole-diastolic murmur or “in tunnel” murmur. Maximum intensity of murmur is found in subclavicular region with irradiation to interscapular region. In an infant, systolic component is exclusive.

*X-ray findings:*

* Heart is normal or slightly enlarged. Left middle arch is elongated. Pulmonary circulation is normal or slightly increased.

PDA with considerable shunt

* polypnoea, recurrent respiratory infections, profuse transpiration, hypotrophy or short stature and cardiac insufficiency. It manifests frequently after 2 – 3 months of life. Hyperpulsative anterior fontanelle, lowered apical impulse, systolic murmur in the left subclavicular region

which may be followed by short diastolic murmur and accentuated second heart sound are usually found.

*ECG:*

* Biventricular hypertrophy, predominantly left, when the pulmonary pressure is moderately raised and predominantly right in marked pulmonary pressure rise.

*X-ray findings:*

* Cardiomegaly with left atrial and ventricular dilatation. Left middle arch is convex and hyperpulsative. Pulmonary arteries are dilated.

*ECHO-cardiography:*

* Increased volume in left ventricle. Presence of Ductus Arteriosus.

*Clinical manifestations in children*

* When the diameter of the duct is small or moderate (under 6-7 mm) shunting is less and functional disturbance is little. Characteristic systolo-diastolic murmur in the left subclavicular region is found. Apical impulse, arch of aorta in the suprasternal fossa and pulse are

hyperpulsative.

* When the diameter of the duct is more than 7 mm, the left-to-right shunt is significant. Pulmonary pressure equals or increases higher than systemic pressure. Hypostature. In the history we can notice repeated respiratory infections. Dyspnoea on effort and palpitation can

be seen. Murmur in the left subclavicular area continues to be harsh and intense. Pulmonary component of the second heart sound is accentuated.

*ECG:*

* ECG depicts the overloading of left ventricle and pulmonary veins in the diastole (high R waves, sharp and asymmetric T waves in the left precordial leads, deeps waves in the right leads).

*X-ray findings:*

* Left atrium and left ventricular dilatation. Ascending aorta is dilated. Pulmonary hypervascularisation.

Transposition of Great vessels (TGV).

* Transposition of Great vessels consists of abnormal origin and positions of aorta and pulmonary artery. Aorta is situated anteriorly to pulmonary artery and originates from right ventricle, and pulmonary artery from left ventricle. Among the cyanotic heart disease this is

the second most frequent anomaly. Predominant in males.

Two principal types of transpositions are described:

* 1. Complete transposition or D-transposition: This is a rare form characterized by aorta originating from right ventricle and is situated right to pulmonary artery, which normally should originate from left ventricle.
* 2. Corrected transposition or L-transposition: this may occur with atrio-ventricular or ventriculo-aortal abnormality. The aorta originates from the right ventricle and is situated anterior and left to pulmonary artery. The aorta originates from the far left end of the right

ventricle which concomitantly corrects the functional transposition.

*Clinical manifestations*

* Severe progressive cyanosis which gets worse or intensifies on crying. This manifests in the first days of life.
* White and black spots on mucosa and bluish-black spots on skin.
* Hypocratic fingers, which are painful and telengiectic. This appears after few months after birth.
* Dyspnoea is a constant sign. Congestive cardiac failure signs may occur in the first few months of birth preceded by gallop rhythm in the heart.
* Deficit physical growth.
* Rapid cardiomegaly.
* In 50% of the cases the auscultatory findings are normal. Second heart sound may be acdcentuated. Ejection systolic murmur may be heard. Intense systolic murmur due to VSD or pulmonary stenosis may be heard.

*X-ray findings:*

* Pulmonary vascularisation may be normal, increased or decreased (in the presence of pulmonary stenosis); the heart is small in the first few weeks of life. Later cardiomegaly may appear. The shape of the heart may appear like an egg on the diaphragm.

*ECG:*

* ECG is nonspecific. Electric axis is deviated to the right. Ventricular hypertrophy, right atrial hypertrophy and biventricular hypertrophy may be seen. Atrio-ventricular block is sometime met with.
* Treatment is by cardiotonics, diuretics, potassium preparations, vit. B1 and B6. Surgical treatment may be palliative (atrioseptostomy, atrial septectomy, pulmonary artery constriction,

aorto-pulmonary anastomosis) and radical (reversing the blood flow at the atrial level or repositioning the great vessels). Surgical treatment is usually given in the first few months to 2-3 years.

# CHD with decreased pulmonary circulation

Pulmonary stenosis:

* Equal predominance to both the sexes. Incidence is 5%.

*Clinical manifestations:*

* Dyspnoea on effort is an early symptom. Dyspnoea at rest may be found depending on the severity of the lesion. In severe stenosis cyanosis, polypnoea, hypoxic signs on minimal effort

(sucking, crying, defecating) may be seen. Right heart failure signs with hepatomegaly, raised JVP and peripheral edema may be seen in critical pulmonary stenosis. On auscultation ejection systolic murmur of II-IV degree in the pulmonary region and split second heart sound are heard. The more the stenosis, the weaker and delayed are closing of the pulmonary valves. In severe stenosis no murmur or closing sound of the pulmonary valve is heard.

*ECG:*

Right ventricular hypertrophy (high R waves in V1 and reverse ration of R and S in V6) is seen.

Presence of Q waves in V1 depict a severe obstruction. High P waves denote right atrial hypertrophy.

*X-ray findings:*

* Moderate cardiomegaly. Bulged left middle arch due to poststenotic dilation of the pulmonary arteries. Normal or poor pulmonary vascularisation depending on the degree of stenosis.

*ECHOcardiography:*

* Right ventricular height and pulmonary and tricuspid valve anomaly can be appreciated.
* *Cardiac catheterization and angiocardiography* confirm the diagnosis.

*Treatment:*

* Right ventricular pressure below 50 mm Hg has good prognosis. If the pressure crosses 60 mm Hg the balloon valvuloplasty is done which has minimum risk factors.

Fallot’s tetralogy

* This represents 10-15% of the cases of CHDs. It is the most frequent among the cyanotic CHDs. In Fallot’s tetralogy there will be right ventricular outlet obstruction (pulmonary valve

stenosis), right ventricular hypertrophy and interventricular communication (VSD) and intact interatrial septum. In Fallot’s tetralogy there will be VSD, pulmonary artery stenosis, over riding of aorta and right ventricular hypertrophy. Fallot’s pentalogy consists all that in tetralogy and ASD. Clinical manifestations are the same. Fallot’s tetralogy is the most frequent and has 3 variants: 1.with pulmonary atresia; 2.classical form with stenosis of different degrees; 3.”red” form of tetralogy (with little infundibular stenosis).

*Clinical manifestations*

* Cyanosis is an essential symptom, it may be present in first few weeks of life (which increases at once on the occlusion of Ductus arteriosus after birth) or cyanosis may appear late at 1 – 1,5

years of life. Hypocratic fingers (short fingers) and secondary nail bed hypoxia may appear at 1 – 2 years of life. In the form of left pulmonary artery stenosis, occasional or due to effort (sucking, crying, playing) appears a hypoxic state (dyspnoeo – cyanotic spells), cyanosis increases, agitation, loss of consciousness, convulsions, hemiparesis (due to infundibular region spasm right ventricle all the venous blood is drained to aorta causing CNS hypoxia).

*Clinical manifestations*

* Dyspnoea is second most important clinical manifestation and will be of different intensity in different patients. The growth retardation and hypotrophy are noted. Squatting position reduces

the systemic venous return and in turn reduces the right-to-left shunt (due to which cyanosis reduces).

* On general physical examination the bulge in the precordial region and apical impulse (apex beat) in the left fourth intercostals space laterally to the mid clavicular line are observed. Systolic murmur in the left margin of the sternum may be heard. Ejection systolic murmur of

III-IV-VI degree can be heard in the same region. The severe murmur indicates that the intensity is less or nothing. Pulmonary component of the second heart sound may be weak, normal or loud depending on the aortic component. Laboratory reports indicate polycythemia, ophthalmoscopy – dilated retinal veins; increased viscosity of the blood is observed.

*X-ray findings:*

* “Boot shaped heart” (normal size, concave left middle arch and apex of the heart lying on diaphragm), pulmonary hypovascularisation and hypertransparent lung fields are seen.

*ECG:*

* Signs of increased right atrial and ventricular flow: sharp and high P waves in lead II and III, positive P waves in V1 and V2 and QRS deviation to right.

*Complications:*

* Tetralogy of Fallot can be met with neurologic complications like anoxic attacks, cerebral abscess and cerebral vascular thrombosis. Other complications are infections, bacterial endocarditis, pulmonary tuberculosis (favoured by pulmonary hypovascularisation), pyaemia

in lower lobes of lungs; spontaneous hemorrhages and congestic cardiac failure.

*Treatment:*

* Medical treatment mainly aims at prevention and treatment of dehydration, paroxysmal dyspnoeic spells, prevention of bacterial endocarditis and combating hypochromic anemia.

Surgical treatment in the case of severe disease is given before the second year of life; aorta or subclavian artery anastomosis which ameliorates pulmonary perfusion may be performed.

After 2 years of life radical surgical treatment is indicated: VSD closure, dilating the infundibulo-pulmonary stenosis. Β-blockers and anticoagulant therapy are indicated.

*CHD without changes in pulmonary circulation.*

Isolated Aortic Stenosis.

* Isolated aortic stenosis constitutes 3 – 6% from all CHDs. Three forms of anatomic variants are observed in aortic stenosis: valvular, subvalvular and supravalvular (very rare). Male/female ratio constitutes 3/1.

*Clinical manifestations:*

* If the diameter of the aorta is less than the 1/3 of the normal caliber it leads to dyspnoea on effort, vertigo, palpitations, unconsciousness and syncope. On percussion the heart is enlarged. Apical impulse is strong and lower in position; on auscultation – intense holosystolic murmur

of IV-VI degree in the second right intercostals space is heard. It is associated with thrill. The murmur radiates to the second left intercostals space and apex. The second heart sound is normal in little stenosis but diminished in severe stenosis. Pulse is weak and delayed. Systolic blood pressure is lowered.

*ECG:*

* Left ventricular hypertrophy signs are seen. Short S-T segment and inverse T waves in D1, aVL, V5, V6 which signifies the severity of stenosis.

*X-ray findings:*

* Moderate cardiomegaly. Left ventricular hypertrophy.

*ECHOcardiography:*

* Calcified aortic valves. Size, form and the surfaces of the bicuspid aortic valves can be appreciated. Aortic dilation can be seen. Echo Doppler measures the pressure gradient between left ventricle and aorta.

*Evolution:*

* Little stenosis has good prognosis. Severe stenosis may result in cardiac failure, rhythm disorders or coma. Bacterial endocarditis worsens the prognosis.

*Treatment:*

* Medical treatment aims in treating the cardiac failure and coronary insufficiency. Surgical treatment may be indicated in medium stenosis and is a must in severe stenosis.

*Check-up:*

* In the less severe forms 2 times visit in a year to a cardiologist, ECG, Echo, blood tests, urine analysis are recommended. In the severe forms cardiologist consultation is recommended. Abstinence from sports or strain physical effort are recommended. Prophylaxis for

endocarditis throughout the life is prescribed.

Coarctation of Aorta

* Coarctation of aorta can present with various degrees of stenosis usually in isthmus under the origin of left subclavicular artery in the zone where ductus arteriosus connects.

For coarctation of aorta are characteristic:

* a) ventricular hypertrophy;
* b)collateral circulation between subclavian artery and internal mammary artery, which assures the sufficient blood supply to the regios denied by obstruction. If the collateral circulation is

insufficient then the prognosis is reserved especially in the infantile form (preductal form). In the postductal form (adult form) then develops collateral circulation in intrauterine life which irrigates the descending aorta. In the preductal form (infantile form) of coarctation of aorta till the stenosis is irrigated by the left ventricle and the descending aorta by the ductus arteriosus.

Also:

* c)left atrial pressure and the pulmonary capillary pressure are high reflecting the high telediastolic pressure in the pulmonary bed.

After the birth, the aortic resistance rises rapidly and pulmonary pressure falls progressively. The shunt may be left-to-right or bidimensional.

Coarctation of aorta is a relatively frequent congenital anomaly (7 - 10% of all CHDs). Male/female rate is 2:1.

# Preductal type of coarctation (infantile type).

Clinical manifestations occur early in infants due to severe cardiac failure (dyspnoea, generalized cyanosis). Brachial and radial artery pulse and dorsalis pedis artery pulse are absent. Pressure is less than 20 mm Hg. This is absent in severe cardiac failure. Oscillometry shows that the femoral artery pressure is 1/3 – 1/2 of brachial artery. Systolic murmur of II-III degree can be heard in the second – third left intercostals space, parasternal and interscapular regions. The murmur changes accordingly to the malformations.

* *ECG:*

*Paraclinically:*

Right ventricular hypertrophy in first few months.

* *X-ray findings:*

- Cardiomegaly with increased pulmonary vascularisation is seen.

* *Cardiac catheterization and angiocardiography* (if necessary) permits to see the type of coarctation and other associated malformations.

Medical treatment aims to alleviate cardiac failure. Surgical treatment: resection of the stenosed part or insertion of dilating ring in the stenosed part of the aorta. For the adult type the surgical intervention can be proceeded with from 4 – 15 years.

**Bibliography:**

1. Nelson Textbook of Pediatrics 21th Edition
2. . Parks Pediatric Cardiology, 2014
3. Susan M., White, Andrew J. Washington Manual TM of Pediatrics, The, 1st Edition, 2009, Lippincott Williams & Wilkins.
4. Colin D. Rudolph. Rudolphs Pediatrics, The 21 st Edition, 2003.