

FROM PHYSIOLOGY OF DISEASE TO SYSTEMIC PATHOBIOLOGY: HISTORY AND CURRENT TRENDS IN PATHOPHYSIOLOGY

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SUMMARY

A paper describes the main events and periods in the history of Pathophysiology as a curriculum element and research area. The national schools of Pathophysiology in Russia, continental Europe, Asia and British-North American world are compared, their history discussed. The evolution of Pathophysiology towards Systemic Pathobiology, its crisis and perspectives are evaluated. The priority of Russian clinical and experimental researchers of late XIX century in foundation of Translational Medicine is supported. The necessity in combined programmes of Pathobiology for current education of medical researchers from biological and medical backgrounds is discussed. The experience of innovative teaching/learning of Pathophysiology at Saint Petersburg State University and Zagreb University is analyzed.

Key words: anatomic pathology - history of medicine - medical education – pathophysiology – pathology - systemic pathobiology - translational medicine

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Pathophysiology as a science and curriculum discipline stands in front of biggest challenge of its history. In genomic and post-genomic era it extended far beyond the constraining limits of its historical name and embedded many aspects of Pathochemistry, Immunopathology, Pathobiophysics and Pathoinformatics, intermingling with Translational Medicine. Similar process prevails in Anatomic Pathology, terminating the historical period of ramification between these two sisters branches of Pathology.

HOW TO INTEGRATE FACETS OF KNOWLEDGE INTO MORE COMPLETE VIEW OF THE NATURE OF DISEASE STATES

Teaching/learning of Pathology should be modernized in accordance with the needs of nowadays, under the bias of its integrative role for Medicine, analogous to that of Systems Biology among non-medical Life Sciences. “Omics” studies gave a possibility of concretization to many classical pathophysiological notions, like reactivity, constitutio corporis and others. Current Pathophysiology grew into clinics (via laboratory and functional diagnostic tests, which are in fact a sort of controlled clinical experiments). Thus, physicians of Functional Diagnosis, Clinical Immunology, Clinical Genetics and Clinical Biochemistry services, those of autopsy units – stand in fact very close to pathobiologists and should be re-named into clinical pathologists. This term is entirely applicable to all above-mentioned specialists, and not only to anatomic pathologists, as it is currently narrowed and thus misused in some countries (Orlov et al. 2011).

ISP-2006 Declaration (2006) adopted by Beijing Congress of the International Society for Pathophysiology

says: “Pathophysiological analysis, the integration of regulatory homeostasis and homeodynamics of body processes and the interconnectivity between them lays down a solid approach towards a comprehensive vision and a more complete understanding of the etiology and pathogenesis of disease. Emerging important biomedical principles bring together both clinical and preclinical knowledge and, directly guide students along the path of evidence based medicine. The rapid expansion of a scientific knowledge related to multiple facets of a complex pathobiological phenomenon increasingly enables a quantitative estimation of relevant processes within an integral body system”. Later the Shanghai Declaration of 2009 International Symposium on Pathophysiology Teaching, adopted by 2010 Montreal Congress of ISP (2010), stated that there is a “necessity to improve biomedical education concerning its scope, quality and quantity in the postgenomic era”.

Every diagnostician during a routine clinical work has to compose a conceptual model of disease in order to explain and combine data for comprehension of a case. But, such modeling is inherent to Pathophysiology; hence competence of diagnostician is based on it. This brings us back to the classical words written as early as in 1905 by one of the earliest pathophysiologicalists, an author of the first Russian textbook in this discipline, translated into European and Asian languages: Vladimir Valerianovich Podvysotskiy (1857–1913), who said (Podvysotskiy 1905): “Every special pathologist, that is, every practitioner, standing at the bedside of a patient, must necessarily be to some extent, also the general pathologist, unless he wants to be really useful to the patient, if he wishes to treat the disease not according the learned prescriptions, but individually each concrete patient ...” (Figure 1).



Figure 1. V. V. Podvysotskiy

Looking back into History, one feels that our branch of medical science is not very old. The term “pathologic physiology” was first coined in a book of 1617 by a Dean of Medical Faculty at Montpellier, Jean de Varanda (aka: Varandal, Johannes de Varandaeus, 1560–1617) (Figure 2). But, even earlier a genius French physician Jean-François Fernel (Fernelius) (1497–1558), a thinker immortalized in the history of science for his correct prophecy that: «Life is a week fire, burning without flame», also wrote in 1542 in his «De naturali parte medicinae» that «there must be special kind of Physiology for life of sick person». It is believed that first textbook in Pathophysiology appeared in Halle, in 1791-99 and was written by August Friedrich Hecker (1763–1811), later medical advisor of Prussian king. The same scientist has established the first periodical journal in the field (*Magazin für die pathologische Anatomie und Physiologie*. Altona, 1796) (Shubert 1989). Later constitution of Pathophysiology as an academic discipline was related to Louis Cailliot's two volumes of French monograph: “*Elémens de Pathologie generale et physiologie pathologique*” 1819.

Holistic approach to patient, disease and education is traditional for Russian Medicine. The very first departments of pathophysiological profile in Russia were combined and included Anatomic Pathology and introductive

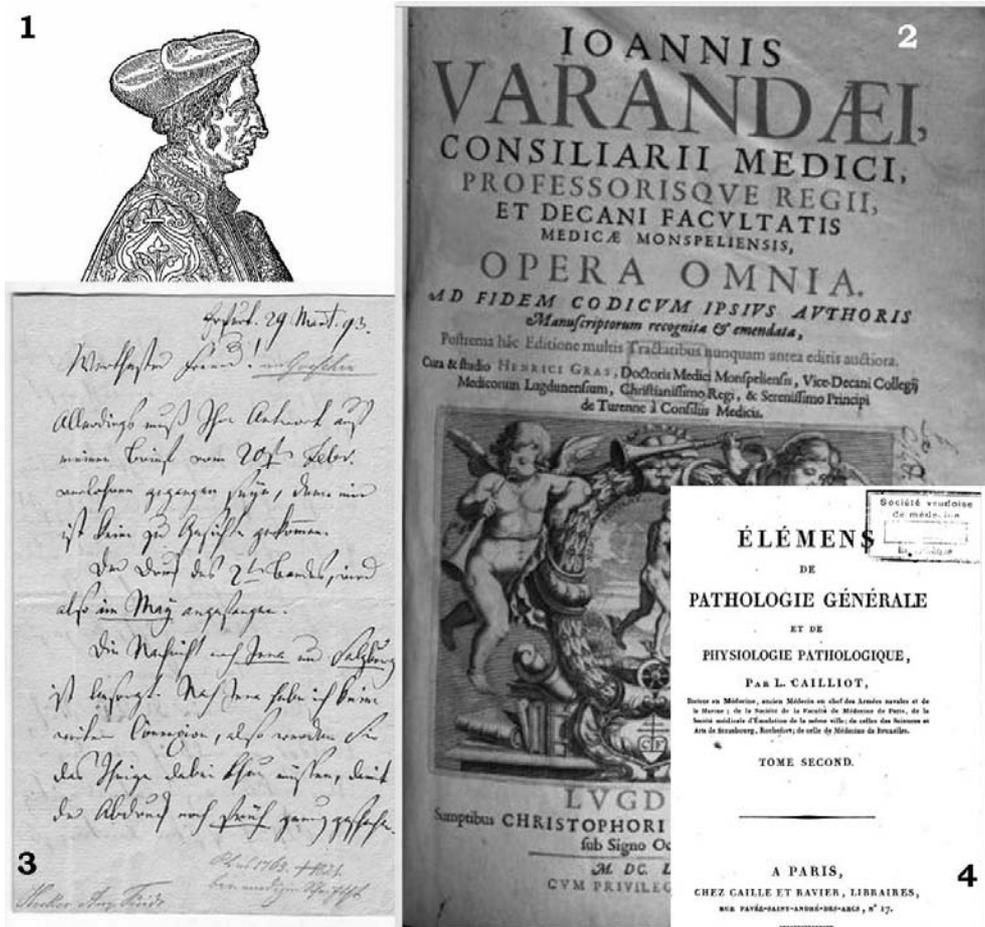


Figure 2. First steps to Pathophysiology. 1 – J. F. Fernel; 2 – book by J. de Varandal; 3 – hand script by A.F. Hecker dedicated to publishing of his book, 4 – title page of book by L. Cailliot

course of Clinical Medicine along with General Pathology and/or Pathophysiology. First domestic titled Doctor of Medicine (and foremost Russian pathologist, who has coined in Russian language the term “Pathologia” itself) was Thoma Ivanovich Barsuk-Moiseev (1768–1811), who taught Pathology at Moscow University (since 1796) within the Department of Internal Medicine. In 1804 his disciple Sergei Alexandrovich Nemirov (1772–1810) headed there new established Department of Pathology, Therapy and Clinics and published first domestic textbook in General Pathology (*Primae lineae pathologiae generalis*, Moscow, 1806). First course of Pathologic Physiology in our country was established in Kiev in 1845 by M.I. Kozlov at the joint Chair of Pathologic Physiology and Anatomic Pathology and later in 1849 by Alexei Ivanovich Polunin (1820–1888), also in Moscow University, within the “Department of Anatomic and General Pathology and Therapy” (Figure 3). Since 1869 Polunin - in Moscow and Nikanor Adamovich Hrzhonshevskiy (1836-1906) - in Kiev separated the General Pathology from the joint departments and established autonomous Chairs of General Pathology (first ones in the world) (Bataev 2001, Zaiko et al. 2015).

Later progress of Pathology (first department of “Allgemeine Pathologie”, first academic institute and first scholar journal in this field, established in 1846) is traditionally related to the name of Rudolf Ludwig Karl Virchow (1821–1902), commonly titled as “Father of Pathology”. But, do we always remember that the Father gave birth to twinned girls, not to a single child?

Indeed, he wrote in a paper of 1858 depicted on Figure 4: «Pathological Physiology never can be constructed on Anatomic Pathology. Pathological Physiology has only two pathways: clinical observations and

experiment. That’s why Pathological Physiology does not flow out of Anatomic Pathology... It is great autonomous and extremely important science... based on clinical facts and experiments”. And later: “Under this name we should mean the whole really scientific theoretical medicine, bearing in mind that theoretical does not mean hypothetical: it is sourced out of evidence, not out of voluntarism” (Virchow 1858). In fact, these words witness for Virchow’s broad understanding of Pathophysiology, beyond the narrow “Physiology of disease”, which definition is just confined to certain methods. Virchow not only gave birth to both branches of Pathology, but in fact also predicted their future “divorce” and possible pathway of current re-integration.

CONCEPTS AND VISIONS OF PATHOPHYSIOLOGY IN CONTINENTAL EUROPE

Pathology rooted in Morphology, because autopsy since the works by Antonio Benivieni (1443-1502) and microscopy in early XIX century revealed some loci and visible elements of disease. But this was not enough for comprehension of systemic disorders and anatomically invisible signal relations between body elements. Systemic approach promoted the involvement of Physiology and birth of Pathophysiology (Foucault 1963). On this way we shall mention the role of two French physicians (Figure 4). First was François Magendie (1783–1855), a founder of Experimental Physiology and author of foremost textbook in this field (1817). He developed experimental approach, later adopted by Pathophysiology and insisted that “Individuals are very different, even within limits of health” which preceded the doctrine of reactivity, crucial for Pathophysiology. Another one was François Joseph Victor Broussais (1772–1838), who first



Figure 3. Th. I. Barsuk-Moiseev (left) and A. I. Polunin

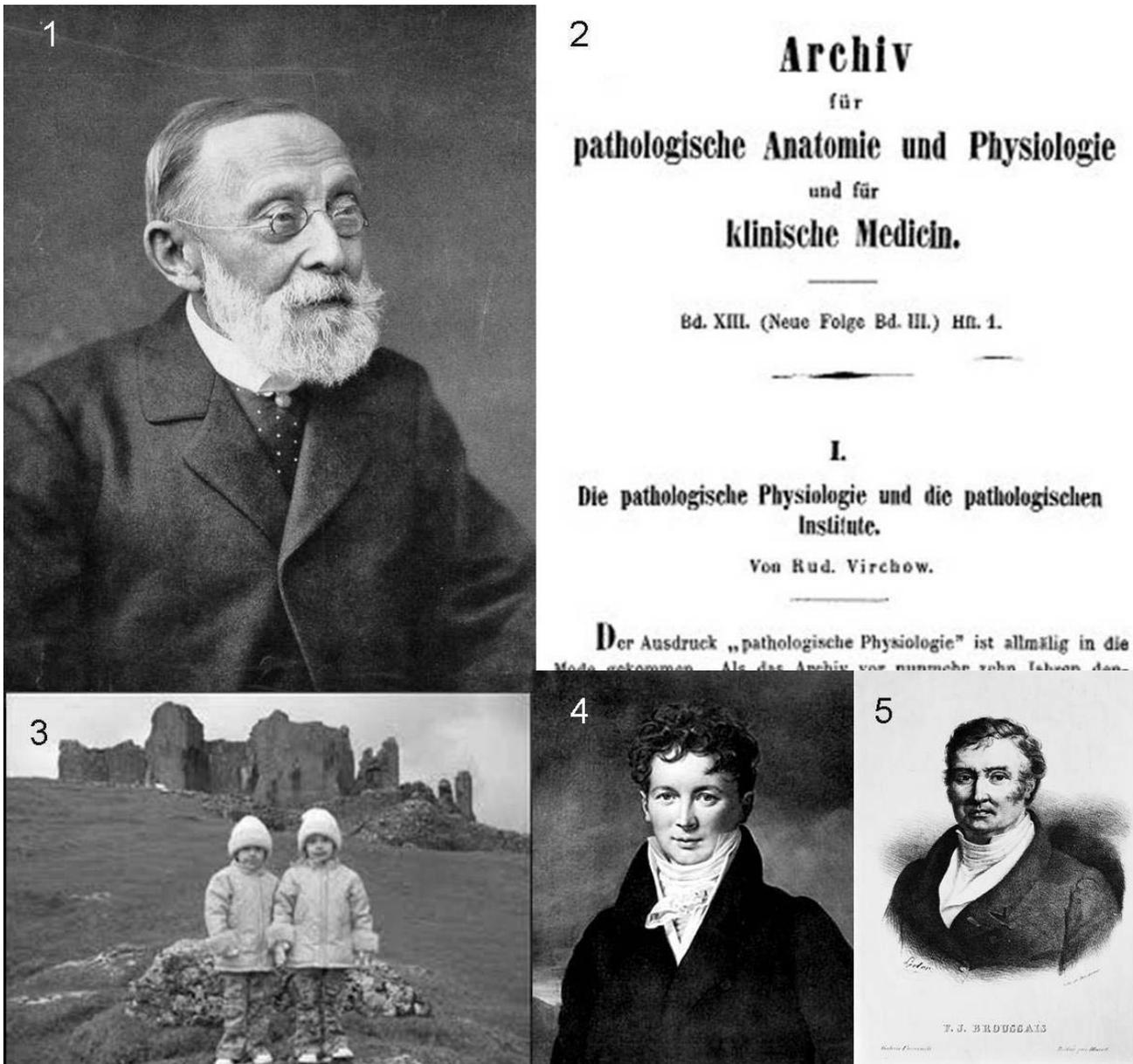


Figure 4. 1 – R. Virchow, 2 – title page of his article on interrelations between Pathologic Physiology and Anatomic Pathology (1858), 3 – his twinned “creatures”, 4 – F. Magendie, 5 – F.J.V. Broussais

guessed that local lesions via some signals may cause disorders on the distance from the foci of primary injury. In fact he understood that Anatomic Pathology can not describe some invisible (humoral) signals, coordinating the cell reactions in organism. This was a concept of the systemic action of “excitation, caused by local inflammation”, proclaimed in 1808 in his tractate “Histoire des phlegmasies chroniques.” Moreover, Broussais insisted that disease is not just a physiological life, disturbed by some pathogenic factor(s), but an autochthonous process, going on according its own laws. Having no thesaurus of Cybernetics and Informatics at his disposal (because these sciences did not yet exist), Broussais postulated, that not only local lesions may cause diseases, but also “non-local disorders of the organism’s Economy”. Those ideas were cornerstones of coming Pathophysiology (Churilov 2009).

R. Virchow expressed the whole atmosphere of the epoch in the following phrase: “If a pathological anatomist does not want to settle for his dead material, closed in simple spatial relations, he is left with no choice but to become at the same time a pathological physiologist” (Virchow 1858). And no surprise that it was his closest pupil, Julius Friedrich Cohnheim (1839–1884), who became first one in the West and developed biomicroscopy of alive experimental objects by the methods we still use in teaching course of Pathophysiology (Figure 5). His Department of Anatomic and General Pathology at Kiel (1868) was at least partially pathophysiological one.

Similar process in Austro-Hungary lead to creation of the Institute of General and Experimental Pathology in Vienna (1873), which was inspired by a strict opponent of R. Virchow, founder of “humoral Pathology” Karel von Rokitansky (1804–1878), who also understood that

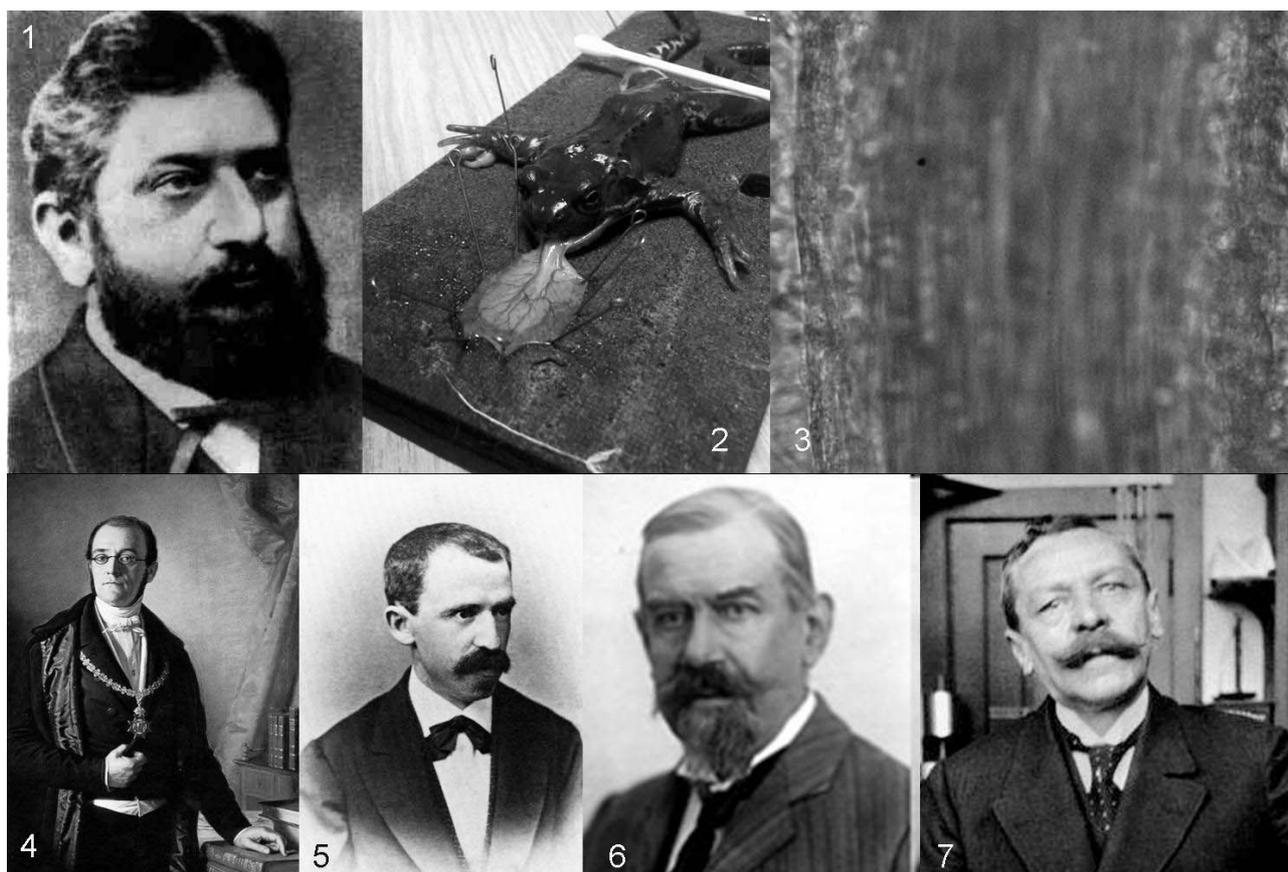


Figure 5. 1 – J.F. Cohnheim; 2 – his model of inflammation and 3 – margination of white blood cells observed in this model (2–3 images by V.J. Utekhin & L.P. Churilov); 4 – K. von Rokitansky; 5 – S. Stricker; 6 – R. Paltauf; 7 – A. Biedl

morphological findings are descriptive and insufficient for comprehension of the diseases, especially because of importance of chemical (humoral) communication of cells, undetectable by microscopes of that period. First director of this Institute, Salomon Stricker (1834–1898) realized the necessity of close collaboration between experimental pathologists and clinicians, which idea was too brave for many of his clinical colleagues (Peterlik 2004). Later this Institute due to efforts of Arthur Biedl (1869–1933) and Richard Paltauf (1858–1924) made next step and started research in the field of Pathochemistry (see below).

RUSSIAN SCHOOL OF THOUGHT AND CONTRIBUTION

Meanwhile, in Russia first pathophysiologicalist of the East, young (29 years old) Victor Vasil'evich Pashutin (1845–1901) created the first Department of General and Experimental Pathology (November 14th, 1874 in Kazan University) and 5 years later reproduced it in Military Medical Academy of Saint Petersburg. Pashutin's departments in Kazan and Saint Petersburg were in fact the first autonomous academic departments of Pathophysiology in the world. He published in 1878 famous two volume textbook "Lectures in General Pathology (Pathological Physiology)" (Pashutin 1878, 1881) – and later was a teacher of Ivan Petrovich Pavlov (Figure 6).

With such a teacher, it looked natural that the former, known worldwide as a physiologist, nevertheless emphasized that: "only in Pathology all real facets of living organism can be entirely displayed and comprehended" (Gorizontov 1952). It is easy to understand why I.P. Pavlov (1849–1936) supported the idea of organizational "divorce" between Anatomic Pathology and Pathological Physiology departments within Russian medical schools. Here is another fragment from his renowned letter of 31 January, 1934 to pathophysiologicalist Serguei Ionovich Chechulin (1894–1937): "Pathophysiology can not and should not be just a supplement to Anatomic Pathology. Nowadays it would be unforgivably anachronistic... We must remember that we had the honor to be the first who separated independent chair of Pathological Physiology from that of Anatomic Pathology – and with great success. And it would be strange if after increasing switching to this division abroad, for some reason we would return to the old-fashioned modus" (Perepiska 1970) (Figure 7).

For a long time the methodological options for bedside studies were scarce, so generations of physicians understood Pathophysiology as a science of lab and vivarium only, unlike Anatomic Pathology, which early integrated in clinics. This led to fornication between two sister branches of Pathology. Teaching of Pathology and clinical subjects separated.



Figure 6. V.V. Pashutin, the first department of Pathophysiology and Pashutin's textbook

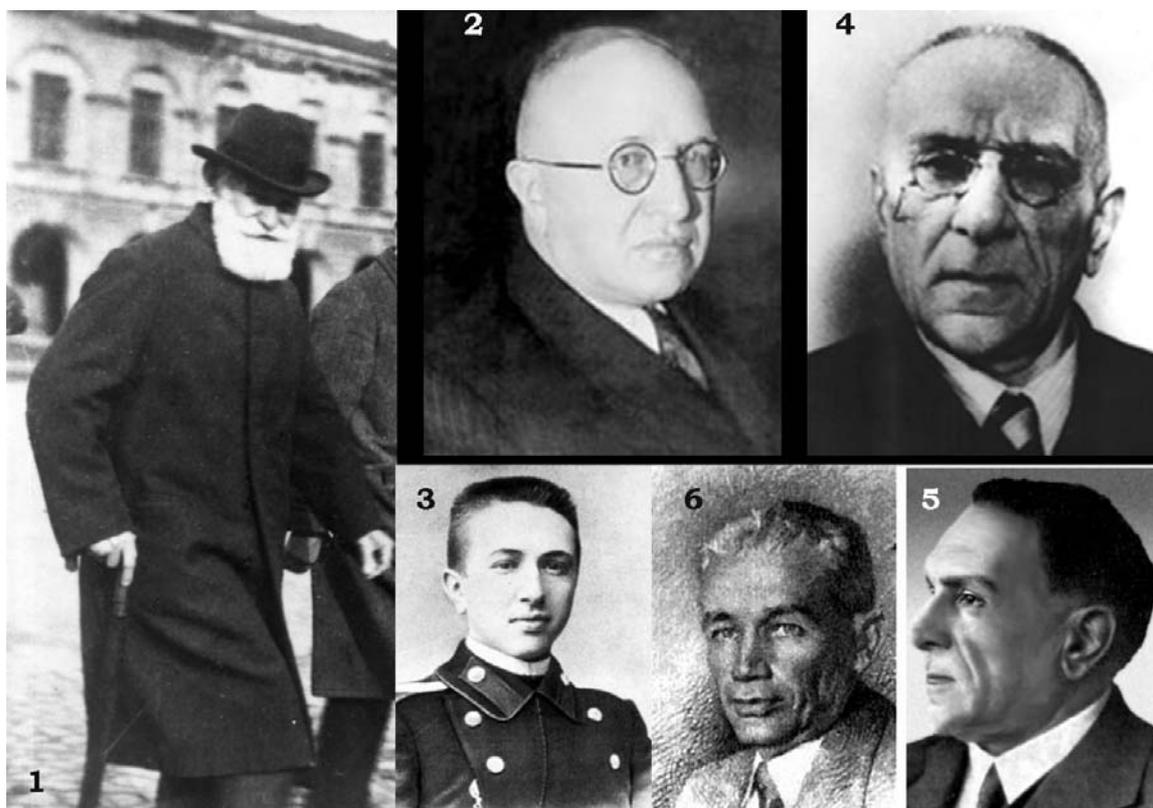


Figure 7. Initiators of separation between Anatomic Pathology and Pathophysiology departments in the USSR. 1 – I.P. Pavlov walking to give a lecture at Leningrad State University; 2–N.N. Anichkov; 3 – the same in youth; 4 – his co-author in cholesterol feed model of atherosclerosis, S.S. Khalatov; 5 – the same in youth; 6 – A.A. Bogomolets

In the USSR until the academic year 1924/25 two branches of Pathology in universities were taught within the frames of single departments (Churilov et al. 2004), but later some quite remarkable events occurred, worth to mention here.

It was a story of cooperation and separation of two brilliant pathologists, which finally catalyzed a divorce not only interpersonally, between them, but also between their fields of interests. These were Semyon Sergeevich Khalatov (1884-1951) and Nikolay Nikolaevich Anichkov (1885-1964). In 1912, when both were very young (Khalatov, earlier graduated from Saint Petersburg University, to that moment was a graduate student and Anichkov – postgraduate fellow of Saint Petersburg

Emperor's Military Medical Academy), their fruitful cooperation resulted in a historical breakthrough. On September 21st 1912 Khalatov reported the creation of first successful atherosclerosis model in cholesterol fed rabbits. This discovery immortalized their names, but their union was not long-living. Anichkov, who was mainly pathomorphologist and Khalatov, who was experimental pathophysiologicalist, disagreed in interpretations of their model as well as in subsequent theories of atherogenesis and even became academic opponents. Soon they headed departments of General Pathology at different medical schools (Anichkov – in Leningrad and Khalatov – in Moscow) (Churilov & Stroev 2012). In 1924 Khalatov and his energetic supporter, I.I. Mechni-

kov's and V.V. Podvysotskiy's disciple and discoverer of antibody-mediated stimulation of endocrine cells, eminent pathophysiologist Alexandr Alexandrovich Bogomolets (1881–1945) initiated re-nomination of the Department of General Pathology in Moscow into "Department of Pathologic Physiology". Few eminent pathomorphologists (including N.N. Anitchkov, A.I. Abrikosov, I.V. Davidovskiy) not only were against this proposal, but even insisted on the opposite: to cut down Pathophysiology course in order to broaden the teaching of Anatomic Pathology. Khalatov probably could step back, and the whole subsequent history of Pathology in our country may go the same way as in Western countries; with combined departments and long preponderance of Anatomic Pathology. But his allies, Bogomolets and Chechulin, involved strong helpers. One of them, of course, was a Nobel Prize winner I.P. Pavlov, whose considerations on this matter were cited above and influenced greatly on the opponents to the benefit of Pathophysiology (Gorizontov 1952). Another one was a friend and chief of Bogomolets at the newly established, first in the world Research Institute of Blood Transfusion (1926). It was experimental gerontologist and old Bol'shevik, Lenin's comrade-in-arms and philosophical opponent, physician by his education – Alexandr Alexandrovich Bogdanov (1873–1928). Bogdanov's experiments in blood transfusion were highly appreciated by Soviet government, because of their definite applied significance for battle medicine (later during World War II they supplied the USSR with the best blood transfusion service in the world). Bogomolets became a head of experimental department under Bogdanov at his Institute. Few years later, in 1928 Bogdanov dramatically perished as a result of risky self-experiments with blood exchange, but to the moment of discussion about future of Pathology teaching he was in zenith of his research activity and on the top of state recognition. Also Bogdanov was one of the world leading scientists in the field of systems approach, a pioneer of scientific management (Tyukin et al. 2010A, Tyukin et al. 2010B). His proto-cybernetic ideas influen-

ced Anatoliy Vasil'evich Lunacharskiy (1875–1933), People's Commissar of Education in Soviet government and Bogdanov's brother in law (since their common exile to Vologda in imperial times) (Figure 8).

Pathophysiologists Khalatov, G.P. Sakharov (1873–1953) and Bogomolets wrote a letter to Lunacharskiy with the motivated request to divide the Departments of Pathology on those of Anatomic Pathology and those of Pathophysiology in all Soviet universities. And government approved this proposal, beginning from the year 1926. After World War II this approach was adopted in many Eastern European and Asian countries, influenced by educational system of the USSR – and Departments of Pathophysiology were established in universities and medical schools on large territories – between Jena in DDR and Shanghai in PRC. A.A. Bogomolets became the leading Soviet pathophysiologist, he is considered to be main creator of Pathophysiology teaching system in our country. Bogomolets was a "root" of the most multi-branched school of domestic pathophysiologists. He published first pathophysiological textbook (1921) and foremost practicum (1937–1938) in the USSR. Also he developed original concept of somatotype based on the status of active mesenchyma. His original theory of ageing based on connective tissue wear made him one of the leading domestic gerontologists (Churilov & Stroev 2013). Pathophysiological departments, not only in the USSR, but in many universities of former socialist countries were founded by his disciples. For example, figure 9 shows Nikolay Nikiforovich Zaiko (1908–1991), who established first Department of Pathophysiology in Germany (Friedrich Schiller University, Jena, 1955) and Nikolay Aleksandrovich Feodorov (1904–1983), who initiated the first training program in Pathophysiology for medical teachers of China (1956). Hence, the local events in the field of Pathophysiology teaching had some global consequences, maybe because they took place in revolutionary period. The details of the History of Pathophysiology in our country can be found elsewhere (Piontkovski & Shilinis 1970).

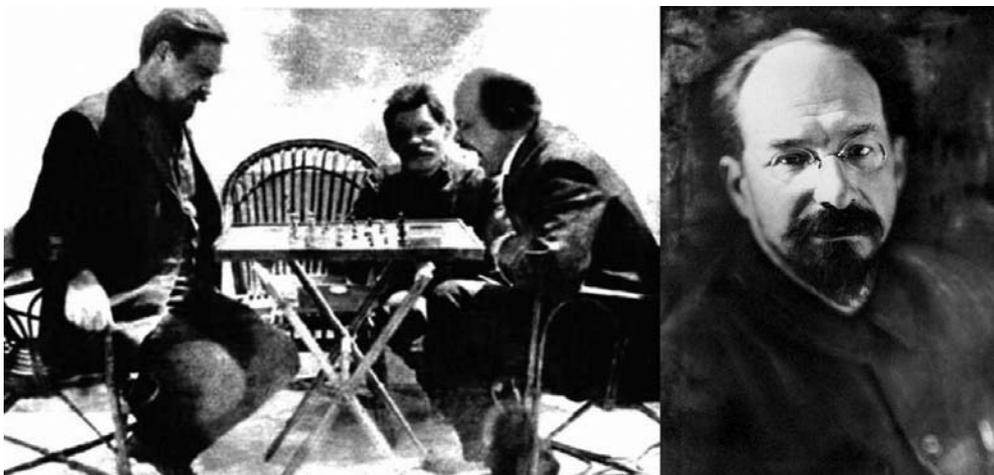


Figure 8. Some friends of Pathophysiology: left – A.A. Bogdanov (Malinovskiy) playing chess (white figures) against V.I. Lenin (Ulyanov) (blacks, just yawned – I hope, not a queen!). famous writer A.M. Gorky (Peshkov) is sitting between players; right – A.V. Lunacharskiy (Antonov) in 1920



Figure 9. Bogomolets' pupils – originators of Pathophysiology teaching abroad. Left: N.N. Zaiko; middle – group of first Chinese pathophysiologists with their teacher N.A. Feodorov (arrow); right – N.A. Feodorov

TWO SISTERS: PATHOMORPHOLOGY VERSUS PATHOPHYSIOLOGY

Pathophysiologist and Anatomic Pathologist are, of course, brothers in reasoning mind. Although their tasks both in clinics and in labs are different, symbiosis of them constitutes a field of Pathology. It is a basis for clinical reasoning and a bridge between scientific and clinical approaches. In the beginning of XX century delineation of Pathophysiology was a hot topic for Biomedicine. But it does not mean that separation of these branches is eternal or always would be beneficial for medical teaching and biomedical research, although their tasks and methods still differ in clinics and in research as well. Methodological progress of the last decades made it possible profound investigation of living person in clinics with minimal invasiveness. Current achievements of Pathochemistry, Medical Genetics, Immunopathology, Bioinformatics, Biophysics and “Omics”– made it possible both for Pathophysiology and Anatomic Pathology spread far beyond the limitations of their historically given names, and intermingle in medical education and research (Figure 10).

The British system of medical education always was distinct from continental one. The thesaurus of British-born medical doctors and their continental colleagues never was identical. The phenomenon which is called “white thrombus” on continental side of English Channel is at the same time called “platelet plug” in Britain and all its former colonies, including USA. It does not mean that medical doctors living on particular shore of the sea are more (or less) sophisticated. But it means difference in their thesaurus and their traditions. And this situation caused some impact on development of Pathophysiology also. Outside of continental Europe and Asia, where influence of German, French and later – Soviet approaches in medical education made the term “Pathophysiology” common for all medical and veterinary specialists, this term never was as popular in medical community as in Eurasia. Of course, there were brilliant experimental and clinical pathologists, which in fact could be called “pathophysiologists”. For example, in North America these were: Silas Weir Mitchell (1829–1914), who obtai



Figure 10. The famous sculpture by Vera I. Mukhina “Worker and Collective Farm Girl” (1935-1937) as a symbol of Pathophysiology and Anatomic Pathology intermingled

ned first experimental model of diabetic cataract as early as in 1860; William Osler (1849–1919), who reformatted medical education in North America according European schedules and was a pioneer of Clinical Pathology; and, of course, direct pupil of R. Virchow and J.F. Cohnheim – Willoughby Dayton Miller (1853–1907), who was globally the first experimental pathophysiologist in Dental Medicine and discovered causes

and conditions of cavities (Churilov et al. 2010). But, no one of them self-named as “pathophysiologist”, unlike did their Eurasian colleagues and contemporaries involved in Experimental Pathology.

It seems to be minor and insignificant thing: a name. «What's in a name? that which we call a rose by any other name would smell as sweet...». But, as it was stated by Shakespeare's Juliet, a name is of great importance! For many decades all departments of Pathology in medical schools of North America were predominantly or exclusively pathomorphological. The tasks and mission of Pathophysiology were distributed between them and departments of Physiology, Biochemistry etc. Such a system did not stay any space for Pathophysiology as autonomous discipline. W.D. Miller, mentioned above, is commemorated with a bronze monument in USA, but still is characterized in American texts as an “oral microbiologist”, although he studied not only etiological agents, but also roles of conditions and reactivity in mechanisms of cavities and did it experimentally. This “tyranny of methods” caused much later coming of Pathophysiology into American medical schools, compared to Eurasian ones. For example, in Harvard course of Pathophysiology was first established as late as in XXI century (Shields et al. 2004). After world wars of last century and social cataclysms occurred in Europe and Asia after these wars a great number of medical doctors, educated in Old World, migrated across the oceans. Of course, they brought into North America some elements of their thesaurus and scope of ideas, including appreciation of Pathophysiology in Virchow's and Pavlov's spirit as a “great autonomous and extremely important science”, which “never can be just a supplement to Anatomic Pathology” (see above).

First person in American medical teaching tradition, who appreciated this, was, probably, Stanley Leonard Robbins (1915–2003); whose centennial

jubilee was celebrated recently (Kumar 2004). This most influential teacher of Pathology stated: “Lesions do not arise in cadavers!” (1957) and later: “But the study of Morphology is only one facet of Pathology. Pathology contributes much to Clinical Medicine. The pathologist is interested not only in the recognition of structural alterations, but also in their significance, i.e., the effects of these changes on cellular and tissue function and ultimately the effect of these changes on the patient. It is not a discipline isolated from the living patient, but rather a basic approach to a better understanding of disease and therefore a foundation of sound clinical medicine”. Although he was criticized for the lack of descriptive Pathomorphology in his books by those colleagues, who were constrained with old understanding of Pathology as Pathomorphology only, Robbins changed (since 4th edition of 1974) even the name of his textbook from “Pathology” to “Pathologic Basis of Disease”, which was definite step into field of Pathophysiology. This approach was traditional for continental Europe and for historically non-British part of Asia as well, but still awkward for North America (Figure 11).

Interestingly, in Europe the neutral non-aligned state of Austria, which stood very close to early recognition of Pathophysiology autonomy (see above), hesitated to change the name of a branch until late 90ies: Adolf Lindner from Institute of General and Experimental Pathology invented the term “Functional Pathology” and insisted on introduction of such a subject into mandatory part of national M.D. curricula (1980). In 1999 the Institute of General and Experimental Pathology was renamed into Institute of Pathophysiology with the idea that “the name to be understood throughout the world and to reflect the fact that departmental research and teaching activities represent a specific discipline in the field of biomedical science” (Peterlik 2004).

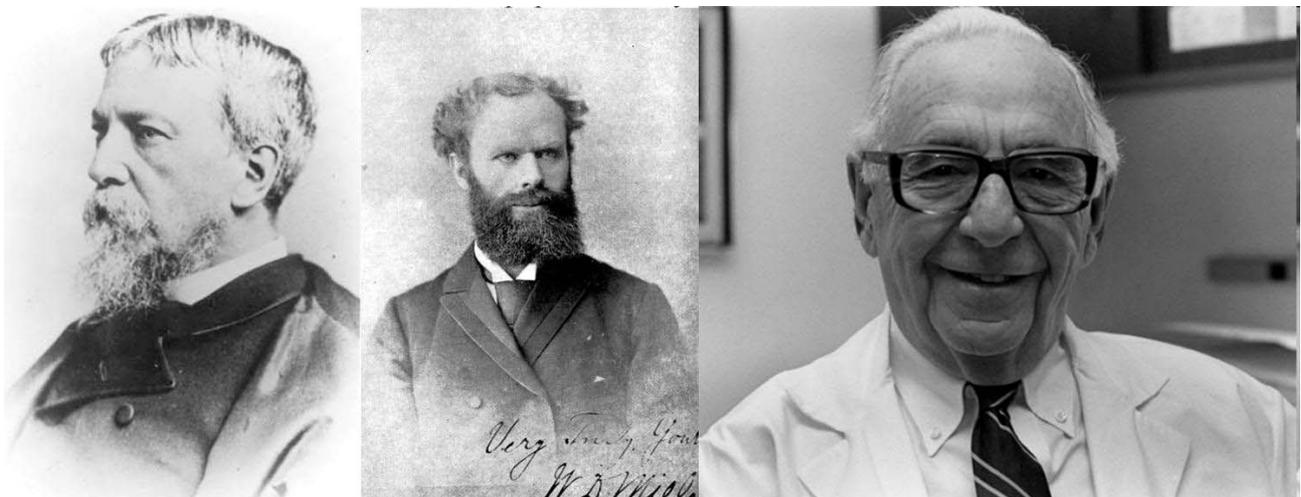


Figure 11. The roots of Pathophysiology in North America left to right: S.W. Mitchell, W.D. Miller and his autograph, S.L. Robbins

NORTH AMERICAN CONCEPTS AND NEW METHODOLOGIES

On course, de facto North America through all XX century was in vanguard of experimental studies of the causes and mechanisms of diseases, although the research of this kind never was called in local medical community “pathophysiological” one.

And when in late XX age research scientists of USA, not accustomed on university bench to the word “Pathophysiology”, finally decided that an area of clinically significant research, based on holistic ideas taken from Clinical Medicine and on molecular/cellular technologies taken from natural science need special designation, they invented for this branch a new name: Translational Medicine (1990).

In fact, Translational Medicine is nothing else, but Clinical Pathophysiology armed with modern cellular and molecular methods. One of the first representatives of Translational Medicine de facto was Sergey Petrovich Botkin (1832–1889), and it happened as early as in second half of XIX century. In 1860 he organized at Military Medical Academy a clinical and experimental physiological and biochemical laboratory, methodologically stood on the top of Physical and Chemical Biology of that time and oriented on systematic studies in Clinical Pharmacology and Experimental Therapy with bidirectional bench-to-bedside flow of ideas and methods. Many pathophysiologists and physiologists, including I.P. Pavlov and S.M. Lukyanov (see below) went through it. S.P. Botkin, known for his aphorism: “Treat a patient, not disease”, can be also regarded as a pioneer of Personalized Medicine, although this term, since it recently came in fashion, also seems to be new one. Hence, terminological innovations which came into medical thesaurus from USA in the end of XX century represent a kind of “old wine in new wineskins” for the medical communities having long pathophysiological tradition.

Even in the period when majority of pathophysiologists thought about autonomy of their discipline, as an

important step into nearest future, there were also most profoundly thinking scientists, who already prophesized the step coming after next one, in remote future of Pathophysiology. In Germany it was Bernhardt Naunyn (1839–1925), whose school of experimental Pathophysiology (at Königsberg and later at Strasbourg) worked with biochemical methods and on metabolic problems. This person and his brightest pupil, Oskar Minkowski (1858–1931) were able to foresee that the future of Pathophysiology is in the field of biochemical and genetic methods (by the way, Naunyn authored genetic concept of diabetes mellitus and Minkowski created its first experimental model) (Utekhin et al. 2013). In Russia a Botkin’s disciple Sergei Mikhailovich Lukyanov (1855–1935) at Warsaw University proclaimed that “behind morphological structure always is lurking physical and chemical structure”, thus he centered the experimental studies of his General Pathology Department in metabolic and cytological fields and stated future confluence of Pathophysiology and Pathomorphology on chemical background (Churilov 2015). It was not surprising, that Russian and Polish pathophysiological Vladimir Karlovich Lindeman (1868–1933), earlier related in his pathophysiological career both to Naunyn’s and to Lukyanov’s schools, wrote in 1911–1915 that in his opinion Pathophysiology in future will absorb Biochemistry of diseases, transforming into Pathochemistry (Figure 12) (Churilov 2015). Of course, Austro-Hungarians R. Paltauf and A. Biedl, mentioned above, were among precursors of Pathochemistry also.

Many years after them, in a new century again one may ask: what is Pathophysiology nowadays (Orlov et al. 2011)? Of course, it is no longer just “physiology of disease”. Modern Pathophysiology spreads far beyond the limits of its original name. It is integrated not around certain (for example, physiological) methods, but around a key concept. The central concept in pathophysiological education in our understanding is a primary pre-programmed imperfection and pathogenic potential of protective mechanisms themselves. Because the genetic knowledge of our body is imperfect and incomplete, a

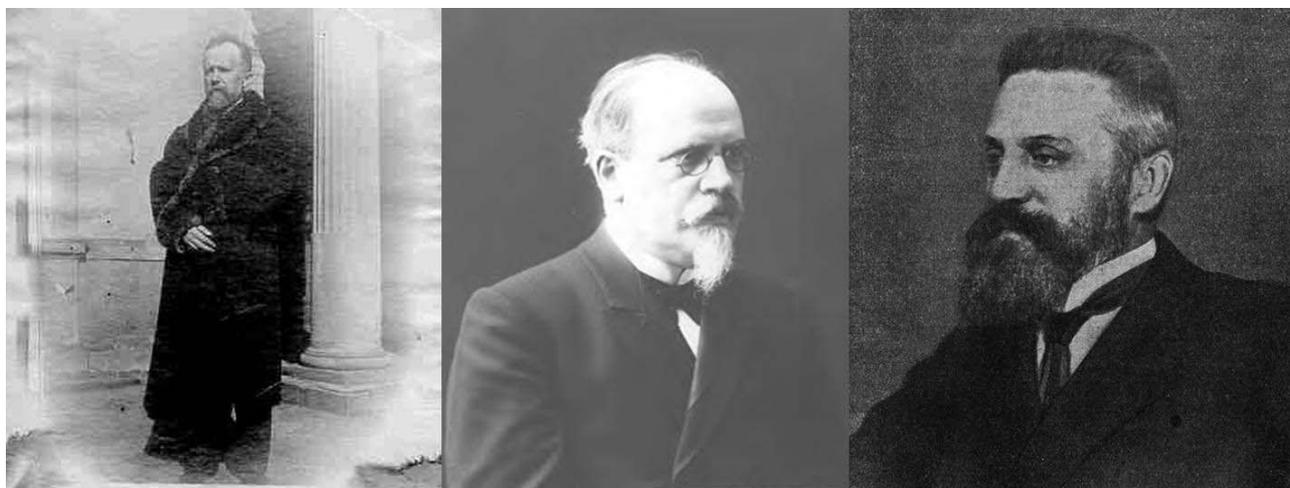


Figure 12. First precursors of Pathochemistry, left to right: B. Naunyn, S.M. Lukyanov, V.K. Lindeman

patient may suffer from imperfect defense not less, but more, than from primary injury. Pathophysiology, when it is understood as a doctrine of body imperfection, implants reasonable pessimism in learning mind of a medical student and physician (Churilov 2015).

The main idea of our science in fact was brightly expressed by most eminent pathophysiologist of XX century (one of those who transferred European custom of Pathophysiology across the ocean): Hans Hugo Bruno Selye (1907–1982): “On the contrary to common opinion, the Nature does not always act in an optimal way. Neither on cellular, nor on interpersonal levels we do not always know: what is worth to fight for...” (Selye 1960) (Figure 13).

Whatever organ or system a pathophysiologist will regard and whatever mechanisms of disease are studied – everywhere one can see that there is no “kind uncle” inside the body, moreover – the same “uncle” maybe both friend and foe in different situations or even at the same time, but for various parts of an organism. It is not enough to recognize that disease elicits defensive reactions which can cause secondary harm for self (which is known as autopathokinesis principle). More subtle but not less important aspect is that often both defensive effect and self-alteration are brought in by the same program or caused by identical mechanism. A bright example is hypoferremia in fever, which is definitely essential for defensive effect of fever on antimicrobial immunity, but at the same time harmful for erythropoiesis. Hence, because every defense has a price, the same manifestation of a compensatory reaction may be preferentially useful or preferentially vicious under different situations or in relation to various organs. It may result in great difficulty for a physician, who shall evaluate similar symptoms in different ways and either support, or suppress the same mechanism in various cases. A good example is dyspnoea, which can be sanogenic and medically supported in croup, but pathogenic and medically suppressed in lung edema (Churilov 2015).

Integrative role of Pathophysiology in Medicine, in our opinion, is analogous to that of Systemic Biology among non-medical life sciences. Systemic Biologist does not know Zoology better than zoologists or Genetics more profoundly than the specialists in this field. But he shall be aware enough in these and many other concrete branches of Biology for making valuable interdisciplinary ideas, concepts and experiments. Modern Pathophysiologist has to be a Systemic Pathobiologist (Orlov et al. 2004)

The subject of Pathophysiology can be defined on different principles, which was done previously by many authors (Piontkovskii & Shilinis 1970). We feel it necessary to point that Pathophysiology in fact is first of a science studying technical faults and technological defects inherent to living systems. Functional and molecular consequences of the body’s technological imperfection constitute the matter of Pathophysiology, regardless of physiological, biochemical, biophysical,



Figure 13. H.H.B. Selye in Moscow, in deep thoughts under I.P.Pavlov’s portrait (1961)

immunological or genetic methods used by scientists for their explore (Churilov 2015). In normal Physiology one primarily deals with adaptation, but in Pathophysiology – with the costs of adaptation (Figure 14).

At the same time, everything, which deals with etiology, pathogenesis and/or models of typical pathological processes and diseases, belongs to sphere of Pathophysiology. That’s why modern teaching of Pathophysiology should emphasize its core position within Pathobiology - as that of Systemic Pathobiology. In this entity Pathophysiology intermingles with Pathochemistry, Immunopathology, Clinical Genetics, Pathomorphology and other concrete facets of Pathology. In outer circle of this system there are Clinical Disciplines (Figure 15).

Moreover, the substances in metabolism are not only bricks or fuel by their roles, but signals or better to say messages as well. A cell has its own natural Informatics, created by evolution. Any pathological process is dualistic: it has not only substantial-energetic side, but also informational one (Churilov 2009). And who must teach Pathocybernetics and Pathoinformatics? There are no such departments or disciplines in structures and curricula of world medical schools. It means that Pathoinformatics is also a facet of Pathophysiology nowadays (Figure 16).

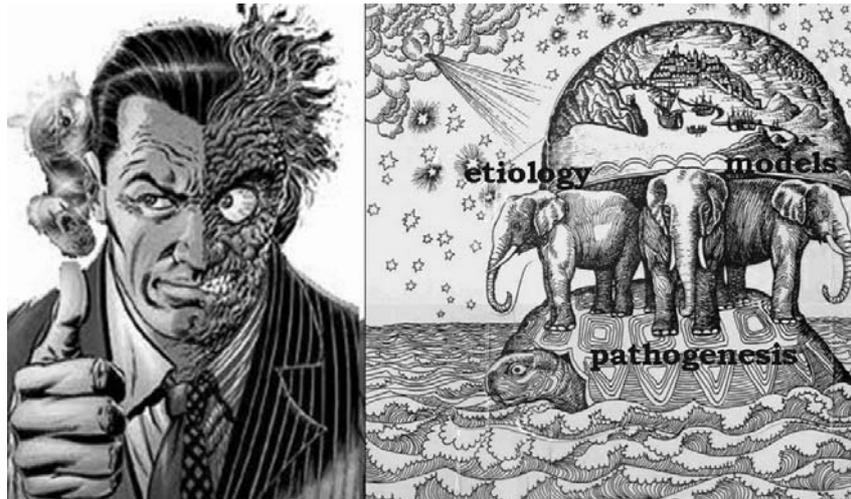


Figure 14. Left: Pathophysiology as a doctrine, insisting that inside the organism every Dr. Jekyll is also Mr. Hyde at the same time. Right: etiology, pathogenesis and models – three elephants, discriminating pathophysiological items from non-pathophysiological ones

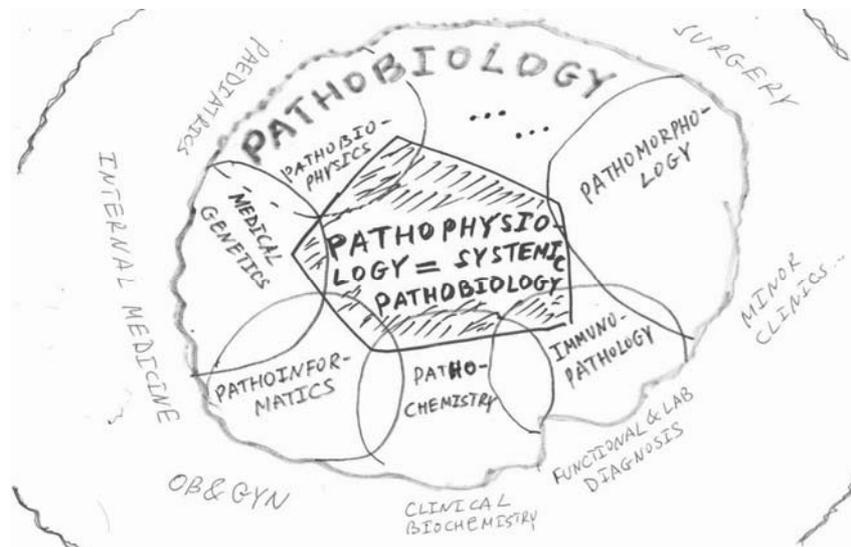


Figure 15. Ptolemaic heliocentric system of medical knowledge or “Every heron bird praises its own bog...”

CURRICULAR POSITIONING AND CONDITIONING FOR TRANSLATIONAL MEDICINE

Existing curricula of M.D. programs in many countries are five or six years long, they usually start with basic courses followed by clinical ones. So, students are in need to study the two different frames of references, the scientific and the clinical ones. But, medical professional way of reasoning and scientific way of reasoning in experimental science – are not identical, otherwise biomedical scholars could treat patients instead of medical practitioners, which is not the case nowhere in the world. The scientific system of reasoning is error-prone, based on controlled experiment, it is time unlimited, and not driven by the benefit of object. As a result, it has a high degree of experimental freedom. A scholar is bad one if he does not mistakes or if he is afraid to be wrong, because chain of intentional tests and mistakes is a normal course of experimental work for any naturalist.

In academic fundamental science the true is more important than a benefit (you can even destroy an atom in order to reveal its real structure). Alfred Bernhard Nobel (1833–1896) noticed the positive effect of nitroglycerine on his angina pectoris (and documented it in his letter to his brother Ludwig), but finally invented an explosive, not anti-ischaemic drug.

In fundamental science thinker always has enough time to reveal the true. You will search for as long as you need, finally your pupils will finish, if not yourself.

The clinical reasoning tends to avoid risk and mistakes, it is time constrained within the natural course of diseases, and driven by the patient’s benefit, not by the desire of scientist to rich the ultimate truth. The duration of search and thinking is limited with the natural course of a case. Patient’s benefit in clinics is prior to truth. Investigation of the organism is limited with the necessity to spare patient and his/her interests. As a result, physician almost always has to start action having no complete information about the case (and principally having

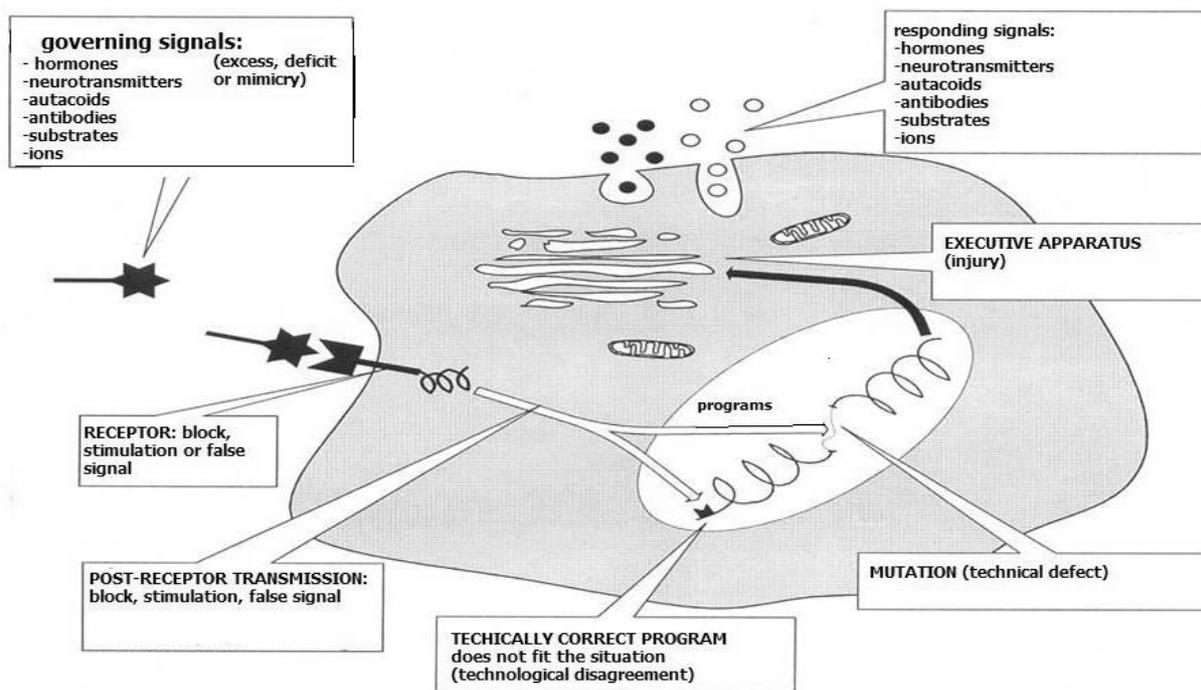


Figure 16. Pathoinformatics of the organism. Cells are programmed systems, giving the responses within the limits of their libraries of programmed stereotypes. Lack, excess and mimicry of signals, as well as disorders of reception, post-receptor transmission, technical defects and technological inconsistency of programs and faults of their execution may cause diseases



Figure 17. Left and middle: Gnosological dilemma of “kind doctor” (from “Soyuzmultfilm” cartoon) versus “crazy scholar” (from Hollywood movie). Right: doctor N.Ya. Chistovich (sitting left) and scholar I.I. Mechnikov

incomplete knowledge of drug and disease itself). That is exactly what Hippocrates meant under his famous words: “Vita brevis, ars longa, occasio praeceps, experimentum periculosum, iudicium difficile” (Hippocrates 1868).

Hence, clinical reasoning operates within very narrow frame of research freedom, tends to minimize the risk of mistake (“Primum non nocere”). But, although doctor’s reasoning is not precise, it is ethically enriched in comparison with reasoning of an academic scholar (Churilov et al. 2008).

The difference and even contradiction of scientific and clinical reasoning was first noted by an outstanding Russian internist Nikolay Yakovlevich Chistovich (1860–1926) in his “Clinical lectures” of 1918 (Figure 17) (Christovich 1918). Chistovich came to this idea

after discussions with great pathophysiologist, Associate Professor of Saint Petersburg University Ilya Il’ich Mechnikov (1845–1916), who was not medical doctor, but evolutionary biologist by his education.

These are challenges and important regulatory forces for medical students and physicians. In current situation, with rapid progress of fundamental natural science and under the pressure of humanitarian and judicial fighters for patient’s rights – this discrepancy between academic scholarly logics and logics of applied practical medicine is getting more and more obvious with every year. Trevor G. Marshall in his recent article entitled “The science of safety” - is it realistic to expect medicine to change to a science-base from its evidence-base?” wrote about real danger of the interpretation of evidence-based

medicine as a medicine of authoritative stereotypes, warning that this may close any possibility of creation and experiment for Clinical Medicine and retard its progress (Marshall 2013).

In view of this challenge we interpret the role of modern Pathophysiology as bridging scientific and clinical modes of reasoning. It stands in the middle of M.D. programs in order to achieve a compromise between scientific and clinical reasoning after years of basic and before years of clinical studies. Sometimes it seems that common sense plus knowledge in fundamental science is enough to start clinical studies. In reality clinical reasoning of medical doctor never can be constructed on the base of common sense. Common sense tells the doctor that thick membrane should be less permeable, than thin one, but Pathophysiology insists on the opposite: in glomerulonephritis thickening of glomerular membrane results in paradoxical proteinuria due to loss of repelling effect. Indeed, many medical doctors will agree with a physicist Stephen William Hawking, who said: "But common sense is just another name for the prejudices that we have been brought up with" (Hawking 2015). As we already mentioned, Pathophysiology in our understanding is a part of medical curriculum, putting reasonable pessimism into doctor's mind. And the necessity of this pessimism is clear, if you will think about incomplete knowledge about a disease, about an individual, or about a drug – versus complete responsibility of a medical professional acting in strict time limits (see above). Do you prefer to be treated by an optimistic doctor, who does not care of worst possibility, or by a pessimistic one, who is aware of worst variants and is ready for the worst in advance?

PATHOPHYSIOLOGY AT THE SAINT PETERSBURG STATE UNIVERSITY

To respond on current challenges posed in front of Pathophysiology, the teaching of our discipline definitely needs modernization.

On January 28th, 1724 Senate of Russian Empire adopted Tsar's edict, prepared by personal physician of Peter the Great, Dr. L.L. Blumentrost (1692–1775), about the foundation of the first classical university in Russia: "... two buildings: University and the Academy are being built for Arts and Sciences. There will be 4 faculties to create in the University: 1 – Theology, 2 – Law, 3 – Medicine, 4 – Philosophy..." (Tishkin 2001).

Tsar Peter I made only one correction of the text: he omitted Theology with a note: "Theology – to Synod!" However, in Russia sometimes even royal edicts wait long for their realization: and Faculty of Medicine was founded in Saint Petersburg State University in 1995, 270 years after proclamation of Emperor's will. It was done by eminent Russian physiologist and pathophysiological, academician Yuri Victorovich Natochin (Figure 18).

Department of Pathology with 3 courses of Pathophysiology, Anatomic Pathology and Forensic Medicine was established at Medical Faculty in 1997 (Markov 2012).

We understand our mission in teaching Pathophysiology as a prerequisite of Translational Medicine in order to establish full possibilities for clinical training of our students and provide for them broadened options of research activity. The main trends of our development in last 20 years were reintegration of two branches of Pathology with clinical disciplines (Figure 19); innovative teaching technologies with elements of project-oriented learning; protection of classical course of real teaching experiments with animals and classical heritage of General Pathology. Of course, we have large library of computer teaching programs and movies. But, in our opinion, computer cartoons can not substitute real handwork of student's team during the experiments on small laboratory animals. In fact interactive teaching is a mode including "third system", besides teacher and student. Such system must be autonomous and hardly predictable in its behavior. Computer program is much simpler variant of "third system" in interactive teaching/learning of Medicine, compared to cadaver for real manual dissection, experimental animal for Pathophysiology or living patient – for Clinics. If teacher wants to provide conditions for formation of real medical doctors, it is not enough to use simplified computer imitations. Nothing can substitute real risk, real stress and real unpredictability of non-virtual teaching experiments. "Experimentophobia", which appeared in medical education of some countries under the flag of humanism, is emphatically detrimental for modern teaching, because it may finally lead to (and already leads to) mass production of "virtual" physicians, able to play some formal role, fill in official forms, pronounce clever words, but not able to perform real actions for the benefit of patient in actual, stressful and volatile situations (Churilov et al. 2008). In the XIX century founder of the Russian system of medical education great surgeon Nikolay Ivanovich Pirogov (1810–1881) ridiculed those professors who, instead of involvement of real patients, demonstrated the technique of amputations slicing the turnips (Balakhonov et al. 2011). Computer game looks very innovative, but principally it is no better than turnip slicing, if compared to work with real living objects.

In the USSR and later in Russia there were different approaches to the problem of integrated interdisciplinary teaching at medical school. Some schools (at Moscow, Novosibirsk and Kaunas) had not always positive experience with attempts to train physician-biochemist, physician-cybernetist or physician-biophysicist with limited clinical training and narrowed perspectives of employment (to non-clinical units only) (Churilov et al. 2014). Sometimes "integration" between Pathophysiology and Anatomic Pathology proceeded on the basis of the administrative principle of "who is more important – that's right". In fact it manifested in engulfment of one discipline by another, a subject taught by professor standing higher in a local administrative hierarchy of certain school always prevailed, and another one was ousted out into postgraduate curricula or squeezed within limited academic credits.



Figure 18. Left: founders of Saint Petersburg University: Peter I (top) and Laurentiy Laurentievich Blumentrost (bottom). Middle: acad. Y.V. Natochin, who realized an idea of Medical Faculty creation. Right: main building of Medical Faculty



Figure 19. Wrong and right way of interdisciplinary integration

In our opinion, right way of integration between Pathophysiology and Anatomic Pathology is via absolute equality and involvement of a third part (Figure 19), which is Clinician. In our department an experienced clinical physician is employed as Professor of Clinical Pathology. He takes part in teaching together with pathologists. Good old lab classes in Pathophysiology with teaching experiments on laboratory animals are combined to early start of Clinical Pathology (in 5th term), with case history analysis and even lectures co-delivered (half by half) by both pathologist and clinician with demonstrations of real patients and discussion of cases by clinician, pathologist and audience.

With these ideas in mind, course of Pathophysiology was re-formulated in our innovative teaching complex.

We published three volume textbook of Pathophysiology (Figure 20) with non-traditional division of the course into General Pathophysiology with fundamentals of Immunopathology which is devoted to typical pathological processes (Churilov 2015), Pathochemistry which is broadened course of Pathophysiology of Endocrine and Metabolic Disorders with clinical correlations (Zaichik & Churilov 2007) and, finally Mechanisms of Diseases Development which is pathophysiological basis of concrete clinical disciplines – Hematology, Oncology, Cardiology, Pulmonology etc. (Zaichik & Churilov 2005).

Our teaching complex “Pathophysiology”, suggested to students, includes also Practicum in Experimental Pathology - a guide for labs and teaching experiments with correlations from laboratory and functional diagnosis,

TEACHING COMPLEX "PATHOPHYSIOLOGY"
by A.Sh. Zaichik & L.P. Churilov

has been recommended by Russian Health Ministry for medical schools of Russian Federation It consists of 3 volumed textbook:
vol. 1: General Pathophysiology
vol. 2: Pathochemistry
vol. 3: Mechanisms of Diseases and Syndromes
Practicum "Introduction into Experimental Pathology"
Electronic CD "Immunology & Immunopathology"

- Pathophysiology as a science of human body imperfection
- Systemic review of technological faults and technical mistakes of the organism
- Human Reactivity as core meaning of the whole course
- Forest, not just trees – history of ideas prevails over list of facts
- Interdisciplinary approach with links to other basic & clinical sciences
- Not only disorders of cellular Physiology and Biochemistry, but also disorders of cellular Informatics reviewed

Theory

Clinics

Figure 20. Left: teaching complex "Pathophysiology", right: principle of continuous teaching of Pathophysiology through entire medical curriculum. Sidebar below shows combined lecture delivered together by pathologist and clinician

electronic compact discs with interactive teaching and testing programs in Immunology and Immunopathology ("Immunology Live") and Neuromorphology/Neuropathology ("Professor Virchow's Castle" – in genre of a quest game). Also it includes a Supplement for Students of Dental Medicine ("Mechanisms of Stomatological Diseases") and a set of 24 multidisciplinary colored teaching posters in General Pathology (Figure 21).

Pathophysiological knowledge in all elements of our teaching complex intermingles with pathomorphological and clinical correlations and with History of Medicine. The history of ideas prevails over the list of facts, in order to describe «a forest, not just the trees». During last decade this teaching complex was widely accepted in Russia and ex-USSR states with its elements re-published 19 times. In 2014 we added to complex "Pathophysiology of Immune System" and "Systemic Pathology of Connective Tissue" and in 2015 prepared "Pathophysiological Basis of Oncology". In our teaching posters pathophysiological, pathomorphological, clinical and historical data are fused. Local net of digital TV-microscopes gives instant video archive of experimental results added to student's protocols of lab studies; the best results are

included into teaching posters. The posters, positioned not only at classrooms, but also in other parts of Faculty space, broadened the educational environment, activated self-studies of students. The motivation of students increased, because along with classical data and data of teacher's research every poster contains a bit of student's own research also (Figure 21).

On November 10th, 2009 President of Russia, alumnus of our University adopted "The Law of Two Universities" (Federal Law of Russian Federation 2015), thus giving to Moscow State University and St. Petersburg State University status of governmental units, complete autonomy and independence of any Ministries and their control over curriculum and syllabus. The law promoted creation of new curriculum and syllabus in these eldest classical universities of Russia. We introduced new standard of medical education, where cancelled or squeezed radically many pre-medical disciplines of general education and instead gave much more time for Pathology and introduced many new disciplines like Molecular Biology, earlier absent in standard Russian medical curricula (Educational standards 2015). These changes provided enough time in order to widen training



Figure 21. A sample of teaching poster, devoted to anaphylaxis

in biomedical sciences, without any limitation of clinical courses. Today in our school teaching of Pathophysiology and Anatomic Pathology, in fact, is not concentrated in certain year, but represents a non-interrupted line of compulsory and elective courses, starting in 4th term and ending in 11th term (Figure 20).

In 4th semester we teach General Immunology (2 credits), in 5th and 6th in parallels – General and Syndromological Pathophysiology and Anatomic Pathology (6.5 credits each), in 7th semester comes Introduction into Endocrine and Metabolic Pathology (1.5 credits), in 8th – Systemic Pathology of Connective Tissue (1.5 credits) and General Oncology (2 credits), later goes Clinical (Nosological) Pathology (2.5 credits). Besides these courses, we also suggest to the students a variety of electives for every year: beginning with Introduction into Stem Cell Studies and ending with English for Medical Students based on pathophysiological and clinical terminology. For the last elective course we published together with our graduates from USA a teaching guide with an audio CD (Figure 22) (Churilov et al. 2012).

CURRENT TRENDS AND INNOVATIONS IN PATHOPHYSIOLOGY

This broadening of biomedical courses does not cut anything from clinical disciplines. Vice versa, we introduced also some innovations, increasing clinical training: sub-residency for 6th year (minimum time on bench, maximum – at bedside) and expanded time limits reserved for

work on graduation thesis. Graduation project is not the element of standard domestic medical curricula at other Russian medical schools. But in our University every medical student in order to obtain M.D. Diploma in General Medicine not only has to pass successfully all conclusive exams, but also must prepare and defend graduation paper. The thesis is an original research not necessarily in a clinical discipline, but also in Pathophysiology, Anatomic Pathology or any other biomedical science, although all graduates get Diploma of a practitioner.

Of course, not all things go smoothly. Some colleagues from other departments sometimes are close to ask us: “Why do you, pathologists, put your nose in everything and penetrate into all courses? Do you want more staff units, more hours and more money?” And our answer is: “We simply are not afraid to have more job and more troubles. And we invite you teach with us”. Almost all our courses are interdisciplinary; it means that people of different other specialties, both clinicians and theoreticians from various departments as well as guest lecturers teach together with us, within the time limits of our department.

Practical organization of health care into branches and sub-branches has generated a compartmentalization of medical profession. Unlike other natural sciences, Medicine still did not elaborate a unified thesaurus and language identically accepted by all its subsets. I call this “Mikluho-Maclay’s paradox” after Nikolay Nikolayevich Mikluho-Maklay (1846–1888), Russian anthropologist, ethnographer and naturalist, who was very impressed when he discovered, that Papuans of adjacent villages use

different dialects and do not understand each other. Unfortunately, medics still are looking like that Papuans in comparison to physicists, chemists and mathematicians. Such common thesaurus, as a pre-requisite of new thinking, in our opinion, should be based on the sub-language of Pathology, mainly on thesaurus of Pathophysiology and Anatomic Pathology. Our disciplines represent a natural bridge, which reduces the growing dichotomy and combines in learning mind scientific and clinical thinking on the background of common language (Balakhonov et al. 2011). To promote this tendency, we published "Explanatory Vocabulary of Eponyms and Figurative Expressions in Pathology and Clinical Medicine" (Churilov et al. 2010) which was re-published in 2015 and became a part of official portal "The Russian as State Language" (Figure 22). Currently our "Large Explanatory Biological Dictionary with Selected Medical Terms", created together with Biologists, is in press.

Our experience witnesses that there is a large and still unsolved problem in training of specialists for the field of Translational Medicine (Churilov et al. 2014).

In classical biological education the courses of Pathophysiology, Anatomic Pathology and Clinics are absent. In modern medical curricula teaching/learning of research technologies, currently used by Molecular and Cell Biology is very limited and superficial. As a rule, a biology graduate is not able to be effective in translational medical studies, because of "innocence" in clinical medicine, or very poor knowledge of systemic holistic medical concepts, medical ethical standards and biology of human being. At the same time, medical graduates are ineffective in this field also, because of their poor knowledge of modern research technologies and mathematical analysis of results. It makes them unable to formulate tasks, evaluate data and use research resources and methods properly. Due to this, development of Translational Medicine is retarded by lack of competent staff, at least in our country (Churilov et al. 2014).

Newly available "visibility" within the integral human body provides a new horizon that should be systemically integrated with the classical interpretations. It is high time for elaboration and introduction of new inter-faculty based M.S. programs in the field of Pathobiology (and/or clinical residencies in the field of Translational Medicine) open both for bachelors of Biology and for postgraduate medical students. Within their individual educational trajectories, the graduates of such admixed programs will combine the advantages and compensate for weak facets of medical either biological background and achieve M.S. degree in Pathobiology & Translational Medicine. Novel two-way teaching/learning clinical practice based approach seems to be resistant to main pitfalls of classical education. In some countries the problems of incompetence of medical or biological graduates in Translational Medicine and necessity of combined training programs in Pathobiology were appreciated long ago (Gray & Bonventre 2002). For example, similar programs are already in function at University of Helsinki and Johns

Hopkins University, the qualification of "pathobiologist" became official in Greece etc. Such programs may help to overcome the gap between education of medical doctors and that of biological scientists. In Russia we are still too conservative and retarded in individualization of existing curricula: our application of 2011 for elaboration of Pathobiology program did not get support. But we will try again!

Of great value and importance for us is an experience of our Croatian colleagues, recently published in Russia and presented during their guest lectures (Kovač 2010, Kovač 2013, Kovač 2014).

The algorithmic workout-based problem seminars, introduced in Zagreb University, give convenient way to deal with complexity of reactivity and diseases, making 4 interdependent steps (exposition of problem, repetition of relevant knowledge, and comprehension of pathogenesis with feedback integration). This is real training in clinical reasoning on pathophysiological basis (Kovač 2010). Algorithmic pathways often converge to more or less identical intersection points, the typical pathologic processes or corresponding etiopathogenetic clusters (EPC). The EPC approach has much common with so called "graphs of logistic structure of typical pathological processes", which were introduced in practice of Pathophysiology teaching in Soviet medical schools of 70ies. They have a multiple redundant inputs and multiple equifinal exits, so they demonstrate some targets of therapeutic interventions. According Z. Kovac, these are around 100 of mosaic blocks, interplaying in all nosological forms, like elements of Mendeleyev's table adjoined in any substance, so they give strong impetus to systemic autonomous analysis of clinical and pathophysiological problems by students (Kovač 2014).

The key clinical, research and judicial document of Medicine is a case history, a joint product of clinical and scientific reasoning, an object of legal analysis. Large archive of old and modern case histories is kept in our department and discussed during seminars and lectures. It plays also ethical and deontological roles: for example, our collection includes case histories written personally by classics of domestic Medicine: Dr. Botkin and Dr. Valdman, as well as case histories, produced during siege of Leningrad on the backsides of military topographic maps (Figure 23).

Case history is an instrument of linkage between pathophysiologist, pathomorphologist and clinician, a bridge between different generations of physicians.

Of great importance for the whole pathophysiological society is a unique project, realized in Croatia, with academic analysis, processing and systematization of 1165 case histories (Kovač 2013). The collection of their scientifically prepared fragments is a valuable teaching material. There are no analogues of such material in our practice. We plan to publish selected case histories with comments of our Croatian colleagues in Russian periodical literature as a serial teaching material, thus inculcating their valuable experience in Russia.



Figure 22. Left: English for medical Students with audio-CD, based on pathophysiological and clinical thesaurus; right: Explanatory Dictionary of Medical Eponyms and Figurative Expressions in Pathology and Clinical Medicine

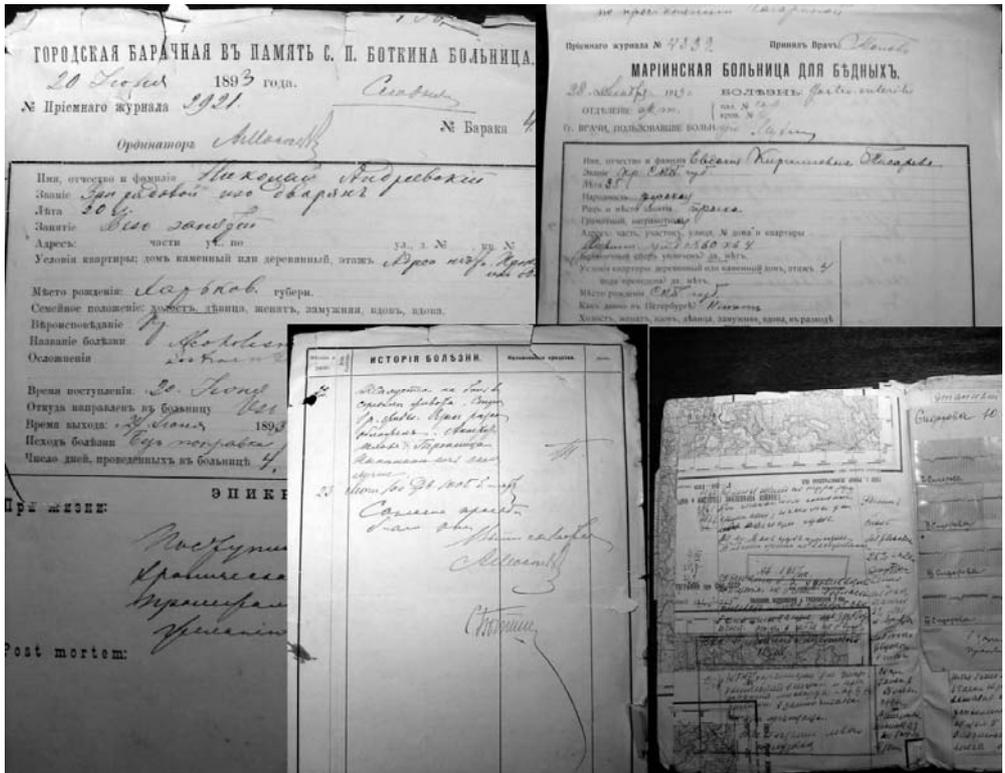


Figure 23. Case histories dated by 1893, 1913 and 1942 from our collection. Bottom left: Botkin’s autograph in case history of 1893; right: case history of 1942 from besieged Leningrad, written on backside of topographical maps

Hence, both Russian and Croatian colleagues collected considerable experience in interdisciplinary project-oriented and algorithmic teaching/learning of Pathophysiology.

In cooperation we are able to respond adequately on challenges standing in front of Pathophysiology nowadays.

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