

Министерство здравоохранения республики Беларусь  
Учреждение образования  
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии  
Обсуждено на заседании кафедры  
Протокол №7 от 30.08.2017

**МЕТОДИЧЕСКАЯ РАЗРАБОТКА**  
Для проведения занятия со студентами  
3 курса ФПСЗС, обучающихся на английском языке  
по патологической физиологии

**Тема: Роль наследственности в патологии**

**Theme: The role of heredity in pathology**

Время 3 ак. часа

**Actuality of the theme.** Hereditary factors play an essential role in human pathology. About 2000 different hereditary diseases are known now. 4 % of new-born suffer from these or other genetically conditioned defects. This testifies importance of ability to participate in exposure methods of hereditary diseases, study ways of their prophylaxis and cure principles. Heredity pathology plays an important role in development of such hereditary conditioned diseases, as atherosclerosis, essential hypertension, rheumatism, diabetes mellitus, gout. Multifactorial disorders result when small variations in genes combine with environmental factors to produce serious defects.

**Learning goals of the lesson:** to study the etiology and pathogenesis of hereditary and congenital diseases, as well as violations leading to pathology of intrauterine development.

**Educational goals of the lesson:** formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

**Objectives of the lesson:**

1. To know mechanisms of emergence and development of hereditary and congenital diseases.
2. To know critical periods of intrauterine development.
3. To know etiology of congenital malformations.
4. Be able to uncover mechanisms of teratogenesis.

**To repeat the following questions from related disciplines to ensure absolute mastery of the material:**

1. Intrauterine development I (histology, cytology, embryology disciplines).
2. Genetic apparatus of cell, encoding of hereditary information (medical biology and genetics discipline).

**Control questions of the lesson:**

1. A concept of hereditary, congenital diseases and phenocopies. Mutagenic factors.
2. Mechanisms of hereditary pathology. Antimutagenesis.
3. Mono- and polygenic hereditary diseases. Penetrance and expressiveness.
4. Chromosomal diseases. Hereditary predisposition to diseases.
5. Hereditary diseases of connective tissue.
6. Methods of studying hereditary diseases, principles of prevention. A concept of gene therapy and "genetic engineering".
7. Pathology of intrauterine development. A concept of antenatal pathology.

**Calculation of study time**

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

## Additional materials:

### HEREDITARY DISEASES

**Genetically determined diseases** — the diseases, which are caused by genetic factors. Their transmission to descendants may be limited in the case of impaired reproductive capability of the patient.

**Hereditary diseases** — are diseases transmitted to the next generations which are based on structural changes in DNA.

**Congenital diseases** – disease and developmental abnormalities which are manifested just after the birth. May be hereditary and non-hereditary.

### The etiology of hereditary diseases

**Causes of hereditary diseases** are factors which may cause mutation – **mutagens**. A risk factor for the emergence and implementation of the mutation action is the failure of repair systems (genetically determined or acquired) or a violation of the regulation of gene activity (epigenetic mechanisms).

### Mutations

**Mutation** — is a strong spasmodic change of genetic apparatus (not connected with cell division or usual recombination of chromosomes) and is a material basis of genetically determined diseases.

#### *Etiology*

Mutagens – are etiological factors, which cause a mutation.

By etiology distinguish spontaneous and induced mutations.

**Spontaneous** (or natural) are called mutations arising spontaneously due to natural conditions of the external and internal environment. For example hormonal factors (endocrine diseases mother diabetic embryo- and fetopathy); somatic maternal disease (cardiovascular, respiratory, digestive, urinary and other systems); endogenous chemical mutagens which are formed in the body during metabolism – peroxides and free radicals (automutagenes). «Overripeness» of germ cells: are basis on processes that lead to desynchronization of ovulation and fertilization. Age of parents: it is known that mothers aged 35 years and under 17 years has increased frequency of gametic genomic mutations. There is a relationship between the father's age older than 40 years and the frequency of monogenic diseases.

**Induced mutation** – a mutation caused by special direction of the impact of physical (ionizing radiation), chemical (pesticides, industrial connections (formaldehyde, benzol and other); drugs (cytostatic drug, connections of mercury, arsenic and other)) and biological mutagens (DNA and RNA viruses: measles, chickenpox, mumps, infectious mononucleosis, rubella).

Feature of chemical mutagens consists in that their effect is dependent in dose and cell cycle stage. The higher dose of the mutagen, the stronger the mutagenic effect. The most sensitive to mutagens step of DNA synthesis (S-phase).

#### *Classification of mutation*

By etiology: spontaneous and induced.

By type of mutated cells: gametic, somatic, mosaic.

By value: favourable, pathogenic, neutral.

By levels of genetic material organization: gene, chromosome, genome.

### Gene mutations

**Gene mutations** (point mutations) — mutation involving a change in a single nucleotide base within a gene.

1. By the nature of the changes:
  - deletion is a loss of segment of DNA;
  - duplication is doubling of segment of DNA;
  - inversions are a turn of segment of DNA on 180°;
  - insertion is an insertion of additional segment of DNA;

- transversion is replacement in DNA of purine basis on pyrimidine or vice versa.

2. On the consequences: neutral, regulatory, dynamic, missense mutations, nonsense mutations.

Missense mutation – altering the coding sequence resulting in substitution of one functional codon for another.

Nonsense mutation – altered DNA codes for a stop codon that causes premature termination of protein synthesis.

**Chromosomal mutations** are **structural** alterations of **chromosomes**:

- deletion is a loss of area of chromosome,
- duplication is doubling of separate area of chromosome,
- inversions are a turn of separate areas of chromosome on 180°
- translocation is a change of position.

**Genome mutation** (polyploidy, aneuploidy) are changing **the number of** the structurally unchanged **chromosomes** in a genome.

**Polyploidy** — is multiplying the complete set of chromosomes multiple of the haploid (3n, 4n, 5n). Causes of polyploidy are double fertilization or absence of the 1<sup>st</sup> meiotic division. Result in the lack of viability of organism and are reason of spontaneous abortions and stillborn.

**Aneuploidy** – a change of amount of chromosomes is in one or a few pair not-multiple haploid (2n + 1, 2n-1). It is most widespread class of mutations, the basic forms of chromosomal illnesses.

**Monosomy** – the presence of only one of the two homologous chromosomes (Turner syndrome)

**Trisomy** – presence of three homologous chromosomes in karyotype (21 – Down syndrome, 13 – Patau syndrome, 18 – Edwards syndrome).

### **Antimutagens**

**Antimutagens** – a **substance** capable of **suppressing** spontaneous and inducing **mutagenesis**.

Antimutational mechanisms

1. Neutralization mutagen prior to contact with the DNA (e.g. by increasing the activity of enzymes detoxifying mutagens).
2. Enhancing the stability of DNA to mutagens (duplication of the structural elements of the genome, the matrix principle of biosynthesis, the ability to repair, regulation of gene activity).
3. Prevents the conversion of indirect mutagens in the true

Examples of antimutagens: amino acids (arginine, histidine, methionine), enzyme (peroxidase, NADPH oxidase, catalase, glutamineperoxidase), some medicaments (sulfonamides, interferon, antioxidants), Vitamins E, C, A, K

### **Classification of hereditary diseases**

There are hereditary, congenital, familial and sporadic diseases.

Congenital diseases – are conditions that already exist at birth. Congenital diseases may be caused by hereditary and non-hereditary factors (birth defects that occur due to teratogenic effects of external factors, congenital infections). At the same time, not all hereditary diseases are congenital.

Family diseases – are diseases among family members (including family members from two to several generations). They can be hereditary and non-hereditary.

Working **classification of hereditary diseases** (E.D.Goldberg, 2009)

- single gene diseases
- chromosome diseases
- multifactorial diseases
- genetic diseases of somatic cells
- diseases exhibited atypical inheritance

**Single gene disorders** – caused by a **mutation of a single gene**.

**Chromosomal diseases** – caused by chromosome and genome mutations.

**Multifactorial diseases** – a hereditary predisposition.

**Diseases exhibited atypical inheritance** – caused by such phenomena as mitochondrial genetics, genomic imprinting, uniparental disomy, triplet repeat expansion.

**Mitochondrial disease** – a heterogeneous group of diseases characterized by genetic and structural-biochemical defects of mitochondria, violation of tissue respiration. The main causes of mitochondrial disease include mutations of mitochondrial genes, nDNA gene mutation required for mitochondria, violation of intergenomic interaction, which may cause a phenomenon of depletion (depletion of mtDNA copy number), as mtDNA synthesis is under the control of nDNA.

**Genomic imprinting** refers to an epigenetic mark that distinguishes parental alleles and results in a monoallelic, parental-specific expression pattern in mammals. Genomic imprinting also subjects mammals to a greater genomic risk because a mutation in one allele (either genetic or epigenetic) can result in the absence of one or more gene products. The most well-known conditions include Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome, Silver-Russell syndrome.

**Uniparental disomy** occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent.

**Triplet repeat expansion** occurs during multiple stages of human development in different cell types, and is sensitive to the gender of the parent who transmits the repeats. As the triplet repeat expands with successive generations there is increasing dysfunction of the gene and worsening of the clinical symptoms. An example is Huntington disease, fragile-X syndrome.

**Monogenic diseases** – are determined by a single mutant gene and occur in a particular action (often specific) and obligatory environmental factor (pollution physical and chemical factors, nutrients, supplements, drugs). Examples: lactose intolerance, lack of  $\alpha$ 1-antitrypsin.

The clinical picture of a specific monogenic hereditary disease can vary. Genetic causes of the polymorphism can be the phenomenon of interaction of main genes and modifiers genes, as environmental factors.

Genetic heterogeneity (genocopy) can be determined by mutations in different genes (interloci heterogeneity) or multiple allelism of individual particular gene (intralocus heterogeneity). Interloci heterogeneity is known for hereditary forms of epilepsy (about 20 genes including mitochondrial). Along with genocopies can occur phenocopies of gene diseases.

**Phenocopies** – those diseases, which are caused by environmental factors and have a clinical picture similar to known hereditary diseases.

The opposite condition, when the mutant genotype of the individual do not develop the disease as a result of environmental influences (drugs, diet, etc.), is defined as **normocopying**.

The phenomenons of gene expression variability are including penetrance and expressivity.

**Penetrance** – is the probability of phenotypic manifestations of the abnormal gene, the ability of the gene to be realized in a sign. It shows the percentage of the abnormal gene carriers reveals a pathological phenotype. Incomplete penetrance is determined by genotypic environment of the gene, ie, a person can be the abnormal gene carrier, but the gene is not manifested due to the modifying effect of other genes.

Expressiveness - a severity of manifestations of the abnormal gene. For example, in six-fingered the sixth finger may be short as a weak manifestation of inherited sign.

**Polygenic disease** – are determined by many genes the result of interaction of normal or modified (mutated genes), each of which alone does not lead to the development of the disease). Individual becomes ill by polygenic disease when the "threshold of the disease."

## **Single gene disorders**

### **Autosomal Dominant Disorders**

**Marfan syndrome** is an autosomal dominant connective tissue disorder involving the cardiovascular, skeletal and ocular systems, the integument, lungs and dura. In 90-93% of cases is caused by mutations in FBN1. Main manifestations include aortic aneurysm and dissection, ocular lens dislocation and long bone overgrowth, usually associated with normal intelligence.

### **Autosomal Recessive Disorders**

**Phenylketonuria (PKU)** is an autosomal recessive metabolic genetic disorder characterized by a mutation in the gene for the hepatic enzyme **phenylalanine hydroxylase (PAH)**. This enzyme catalyzes the conversion of phenylalanine to tyrosine. The absence of PAH leads to accumulation of phenylalanine and tyrosine to become an essential amino acid. Clinical manifestations are postnatal growth retardation, moderate to severe mental retardation, recurrent seizures, hypopigmentation, and eczematous skin rashes.

### **X-Linked Disorders**

**Vitamin D-resistant rickets** – is X-linked dominant caused by mutations in phosphate regulating endopeptidase homolog X-linked, FGF23, and dentin matrix acidic phosphoprotein gene respectively. Typical signs are observed from the first months of life: radiological signs of defective mineralization on cartilage growth plates (rickets) and bones (osteomalacia) and alterations of the phosphocalcic homeostasis in spite of a satisfactory vitamin D status. The clinical phenotype combines bone deformities, mainly at the lower limbs.

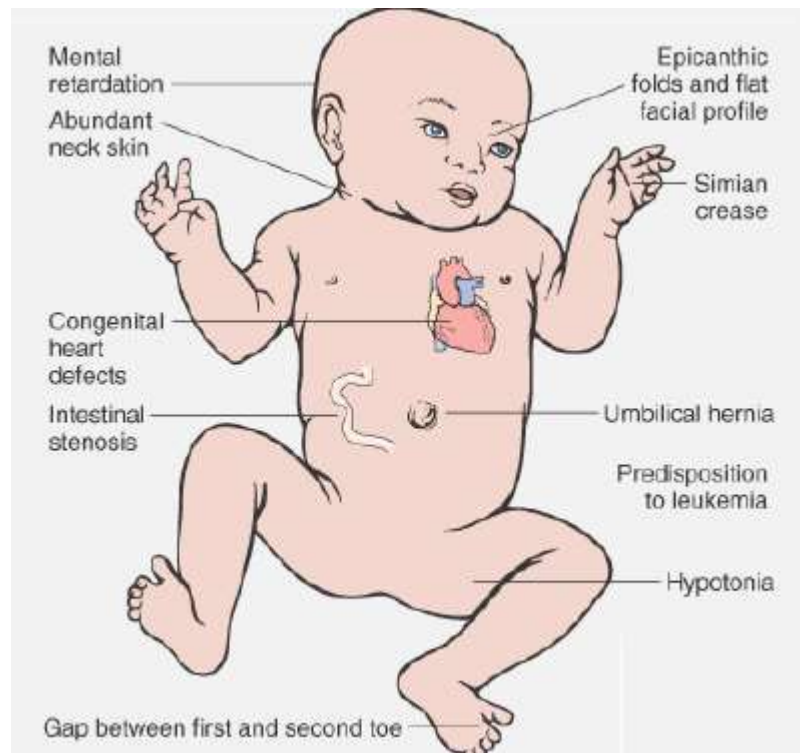
**Hemophilia A** – X-linked recessive disorders with a deficiency of factor VIII (antihemophilic globulin). It is characterized by hematoma type of bleeding. Recurrent bleeding in the large joints (hemarthrosis) lead to ankylosis. Large inter- and intramuscular, retroperitoneal hematoma with subsequent destruction of the soft tissues, severe and frequent spontaneous bleeding, persistent recurrent gastrointestinal bleeding and kidney.

### **Chromosomal disease**

**Cri du chat syndrome** – chromosome 5p deletion syndrome, 5p minus syndrome or Lejeune's syndrome, is a rare genetic disorder due to a missing part of chromosome 5. The syndrome gets its name from the characteristic cry of affected infants, which is similar to that of a meowing kitten, due to problems with the larynx and nervous system. About 1/3 of children lose the cry by age 2. Other symptoms may include feeding problems (due to difficulty swallowing and sucking); low birth weight and poor growth, growth retardation; microcephaly; severe cognitive, speech, and motor delays, behavioral problems such as hyperactivity, aggression, tantrums, and repetitive movements.

### **Down syndrome**

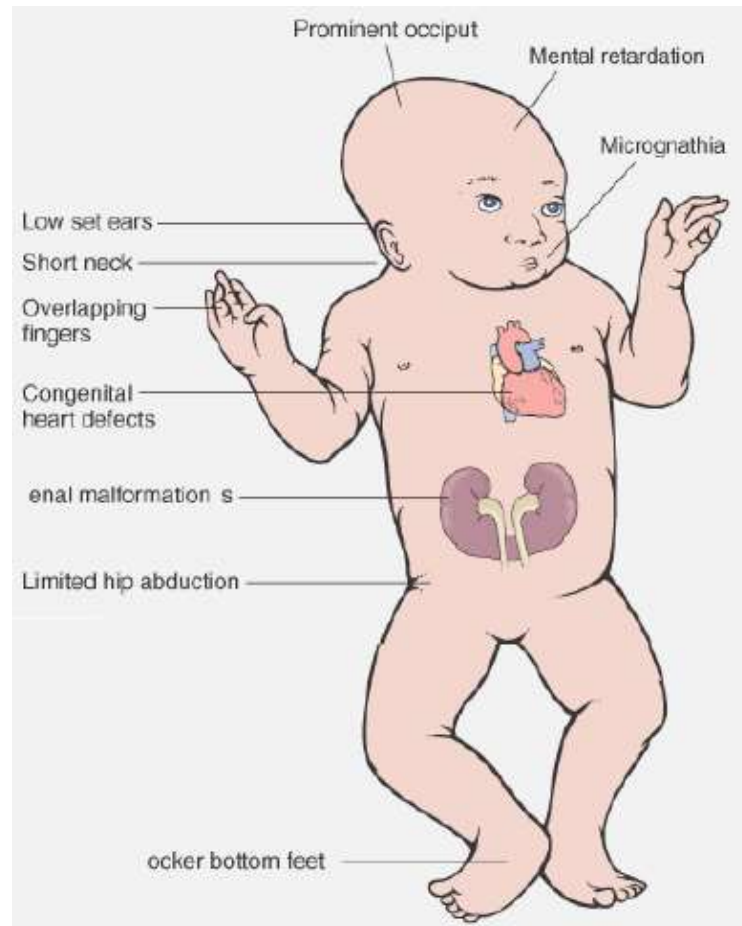
Down syndrome is the most common of the chromosomal disorders. Approximately 95% of affected individuals have trisomy 21 (due to nondisjunction), 4% of cases Robertsonian translocation t(14;21)(q10;q10), 1% of cases – mosaicism. Manifestations: mental retardation, epicanthic folds, flat facial profile, macroglossia, Simian crease, combined atrial and ventricular septal defects (major factor affecting survival in early childhood). Persons have increased risk of Hirschsprung's disease, duodenal atresia, leukemia, Alzheimer's disease by 35 years of age in most cases. All males are sterile; females have a 50% chance of having a child with Down syndrome.



**Figure 3 – Trisomy 21: Down syndrome (Kumar V., 2005)**

### ***Edwards syndrome***

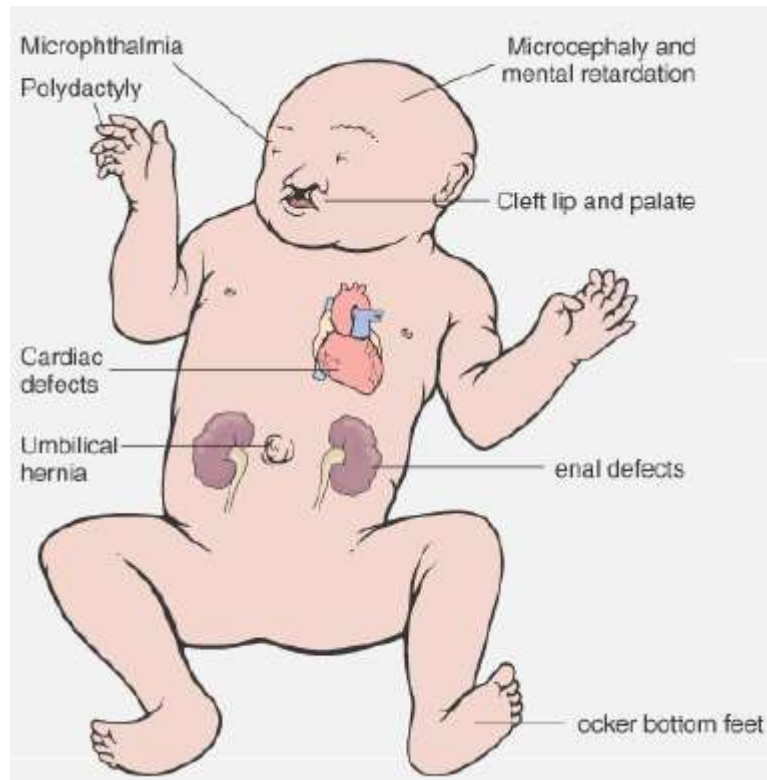
More than half born die by 2 months of age, survival beyond 1 year is rare. Trisomy 18 is due to non-disjunction in approximately 80% of cases, mosaicism in 10%, translocation in 5%, and trisomy 18 plus sex chromosomal aneuploidy in 5%. Manifestations: craniofacial dysplasia (micrognathia, short neck, low-set malformed ears, unilateral cleft lip and palate, dolichocephaly – long narrow cranium); skeletal malformations (radial aplasia, camptodactyly (crossed, flexed fingers), foreshortened dorsiflexed great toe); obligatory cardiopathy (ventricular septum defect and valvular defects); intestinal and renal malformations.



**Figure 4** – Trisomy 18: Edwards syndrome (Kumar V., 2005)

### ***Patau syndrome***

In most cases is found trisomy 13 caused by non-disjunction, in approximately 20% of cases translocation of chromosomes 13 and 14, mosaicism is found in less than 10%. Clinical signs: facial dysplasia (bilateral cleft lip and palate, microphthalmos, coloboma, microtia, hypertelorism). cerebral symptoms (rhinencephalon (absence of the olfactory bulb) holoprosencephaly (fusion of the frontal lobes)), internal malformations of kidneys, urogenital tract and heart, polydactyly (supernumerary fingers), rocker-bottom feet.



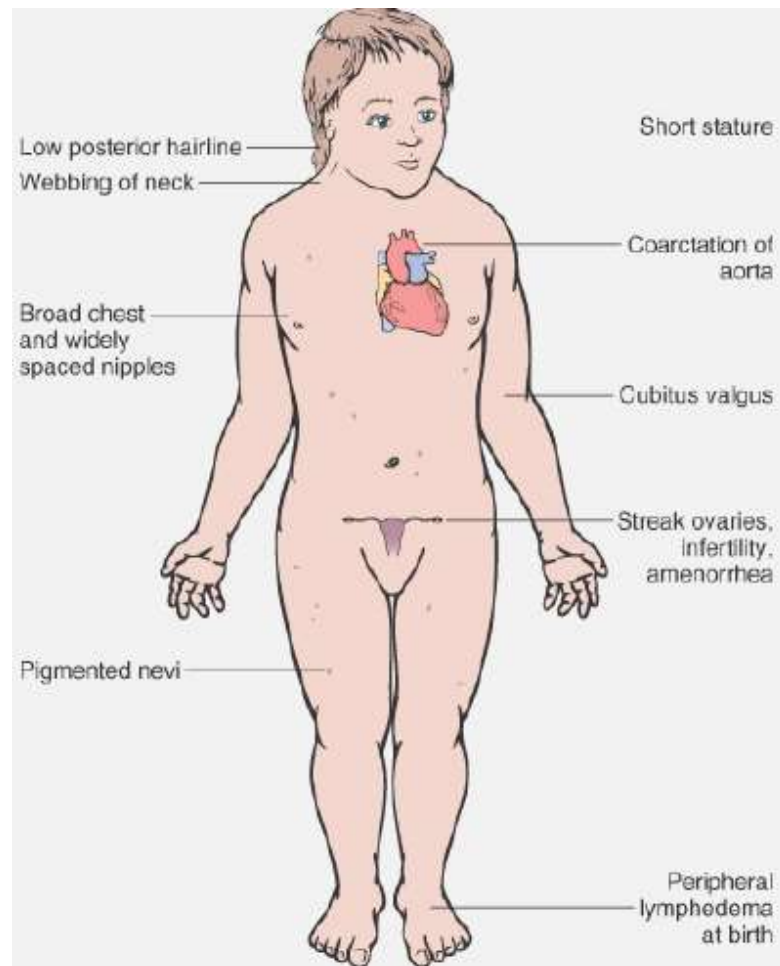
**Figure 5** – Trisomy 13: Patau syndrome (Kumar V., 2005)

### ***Klinefelter syndrome***

Around 80% are 47,XXY, 10% are mosaic, and the remainder is 48,XXYY, 48,XXXY, 49,XXXYY, and 49,XXXXY. Manifestations: patients are phenotypic males, sex chromatin-positive, may be eunuchoid; typically hypospadias and small testes with tubular dysgenesis, patients are sterile due to azoospermia or oligospermia.

### ***Turner syndrome***

Turner syndrome is a monosomy of sex chromosomes. 45, X/O (usually is nondisjunction of the paternal gamete). Clinical signs: swelling of the hands and feet at birth, skin fold in the neck, short stature (140 cm), patients are phenotypic females with rudimentary ovaries, leading to primary amenorrhea (infertility) failure of breast development, and a low hairline on the back of the neck; congenital heart disease, sometimes reduced mental development.



**Figure 6 – Turner syndrome (Kumar V., 2005)**

### **The pathogenesis of genetic diseases**

The pathogenesis of genetic diseases associated with the primary effect of the mutant allele. The pathogenesis of genetic diseases can be summarized as follows: the mutant allele – a pathological primary product (qualitative or quantitative) – a chain of subsequent biochemical processes – cells – organs – body.

The primary effect of any (nuclear and mitochondrial) mutant alleles can be shown in four variants:

- 1) quantify excessive synthesis of the polypeptide chain (protein);
- 2) synthesis of abnormal primary structure of the polypeptide chain (protein);
- 3) absence of synthesis of the polypeptide chain (protein);
- 4) quantitatively insufficient synthesis of the polypeptide chain (protein).

In an excess amount of produced protein the pathogenesis of the disease will generally is caused by hyperproduction of gene activity. Example: at primary hemochromatosis is synthesized excessive amount of globin, resulting in overload of red blood cells by hemoglobin and, respectively, by iron → increased blood clotting, developed hemosiderosis of parenchymal organs.

Abnormal protein leads to functional disturbances in the system. Example: sickle cell anemia – replacement of hydrophilic glutamic acid to hydrophobic valine in the globin structure alter the functional properties of hemoglobin (reduced solubility, increased polymerization) → it crystallizes in insufficient oxygen → erythrocytes become sickle-shaped and are aggregate thrombosing capillaries etc.

Absence of production of the primary product is expressed in the accumulation of toxic precursor-products. For example, phenylketonuria.

Insufficient production of the normal primary product. Example: hypocatalasemia (low levels of catalase in blood) is accompanied by recurrent infections, ulceration of gums and oral mucosa.

Mutations in the genes of the morphogenetic controlling lead to congenital malformations (polydactyly, Holt–Oram syndrome, Laurence–Moon syndrome). The initial link of congenital

malformations is associated with impaired cell differentiation. Programmed in the genome, cell differentiation, and then organogenesis is implemented by changing the activation and inactivation of certain genes in a strictly limited time intervals (relative to ontogenesis). If the primary product of the morphogenetic gene is abnormal, do not follow the differentiation of cells that necessary for further proper development of organ.

### **Pathogenesis of congenital malformations**

Ways of teratogenic effects realization. All kinds of damaging effects by primary mechanism can be divided into two groups:

- 1) genetic injury;
- 2) epigenetic effects through non-genetic molecular structure of cells, ie, all types of violations of the metabolism dynamics or molecular structures on postgenetic level.

All types primary genetic and epigenetic disorders in teratogenesis realized in one of the six stages of germ development:

- 1) violation of cell viability,
- 2) violation of determination,
- 3) cell proliferative disorder,
- 4) violation of differentiation,
- 5) violation of organization and intercellular interactions,
- 6) violation of migration of cells and cell layers.

It is assumed, that the primary molecular mechanism of teratogen action completely determines cell stage at which occurs realization of damage.

### **Critical periods of development**

**Critical periods of development** – are periods of heightened sensitivity of embryos to the action of endogenous and exogenous damaging factors. Critical periods coincide with the periods of the most intensive organs formation and mainly associated with the periodicity of manifestation of morphological nuclear activity.

There are three groups of the external environment actions:

- 1) damaging effects resulting in death or pathology;
- 2) modifying effects causing non-pathological abnormalities – mutations;
- 3) determinate action of the environment, provide normal development and influence on the body resistance (oxygen supply, power, temperature, etc.).

**Critical periods** are associated with the following events:

1. **determination of new phases of development** (activation of new part of genetic information, which ensures the development of organism to next step).
2. **change the type of trophic and intensification of metabolism.**
3. **reduction of regulatory activity.**
4. **slowing process of growth structures**, leading to a transition to a new stage of development.

Critical periods are characterized high metabolic activity and promoted sensitiveness to the action of damaging factors.

Congenital malformations associated with critical periods of development are due to:

- 1) violation of the cell division (growth disturbances of individual germs);
- 2) violations of cell migration (change of the spatial relationship of organs and tissues);
- 3) abnormal lines of cell and tissue differentiation (appearance of abnormal structures or atypical ratio of normal);
- 4) break of correlations between cellular components, the rudiments of organs and tissues;
- 5) changes in the physiological processes of cell death (lack of "reverse development" of the embryo provisory structures);
- 6) violation of metabolic processes (very significant, but may pass without the expressed morphological violations).

In human ontogenesis are several critical periods of development:

1. Development of germ cells (ovogenesis and spermatogenesis). Genome mutations can cause the formation of defects and make development impossible.
2. Fertilization (1<sup>st</sup> day). This period may be violation of cytoplasm segregation, of blastomeres determination and their subsequent differentiation.
3. Implantation (7-8<sup>th</sup> day of embryogenesis). There is a change on histiotrophic nutrition. Die about 30% of embryos. In this period the axial buds and ovoimplantation is developed. The process of implantation can be violated due to:
  - abnormalities of uterus structure of (infantilism, bicornuate or arcuate uterus, walls in uterus);
  - endometrial trauma (the inner layer of uterus) as a result of induced abortion, and inflammatory diseases (chronic endometritis);
  - metrofibroma;
  - uterine scar after cesarean section and other operations.Stress, emotions, heavy physical activity by pregnant can blocked implantation
4. Formation of placenta (3-12<sup>th</sup> week). Changing type of nutrition to hematotrophic. Die about 25% of the embryos.
5. Histogenesis and organogenesis (from 3<sup>rd</sup> week to 8-9<sup>th</sup>), stage of intensive growth of brain (15-20<sup>th</sup> week). Hazards during this period can cause a variety of abnormalities (cardiovascular, respiratory and other systems), which is associated with heterochronic anlage. The fetus take new reflexes, formed anlage of cerebral cortex, forming medullary hematopoiesis, activates metabolism. In this stage can be malformations of central nervous system. However, brain, endocrine, and reproductive systems of the fetus can be damaged at any stage of development.
6. Formation of main functional systems (20-24<sup>th</sup> week) – damage arising due to the fact that material of many organs is in determination of cell differentiation. At this time, actively growing pregnant uterus. Hazards include abnormalities of placenta location, such as low-lying.
7. Perinatal period – from full 22 weeks (154 days) of fetal life to 7 full days after birth. Dangerous for the fetus are the last weeks of fetal life, when there is a dissociation between the relatively rapid increase in fetal weight and stop of placenta growth. Disorders of pregnancy can cause by complications such as recurrent threatened miscarriage, late gestoses, placental insufficiency, and placental abruption.
8. Newborn period.

***In pathophysiology are marked 5 critical periods:***

1. First week of pregnancy – pre-implantation period of embryogenesis or tube
2. From 3 to 9 weeks – a period of great organogenesis.
3. 3 months pregnant, during which the formation of the placenta are end and its function is characterized by a high activity.
4. 20-24 weeks time of formation of fetal functional systems.
5. from full 22 weeks, when there is dissociation between the relatively rapid increasing a fetal weight and stopping of placenta growth, to the first 8 day after birth — period of adaptation to new external environment, with which it occurs after birth.

Typical manifestations of antenatal pathology are congenital malformations – rough anatomical changes in organs and tissues (or organ systems), leading to dysfunctions.

Depending on the timing of fetal pathology occurrence distinguish the following its forms: gametopathy and kymatopathy (blastopathy, embryopathy, fetopathy).

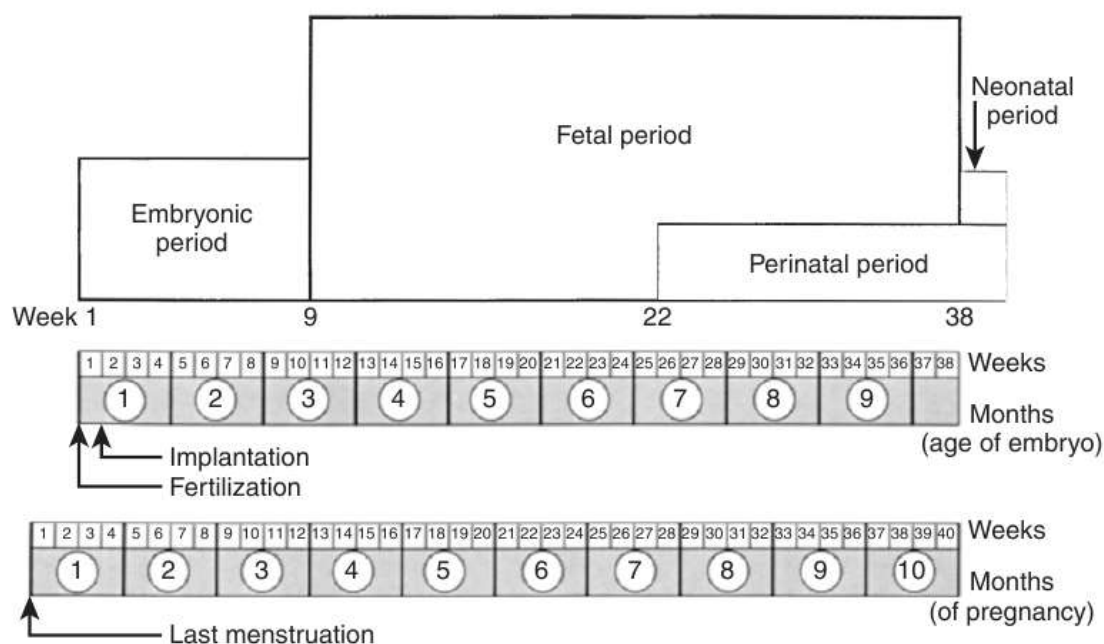
Prenatal period is the period of fetus development beginning with the moment of fertilization to the birth of the child. Normally, prenatal period lasts for 40 weeks (280 days). Born a child earlier 38<sup>th</sup> week is premature; if more than 42 weeks – overmature.

Prenatal period is subdivided into 2 periods:

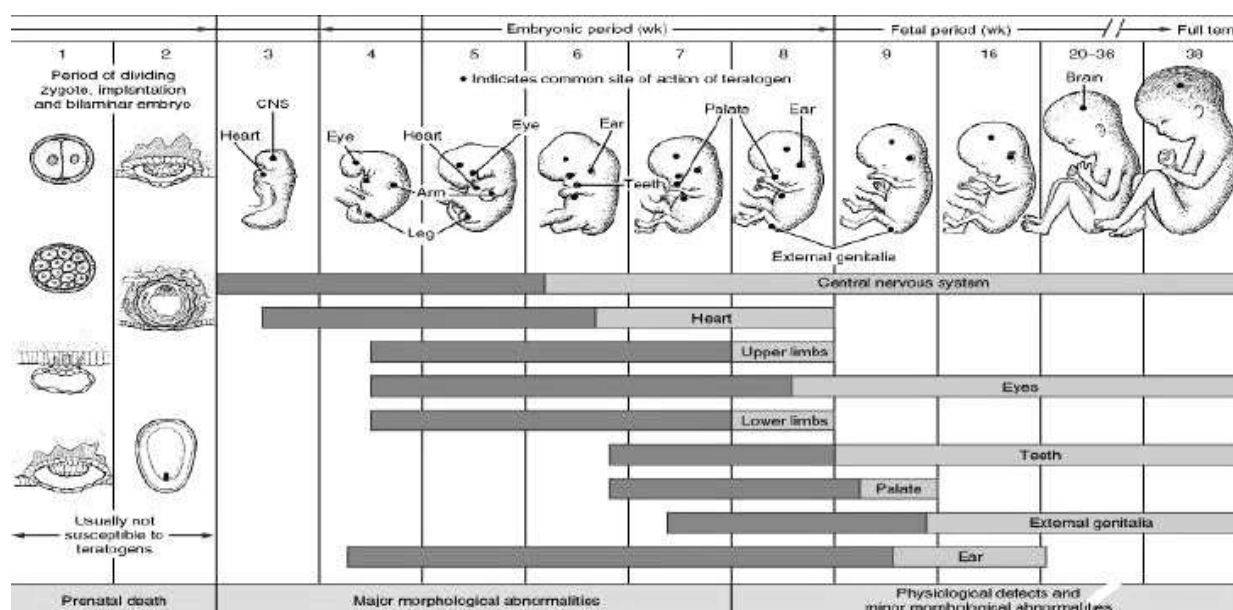
- progenesis (gametogenesis) – period of maturation of ovum and sperm;
- kymatogenesis – period of development fertilized ovum.

There are several periods in the kymatogenesis

- blastogenesis – from the 1st to 15th day;
- embryogenesis – from the 16th day to full 8 week (56 days);
- fetogenesis – from 9 to 40 week.



**Figure 7** – Human development (From R.A. Polin et al., 2011)



**Figure 8** – Schematic illustration of the sensitive or critical periods in prenatal development (From K.L. Moore, 1977)

### **Gametopathy**

It is all kinds of damage to the male and female gametes (ovum and sperm) arising during ova- and spermatogenesis before fertilization. Gametopathy caused mainly by mutations. Heavy damage of gametes can lead to their death, infertility and miscarriages. Gamete with a defect gene or genes may cause hereditary congenital malformations.

### **Blastopathy**

The main outcomes blastopathy are:

- empty embryo sacs (they are formed due to aplasia or early death embryoblast with subsequent resorption);
- hypoplasia and aplasia extraembryonic organs (amnion, yolk sac);

- **twin defects** (symmetric and asymmetric, that is, in whole or in part are not separated twins);
- **ectopic pregnancy** (implantation of the fertilized egg in ovary, fallopian tube, rudimentary uterine horn and internal os of uterus) or violation of the implantation depth (surface, unusually deep).  
Most of the embryos, damaged by blastopathy, are **eliminated by spontaneous abortion**. Twin defects occur as conjoined twins.

### **Embryopathy**

Embryopathy is characterized by impaired formation of organs. It is **lead to death of embryo or congenital malformations**. The degree of severity of birth defects varies from slight variations in structure of organs to severe changes in many organs, which are fatal.

Microanomalies of development (stigma of dysmorphogenesis) – are morphological changes not accompanied by dysfunction. For example: telangiectasia, freckle, low growth of hair on the forehead or neck deformation ears, mongoloid and antimongoloid slant, epicanthus, arachnodactylia and others.

Congenital malformations include developmental disorders:

- **aplasia** – complete congenital absence of an organ or its part;
- **agenesis** – complete congenital absence of an organ and its rudiment;
- **hypoplasia** – underdevelopment of organ, manifested by **deficit of relative weight or size of the organ**;
- **hypertrophy (hyperplasia)** – **increase in relative weight (or size)** of the organ by increasing the number (hyperplasia) or volume (hypertrophy) of the cells;
- **atresia** – the complete **absence of a channel** or a natural orifice;
- **stenosis** – **narrowing channel** or orifice;
- **non-separation of limbs or their parts**, starting with the Greek prefix syn, sym (together), for example, syndactyly – non-separation of fingers;
- **ectopy** – **displacement of organ**, its location in an unusual place (for example, location of the kidney in the pelvis, location of the heart out of the chest);
- **persistence** – saving embryonic structures that normally disappear to a certain period of development. One of the forms of persistence is dysraphia (arrhaphia) – cleft of embryonic fissure (cleft lip, palate, spine, urethra);
- **heterotopia** – the presence of cells, tissues or whole parts of organ in another organ or in those areas of the organ where they should not be (for example, areas of the pancreas in Meckel's diverticulum);
- **hamartia** (from the Greek. gamartus – error) – incorrect ratio of tissues, accompanied by the tumorous growth.

### **Fetopathy**

Fetopathy has following features:

1. Rare birth defects in humans caused by teratogens in the fetal period;
2. Any **damage** in this period entails development of **defects at tissue level**. In this case, there may be a **wrong ratio of tissues in organ or delay of their maturation**.
3. The **presence of** predominantly **generalized forms of infections**. Characterized by multiple foci, mainly alterative inflammation in parenchymal organs, or the presence of generalized granulomatosis (eg, congenital listeriosis);
4. **Infectious** and toxic processes are **accompanied by severe hemorrhagic diathesis** (petechiae on skin and mucous membranes, bleeding in internal organs);
5. A delay of involution and excessive proliferation of cells in the foci of extramedullary hematopoiesis
6. Hypertrophy and tissue **regeneration** is **mainly due to hyperplasia of mesenchymal elements**, which leads to excessive development of **connective tissue** (eg, in mucoviscidosis – accrementition of elastic and fibrous tissue in pancreas).

### **Methods of prenatal diagnosis and prevention of congenital diseases.**

Preventive measures by means medical genetic counseling (MGC), in which the patients or their relatives receive information about hereditary diseases, consequences, probability of inheritance, as well as methods of prevention and treatment.

Periconceptional prevention is aimed at providing optimal conditions for germ cell maturation, their fertilization, formation and implantation of the zygote, early development of the fetus.

It includes:

- MGC, including the study of genealogy, determination of karyotype and leukocyte antigens at spouses;
- Diagnosis of viral and bacterial infections and their timely treatment;
- Exclusion of occupational hazards;
- Diet therapy and vitamin therapy, folic acid (up to 4 mg per day).

Prenatal diagnosis evaluates the fetal condition. There are indirect and direct methods.

**Indirect methods (examination of pregnant women) include:**

- **Obstetrics-gynecology.**
- **Medical-genetic** (genealogical, cytogenetic, molecular-biological).
- **Bacteriological and serological.**
- **Biochemical** (tests were screened for alpha-fetoprotein, human chorionic gonadotropin, estriol et al.).

**Direct methods** (examination of the fetus) are divided into **non-invasive and invasive.**

The main non-invasive methods is the **ultrasound examination** (87% accuracy). Ultrasound screening is carried out in order at least three times during pregnancy: 10-14 weeks of pregnancy – estimated gross malformations, fetal nuchal translucency (3 mm or more – an important marker of chromosomal aberrations in the fetus); 18-21 weeks – identify congenital abnormalities, oligohydramnios and polyhydramnios, fetal hydrops, ventriculomegaly, placental insufficiency etc .; 32-35 weeks – the detection of late manifestations of congenital malformations and functional assessment of the fetus.

**Invasive methods include:**

- **Chorion biopsy and biopsy of the placenta** (10-14th week of pregnancy, or 20-22 weeks) performed transabdominal or transcervically – aspiration of chorionic tissue or placenta with a needle under ultrasound guidance.
- **Amniocentesis transabdominal** (optimally 15-18 weeks) – puncture of the amniotic cavity to obtain amniotic fluid and contained therein fetal cells.
- **Cordocentesis** (optimally 22-24 weeks) – is a procedure for blood collection from a vein in the umbilical cord of the fetus under ultrasound guidance.
- **Fetoscopy** - examination of the fetus through an endoscope inserted transabdominal into the cavity of the amnion, biopsy of fetal tissues (liver, spleen, skin, muscle, etc.).

### **Principles of treatment of congenital diseases.**

Common approaches to the treatment of hereditary diseases are similar to the approaches to the treatment of diseases of any etiology:

- symptomatic
- pathogenetic
- etiotropic

Applied to hereditary diseases in a separate group can be identified surgical methods, because sometimes they act as symptomatic therapy, sometimes – pathogenic, sometimes – and the one and the other.

#### **Pathogenetic treatment**

- Correction of the exchange at a substrate level (for phenylketonuria prescribes a diet low in phenylalanine).
- Correction of the exchange at the gene product level (compensation product (or adding) for violations caused by abnormal enzyme that does not provide the production of the product, or other biologically active compounds, eg, treatment by thyroxine in hypothyroidism).
- Correction of the exchange at the enzymes level (used for the correction of inherited metabolic diseases in which known functionally abnormal enzyme (enzymopathies)).

- Modifying enzyme activity. Induction of enzyme synthesis can be used to enhance residual enzyme activity by administering drugs. For example, phenobarbital and related drugs stimulate the function of endoplasmic reticulum and synthesis of a specific enzyme. For the treatment of Gilbert syndrome and Crigler-Najjar phenobarbital used to reduce the level of bilirubin in the blood plasma. Inhibition of the enzyme synthesis is used to treat acute porphyria, biochemical basis of which is the increased production of amino levulinate synthase. Hematin inhibits the synthesis of this enzyme and quickly relieves acute attacks of porphyria.

- Compensation for the enzyme

#### **Etiotropic treatment: cell and gene therapy**

Etiotropic treatment of hereditary diseases can be carried out at the level of cells or genes.

The term "cell therapy" refers to a method of treatment by transplantation of cells. Transplanted cells retain the genotype of the donor therefore transplant can be viewed as a form of gene therapy, because it leads to a change in the somatic genome.

Gene therapy – a method of treatment by administration of additional genetic information into the cells of the individual at the level of DNA or RNA (genetic engineering structures), or by changes in expression of genes.

Genetic engineering – a set of methods and techniques, including techniques for producing recombinant ribonucleic and deoxyribonucleic acids, by isolation of genes from an organism, implementation of manipulations with genes and introducing them to other organisms.

There are currently four areas of etiotropic treatment:

- transplantation of allogeneic cells (cell therapy);
- the introduction of genetically engineered structures in the tissue of the patient (gene therapy);
- transplantation of transgenic cells with the target of genetic engineering design (combination therapy);
- changes in the expression of genes (gene therapy).

#### **Cell therapy**

Hematopoietic stem cell transplantation is used as an effective treatment of hereditary metabolic diseases, mainly the lysosomal storage diseases and peroxisome. Hematopoietic stem cell transplantation is used in the treatment of the following diseases: Fanconi anemia, primary immunodeficiencies, hemoglobinopathies. Despite numerous clinical trials of cell therapy approved treatment protocols (cell type, quantity, method of administration of the cells, the timing of re-introduction) for particular nosological forms are no.

#### **Gene therapy**

Gene therapy by administration of genetically engineered constructs into cells and tissues of the patient (transgenic in vivo) can stimulate the growth of tissue, organ function. In this type of therapy created functionally capable genetic constructs (genetic vector) in the laboratory. These constructions must contain the target gene (or its main part), vector, promoter.

Gene therapy has been tested as presented primarily for the treatment of cardiovascular diseases: coronary heart disease and chronic lower limb ischemia.

Therapeutic angiogenesis in the treatment of critical limb ischemia was carried out by different authors by administering native DNA encoding the protein Vascular endothelial growth factor, gene Fibroblast growth factor, recombinant constructs based on different adenoviruses with genome angiogenin.

#### **Treatment by transgenic cells**

Treatment by transgenic cells with the target genetic engineering structure may be called combination therapy. To implement this type of cell gene therapy is necessary to carry out the introduction of the target gene into a cell. Such combination combines the properties of cell vector, gene function and effect of cell therapy.

Transgenic (transfer of genetic material) in vitro directed to somatic target cells, previously isolated from an organism (e.g., resected liver, lymphocyte culture, bone marrow culture fibroblasts, tumor cells).

Finite procedure through gene therapy transgenic somatic cells in vitro - is reimplantation of transgenic target cells. It can be organotropic (liver cells are injected through the portal vein) or ectopic (bone marrow cells are injected through a peripheral vein).

### ***Changes in gene expression as a method of treatment***

Changes in gene expression can be achieved by pharmacological modulation or RNA interference. Today we can talk about three directions:

- increased expression of the gene determining disease;
- increased expression of the normal gene to compensate effect of a mutation in another gene;
- decreased expression of abnormal dominant gene.

### **Questions for self-control of knowledge:**

1. What is role of conditions and reactivity of organism in occurrence of hereditary diseases?
2. What is significance of heredity in development of multifactorial diseases?
3. Give characteristics of endo-and exogenous causes of birth defects.
4. What are cellular and tissue mechanisms of teratogenesis?
5. Describe manifestations of diabetic embryo- and fetopathy.
6. What processes is bases on "overripeness" of sex cells?
7. What is effect of ionizing radiation on prenatal development?
8. What is etiology and pathogenesis of fetal alcohol syndrome?
9. What is role of viruses in pathology of fetal development?
10. What is prevention and prenatal diagnosis of congenital malformations?
11. What is significance of critical periods in pathology of embryo and fetus?
12. What are causes of stillbirth.
13. What is role of environmental protection in prevention of hereditary diseases?
14. Is there a correlation between pathology of fetus and harmful influences on mother?

### **Tasks for self-managed student work:**

1. Genotype, constitution and somatic pathology.
2. Features of placenta as an immune barrier.
3. Relationship of fetal pathology with harmful influences on the mother's organism.

### **Literature**

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