1. General etiology of diseases

Genetic component is nearly always present → genetics is an integral part of pathophysiology

Environmental component interacts with the genetic one in a complex manner

“Gross (large)” and “small” factors could be distinguished both among genetic and environmental factors (Fig. 1)

<table>
<thead>
<tr>
<th>Genetic factors</th>
<th>Environmental factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pathologic gene Mendelean disease</td>
<td>large trauma, intoxication, virulent infection…</td>
</tr>
<tr>
<td>Multigenic diseases</td>
<td>polluted environment, overeating, physical inactivity, smoking, psychic stress…</td>
</tr>
</tbody>
</table>

Heterogeneity of diseases is increasingly apparent, both in diseases from one large factor and from several small factors. Heterogeneity is both intragenic (multiple alleles) and intergenic (heterogeny)

5 types of diseases conditioned by genes: chromosomal anomalies, monogenic diseases, multifactorial diseases, mitochondrial defects, diseases produced by somatic cell mutations

2. Mutations in germ line and somatic cells

Gene (DNA) function is more stressed now in genetics compared to the simple fact of familial transmission (whence genetics originated) → a broader definition of genetics

Mutations in germinative and somatic cell lines (Fig. 2)
3. Molecular physiology of a gene
Molecular organization of an eucaryotic gene (Fig. 3)

Isomorphic proteins specific for developmental stages and tissues (Fig. 5)

4. Regulation of gene activity (of gene expression) and its pathology

Gene expression must be regulated during development, tissue specialization, under the influence of exogenous factors and xenobiotics (= synthetic compounds foreign to the body).

Regulation of gene expression is realized mainly by regulation of:
- starting of interaction of RNA polymerase with its promoter = initiation of transcription
- splicing

Initiation of transcription is the most important. Development of the embryo and all differentiation are regulated by means of transcription initiation.
Role of transcription factors

TF = specific proteins necessary for polymerase II to initiate transcription. Binding of TF to specific sequences = responsive elements → interaction among the proteins of general transcription machinery → initiation of transcription. RE are localized generally in promoters and enhancers (Fig. 6).

Influencing of gene expression by exogenous factors:

- Corresponding TF are produced and stored in advance and must be activated under the influence of external signals to the cell.
- Polycyclic carbohydrates → binding to TF and activation → expression of the genes of the cytochrom P450 system → synthesis of monooxygenases → oxidation of the acting xenobiotic (possibly its transforming into an active carcinogen)
- Farmacogenetics and ecogenetics

Types of transcription factors:

- Activators (Fig. 9)
- Repressors – critical regulators of cellular growth and differentiation
Different genes react to the same regulatory stimulus:
they have a common responsive element reacting to the
same transcription factor
Tissue → specific TF → tissue specific proteins
are produced
A single RE among all others suffices usually to
activate a gene. Sometimes more than one copy of the
same RE are present → expression is proportional to
the number of copies occupied

Example: Heat shock of cells → activation
(by phosphorylation) of a transcription factor HSTF →
activated HSTF binds to its RE (labelled here HSE) →
forming/stabilization of initiation complex →
expression of about 20 genes

A single gene may be regulated by many different
control circuits (i.e., transcription factors),
sometime differently in different tissues
A combination of a few regulatory genes may regulate
a large number of structural genes

Example: Heavy metals → unknown TF →
activation of RE (called MRE) → expression
of the gene called MT (metallothionein)
Glucocorticoids → steroid receptor = TF →
RE called GRE → expression of the same
metallothionein gene
Phorbol esters → TF AP1 → RE TRE →
expression of the metallothionein gene

A single gene may be active in some type of cells, inactive in
another type (Fig 11)
Examples of pathogenic mutations
Mutations of transcription factors → improper activation or blocking of activation of transcription
Mutated protooncogenes → anomalous TF production → enhanced expression of „proliferation“ genes → malignant transformation of cells

Pituitary dwarfism (Fig. 12):
Mutation of the gene coding for Pit1 TF → derangement of the expression of genes coding for growth hormone and prolactine and for the development of hypophysis (Fig. 13)

Examples of pathogenic mutations in regulatory mechanisms
1 Mutations in regulatory genes
A Pituitary dwarfism:
regul. gene transcr. factor pit-1 expr. genes coding for growth horm. prolactin thyreoidal functions

B Testicular feminization:
regul. gene receptor for steroid. hormones (testost.) genes coding for sexual features

Thrombembolic diathesis (Fig. 14): Mutation of RE 5G → 4G in the gene for PAI-1 (plasminogen activator inhibitor) → derangement of binding of repressoric TF → the gene for PAI-1 is expressed excessively → plasminogen activator is depressed → lack of plasmin → degradation of fibrin is depressed → production of thrombi

Mutations in exones → substitution of aminoacids → a qualitative change of a protein
Mutations in introns and flanking sequences → changes of regulatory regions → a quantitative change of expression