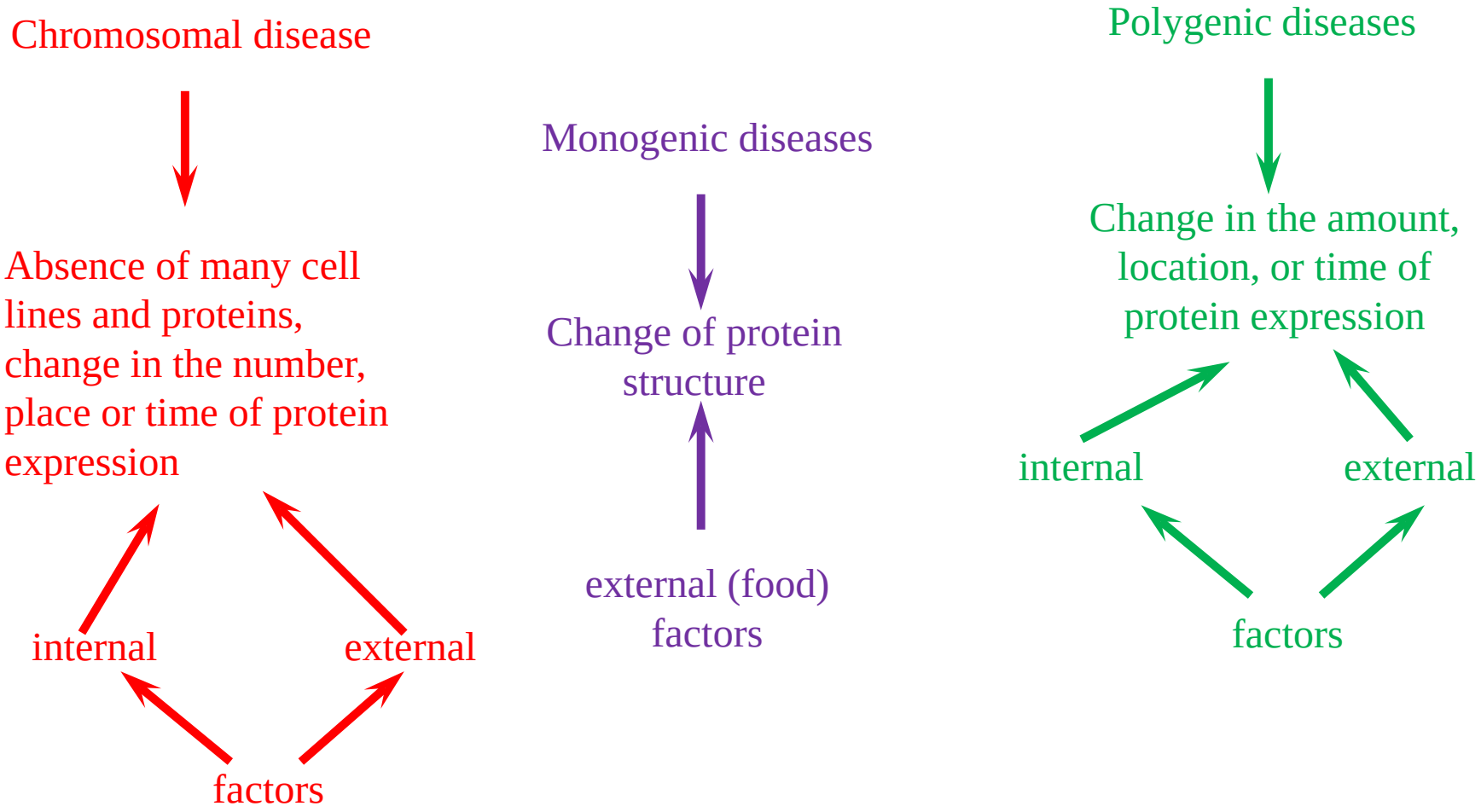
Multifactorial diseases

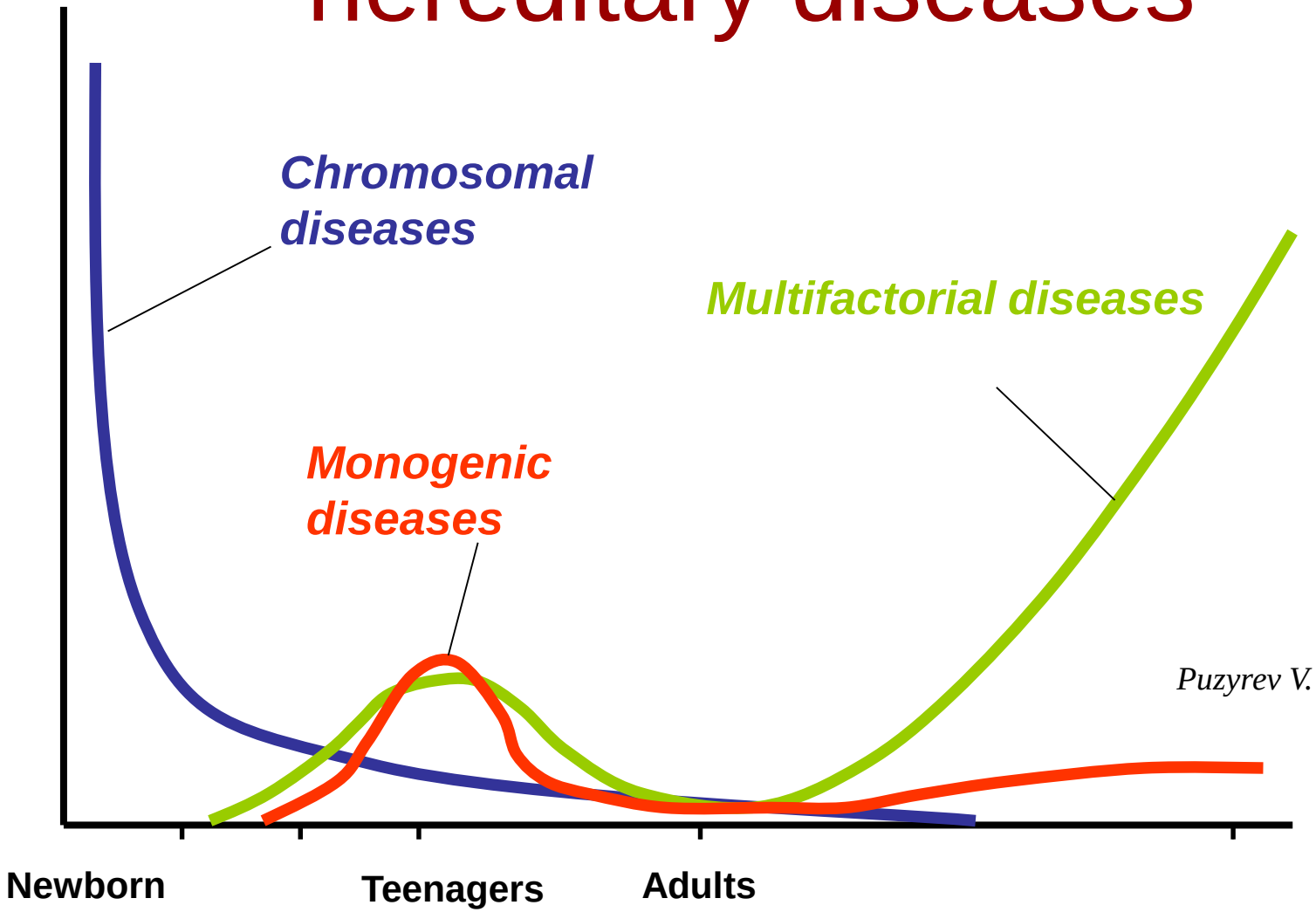
Molecular basis of diseases



Multifactorial diseases (MFD)

Hereditarily predisposed, multifactorial diseases (Complex genetic disorders) with a polygenic type of inheritance, resulting from a combination of actions: genetic predisposition and various pathogenetic factors (infectious, environmental, alimentary, etc.)

The age of the onset of hereditary diseases



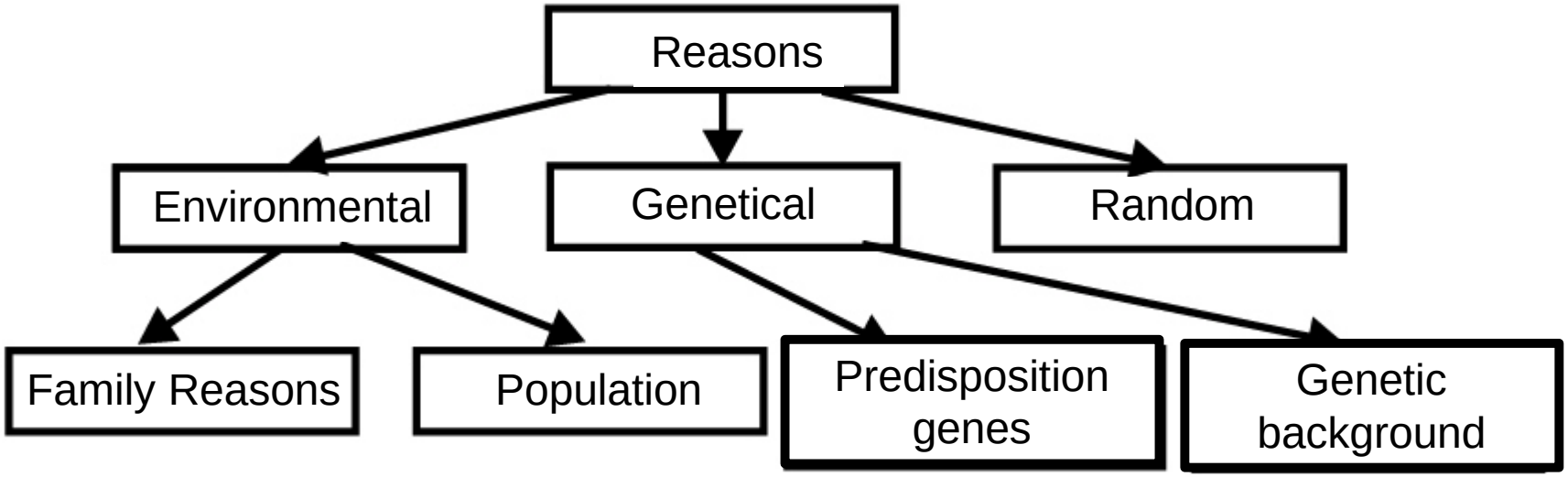
Puzyrev V. P., 2006

PROPERTIES OF MULTIFACTORIAL DISEASES

- IN ETIOLOGY, THE ROLE OF CHANGES IN THE GENOME IS IMPORTANT
- PREDISPOSITION DEPENDS ON A LARGE NUMBER OF GENES
- PREDISPOSITION IS REALIZED UNDER THE INFLUENCE OF A LARGE NUMBER OF ENVIRONMENTAL FACTORS
- THE NATURE OF INHERITANCE IS NOT EXPLAINED BY MENDEL'S LAWS ALONE

CORONARY HEART DISEASE
HYPERTENSIVE DISEASE
BRONCHIAL ASTHMA
DIABETES MELLUTES II
SCHIZOPHRE
NIAMANIC-DEPRESSIVE PSYCHOSIS
EPILEPSY
PSORIASISSYSTEM CONNECTIVE TISSUE
…

MULTIFACTORIAL DISEASES



Multifactorial diseases depend on

Polymorphism of genes and their totality (genotype), consisting of the genes of the mother and father;

Mechanisms of interaction between allelic and non-allelic genes of mother and father, between individual genes and genotype as a whole;

Modifying the influence of environmental factors on the action of genes in the case of their plasticity (and elasticity) – the ability to change (not change) its action in response to the action of the environmental factor.

The causes of polymorphism

Genetic heterogeneity (diversity of genetic causes) due to:

- interaction of allelic paternal and maternal genes (genes located in identical loci of homologous chromosomes);
- multiple allelism (polymorphic gene loci, which are modified with varying degrees of alleles);
- multiple mutations of the same gene (gene copying).

The causes of polymorphism

- ✓ Polidocanol or genecopoia trait or phenotype. Different mutations in genes located at different loci on both the same and different chromosomes cause the same trait or phenotype.

- ✓ Violation of differentiated gene expression-the sequential transfer of genetic information from a DNA molecule using different types of RNA to polypeptides. Gene expression disorder can occur as a result of mutation in any link of this chain.

- ✓ Genomic imprinting (genomic memory). The formation of the trait and phenotype depends on whose hereditary material (maternal or paternal) is transmitted to the individual.

Types of relationship	Number of common genes
Monozygotic twins	1
Parents – children, sibs, dizygotic twins	1/2
Grandfather – grandson; uncle, aunt – nephew, niece; half – siblings	1/4
The cousin in which siblings	1/8
Sibs ' second cousin	1/32

Comparison of genetic variability responsible for monogenic and multifactorial diseases

Multifactorial diseases	Monogenic diseases
High frequency in the population (polymorphism)	The frequency of mutations in the population is low
Mutations are not necessary and sufficient	Mutations are necessary and sufficient
Small phenotypic effect	Great phenotypic effect

THE CHARACTERISTICS OF MULTIFACTORIAL INHERITANCE

- ✓ **The phenotype detects accumulation in families, but there is no clear type of inheritance**
- ✓ **The risk is increased if more than one relative has the disease**
- ✓ **Most often the severity of the disease correlates with the magnitude of the risk**
- ✓ **In the case where the phenotype is more common in the same sex, the risk is higher for relatives of probands of the less exposed sex**
- ✓ **The risk is increased in the case of consanguineous marriages**

Conceptual model of the causes of multifactorial disease (F. Vogel and A. Motulski, 1989)

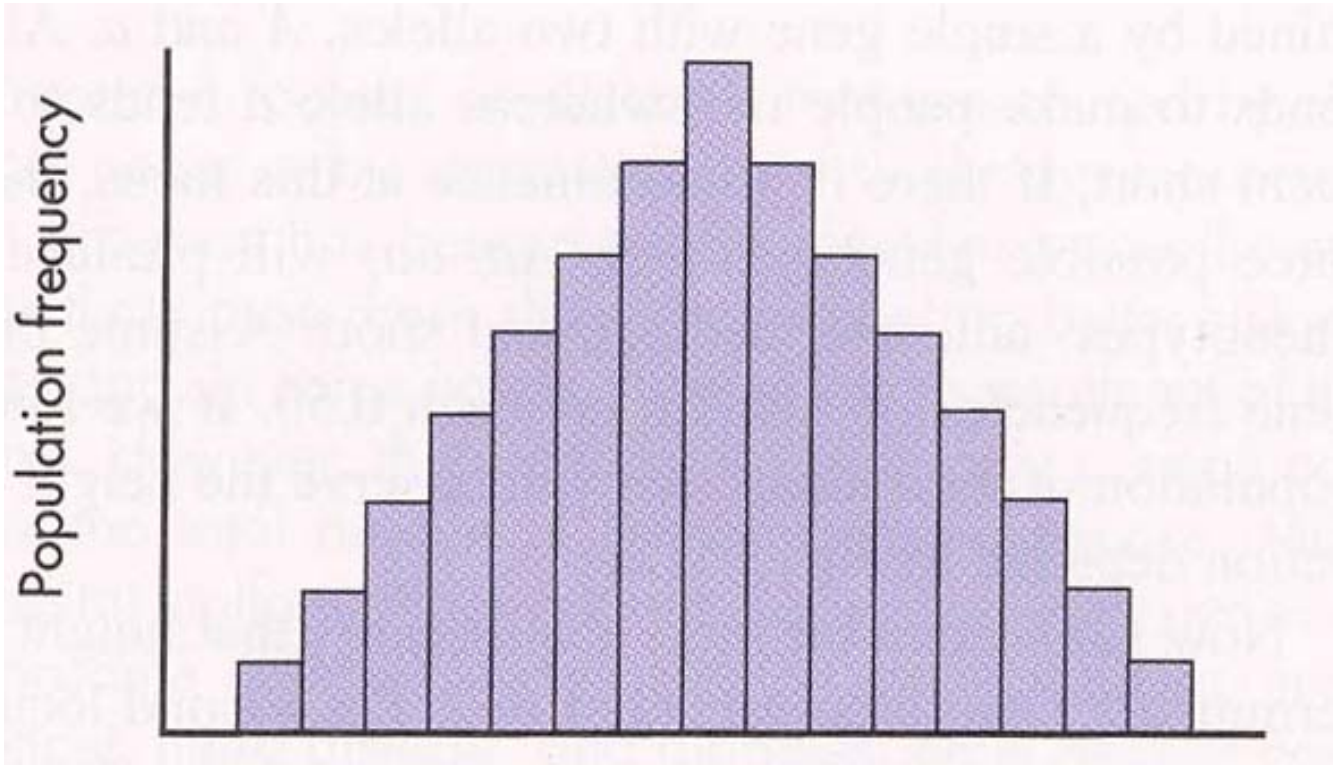
- ✓ Environmental factor
- ✓ Set of genetic factors
  - ➢ The main genes
  - ➢ The genetics problems for linkage ("genetic background»)
- ✓ Random (stochastic) factors

Multifactorial features

- ✓ Signs are formed in the process of interaction of environmental and genetic factors

- ✓ The severity of most signs in the population is characterized by a normal distribution

Normal distribution (theoretical)



THE CONCEPT OF "NORM" IS RELATIVE TO

This is especially true of quantitative features

- Blood glucose
- Blood pressure
- Heart rate
- etc.

The normal blood pressure

At the end of the last century, the norm for blood pressure was up to 160/95 mm Hg. art.

Now the norm of blood pressure to 145/90 mm Hg. art.

Threshold model

- ✓ Most of the diseases are not subject to normal distribution. It is or it is not (for example, myocardial infarction).

- ✓ For diseases with exposure, there is a threshold beyond which the disease develops.

Gene network

A group of co-ordinated genes that control the performance of a certain function of the organism.In each gene network there are several mandatory types of components:

1) the group of genes that make up the core of the network
2) proteins encoded by these genes
3) transmission of signals
4) negative and positive interactions providing autoregulation
5) low molecular weight compounds.

To accumulate information on gene networks, databases are being developed, for example GeneNet which currently has information on lipid metabolism networks, steroidogenesis, erythropoiesis, antiviral response.

Examples of interaction of genotype and external factor

- ✓ Malaria and sickle cell anemia genes
- ✓ PKU and phenylalanine intake
- ✓ Adverse effects of drugs and impaired CYP2D6 function
- ✓ Alcohol intolerance and aldehyde dehydrogenase alleles
- ✓ Smoking, lung cancer and acetylator genotypes

Association of polymorphisms with drug response

Gene	Remedy	Manifestations
Citochrom P450 (2C9) 50 % variability of dose	Warfarin	The homozygotes for the mutant phenotype are at increased risk of bleeding
Gene vitamin K epoxide reductase (VKORC1)	Warfarin	There are a number of single nucleotide polymorphisms associated with an increased risk of bleeding
Protein Transporter of cholesterol esters (gene CETP)	Pravastatin	Efficacy of pravastatin in coronary atherosclerosis
Stromelysin -1	Pravastatin	Rate of restenosis in coronary atherosclerosis
Adducin	Hydrochlorothiazide	Effectiveness in the treatment of hypertension
Potassium channel (MiRP1)	Clarithromycin	Clarithromycin-induced syndrome of an elongated Q-T
Apolipoprotein E	Simvastatin	The presence of the E4 allele reduces the effectiveness of therapy

Assessment of the risk of recurrence of multifactorial disease in the family

The risk in sibs and descendants is equal the square root of the population frequency

population = 0.1%

sibs = 4.0%

Repeated risk in multifactorial inheritance

(Smith, 1971; P.S. Harper, 1984)

Population frequency, %	Heritability, %	Sick parents								
		0			1			2		
		Sick which siblings								
		0	1	2	0	1	2	0	1	2
	80	1.0	6.5	14.2	8.3	18.5	27.8	40.9	46.6	51.6
1	50	1.0	3.9	8.4	4.3	9.3	15.1	14.6	20.6	26.3
	20	1.0	2.0	3.3	2.0	3.3	4.8	3.7	5.3	7.1
	80	0.1	2.5	8.2	2.9	9.8	17.9	31.7	37.4	42.4
0.1	50	0.1	1.0	3.2	1.0	3.4	6.9	6.6	10.9	15.3
	20	0.1	0.3	0.7	0.3	0.7	1.3	0.8	1.4	2.3

Holzinger Formula

$$H = \frac{C_{mz} - C_{dz}}{100 - C_{dz}} \times 100\%$$

H - the coefficient of heritability

C_{mz} - % concordant pairs in monozygous twins

C_{dz} - % concordant pairs in dizygotic twins

E - the influence of the environment

E = 100 - H

formula for calculating heritability coefficient based on twin concordance coefficients

The classical method of assessing the relative contribution of hereditary and environmental factors in the development of the disease remains the twin method

In Sweden, a fundamental study was carried out (Marienberg ME., 1994):

- 21004 twins born between 1886 and 1925. 3298 monozygotic and 5964 dizygotic males, 4012 monozygotic and 7730 dizygotic females.
- Among men, the relative risk of death from CHD when one of the twins died before age 55, compared to those with a twin who did not die before age 55, was 8.1 (95% confidence interval 2.7-24.5) for monozygotic and 3.8 (95% CI 1.4-10.5) for dizygotic.

Among women, the relative risk of death from CHD when one of the twins died before age 65, compared to those with a twin who did not die before age 65, was 15.0 (95% CI 7.1-31.9) for monozygous and 2.6 (95% CI 1.0-7.1) for dizygotic.

Family accumulation in coronary atherosclerosis

- ✓ The incidence of CHD is approximately 2-6 times higher in the families of patients compared to control families.
- ✓ Family accumulation is more pronounced in families of younger probands, i.e. in early coronary heart disease.
- ✓ The probands of the family-women are more pronounced the accumulation.
- ✓ Family history of early CHD (up to 55 years) is the most important risk factor for CHD.

Risk factor

The relative risk (RR) is an estimate of the effect of a specific risk factor (Smoking, diet, genotype, etc.).

RR= frequency of disease in individuals with a risk factor divided by frequency in individuals without a risk factor.

Overall risk

$$X\beta = X_1\beta_1 + X_2\beta_2 + \ldots + X_n\beta_n$$

Xβ - the cumulative risk is due to all of the inputs in the equation variable factor.)

X_i - variable value;

β_i - regression coefficients of these variables.

The equation includes factors that independently affect the risk of developing the disease. Reducing the risk associated with individual factors-reduces the cumulative risk for each individual and the population as a whole.

Hypertension

It is a risk factor for cardiovascular disease, stroke, kidney disease.

It is believed that up to 20-40% of the variability in blood PRESSURE is determined by genetic factors. Hence from 60 to 80% - environmental.

Burdened family history is a risk factor for most multifactorial diseases

	Относительный риск
Cardiovascular diseases	2.0 – 5.4
Breast cancer	2.1 – 3.9
Colorectal cancer	1.7 – 4.9
Type two diabetes	2.4 – 4.0
Osteoarthrosis	2.0 – 2.4
Asthma	3.0 – 7.0

Am J Prev Med - February 2003

MULTIFACTORIAL DISEASES

John Forbes Nash, Jr., winner of the 1994 Nobel prize in Economics "for the analysis of equilibrium in the theory of non-cooperative games»

Diagnosis-paranoid schizophrenia

Prototype of the main character of the film "mind Games»

In schizophrenia, there are no violations of intelligence, there are violations of associative thinking.

Davidenkov S. N. – Russian great therapist

I don't understand a doctor who doesn't use pedigree analysis as it helps a lot in his work.

The increase in the number of narrow specialists will lead to the need for consultations or the introduction of a family doctor.

The use of empiric risk estimates for counseling

- ✓ Exclude chromosomal, monogenic diseases
- ✓ Risk is the population average - in a real family, the real risk may be above or below average
- ✓ Risk may vary across populations
- ✓ The risk increases with increasing genetic proximity to the patient
- ✓ May vary depending on gender

Hereditary burden and prevention

- ✓ Affects individual risk assessment
- ✓ Influences approaches to the prevention and treatment of
- ✓ The higher the genetic component of risk, the more active and early intervention
- ✓ Can determine the specifics of preventive and therapeutic effects

It is impractical to conduct DNA studies of the risk of multifactorial diseases:

- ✓as a mass screening test;
- ✓as a prenatal diagnosis;
- ✓to establish or confirm a diagnosis

Indications for DNA studies at multifactorial diseases

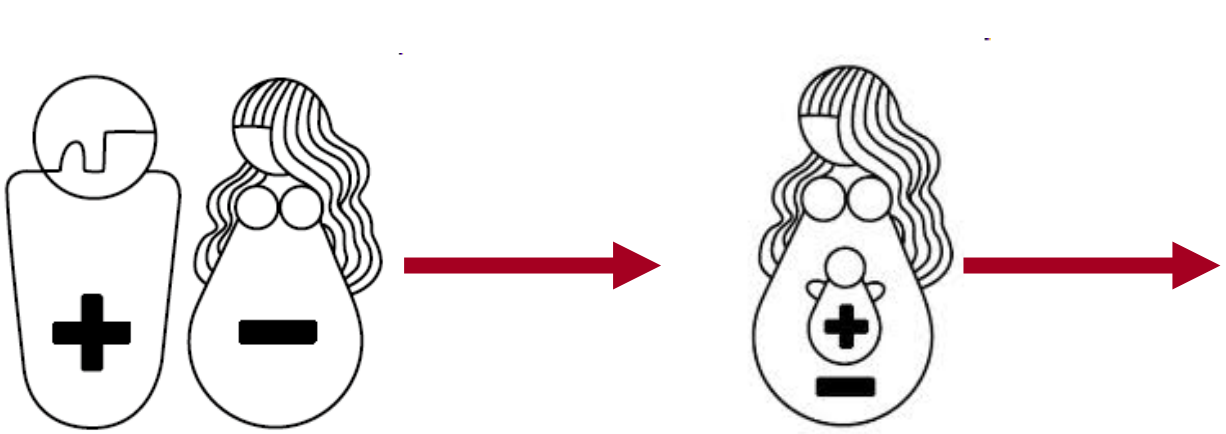
- ✓ patients with early forms of disease;
- ✓ burdened family history;
- ✓ relatives of patients with identified mutations;
- ✓ identified biochemical disorders in proband

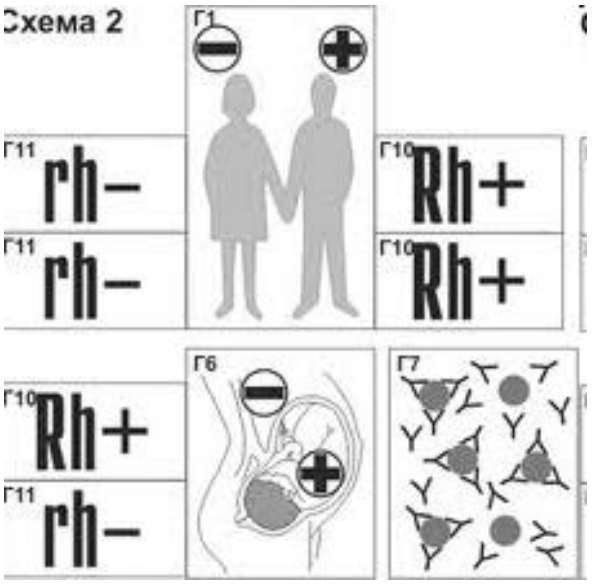
Diseases arising from autoimmune incompatibility of mother and fetus

- ✓ Develop as a result of the mother's immune response to fetal antigens.
- ✓ Fetal blood in a small amount enters the body of a pregnant woman. If the fetus inherited from the father such an allele of the antigen (AG+), which the mother does not have (AG -), then the body of the pregnant woman responds with an immune response.
- ✓ The mother's antibodies, penetrating into the fetus's blood, causing him immune to the conflict.

Diseases arising from autoimmune incompatibility of mother and fetus

Hemolytic disease of newborns





Teratogenic factors

- Chemical
- Physical
- Biological

Criteria of teratogenic factors

- The connection between the action of the factor and the formation of malformation is proved
- Epidemiological studies confirm this link
- The effect of the harmful factor coincides with critical periods of intrauterine development
- With rare exposure to the damaging factor characteristic malformations are rarely formed

Main groups of teratogenic factors

- Drugs and chemicals (tetracycline, trichopol, androgens, mercury, lead, phosphorus)
- Ionizing radiation (radioactive fallout, radioisotope diagnostics, radiation therapy)
- Viral and bacterial infections (herpes, rubella, syphilis, toxoplasmosis)
- Metabolic disorders and bad habits (diabetes mellitus, endemic goiter, phenylketonuria;
- Smoking, alcoholism, drug addiction

Features of influence of teratogenic factors (TF)

- Dose-dependent character.
- For each TF there is a dose of teratogenic action.
- Usually it is 1-3 orders of magnitude lower than lethal.
- Sensitivity to different TF during fetal development may vary.

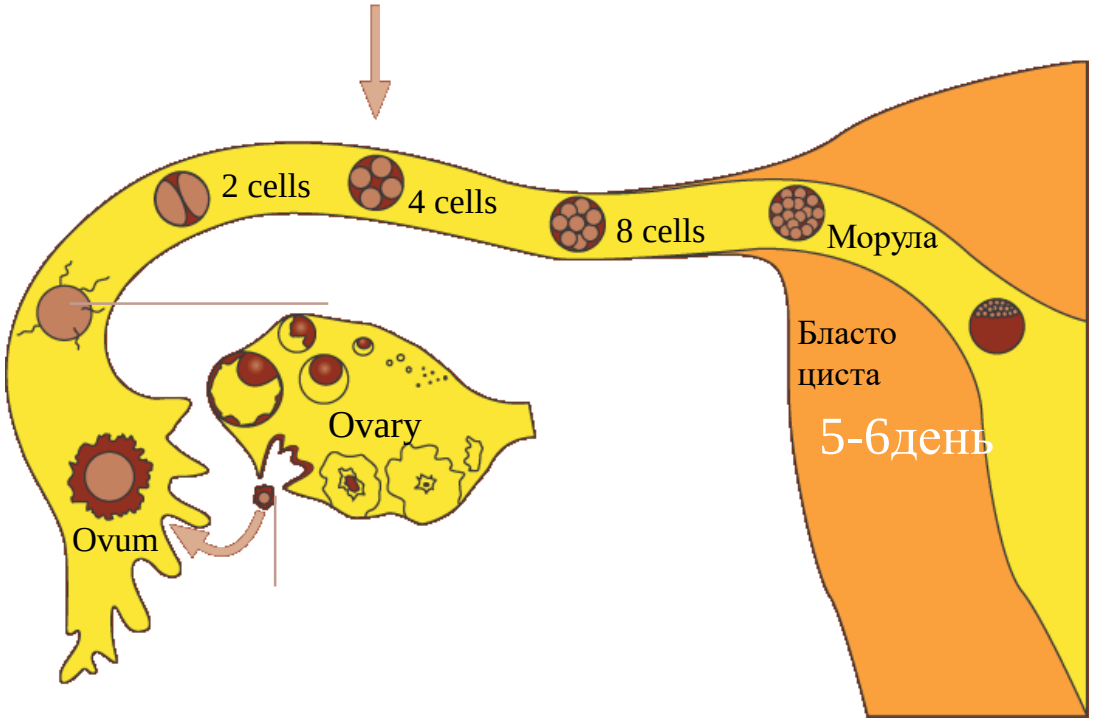
Infectious agents as teratogenic factors do not have a threshold dose and dose dependent nature

Periods of intrauterine human development

- Initial - from the moment of fertilization to implantation of blastocysts (up to 11 days).
- Embryonic (18-60 days after fertilization)
- Fetal (from 9 weeks of pregnancy to birth)

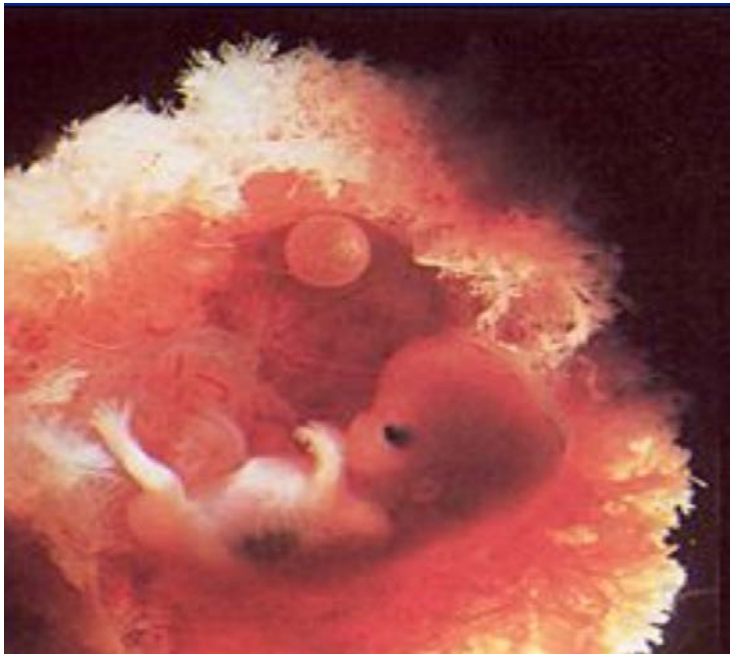
Initial period

It is characterized by large compensatory and adaptive capabilities of the embryo. The law "all or nothing" - when a large number of cells are damaged, the embryo dies, when individual blastomeres are damaged, further development is not violated



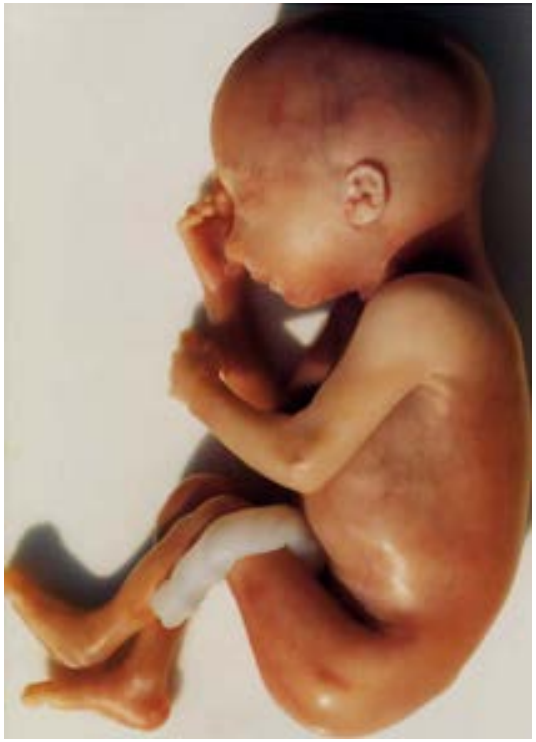
Embryonic period

The embryo is most sensitive to the action of TF.
gross malformations are Formed



The fetal period

Malformations are not characteristic. Under the influence of the external environment, growth inhibition and/ or cell death occurs, which is further manifested by underdevelopment or functional immaturity of organs



Major malformations

- Malformations of the Central nervous system – anencephaly, spina bifida, hydrocephalus. Formed as a result of cleft of the neural tube when folic acid deficiency, infections, diabetes.
- Congenital heart disease - ASD, tetralogy of Fallot, stenosis of the aorta and so on (phenylketonuria, lupus, rubella virus, genetic factors, alcohol, NSAIDs, diabetes mellitus)
- Cleft lip, firm palate
- Congenital clubfoot
- Congenital hip dislocation
- Malformations of the gastrointestinal tract-stenosis of the pylorus, Hirschsprung's disease, atresia of the esophagus, anus, etc.

General approaches to prenatal prevention

1. Environmental protection
2. Family planning (consanguineous marriages, childbearing after 35 years)
3. Prenatal diagnosis – the elimination of embryos with abnormal
4. Identification of heterozygous carriers
5. Periconceptional preparation
6. Invasive and non-invasive methods of intrauterine diagnosis

Periconceptional preparation

- medical and genetic counseling;
- carrier diagnosis and treatment of viral and bacterial infection;
- exclusion of occupational hazards;
- giving up bad habits;
- the intake of folic acid and Tocopherols)

Methods of intrauterine diagnosis

1. Noninvasive method:

- Ultrasound (10-14, 22-24, 32-34 weeks),
- Biochemical marker:
- 9-14 weeks b-HCG, rarr-A From 17 to 19 weeks AFP, 17 MIC, b-HCG, estradiol

2. Invasive method:

- Chorionic villus sampling (9-11 weeks)
- Cordocentesis (22-24 weeks)

Drugs and chemicals

For the transplacental transition are important:

Molecular weight of the drug (up to 600 easily pass, 600-1000 limited, more than 1000 almost do not penetrate). Most drugs are less than 600 and easily penetrate to the fetus. Fat-soluble substances easily diffuse through the placenta (ether, nitrous oxide). Binding to blood proteins. The greater the bond, the slower the penetration through the placenta and accumulation in the fetus.The method of introducing the materialStage of intrauterine development

Categories of drug safety

Risk categories of drug use during pregnancy FDA (Food and Drug Administration)

A - no risk to the fetus;

B - the risk to the fetus is not established in animals or humans;

C - risk to the fetus has not been established in humans; controlled human studies have not been conducted;

D - there is a risk to the fetus, but can only be used at risk to life; it is necessary to assess the degree of risk and benef it;

X-proven risk to the fetus. When pregnancy is contraindicated.

Absolute teratogens

Drugs used in Oncology:

1. Antimetabolites (6-mercaptopurine)
2. Alkylating agents (cyclophosphamide)
3. Antitumor antibiotics (actinomycin, sarcolysin)

Antibacterial drugs during pregnancy (Gurtov B. L. et al. 2004)

Group I - contraindicated in pregnancy: tetracyclines, chloramphenicol, trimethoprim.

Group II - apply only on vital indications: aminoglycosides, nitrofurans, sulfonamides.

Group III - antibiotics without embryotoxic action: penicillins, cephalosporins, macrolides.

Effects of antibiotics

- Tetracycline and its derivatives in the early stages lead to malformations, in the late-slowing the growth of the fetus, the defeat of the rudiments of the teeth, hepatotoxic effect
- Chloramphenicol – aplastic anemia
- Aminoglycosides-ototoxic effect

Hormonal preparation

- Estrogens lead to the development of adenosis and light cell adenocarcinoma of the vagina and cervix in girls

Ionizing radiation

The effect of radiation on the female body occurs according to the General laws of radiation damagea-radiation practically does not penetrate the skin, but is very dangerous if ingestedb-radiation penetrates to a depth of 1-2 cmg-radiation has the greatest penetrating power with the formation of free radicals, leads to gene mutations

Transplacental transfer is the major penetration of the isotopes

Mechanisms of transplacental transition of radionuclides

- Hematogenic pathway-free transfer of isotopes from the mother's blood to the fetal blood through the transplacental membrane (^{131}I, ^{32}P, etc.)
- Accumulation in the tissues of the placenta with subsequent effects on the fetus (transuranic elements)
- Paraplacental transition through fetal membranes and amniotic fluid (radioactive plutonium)

Infection (mechanisms of action)

1. Viruses (cytomegalovirus, herpes, rubella), penetrating to the embryo and fetus, can have a direct teratogenic effect
2. Infection leads to changes in the metabolism and function of the endometrium, which causes a violation of implantation or a violation of the development of the placenta

Infection (mechanisms of action)

3. Viral and bacterial infection can affect the development of the placenta and lead to CKD and fetal STD
4. Bacterial toxins can have a toxic effect on the fetus

Pernicious habits

- Smoking
- Use of alcohol
- Addiction

Smocing

- Tobacco contains more than 600 harmful factors: organic and inorganic acids, proteins, esters, aldehydes, phenols, etc.
- Currently, radioactive polonium has been detected in tobacco smoke
- Nicotine has the greatest impact

Nicotine

- Exposure to nicotine in early pregnancy can lead to impaired egg implantation and spontaneous abortion.
- Abortion and premature birth may be due to increased contractile activity of the uterus when Smoking
- Nicotine leads to contraction of the vessels of the uterus and placenta with the development of placental insufficiency and fetal hypoxia

Nicotine

- Fetal hypoxia is also associated with increased levels of carboxyhemoglobin
- Violation of the development of the placenta contributes to the emergence of CKD and fetal STD
- Nicotine intensively penetrating through the placenta and accumulating in it, penetrating through the amnion, accumulating in the internal organs of the fetus, causes prolonged intoxication

Alcochol

Systematic use of alcohol during pregnancy can lead to the development of fetal alcohol syndrome

Fetal alcohol syndrome

- Violation of the structure and function of the Central nervous system (microcephaly, impaired intelligence, coordination)
- A slowdown, particularly noticeable after the baby is born
- Characteristic anomalies of the facial skull (microphthalmia, elongation of the face, low forehead, underdevelopment of the chin, small saddle-shaped nose, large wide open mouth, strabismus, flattening of the nape)

Pathogeneses of fetal alcohol syndrome

Insufficiently studied. It is known that:

- Ethanol easily penetrates the placenta and blood-brain barrier of the fetus, accumulates in the
- Central nervous system, having a toxic effect
- In the liver of the fetus there is no enzyme alcohol dehydrogenase, which destroys ethanol, so the fetus is exposed to prolonged exposure
- Embryotoxic and teratogenic action has a metabolite of ethanol-acetaldehyde