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EDITORIAL

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: diagnostic 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 (CFRT) 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 molecu-

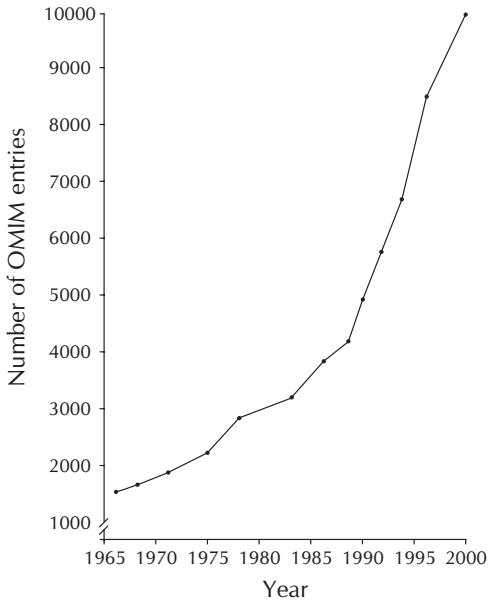

Figure 1. Number of entries in the Online Mendelian Inheritance in Man database (OMIM, ref. 6).

Table 1. Online Mendelian Inheritance in Men (OMIM). Statistics for April 13, 2003 (6)

All entries: 14,351	
established gene locus: 10,651	
phenotype descriptions: 1,282	
other entries: 2,418	
Autosomal entries: 13,446	
established gene locus: 10,027	
phenotype descriptions: 1,161	
other entries: 2,258	
X-linked entries: 802	
established gene locus: 546	
phenotype descriptions: 98	
other entries: 158	
Y-linked entries: 43	
established gene locus: 41	
phenotype descriptions: 0	
other entries: 2	
Mitochondrial entries: 60	
established gene locus: 37	
phenotype descriptions: 23	

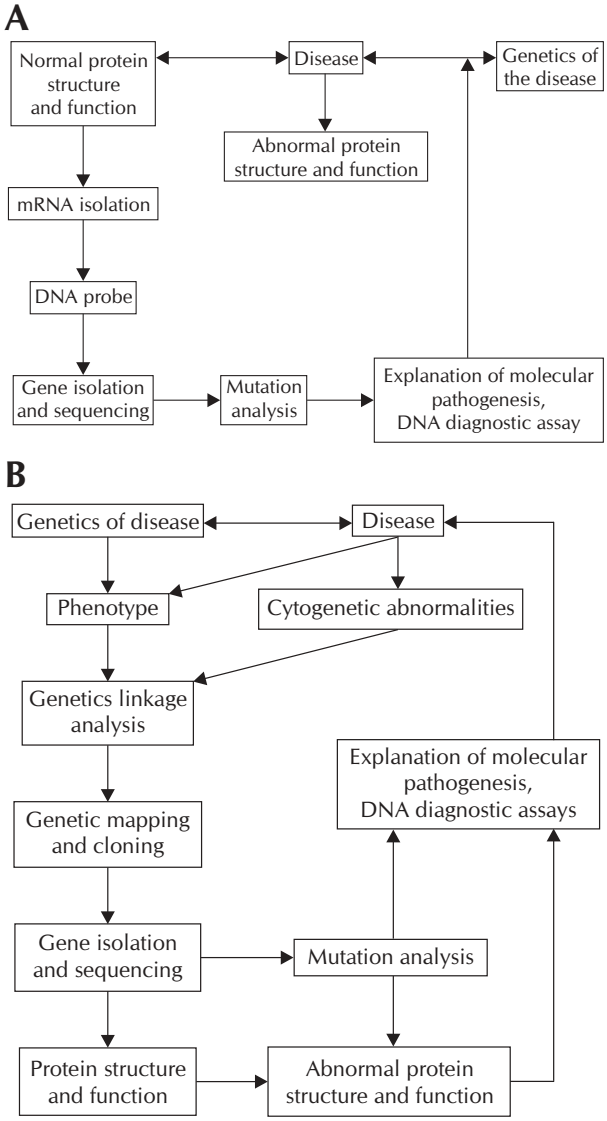

Figure 2. Functional and position cloning. **A.** Gene isolation by functional cloning is based on protein and subsequent mRNA isolation and DNA probe synthesis for the gene identification. **B.** Gene isolation by position cloning is based on genetic linkage analysis, mapping and cloning. Structure and function of normal and abnormal proteins are derived from gene sequencing and mutational analysis.

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

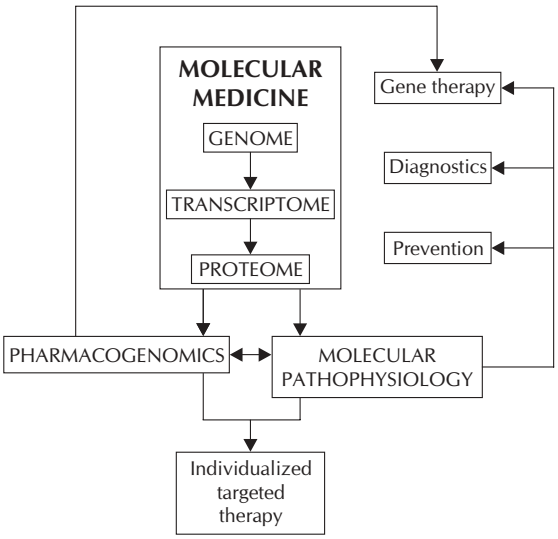

Figure 3. The impact of molecular medicine on medical science and practice.

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 interorganic interactions) (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-

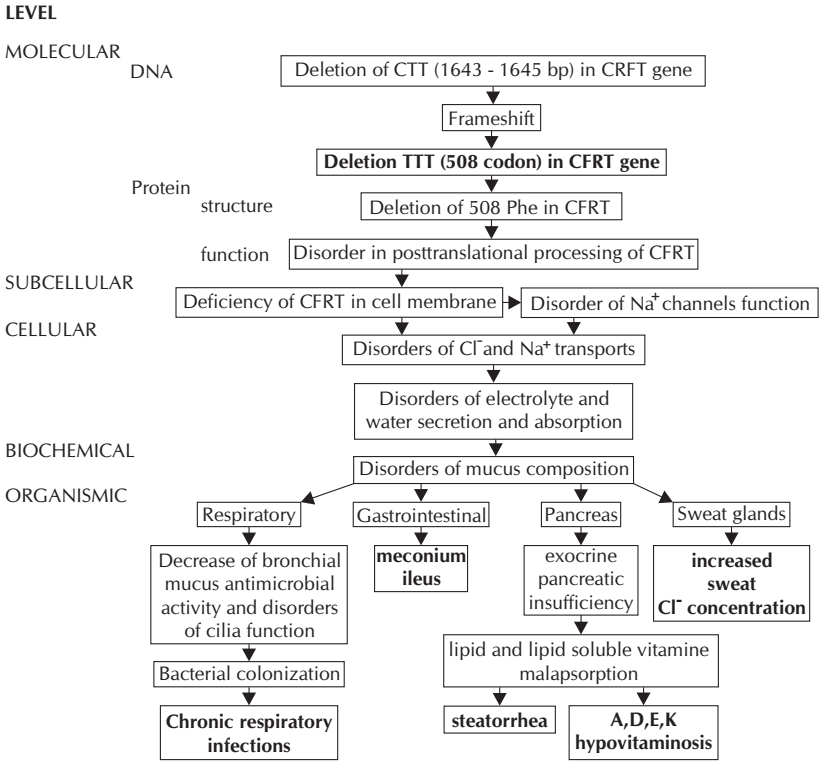

Figure 4. Vertical analysis of pathogenesis (25). Example: cystic fibrosis. Hierarchical levels of organization of the organism (capitalized); genotype and phenotype characteristics (bold); intermediate phenotype (normal). C – cytosine, T – thymine, CFRT – cystic fibrosis transmembrane conductance regulator, Phe – phenyalanine.

Table 2. Factors contributing to genotype/phenotype relationship

Factor	Effect	Pathogenetic involvement	Example	Ref. No.
mRNA QC* efficiency	prevention of availability of abnormal mRNA	abnormality in expression of nonsense and splice-site mutations	*bypass of mRNA CQ in nonsense mutations:*	
			premature polypeptide chain termination with a consequent rapid polypeptide degradation: thalassemic syndromes	27
			truncated protein synthesis in LDL-R†... gene mutations	28
			bypass of mRNA CQ in splice-site mutations:	
			competition with normal mRNA: thalassemic syndromes	27
			efficient mRNA CQ:	
			retention of abnormal transcript in nuclea: splice-site mutations of COL1A1 gene in osteogenesis imperfecta	29
Heterogeneity of mutations	heterogeneity of mutated protein quantity, structure, and function	phenotypic variability of the mutations	*different mutations of the same gene – different diseases:*	
			quantitative hemoglobinopathies	27
			hemorrhagic disease caused by alpha-1-antirypsin Pittsburgh	30
			different mutations of the same gene – one disease with variable expression:	
			variability of cortisol and aldosterone deficiency in congenital adrenal hyperplasia	31
			variability of cystic fibrosis due to diverse mutation of CFTR‡ gene	32
			mutations in diverse genes – similar disease (genocopy):	
			osteogenesis imperfecta	33
			monogenic muscular dystrophy	34
			defective apoB100 and familial hypercholesterolemia caused by apolipoprotein B100 gene and LRL-R gene mutations, respectively	28,35
Modifier gene effects	modulation of pathogenesis	phenotypic variability of the same mutation	influence of genes controlling immune and inflammatory response on lung involvement in patients with cystic fibrosis and 508F mutation	36
Mutated protein function	mode expression of the same gene mutations	expression of mutation in homozygous vs heterozygous constellation	oncogenic effect of p53 tumor suppressor gene mutations with dominant negative effect (mutated protein inactivates the wild protein)	37
Environmental factors	biochemical interactions	modulation of phenotypic expression	euphenic nutrition in phenylketonuria	38
Polygenic disorders	multiple genomic interactions	genomic contribution to common complex disease with increased risk of the disease	*cardiovascular disease:*	
			angiotensin-converting enzyme gene mutations in arterial hypertension	39
			factor V Layden in thromboembolism	15
			infections:	
			mutations in cytokine and cytokine receptors genes and HLA gene polymorphism confer susceptibility/resistance	40
			autoimmune disease:	
			mutations in NOD2 gene confers high risk of fibrostenotic form of Crohn's disease	41
			malignant tumors:	
			multiple gain-of-function and loss-of-function mutations of protooncogenes and tumor suppressor genes, respectively	42

*mRNA quality control.
†Low density lipoprotein receptor.
‡Cystic fibrosis transmembrane conductance regulator.

ciency, which prevents translation of abnormal mRNAs (45). When mRNA QC is bypassed, translation of an mRNA with a nonsense mutation results in premature polypeptide chain termination, whereas mRNAs produced by splice-sites mutations compete with the normal mRNAs (27). The existence of functional mRNA with a nonsense mutation was confirmed by finding of β-globin mRNA with a nonsense mutation at 17th codon in reticulocyte lysate in some patients with β-thalassemia. This mutation was suppressed at translation level in vitro, when seryl-transfer RNA recognizing uracil-adenine-adenine nonsense codon was added in protein-synthesizing cell-free system (46). The experiment illustrates the unambiguousness of genetic code.

Mutations of the same gene are heterogeneous, ie, they result in heterogeneity of the mutation-disease 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 pathogenesis 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-negative effect inactivating a wild protein, the mutation is expressed in heterozygous constellation (37).

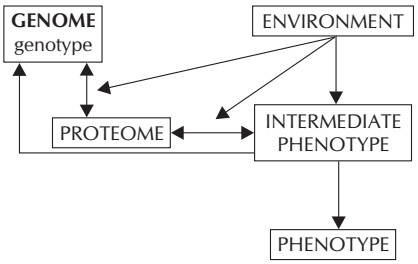

Figure 5. Genotype/phenotype relationship. The complexity of the relationship depends on the number of interactive genetic and environmental factors; it is lower in monogenically and higher in polygenically determined diseases.

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

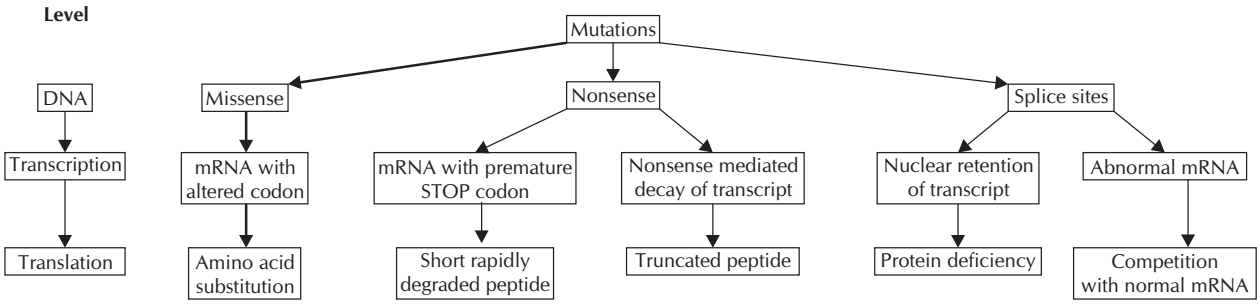

Figure 6. DNA-mRNA-protein relationship. In missense mutations, the consequences on mRNA and protein structure are unequivocally determined by changes in genetic code (bold arrows). In nonsense and splice-site mutations, the consequences depend on mRNA quality control efficiency.

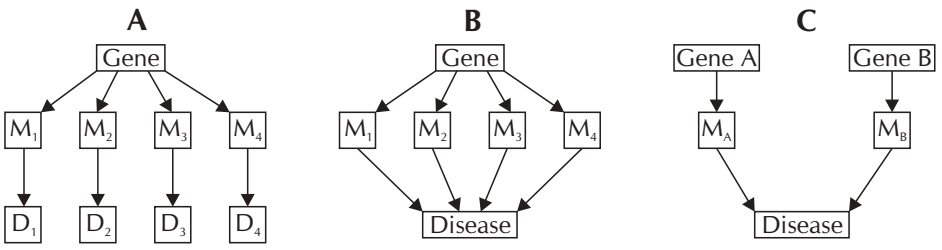

Figure 7. Gene/disease relationship. **A.** Various mutations of the same gene cause various diseases. **B.** Various mutations of the same gene cause the same disease with variations. **C.** Mutations in diverse genes cause more or less similar disease. M – mutation, D – disease.

defined by gene structure, and the latter depends on the relationship in the rates of protein synthesis (translation) and degradation (Fig. 8). Protein synthesis depends 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).

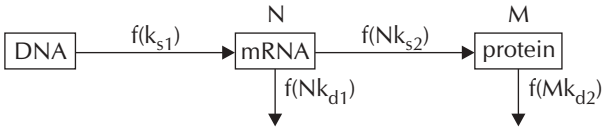

Figure 8. Kinetics of protein synthesis and degradation. N and M – quantities, k_s – rate of synthesis, k_d – rate of degradation, f – function.

Disorders also occur on transcriptional level (transcriptome) (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 therapeutic implications (52,61).

Specific transcriptional factors regulate transcription of particular genes. These factors have a specific tissue distribution, governing tissue-specific gene expression. Signal molecules control the activity of these factors, which thus influence gene expression. Over 2,000 specific transcriptional factors make interactive 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 intracellular signaling pathways are interconnected signaling networks, with sites of signal convergence or divergence. These networks are responsible for pleotropic effects of signal molecules, which involve not only transcriptional regulation of a number of genes, but also the control of various cell functions. Consequently, disturbances in signaling pathways provoke complex disorders in cell functions (63).

Cells adapt to workload by modulating gene expression, ie, the quantity of function per mass of organ (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 hypertrophy 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 pathological conditions (Table 4). The underlying mechanism is the inhibition of initiation of translation and consequent polyribosome disaggregation (80), with simultaneous increase in stress-protein gene expression (81). Inhibition of overall protein synthesis could be a sparing adaptation to energy or substrate deprivation, but it is not clear how it may contribute to cell injury, particularly when the recovery of protein synthesis is delayed.

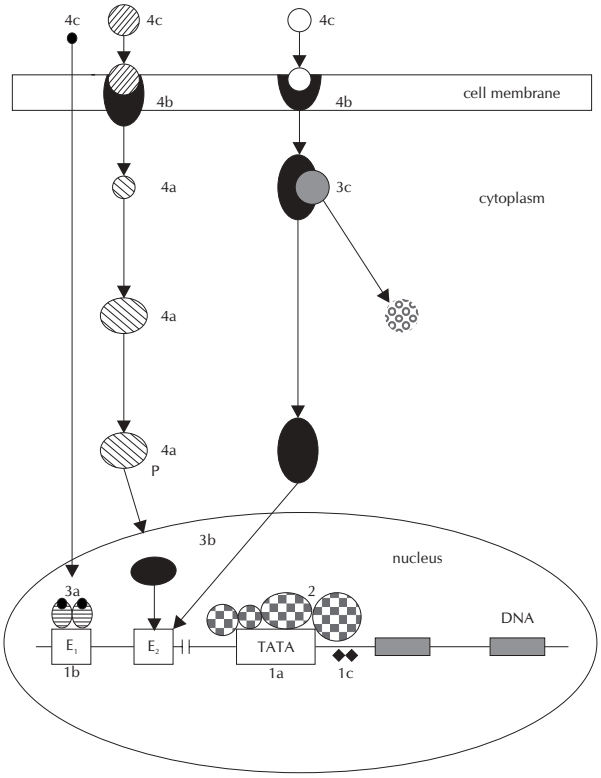

Figure 9. Disorders of transcription (22). **1.** Disorders of DNA structure: 1a. promoter (TATA box) mutation, 1b. enhancer mutation, 1c. hyper and hypo DNA methylation. **2.** Disorders of general transcriptional factors. **3.** Disorders of specific transcriptional factors: 3a. located in nucleus and activated by ligand biding, 3b. located in nucleus and activated by signal molecules, 3c. located in cytoplasm and activated by signal molecules and dissociation of inhibitory subunit. **4.** Disorders of signal molecules and pathways: 4a. intracellular signal molecules, 4b. receptors, 4c. extracellular signal molecules.

Cellular protein quantity depends on the relationship between the rates of synthesis and degradation. The ubiquitin/proteasome pathway of protein degradation plays a key role in the regulation of a turnover of many proteins involved in cell cycle progression, gene expression, and signal transduction, in degradation of misfolded proteins, antigen presentation, and protein catabolism. Disregulation of proteasomic proteolysis contributes to malignant transformation, 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 molecular mechanism underlying pathogenesis of diverse diseases in which protein misfolding or disorders in ER cargo handling are involved (72).

Table 3. Disorders in gene expression

Level of disorder	Effect	Pathogenetic involvement	Example	Ref. No.
DNA structure				
promoters and enhancers of mutations	decrease in the rate of transcription	protein deficiency	thalassemia syndromes	27
mutations affecting mRNA stability	decrease in mRNA availability and in the rate of translation	protein deficiency	thalassemia syndromes	27
mutations in 5' or 3' UTR*	disorders in translational regulation	protein deficiency or excess	hyperferritinemia/cataract syndrome	50
DNA methylation	gene silencing and activation by DNA hiper- and hypomethylation, respectively	changes in gene expression in malignant cells and gene imprinting	loss of ER†... in breast cancer due to ER gene	51
RNA interference	repression of gene expression by small regulatory RNA and antisense RNA	protection from virus	inactivation of p53 RNA	52
		ds RNA		
		carcinogenesis (hypothetical)		
General transcriptional factors	decrease in activity of general transcriptional factors	disorders of DNA repair and general gene expression	transcriptional syndromes	53
Specific transcriptional factors	disorders in regulation of specific gene expression	up- or down-regulation of specific gene expression	HIF‡ in hypoxia	54
		concordant response in various pathological conditions	NF- B§ in inflammatory and immune responses	55
		disorders in gene expression in malignant cells	transcriptional profile of tumors	56,57
Signal molecules	disorders in extracellular and intracellular signaling	pathogenetic mechanism involving extracellular (hormone or cytokine) and intracellular (ras) signaling	disorders of gene expression in diabetes	58

*Untranslated region.
†Estrogen receptor.
‡Hypoxia inducible factor.
§Nuclear factor κB.

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 mutation, 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 from *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	Effect	Patogenetic involvement	Example	Ref. No.
Translation	inhibition of initiation		inhibition of protein synthesis and polyribosome disaggregation:	
		hypoglycemia	in brain in hypoglycemia	67
		starvation	in liver in starvation	68
		hypoxia	in hypoxic kidney	69
Protein degradation	disregulation of proteasomic proteolysis	disorders in protein turnover	disregulation of protein activity by turnover	70
			catabolic reaction to injury and infection	71
Protein folding	disorders in protein processing, endoplasmic reticulum overload	endoplasmic reticulum overload response	disease with accumulation of misfolded protein in endoplasmic reticulum	72
Posttranslational modification:				
in enzyme activity	failure in posttranslational modifications	deficiency in active protein modifications	disorders in coagulation factors due to K hypovitaminosis	73
in cascade activations	inappropriate activation of cascade reactions	amplification of processes with cascade activation (blood coagulation, complement activation, digestive enzyme activation)	disseminated intravascular coagulation	74
			acute pancreatitis	75
in covalent modifications:				
endogeneous factors (glucose or ROS*)	protein glycation, carbonylation	formation of pathogenic products	protein gycation and diabetes complications	76
			protein carbonylation and ageing	77
exogenous factors (bacterial toxins or xenobiotics)	protein inactivation	bacterial infections; effects of xenobiotics	α-subunit of Gc protein ADP-ribosylation by cholera toxin	78
			cholinesterase phosphorylation by organophosporous compounds	79

*Reactive oxygen species.

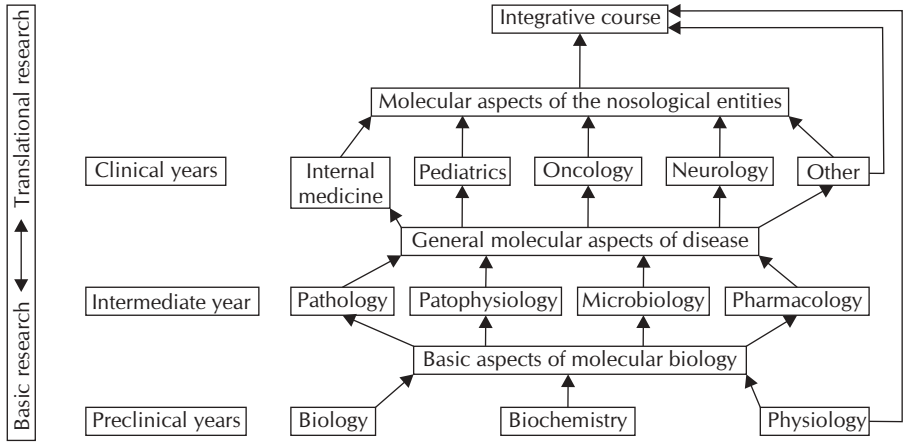

Figure 10. Model of integration of molecular medicine teaching into the medical school undergraduate curriculum. The teaching should be supported by basic and translational research.

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, prognosis, 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-orientated molecular medicine. Domestic medical journals should follow the editorial policy of some leading general medical journals to spread the fast grow-

ing knowledge in molecular medicine by publishing series of reviews dedicated to the clinician education (3,4,12,26). 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.

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