REVIEWS

Progress in Medicine and Biology in the Last Centuries

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On the eve of 21st century it is interesting to analyze recent history of theoretical and practical medicine and to outline possible ways of their future progress. One of the approaches to this task is to consider the relationships between analysis and synthesis in medical sciences in that period. The harmony between accumulation of new data and their generalization is the cornerstone of fruitful development of theoretical medicine and its implementation in clinics.

From this viewpoint, the 19th and 20th centuries are of particular interest. Although previous 16th-18th centuries were also marked with fundamental progress in medical and biological sciences (A. Vesalius, W. Harvey, R. Descartes, G. Morgagni, A. Leuwenhoek, E. Jenner, *et al*.), they were mere streams breaking thousand-year delusions and metaphysical prejudices, which did not confluence into an ocean of scientific data on human being harvested by 19th and 20th centuries. The 19th century is the period of **creation of large-scale universal principles, which laid the theoretical foundation of biology and medicine** (Darwinian evolution theory, Schwann's cell theory, Virchow's cell pathology theory revealing materialistic basis of vital functions in healthy and sick organism, the energy conservation law, *etc*.). This sound theoretical basis caused the turbulent development of physiology, biochemistry, genetics, microbiology, pathological anatomy, pathological physiology, *etc*., which studied life processes predominantly at the organ, tissue, and cell structural level. However, the intracellular processes glimpsed only slightly in some biochemical, genetic, physiologic, and morphological studies.

The new and rapidly accumulated data outlined the basic frames in the study of the causes of disease (etiology), the mechanisms of their development (pathogenesis), the typical general pathological processes (degeneration, circulatory disturbances, inflammation, thrombosis, regeneration, *etc*.), organism responsiveness, constitution, *etc*. However, it was only the beginning of formulation of theoretical cornerstones of medicine: the sprouts of these disciplines were rather amorphous due to lack of the data on intracellular molecular processes. Therefore, many theses were formulated as more or less significant hypotheses and suggestions. This situation resembled similar period in physics, when natural philosophy flourished and yielded a vast number of genial empirical findings. The particular role of 19th century medical and biological sciences is the ultimate statement on material basis of the work of a living organism.

The first, and especially the second half of 20th century were marked with a broad application of modern achievements of physics, chemistry, and technology for solving medical and biological problems. They made it possible to "penetrate" into the depth of cells and obtain principally new and wide data on the processes developed in them under normal and pathological conditions. The most striking feature in the development of medical science in 20th century was focusing the research on more and more fine biological processes, so scientific work was performed not only at the systemic, organic, tissue, and cellular levels, which was characteristic of the past, but also at intracellular (ultrastructural and molecular) ones. Namely this way was marked by widely known modern achievements in biochemistry, genetics, immunology, pharmacology, infectiology, cardiology, morphology, *etc*. Due to methodical progress, modern medicine rapidly approaches to the origin of life and to understanding the most fine and basic mechanisms underlying genesis and control of the functions at all organization levels.

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A peculiar situation is becoming more and more clear: in 19th century, when scientific medicine was in its cradle and had relatively poor amount of experimental data, the scientists tried to make wide generalizations. In 1885, V. V. Pashutin wrote: "Generalizing swings of mind in the sphere of pathologic phenomena are indispensable, because the wealth of experimental data is enormous, and without generalization it tends to become an intellectual ballast, which could be hardly retained in memory" [12]. In 20th century and, in particularly, in its second half characterized with accumulation of mountains of new and precious data, the scientists were far more involved in further accumulation of experimental data than in their theoretical synthesis. While researchers run more and more rapidly at systemic, organ, tissue, cell, and molecular levels, they decelerate and almost stop at the highest (organism) level. However, only this "supreme" level of organization should incorporate and fuse the data collected at the lower structural levels, thereby creating instruments to study such global medical and biological problems as the causes and developmental conditions of diseases (etiology), structural-functional relationships, the mechanisms of development of pathological processes (pathogenesis), directed activity of an organism for recovery of the vital functions (adaptation, compensation of the disturbed and lost functions, and sanogenesis), constitution and responsiveness of an organism, *etc*., which lead to solution of major medical problem, *i.e.* creation of the comprehensive concept of diseases. Hence, 20th century is characterized by a paradoxical breach between huge number of facts in physiology, genetics, biochemistry, morphology, immunology, and other branches on the one hand, and the lack of principal new theoretical achievements explaining these facts, on the other. In this respect, I. V. Davydovskii wrote: "Modern medicine is almost entirely absorbed in analysis, while synthesis lags behind in company with the general concepts, which are indispensable for more or less comprehensive study on the diseases" [7]. Somewhat earlier, a famous biologist E. Wilson made similar prevention: "Future naturalists must be ready for intensive and highly specialized work; however, in future they will vainly wander in a barren desert of specific trifles even more than in the past, if they overlook the broad problems and general targets of their science. These general purposes are the guiding stars of the progress, and although at close distance science looks more and more complex, a broader view shows that its most wonderful discoveries are frequently especially simple" [5].

Such situation can be explained by three basic reasons. First, many scientists stress, that theoretical generalization at the organism level is far more difficult problem than analysis of specific data. Indeed, during last 100-150 years only few of hundreds of medical scientists in our country tried to formulate broad philosophical generalizations (S. M. Luk'yanov, I. V. Davydovskii, G. P. Sakharov, A. V. Speranskii, and few others). Second, no less important is the modern trend to focus the study on the molecular processes, which narrows the range of researchers. The narrow specialization does not stimulate the appearance of broad generalizations falling outside the scope of specialized field, and moreover, it sinks the researchers more and more deeply into the microcosm of particularities. The third and probably most important reason is the fact, that rapid sinking of the scientists into the depth of most interesting and intimate vital processes strengthens their believe that namely this "bottom of life" contains the solution of all problems, which attracted physicians for centuries. The appearance of modern so-called **cellular problems** pretending to explain the very essence of life is not casual. In such conceptions, the most typical is binding the phenomena in a diseased organism with some subcellular alterations. Such approach to solution of pathogenesis of human diseases is characterized by narrow morphologism, i.e. an attempt to reduce the nature of biological phenomenon to one of its features. This is a wrong methodology, since any general phenomenon in an organism results from a number of interrelated changes in various organs and system, so it is principally broader than the local morphologic alterations and cannot be reduced to them. Touching on the problem of cardiac insufficiency, S. P. Botkin wrote: "… calm and attentive observation showed that in many cases the postmortem examination reveals a pronounced alteration of the myocardium in the terms of its adipose degeneration, while the corresponding clinical manifestations were rather insignificant. By contrast, extremely drastic changes of volume and function of the heart can develop without pronounced anatomical alterations of the myocardium" [1]. D. D. Pletnev shared the similar thoughts: "… functional changes of the heart not accompanied by significant anatomical alterations depend on the central neural elements, whose state is determined by numerous environmental conditions" [13]. It indicates that insufficiency of hypertrophied heart can be observed not only at the moment, when it exhausted its resources entirely, but also during the earlier period due to some general reasons originating outside the muscle cells and blocking the work of the heart before the ultimate exhaustion of the cardiomyocytes. There is evidence on importance of extracardiac factors in the origin of insufficiency of the hypertrophied heart [4].

Thus, it would be erroneous to relate the hopes for successful solution of challenging clinical problems entirely with the progress in molecular biology and

pathology. Such progress is the necessary and important step, but it is not a single prerequisite condition to solve these problems. Another factor is deciphering of the complex system of regulator mechanism providing intimate incorporation of specific molecular, ultrastructural, and cellular processes into general scheme of vital activity and determining their individual role. Evidently, the problems of cancer, cardiac insufficiency, genetic pathology, and the like belong to the cellular level. However, is it equally important to realize that in the complex organisms all these problems simultaneously belong to the supracellular level. Such dialectic approach to these cellular problems is explained by the fact that any local changes, the molecular ones included, are rigidly corrected by the regulatory systems in the organism and in vast majority of cases they are blocked or inhibited by the adaptive reactions. Therefore, in many cases, the treatment performed exclusively at the molecular level yields not only successful, but also doubtful results, or downright fails to produce any. There are instructive cases in the history of medicine on many wonderful *in vitro* achievements that could not be matched by the corresponding effects *in vivo*.

Therefore, the modern researches rapidly penetrate into the depth of vital mechanics, but this breakthrough produces almost no effect on the outdated concepts in etiology, pathogenesis, compensation of the lost functions, and general theory of the diseases, which came from the 19th century science and were preserved almost unmodified in the next century. It cannot be excluded that they will live at the beginning of 21st century as well. Nevertheless, the accumulated data grew in quantitative and qualitative aspects and fell far outside the scope of those conventional theoretical notions, which corresponded to their previous volume and quality. Gradually, the old theoretical views become not only superfluous, but erroneous as well, retarding further development of the practical medicine.

For example, before the advent of electron microscopy, the morphological alterations corresponding to fine and dynamic functional modifications rarely could be detected. Now it is obvious that no functional changes, even the finest ones, can occur without corresponding alterations in the nuclear and cytoplasmic organelles. Respectively, the notion on "primary functional changes and secondary morphological alterations" widely spread in 19th century, is no more valid. Thus, the previously prevailing belief on existence of so-called functional diseases lacking a clear structural basis should be rejected. K. M. Bykov wrote: "I stress that the time is not far, when subdivision of all diseases into organic and functional will disappear" [3]. However, this concept of 19th century science was ingrained so strongly in physician minds that nowadays it is impossible to root it out from encyclopedias and textbooks.

However, this problem is of principal importance not only for theory, but also for clinical practice. The point is that although some pathological changes developing at the "lower" levels (molecular, cellular, tissue, organ, and systemic) can be immediately observed at the organism level (severe genetically determined developmental abnormality, traumatic lesions, the effect of potent poisons, *etc*.), in most somatic diseases they are not manifested at the organism level and do not necessitate a direct clinical intervention being compensated by the potent protective mechanisms, which can completely neutralize them and make a patient virtually healthy for many years. In the last case, the disease and the corresponding structural changes develop more or less intensively, but during some period they are completely compensated by the opposite reparative processes and do not manifest themselves functionally and clinically. This period is referred to as the preclinical asymptotic phase of a disease, which sometimes erroneously termed as a "predisease". A disease becomes clinically manifested only when the protective compensatory reactions of the organism begin to decline. I. P. Pavlov wrote: "… really, do not the causes of the diseases usually germinate and start their activity before the patient becomes an object of medical observation?" [11]. Therefore, in reality, a picture may emerge, which is opposite to the general views: the functional (clinical) changes appear not earlier than the structural ones, but only when the pathological process marched a long way in its morphological manifestation. Thus, a general practitioner should always take into consideration the principal fact that the first complains of a patient (the functional disorders) may not be the signals of a starting disease, but the first signs of exhaustion of the compensatory reactions, which attest to a pronouncedly developed pathological process. This notion is substantiated by the fact that in many cases the patients are admitted into hospital in the incurable state, so it is directly related to the early diagnostics of the diseases. It is not casual that more than half-century ago I. V. Davydovskii formulated at first glance paradoxical, but in essence a very deep notion that "diagnostics of the diseases should start not at the patient's bed (this is an accomplished period of medicine), but in the clinic of healthy man" [8].

This reasoning makes clear why the problem of **compensation of the lost functions** on the basis of organ-organ, tissue-tissue, cell-cell, and other connections, plays the key role in clinic. The constellation of these connections arrests, corrects, and annihilates the primary pathological changes, thereby providing homeostasis and supporting health: " … namely the pro-

blem of compensatory and adaptive processes, and hence, the problem of their disturbance or insufficiency (*i.e.*, decompensation) is the central task both in pathology and physiology" [9]. Many decades ago, the similar thoughts (although in somewhat different field) were reported by R. Virchow: "I would consider as obsolete to raise a question on general disease before so enlightened meeting. If somebody among those present still keeps in the intimate convolution of the brain some memory on universal diseases, then on a certain reflection he would immediately conclude, that any patient preserves a larger and even greater part of the normal healthy life, in which the diseased and even dead pieces are only parts of the integral body. It is impossible to discuss pathology in natural terms with those, who do not share this view. … During disease an organism retains more or less pronounced remainder of the healthy vital force. Namely this residual force produces "the reaction" and wages war against the "invader" [6].

Modern data obtained during the study of pathological processes at intracellular, tissue, organ, and system levels and assessed in the context of the integral organism, form the basis for wide generalizations necessitating a radical modernization of many conventional theories of the diseases. Of particular importance is the fact that these generalizations not only constitute a valuable theoretical constrains *per se*, but in their turn, they affect formation of so-called clinical reasoning of a student and improve the guidelines of diagnostic and therapeutic tactics of a practitioner.

One of the most important premises for the development of theoretical medicine is elucidation of the vast variety of structural and functional regulatory connections, which underlie existence of an organism as an integral system. These connections are characterized by an exclusive dynamism: they close and open persistently producing new combinations, which are adequate to the direction of the compensatory and adaptive reactions of an organism in a particular moment. Extremely complete pattern of these connections is the material basis of homeostasis under the varying environment. It explains the most important role of the nervous system as the major linking apparatus, which connects all parts of the body. In the past, the integrative role of this apparatus was overestimated and rather simplified, but nowadays there is a tendency to go to the opposite extreme and neglect it altogether. At present, at the boundary of centuries, the new vistas are open in this principal problem: **neuroimmunoendocrinology**, a novel integral science, is currently formed, which studies the interaction of basic regulatory systems controlling the most important physiological functions. This scientific branch seems to be very perspective in the study of pathogenic mechanisms of human diseases.

Generalization of modern data and further development of medical theory in general, and the theory of disease in particular is currently going on within the frame of the general pathology course, which combines the achievements of all other medical disciplines and, therefore, occupies some **supradisciplinary** position. Naturally, the laws and categories of materialistic dialectics form the ideological and methodological basis of this course.

The most important thing expected from medical science in 21st century is the **decisive step to strictly scientific and highly efficient etiotropic prophylactics and therapy**. This will be a principal new feature of 21st century medicine. Indeed, at present, the real progress of etiotropic therapy is observed only in the field of bacterial infection. By contrast, the overwhelming majority of most important somatic diseases are still treated on the basis of prevailing symptomatic or pathogenic, but not etiotropic therapy (chemotherapy of the tumors without precise knowledge on their origin; drug therapy of enhanced arterial pressure without theory of the trigger mechanisms of essential hypertension; replacement therapy during endocrine diseases; cardiac valve replacement during developing rheumatic process; coronary artery bypass during aggravating atherosclerosis, *etc*.). In this connection, it can be said that despite enormous progress in therapy, surgery, and other medical branches, the patients with severe pathologies are still treated more or less successfully, but reduced suffering and prolonged life do not culminate in the complete recovery.

On the eave of 21st century, we observe the principally new stage of medical development. While in the past we studied the essence of intimate biologic processes and started to interfere cautiously into their course with the desire to correct the disturbances, now and especially in the future, having revealed the basis of elementary pathologic mechanisms, the scientists will correct the pathologic processes more decisively, more scientifically substantiated, and, therefore, much more efficiently. Evidently, nowadays we enter the principally new period of the development of medical science, which is focused mostly on the molecular level of organization. In this way surgery, an ancient "reconstructive" branch of medicine, will achieve its logical completion.

In future work it will be no less important to clear off the above "debts" of the last century on the development of theoretical medicine. Therefore, if 21st century is supposed to be the period of the large-scale analysis, penetration to the origin of life, and directed control of the disturbed intimate biological processes, the success can be expected only in the case, when this

century will simultaneously be the period of great synthesis, comprehensive theoretical generalizations similar to those achieved in 19th century, which can be really termed as the epoch of medical renaissance. If the lag in synthesis will not shorten, numerous scientific efforts will yield only partial results: "… those who tries to solve the partial problems without preliminary elucidation of the general ones, will obligatorily and unintentionally "encounter" these general problems" [10]. A short and generalizing description of the mainstream of modern biology and medicine was formulated by K. M. Bykov: "After accumulation of enormous data on the action of individual organs and tissues, modern physiology approximates to solutions of two major problems: physiology of individual cells and physiology of the entire organism" [13]. This thesis should be the guideline for the progress in two intimately connected directions: study of local (tissue, cellular, and subcellular) changes and elucidation of structural and functional regulatory reactions of the entire organism.

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