Impact of Molecular Medicine on Pathophysiology, Medical Practice, and Medical Education

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This article brings an overview of the influence of molecular medicine on pathophysiology, medical practice, and medical education. Various aspects of the growing impact of molecular medicine on clinical practice are discussed: diagnostical and predictive testing, gene and targeted therapy, and pharmacogenomics. Insufficient data from appropriate clinical studies and evidence-based medicine presently limit the applications of molecular medicine in clinical practice. Incorporation of conceptual and clinical aspects of molecular medicine in undergraduate and postgraduate curricula and a continuing education of medical professionals is an urgent imperative for the demands of medical care quality to be met in near future. The emphasis should be put on bedside-orientated molecular medicine. The prerequisite is translational research aimed to translate basic information into the improvement of healthcare of individual patients and the population as a whole.

Key words: education, medical; genetic screening; genomics; molecular biology; pharmacogenomics

In their 1949 paper “Sickle cell anemia – the molecular disease,” Pauling et al (1) showed that there was a difference in electrophoretic mobility of hemoglobin between normal individuals and patients with sickle cell anemia. They concluded that the disease was caused by the disorder in protein structure. This idea shifted the pathologic basis of disease from cellular to molecular level, and thus the era of molecular medicine begun (2).

The following 20 years were the golden era of molecular biology. The structure of DNA and the genetic code were revealed and central dogma of molecular biology was established, showing the flow of genetic information from DNA to RNA to proteins, emphasizing that nucleic acid are informative macromolecules and proteins are executive macromolecules expressing genetic information (3). However, these great achievements have had little impact on clinical medicine (4). The following paragraph from McFarlane Burnett’s book illustrates the skepticism toward application of molecular biology to medicine (cf. 4):

I cannot avoid the conclusion that we have reached the stage in 1971 when little further advances can be expected from laboratory science in the handling of the intrinsic type of disability and disease.

The isolation of globin genes and the development of DNA techniques (cloning, Southern-blotting, and analysis of restriction fragment length polymorphism) resulted in the explanation of hemoglobinopathies at the DNA level (5).

Further growth of molecular medicine was exponential, as shown by ever increasing number of entries in the Online Mendelian Inheritance in Men (OMIM) database (Fig. 1 and Table 1; ref. 6). The functional cloning of genes was largely replaced by position cloning based on the linkage of DNA markers to a disease phenotype and/or cytogenetic markers (Fig. 2). Position cloning became the basic procedure in gene identification (7). This approach to gene identification and isolation was called “reverse genetic” (8). Gene identification starts from the phenotype and leads to the genotype, with no knowledge of corresponding protein structure and function. This approach has led to the “reverse logic” in terminology. The genes isolated by functional cloning were named after the protein they code for, whereas the names of genes identified by position cloning were derived from the diseases caused by the mutations of these genes. This “reverse logic” misleads students, because it is not self-evident that cystic fibrosis transmembrane conductance regulator (CFTR) gene codes for a normal epithelial protein.

The drafts of human genome published in 2001 (9,10) opened the door for genomic medicine, which rests on the knowledge of structure, function, and interactions of entire genome.

The birth of proteomics represents another crucial step in understanding gene function and molecular...
lar basis of disease. Proteomics is the study of proteome – all proteins, including their relative abundance, distribution, posttranslational modification, function, and interactions with other macromolecules – in a given cell or organism within a given environment at a specific stage of the cell cycle (11).

Molecular medicine changes medical sciences from phenomenological to causal, increasing the precision and predictability of diagnostic procedures, and individualizing and targeting therapeutic approaches (Fig. 3) (12-16). However, the application of molecular biology principles to the basic and clinical medical problems is far from simple. It has a number of limitations arising from the complexity of biological systems (17) and draws many unresolved ethical, legal, and social implications (18,19). The appropriate introduction of molecular medicine into clinical practice requires a proper education of medical students at the undergraduate and postgraduate level as well as within the continuous education of medical professionals (20).

**Impact of Molecular Medicine on Pathophysiology**

The starting point of molecular pathophysiology is the concept that disorders in the structure and function of a macromolecule are the basic disorders in the pathogenesis of any disease. The primary disorder may be a non-repaired DNA damage leading to mutation, or a disorder in DNA reparation, or a change in informative content of the cell due to the mutation of nuclear or mitochondrial DNA or introduction of genetic information (virus infection). Disorders of gene expression regulation, of RNA and protein synthesis
and degradation, and of posttranslational protein modifications play indeed an important role in pathogenesis of various diseases (21-23).

To understand the mechanisms of disease in terms of molecular pathophysiology, the disorders on molecular level should be linked with consequent disorders on subsequent hierarchical levels of the organization of the organism, involving interactions of various functional systems (polysystemic or interorganicism) (Fig. 4). Ascending from the basic level to the organism level, the complexity of the system and the number of possible interactions increase, whereas the predictability decreases (24,25).

The vertical analysis of pathogenesis aims at explaining phenomenology observed on higher levels by establishing causality on basic levels of organism organization. However, such an analysis is presently possible only as a simplified general scheme, often elusive and misleading if specific limitations are not taken into account (17,26).

Genotype/Phenotype Relationship

The central problem in understanding the mechanisms of disease, interpretation of diagnostic assays at molecular levels, preventive procedures, clinical decision making procedures, and counseling is the genotype/phenotype relationship. It involves gene structure (genotype), gene interactions, modifier gene effects, proteome, and effects of environmental factors (Table 2, refs. 17,32,39,43), whose interactions result in an intermediate and expressed phenotype (Fig. 5). Even the expression of identical mutation might be diverse, allowing the prediction of the expression of the mutation only with higher or lower probability (44).

The basic level of the organization of the organism is the DNA structure defining the identity of the organism. The genetic code and its mutations are unequivocal, and the missense mutations result in corresponding changes in protein amino acid sequence. However, immediate consequences of nonsense and splice-sites mutations on messenger RNA (mRNA) and protein structure might be ambiguous (Fig. 6), depending on mRNA quality control (mRNA QC) effi-

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**Figure 3.** The impact of molecular medicine on medical science and practice.

**Figure 4.** Vertical analysis of pathogenesis (25). Example: cystic fibrosis. Hierarchical levels of organization of the organism (capitalized); genotype and phenotype characteristics (bold); intermediate phenotype (normal). C – cytosine, T – thymine, CFRT – cystic fibrosis transmembrane conductance regulator, Phe – phenyalanine.
pressed at translation level in vitro, when seryl-trans-
patients with mutation at 17th codon in reticulocyte lysate in some
free system (46). The experiment illustrates the un-

tense codon was added in protein-synthesizing cell-

erNA recognizing uracil-adenine-adenine non-

ambiguousness of genetic code.

ie, they result in heterogeneity of the mutation-dis-

ease relationship (32). Different mutations of the

same gene may result in different diseases (Fig. 7A) or

cause the same disease with variable expression, which is more often a case (Fig. 7B).

Mutations in various genes may produce more or less similar phenotype (genocopies) (Fig. 7C). The genetic analysis and studies of genotype/phenotype relationship help us understand the diverse patho-
genesis of these groups of diseases and allow formation of appropriate taxonomy (33,34).

The mode of mutation expression depends on function of mutated protein. When the protein has catalytic or quasi-catalytic function (one molecule of protein reacts with a number of substrate/ligand molecules) the mutation is expressed in a homozygous constellation (47). However, when the mutation of the same gene produces a protein with dominant-neg-

ative effect inactivating a wild protein, the mutation is expressed in heterozygous constellation (37).

Table 2. Factors contributing to genotype/phenotype relationship

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>Pathogenetic involvement</th>
<th>Example</th>
<th>Ref. No.</th>
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<td>mRNA QC* efficiency</td>
<td>prevention of availability of abnormal mRNA</td>
<td>abnormality in expression of nonsense and splice-site mutations</td>
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<td>defective apoB100 and familial hypercholesterolemia caused by apolipoprotein B100 gene and LRL-R gene mutations, respectively</td>
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<td>infections: mutations in cytokine and cytokine receptors genes and HLA gene polymorphism confer susceptibility/resistance autoimmune disease: mutations in NOD2 gene confer high risk of fibrostenotic form of Crohn's disease malignant tumors: multiple gain-of-function and loss-of-function mutations of protooncogenes and tumor suppressor genes, respectively</td>
<td>40</td>
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* mRNA quality control.
† Low density lipoprotein receptor.
‡ Cystic fibrosis transmembrane conductance regulator.
The modifier gene effects include complex genomic interactions producing remote consequences of the mutations and contributing to the pathogenesis of the disease on polysystemic level. Environmental factors might either ameliorate or exaggerate the consequences of the mutation, and understanding of these effects allows more or less effective prevention of the expression of the mutation (38).

The pathogenesis of a common complex diseases (cancer, atherosclerosis, arterial hypertension, autoimmune disease, and neurological disorders) involves multiple interactions of environmental and genomic factors. Genomic factors include gene polymorphism and gene interactions at transcriptional level, which create complex interconnecting network of intermediate phenotype (39). The identification of these genomic factors will improve the understanding of the pathogenesis of diseases, and make it possible to identify individuals at risk with regard to both the development and the outcome of the disease.

The recent completion of the draft sequence of human genome will accelerate the identification of genotypes associated with causes and mechanisms of complex diseases (15,39). A single nucleotide polymorphism (SNP), where one nucleotide is substituted for another in a DNA sequence, is associated with a certain phenotype of a disease (15). There are about two to three million SNPs in exonic, intronic, regulatory, and intergenic regions of almost all genes. SNPs only rarely result in variations in amino acids in corresponding proteins and many are associated with various phenotypes of diseases. SNPs are genetic markers. However, studies showing association of SNPs with a certain phenotype of disease still do not provide the evidence of functional genotype/phenotype relationship. A great dispersion of SNPs across genome may point to a relevant genotype, but association between SNP and a disease may also be caused by the linkage disequilibrium. These limitations have to be taken into account when associations between SNPs and disease are interpreted (15,48).

**Disorders of Gene Expression**

Regulation of gene expression is involved in the processes of cell cycle control, differentiation, maturation, and malignant transformation, as well as in response to cellular stress, external signal molecules, cell injury, and adaptation to workload. Gene expression is an interface between genetic and epigenetic factors and it is central to understanding of molecular pathogenesis of disease.

Disorders in gene expression may occur on transcriptional, translational, and posttranslational level. Ultimately, gene expression depends on quality and quantity of the corresponding protein. The former is
defined by gene structure, and the latter depends on
the relationship in the rates of protein synthesis (trans-
lation) and degradation (Fig. 8). Protein synthesis de-
pends on the quantity of mRNA, which is defined by
the relationship between the rates of mRNA synthesis
(transcription) and degradation, and by the rate of
translation. All these factors also have to be taken into
account in the analysis of gene expression (49).

Disorders also occur on transcriptional level (transci-
ptome) (Fig. 9 and Table 3; ref. 22).

Transcriptional regulation by RNA interference
involving interactions of mRNA and small regulatory
RNAs molecules (59) or antisense RNA (60) is the
amazing new field of research, with promising thera-
peutic implications (52,61).

Specific transcriptional factors regulate transcrip-
tion of particular genes. These factors have a specific
tissue distribution, governing tissue-specific gene ex-
pression. Signal molecules control the activity of
these factors, which thus influence gene expression.
Over 2,000 specific transcriptional factors make inter-
active regulatory loops, orchestrating the up- or
down-regulation of transcription in a number of genes
into a concordant cellular response (61).

Many extracellular (e.g., hormones or cytokines)
and intracellular signal molecules are involved in the
control of transcriptional factors activity. The intra-
cellular signaling pathways are interconnected signal-
ing networks, with sites of signal convergence or di-
vergence. These networks are responsible for pleotro-
pic effects of signal molecules, which involve not
only transcriptional regulation of a number of genes,
but also the control of various cell functions. Conse-
quently, disturbances in signaling pathways provoke
complex disorders in cell functions (63).

Cells adapt to workload by modulating gene ex-
pression, ie, the quantity of function per mass of or-
gan (intensity of function of structure, IFS) tends to
remain constant (64). The maintenance of IFS constancy
is a general principle of cell adaptation to workload
underlying the diverse mechanisms of organ hyper-
trophy and atrophy (65,66).

Disorders of Protein Synthesis Degradation
and Posttranslational Modifications

Inhibition of protein synthesis, accompanied by
disaggregation of polyribosomes, is one of the earliest
alterations of cellular function seen in different patho-
logical conditions (Table 4). The underlying mecha-
nism is the inhibition of initiation of translation and
consequent polyribosome disaggregation (80), with
simultaneous increase in stress-protein gene expres-
sion (81). Inhibition of overall protein synthesis could
be a sparing adaptation to energy or substrate depriva-
tion, but it is not clear how it may contribute to cell in-
jury, particularly when the recovery of protein synthe-
isis is delayed.

Cellular protein quantity depends on the rela-
tionship between the rates of synthesis and degrada-
tion. The ubiquitin/proteasome pathway of protein
degradation plays a key role in the regulation of a
turnover of many proteins involved in cell cycle pro-
gression, gene expression, and signal transduction, in
degradation of misfolded proteins, antigen presenta-
tion, and protein catabolism. Disregulation of protea-
somal proteolysis contributes to malignant transfor-
mation, ageing, and catabolic reaction to injury and
infection (70,71).

Protein misfolding due to hereditary or acquired
structural alterations causes disorders of the protein
processing and translocation, and their accumulation
in endoplasmic reticulum (ER), which triggers ER-
overload response. ER-overload response is a key mo-
lecular mechanism underlying pathogenesis of di-
verse diseases in which protein misfolding or disor-
ders in ER cargo handling are involved (72).
Disorders of protein covalent modifications are involved in failure of protein processing into active forms (73), inappropriate activation of cascade reactions (74,75), and formation of pathogenic products (76,77). Covalent modifications of proteins are the primary consequence of action of most bacterial toxins and toxic xenobiotics, being the basic macromolecular disorder in these conditions (78,79).

Molecular pathophysiology should identify molecular targets of etiological factors, modes of interaction between them, and the consequence of the interaction at molecular levels. The understanding of the basic mechanisms of diseases will improve diagnostic and therapeutic approaches, allowing specific analytical or pharmacological procedures to be targeted at relevant molecules.

**Impact of Molecular Medicine on Clinical Practice**

Understanding of human genomics has a growing impact on all aspects of clinical medicine. The knowledge of molecular basis of disease (molecular pathophysiology) will call for redefinition of the now existing nosological entities, which are heterogeneous on the molecular level. Examples are essential arterial hypertension, diabetes mellitus, and various malignant tumors. This would allow selecting the patients for appropriate therapy or stratifying them for trials according to the molecular characteristics of the disease. However, the present limitations in the knowledge of human genomic raise skepticism concerning the perspective of application of molecular medicine in individual patient management (18).

Genomic technology offers highly specific and sensitive methods acceptable for clinically orientated assays. They may be used as diagnostic or prognostic tests and for monitoring of progression of the disease (82).

DNA techniques are the most appropriate methods for confirmation of diagnosis in patients with signs and symptoms indicating a genetic disease (82). However, the limitations of the assays based on DNA technology have to be taken into account. In most cases, the diseases are caused by a number of heterogeneous mutations of the same gene (allelic heterogeneity). Testing methods available for clinical use usually detect the most frequent mutations, lowering the sensitivity of the assays and possibly leading to false negative results. The mutation detection rate depends on the allelic heterogeneity and frequency of new mutations. Positive results, detecting known pathogenic mutations, are confirmatory (26). However, due to diverse genotype/phenotype relationship, the detection of the mutation does not allow the prediction of the severity of disease (36,44). A negative result of the known mutation is equally confirmatory and can be used for selection of a normal embryo resulting in vitro fertilization, from gametes of a heterozygous couple with the mutation (83).

When new mutation is detected, its pathogenetic effect should be proven by linkage analysis in a family study if two or more affected family members are available for testing (82).

When DNA-based diagnostics is used to identify individuals at high risk of a disease, the risk conferred by the mutation should be taken into account. Present epidemiological data are mainly derived from studies...
including different, small populations with diverse frequency of mutations, and inappropriate control groups.

Clinical validity of the testing depends on prophylactic procedures available. Presently, these procedures are not based on prospective randomized studies, which would allow us to draw conclusions in terms of evidence-based medicine (82). For example, conclusion that prophylactic mastectomy lowers the lifetime risk of breast cancer for more then 90% in high-risk group of women is based on a retrospective study with historical control group (84). The conclusion was criticized because the cost-benefit ratio was not discussed, other preventive possibilities (close surveillance or chemoprevention) were not compared, and the life expectancy of women who would eventually develop breast cancer was not taken into account (85).

The perspective of predictive genetic testing is to establish reliable and widely accessible methods for estimation of individual risk for common diseases, and to integrate them in overall medical care (86). The emphasis will shift from diagnosis to prevention, and the present day question "which disease has this patient?" will be replaced by the question "which disease this person may develop?" The answer will be the selection of appropriate, individualized preventive procedure (26).

DNA technology has been applied in cancer diagnostic for detection of oncogene and antioncogene mutations as prognostic factors or for discovering micrometastases of cancers or minimal residual disease in leukemia (87). Transcriptional profiling of malignant tissues by DNA microarray has improved classification of malignant tumors, prognosis, and appropriate therapeutic selections (57,88). Molecular characterization of breast cancer on protein level has been used in the management of patients for a long time, starting with steroid receptor determinations 30 years ago (89,90), and later being supplemented with additional assays (cathepsin D or c-erbB-2 protein) (91-93). Recently, the analysis of serum proteomic pattern has been used to detect ovarian cancer with 100% sensitivity and 95% specificity (94).

Molecular medicine influences various aspects of therapy. It is expected that the most immediate application of human genome project on clinical practice will be pharmacogenomics: the application of genetic information to individualization of drug therapy with an aim to administer the proper dose without causing adverse reactions (95).

The elucidation of molecular mechanisms of disease allows the identification of therapeutic targets and designing drugs that specifically act on the targets. Some examples are antiestrogens (96), humanized monoclonal antibody recognizing c-erbB-2 receptors on breast cancer cell membranes (97), and the highly specific tyrosin kinase inhibitors affecting chronic myeloid leukemia cells with highly expressed bcl-abl tyrosine kinase activity (98).

Gene therapy includes a genetic modification of cells in order to produce a therapeutic effect. The obstacles to gene transfer are access to the target cells, the efficacy of gene transfer, and expression and safety of the procedure in terms of unpredictable consequences of genetic manipulation, particularly oncogenic transformation. The risk of oncogenic transformation was assessed as acceptable on the basis of animal studies (99). However, the development of leukemia in a child after the gene therapy treatment for se-

| Table 4. Disorders in translation, protein degradation, and posttranslational modifications |
|-----------------------------------------------|---------------------------------|-------------------------------------------------|-------------------|-------|
| Disorders in translation | Protein degradation | Protein folding | Posttranslational modification: | |
| Translation | inhibition of initiation | deregulation of proteasomal | disorders in protein | in enzyme activity |
| Protein degradation | disorders in protein | degradation, endoplasmic | processing, endoplasmic | failure in posttranslational |
| Protein folding | endoplasmic reticulum overload | response | reticulum overload | modifications |
| Posttranslational modification: | in enzyme activity | failure in posttranslational | in cascade activations | inappropriate activation of |
| in cascade activations | in enzyme activity | modifications | in cascade activations | cascade reactions |
| in covalent modifications: | endogenous factors | protein glycation, | formation of pathogenic products | protein glycation and diabetes |
| endogenous factors | (glucose or ROS*) | carbonylation | protein glycation and diabetes | complications |
| exogenous factors | protein inactivation | bacterial infections; effects of | protein carbonylation and ageing | protein carbonylation and ageing |
| (bacterial toxins or xenobiotics) | | xenobiotics | | by cholestrol toxan |
| acute pancreatitis | protein phosphorylation by | organophosphorous compounds | | |

*Reactive oxygen species.
vere combined immunodeficiency has raised concern about the risks of gene therapy (100). New promises in gene therapy are drugs suppressing mutations at the level of translation (101), suppression of transcription by RNA interference (52, 61), and stem cell therapy (102).

**Impact of Molecular Medicine on Medical Education**

Medical professionals are faced with complex public, social, ethical, legal, and healthcare issues of knowledge explosion in the field of human genome structure and function (103). It may be expected that by 2010 predictive genetic tests will be available for many common diseases, and by 2020 pharmacogenomic approach to individualized drug therapy the standard procedure (104). In the decision making process, both the physician and the patient will be involved and the appropriate education of both will be necessary (103).

It is widely recognized that present medical school curricula are not adequate to enable medical professionals to meet these challenges (104, 105). Medical professionals should be able to transfer new knowledge into practice rapidly and appropriately, take a role in public education at large, and develop a critical attitude to complex public (ethical, legal, and social) issues of the genomic.

Incorporation of conceptual and clinical aspects of molecular medicine in the undergraduate and postgraduate curricula and continuing education of medical professionals is an imperative if the demands of medical care quality are to be fulfilled in near future (106).

The emphasis should be put on bedside-oriented molecular medicine (107). Translational research is a prerequisite, aimed at translation of basic information into improvement of healthcare of the individual patients and population as a whole (108, 109). The research should primarily address the effects of genetic and environmental factors on expression of the disease in a particular population, taking into account genomic variability and differences in environmental factors, whereas healthcare consequences should be founded on evidence-based medicine.

The molecular medicine topics should be included into various subjects of undergraduate curricula and vertically integrated rather than treated as a separate subject in preclinical or clinical courses (Fig. 9; ref. 106). During the preclinical years (the first two years in Croatia), the emphasis should be put on the basic principles of genomic structure and function. The intermediate subjects (pathology, pathophysiology, pharmacology, and microbiology – the third study year in Croatia) should integrate the basic knowledge of the mechanism and therapy of disease. Clinical subjects (internal medicine, pediatrics, oncology, and neurology – last three study years in Croatia) should incorporate molecular medicine in teaching on relevant nosological entities. The last year’s integrative courses should give an overall knowledge of most common diseases, incorporating all molecular aspects – mechanism, diagnosis, prevention, and therapy of diseases. The vertical integration of this disperse teaching of molecular medicine topics should be programmed, organized, and supervised, with the aim to ensure logical sequence and balance between subjects and avoid unnecessary repetitions.

The problem-oriented tutorials using clinical or research problems taken from literature or clinical records may provide an excellent mode of teaching. Such a model has been developed and used at the Department of Pathophysiology at Zagreb University School of Medicine. The aim of these tutorials is a vertical analysis of pathogenesis from molecular to organism level.

The translational research laboratories should be developed within university hospitals, providing the infrastructure for research training on postgraduate teaching level.

Continuing medical education credits should adequately stimulate the attendance of courses of continuing medical education devoted to bedside-oriented molecular medicine. Domestic medical journals should follow the editorial policy of some leading general medical journals to spread the fast grow-
Many websites provide free access to databases relevant to molecular medicine and point to “hot” papers (110).

In conclusion, one may say that the era of molecular medicine is here to begin. The elucidations of human genome structure and function have to be applied to pathophysiology and clinical practice and introduced into education. It is extremely important for all of us involved in medicine not to miss the opportunity to participate in these efforts.

References


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