95th ANNIVERSARY OF PATHOPHYSIOLOGY IN CROATIA

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SUMMARY

University level of Pathophysiology research and teaching in Croatia had started with the third year of Medical School of Zagreb in academic year 1919/20. Ever since, despite historical changes of the main university stake holder, the state of Croatia, Department of Pathophysiology development progressed and has made visible academic achievements, with a broader effect in medical community. The first 95 years of academic tradition and major achievements are shortly described in this paper. Professor Miroslav Mikulić envisioned Pathophysiology in close relations with Pharmacology and made the pioneering steps of establishing the "double" department at Šalata. His group was academically very pro-active, with strong international scientific participation and recruitment of professionals. The group published the first voluminous textbook of Pharmacology and Pathophysiology, in Croatian. In fifties, professor Pavao Sokolić established clinical pathophysiology within the Hospital Centre at Rebro. Out of "double" department two new departments were founded, the Pathophysiology one was completed with the clinical ward. That institutional move from Šalata hill to the Rebro hill was a necessary gigantic step and a prerequisite for the proper further development. It was in accordance with the concept of the Mikulić’s program of Pathophysiology from 1917. Pavao Sokolić has been remembered for his visions, deep insights into etiopathogenesis, ability to transfer knowledge and friendly relations to students. Sharp intellectual power, emanating charisma, academic erudition and unique clinical competencies made the legendary image of the "Teacher" - as students used to refer to him with admiration. He was second to no one when complex patient issues were to be resolved. Clinical Hospital Centre Zagreb and his Department at Rebro have become a referral point to whom to go to despair. Students recognized in their Teacher the landmark of Croatian medicine, which made a lasting legacy on generations to come. Professor Stjepan Gamulin made molecular medicine the working reality at Rebro. Both in clinical research, and in health system as diagnostic service and tool for all centers in Croatia, molecular measurement in tissue samples came into usage in daily physicians reasoning and therapy prescriptions. Macromolecular aspects of disease have come of age and became clinimetric signs of patients' condition. Professor Gamulin with his group and associated authors wrote the textbook of pathophysiology, which in upcoming 30 years had 7 editions, has become the bestseller in medicine. The textbook was translated and published in English and Albanian. In the most recent book professor Gamulin turned the focus of medical community to clinical epidemiology and a need for retrospective insights into medical efficiency. Medical performance can be improved with the improvement of understanding of underlying etiopathogenetic relations as the foundation of therapy-is the main message.

Following the academic legacy and spirit of three charismatic authorities we established two methods of teaching/learning in medicine. The two methods opened up a new avenue, so important for the era of postgenomic plethora of information and demands of precision/personalized medicine. Methodology has been introduced timely. It is student-friendly and usable for advanced types of education. Problem based algorhythmic matrices stimulate analysis and resynthesis of etiopathogenetic pathways. Graphic presentation of the solution integrates horizontal, vertical and longitudinal aspects of the problem. The companion textbook in the form of problem solver has been published in 3 editions, and contains 128 study solved cases. It was published in English, as well. Out of algorhythmic analysis the etiopathogenetic clusters (EPCs) are composed of etiopathogenetic pathway analysis. EPCs are natural units of disease development, the crossing points of processes. They are integrative hubs which tend to make networks of EPCs. Four volume textbook has been published, which elaborates 91 EPCs with 1165 study cases. Unique approach in the first 95 years was defined as Zagreb School of Pathophysiology. It made visible effect outside academia and recognizable image at the international level, in scientific, educational and practical aspects of activities.

Key words: “double” department at Šalata - clinical pathophysiology within the Hospital Centre - molecular medicine the working reality - Problem based algorhythmic matrices - the etiopathogenetic clusters - Zagreb School of Pathophysiology

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Historical prospective and framework of pathophysiology start up in Croatia

Understanding of human body structure and function in health and disease states makes a reliable foundation for the rational diagnostic and therapy interventions. It took a long evolution of medicine, both practical and conceptual, before the time of , for example, successful transplantation medicine was possible. Understanding of biomedical phenomena has been a tantalizing goal of physicians ever since the early steps of human civilization till the present day. Medical knowledge has been generated and recorded from the beginning of written history. Until the 20th century medical knowledge basically was empirical, thus observational type of knowledge. Such type of knowledge is descriptive, it relies on immediate sensory information (visual, auditory, etc) on symptoms, disabilities, and outcomes (etc), which physicians carefully recorded and followed. Practical skills of „herb-doctors“, „knife-doctors“ and „word-
doctors" were simple, short of underlying mechanisms and systematic views, yet resourceful experience that was passed from generation to generation of practitioners, in style of trade and traditional learning/teaching of medicine. Empirical biomedical knowledge has accumulated in copious amounts (like Hippocratic collection, Cannon of medicine, etc). Understanding of such body of data, which is not rarely in self-contradiction, remained an intellectual challenge and a lasting quest for a coherent vision of underlying processes. In addition, empirical knowledge very often is in the form of tacit knowledge, which is taken as a rule that is valid for a certain set of conditions. Tacit knowledge does not rely on measurements, discussions and experiments. It is rather a given recipe, a non-declarative "wisdom" habituated from observations and/or interventions. Attempts to integrate and understand basic principles of empirical phenomenology were, very often, related to a dominant conceptual framework and broader culture which prevailed in given historical era (like Egyptian, Hindu, Islamic, Occidental, etc). Those attempts were guided by opinions and authorities of an individual medical school philosophy (Hippocrates, Galen, Avicenna, Virchow, etc). The chaotic confusion in empirical art of medicine awaited the advent of appropriate scientific methodology and advancements in general biology understanding the life phenomena.

Western civilization institutionalized a systemic approach to human knowledge by development of the university system. The grand starting point of advanced studies was marked by the opening of the University of Bologna in the year of 1088. In the course of the following almost ten centuries, history has witnessed impressive achievements in all avenues of human interests, including the medicine. Universities have procured environment, libraries, auditoria, laboratories, study system, curricula (etc), with the idea to materialize the triple university mission, which includes the research (generation of knowledge), the education and the application of knowledge. The triple mission and achievements have justly elevated the university system to the one of the highest points in the hierarchy of human values. In the last two centuries the university mission has triumphed in practical application of knowledge, especially related to energy usage, technology of human society needs (like transportation, food production, pharmacy, etc), information transmission and management, etc. There is no doubt that scientific systematization and methodology have opened new visions, horizons and civilizations artifacts have been created. Started with Claude Bernard (1813-1878) medicine was enriched with the experimental scientific method as a dominant type of knowledge-generation mechanism and way of a thinking (Rall 2016). Scientific methodology was systematically introduced and expanded into all areas of medicine and related research. Carried-on body of empirical knowledge in medicine was to be re-evaluated, new insights into mechanisms were to be established and new theoretical concepts and frameworks were to be created. In the 19th and 20th century physics and chemistry have rapidly advanced to the level of general rules and laws (like laws of gravitation and electromagnetism, laws of thermodynamics, equivalency of mass and energy, etc), with high power of prediction of system behavior in various conditions. Out of these fast developments great expectation were imposed to the general biology and human biology as well. A common sense reasoning that life phenomena ought to be reducible to the level of physically and chemically measurable system of molecules and forces interactions, has become a guiding myth and vision for generations of scientists, physicians and students of life sciences.

Presently, the nature of human body biology has been studied from various experimental, clinical and epidemiological, anthropological (and so on) approaches. Those approaches apply myriads of experimental models, dealing with questions at various levels of organismic organization (macromolecular, genetical, cellular, organ-system, etc). Each method generates facets of knowledge and widens the concepts. Each method tends to apply as rigid as possible control system, in order to generate knowledge which is reproducible and reliable. Nevertheless, those facets of knowledge are methodologically conditioned and they are valid for given investigation model and methods applied. They do not lead to a straightforward understanding of the life phenomena as the whole system. Studies of organismic functional performance are faced with the complexity issues in putting together elementary data. It seems that new methods and tools are to be developed for research and construction of integrative knowledge of complex system functioning as the whole body. In medicine, both physiology and pathophysiology, as integrative academic disciplines use a chimerical approach and standpoint in their interpretation of research/study contents. They try to fuse both reductionistic scientific data and whole body phenomenology into comprehensive visions and concepts. The whole body aspect imposes additional methodological requirements to fit criteria of controllability, reproducibility and homogeneity of acquired data.

Medical School University of Zagreb (established in the academic year 1917./18.) from the very beginning was fully aware of the trends in biomedical sciences at the beginning of the 20th century (Figure 1). The forefathers of the medicine in Croatia clearly understood differences between the empirical and scientifically based knowledge in medicine (Kovač 2011). They foresaw and paved the pathways of development in three directions; basic biomedical sciences, clinical sciences and public health sciences. That was the core of the future medicine, which was applied on institutional development, curricular contents, programs and plans, personnel training and coaching and practical participation in the public health system providers. Special attention was devoted to international scientific collaboration and academic networking. The course of Pathophysiology
Figure 1. Chronology of the first 95 years of important events and processes in development of the Department of Pathophysiology Medical School University of Zagreb aligned with the statehood alterations in Croatia. Since the State of Croatia is the main stakeholder of the university, geopolitical conditions and stability have been indirectly making a significant influence on academic performance.

Figure 2. The first step of Pathophysiology in Croatia. In the year 1919/20, professor Miroslav Mikuličić held classes for the first Third year of Program for medical students in newly founded Medical School of Zagreb. A) Frontpage of Syllabus; B) Weekly schedule of Pathophysiology in autumn semester; C) Weekly schedule of Pathophysiology in spring semester.
Figure 3. Department of Pathophysiology and Pharmacology at Šalata A) Professor Miroslav Mikuličić in front of his „double“ institute; B) Mikuličić’s program for Pathophysiology and Pharmacology, 1917; C) 7 functional units of Mikuličić’s double institute - a segment from the Program.

started in the 1919./20. academic year, as the course for the first enrolled generation of students of medicine (Figure 2). Ever since, continuously, pathophysiology has been thought, un-interruptedly even during the wars (The Second World War 1941-1945 and Homeland War 1991-1995), which seriously harmed the people, the society and the state of Croatia. The first 95 years of Pathophysiology went through fruitful development of the Department, careful recruitment of professionals, introduction of appropriate methods for clinical research, research and development of own teaching/learning methods, and establishment of clinical integrative discipline and branch of medicine.

Duble department of pharmacology and pathophysiology at Šalata – the vision of Miroslav Mikuličić

Miroslav Mikuličić (1883-1955) was the fourth elected professor of the newly founded Medical School in Zagreb (Figure 3). He was born in Bakar, Croatia, to a well-to-do family of the ship owner and the city major. As a child prodigy, ever inquiring pro-active spirit, he never stopped to pursue his academic interests. He received his higher education in natural sciences at the University of Jena. In 1905 Mikuličić was awarded the PhD degree (in Lat. Doctor Rerum Naturalium). His final collective exam was in fields of zoology, botanics, geology and paleontology. He shortly practiced as a secondary assistent researcher in the Institute of Zoology, Comparative Anatomy and Physiology in Nice, France. Thereafter, he enrolled into study of medicine at the Medical School University of Graz, Austria. He completed medical education in 1912, and received the MD-degree with excellence (sub auspiciis Imperatoris, i.e., a special title awarded to students who achieved top grades in all exams in gymnasium and during the university studies). In his free time, during medical studies in 1905-1906, Miroslav Mikuličić used to volunteer in the Hospital Santo Spirito in Rijeka, Croatia (Dugački 2009). He also volunteered at the Department of Surgery in Graz in 1910-12. As a doctor of both natural sciences and medicine, in 1912, he joined to Oto Loewi group at the Institute of Pharmacology and Pharmacognostics, a university of Graz, from where he published several papers. Shortly after, Mikuličić was recruited as a teacher-assistant at the Department of Pathophysiology, headed by Professor Rudolf Klemensiewicz (1848-1922), and published two papers in Archiv für Experimentelle Pathologie und Pharmakologie. That
Graz period was important for his concept of pathophysiology and pharmacology in Zagreb. For a long time, he stayed in good personal relations and shared common academic interests with his Graz friends. When Oto Loewi was awarded Nobel prize for physiology and medicine in 1936 for mechanisms of neurotransmission, Mikuličić invited the laureate Loewi to visit his Department at Šalata. On June 11, 1937 Oto Loewi gave lecture “On hormonal mechanisms of neuron stimulation” in Zagreb. Mikuličić proudly presented the concept and achievements of the Department in last 20 years since the foundation (Vučak 2017).

Figure 4. The first textbook in Croatian for Pharmacology and Pathophysiology. Ivo Ivančević published in 1948. voluminous textbook, that elaborates programs of the two study subjects. It consisted of 39 chapters and 944 pages

When he was invited to organize department which will deal with pathophysiology and pharmacology for the first University Medical School in Croatia in 1917, Mikuličić had a quite clear concept and vision, as well as working experience for such a challenge. He was given the space within one of already existing buildings at Šalata for the future department (Figure 3). His heterogeneous and comparative education in natural sciences and medicine and practical experience of several academic environments had helped him in development concepts, guidelines and visions of the future department and curriculum. He wrote the extensive program-document „THE FOUNDATION, DEVELOPMENT AND SCOPE OF THE INSTITUTE FOR GENERAL EXPERIMENTAL PATHOLOGY (PATHOLOGIC PHYSIOLOGY) AND PHARMACOLOGY AT THE ROYAL UNIVERSITY OF ZAGREB” (Figure 3B and 3C). He envisioned basic research laboratory with close interaction with human pharmacological and clinical investigations, to be organized side by side. The structure of the Department and study programs are outlined in the Program. In drafting the document Mikuličić consulted several experts in Europe, and received many supports to the concept. For example Ludwig Aschoff wrote: „An sich finde ich es einen glücklichen Gedanken, dass Sie die pathol. Physiologie – so muss es heissen, und nicht experimentelle Pathologie – mit der experimentellen Pharmakologie vereinen. - Auch ich bin der Meinung, dass die Pharmakologie in erster Linie berufen inst. pathol. Physiologie zu lehren. Freilich wird auch der Kliniker sich dieses Gebiet nicht nehmen lassen, da er das wertvollste Object, nähmlich den Menschen, in seiner Beobachtung hat. - Auch die pathol. Anatomie wird auf Grund rein morphologischer Befunde zu pathol. physiologischen Fragen Stellung nehmen müssen.- Wenn aber die Pharmakologie die pathol. Physiologie mit übernimmt, besser gesagt, die Pharmakologie nur einen Teil, der pathol. Physiologie darstellen soll, andererseits die pathol. Physiologie die Verbindung mit der pathol. Anatomie nicht verlieren soll, so ist engstes Zusammenarbeiten der beiden Disziplinen, wenn möglich unter einem Dach erwünscht. - Das ist der Vorzug des Virchowschen Instituts in Berlin.- Ähnlich ist ja auch das Rockefeller-Institut in NEW-YORK eingerichtet. - Jedenfalls kann ich Ihnen nur wünschen, dass Sie einen tüchtigen, für pathol. Physiologie interessierten pathol. Anatomi gewinnen können……“. During his time, the concept presented in the Program was materialized partially, due to suboptimal funding and turbulent changes in the government administration, the main stake holder of the University (see Figure 1). Mikuličić contributed to development of the Department by convincing Croatian people in diaspora to help purchasing necessary research equipment. South American Croats contributed with X-ray machine and some other instruments. He drafted manuscripts of study material that was published

1 Pathologist from Freiburg, Ludwig Aschoff (1866-1942) wrote to Mikuličić: „I think your concept to call the subject pathophysiology is much better choice than experimental pathology – and it should be so named, and it is a good choice to put it together with experimental pharmacology. Also, I think that pathophysiology could be efficiently studied through pharmacology. Certainly, I would not give this study area to doctors in hospitals, because they have the most valuable resource in their consideration, i.e. human being. Equally, pathologic anatomy should take position of asking the questions to pathophysiology because of clear reasons which are coming from morphological analyses. However, if pharmacology intermigles with pathophysiology, better to say, pharmacology should be just a part of pathophysiology, and on the other hand, pathophysiology should not lose its connections to pathologic anatomy, and it would be desirable condition to have tight interactions of both disciplines and to have them both under the same roof, whenever possible. This is strategy of Virchows Institute in Berlin – and similar is orientation of the Rockefeller Institute in New York. In any case, may I just wish you to attract skilful pathologic anatomists for pathophysiology“. (Translated by the author).
as student-edited material of 512 pages (Dugački 2009). Due to his persistence in his demands and ideas of how medical school should recruit future staff, Miroslav Mikulić came into severe conflicts with superior academic authorities. It was recorded that he was three times retired and then two times re-activated in his professional career. Those social swings and some personal health problems certainly contributed to a partial materialization of his program. His successors continued in building up the components of the program. Professor Ivo Ivančević published the voluminous textbook of Pharmacology and Pathophysiology in 1948 (Figure 4). Dr Vladimir Sertić (1891-1983) during his research at the Mikulić’s Department at Šalata discovered several bacteriophages, and later on, he continued that research at Sorbonne University in Paris. He proposed a classification of bacteriophages and earned the international fame. His bacteriophage ФX174 turned out to be the first sequenced organism ever. Namely, Frederick Sanger, was awarded his second Nobel prize in the year 1980, for dideoxy chain-termination method, by which he group to sequenced 5386 nucleotides of single-stranded Sertić’s bacteriophage ФX174 (Lacković & Klarica 2014).

On the other side, the clinical component, envisioned by the Program of Mikulić’s Department, remained non-materialized. It waited for opening of the new university hospital located at the hill of Rebro.

**Clinical pathophysiology at Rebro - the life mission and legendary achievements of Pavao Sokolić**

Pavao Sokolić (1907-1977) may be considered as the most dedicated follower of Mikulić’s vision and concept of a physician-scientist (Figure 5) (Kovač 2011, Gamulin 2010). In his mature professional years, he was able to put the vision into the working reality, despite the unfavorable academic framework of a communist regime in decades following the Second World War. Professor Sokolić ignited the lasting enthusiasm and a creative spirit in many medical student generations to come. He taught the pathophysiology as the „bridge between the clinical and basic sciences“, and paved the ways of thinking, education and practice which will later on be called „evidence-based medicine“. He separated the Chair of Pathophysiology out of the „Mikulić’s double department“ and moved activities into the hospital environment. Hospital Rebro, later on the University Hospital Centre Zagreb (KBC Zagreb), became the home of Pathophysiology. It was a win-win alliance, which operated with difficulties. On the one side, the regular city hospital of Rebro gained the group dedicated to study scientifically etiopathogenetic foundations of disease, it became, herewith, the focal and referral point of attractive clinical and academic activities. Pathophysiology as the branch of medicine and study discipline, on the other hand, was clearly directed to reduce already growing gap between clinical practice and basic sciences. It became the clinical subject. The physician-scientist became the reality. Sokolić’s determinations and personal charisma enabled such approach and trend in Medical School of Zagreb, which, one may say - anticipated a general „translation movement in medicine“, in the first decades of the 21st century. Difficulties encountered in hospital environment were numerous, including misunderstandings of both the mission and the practical role of pathophysiology, misconceptions regarding clinical specialization, budgeting and labor distribution issues, working space allocations (clinical ward, research laboratory, animal facility, and library), etc. Professor Sokolić considered those difficulties as necessary and unavoidable hurdles and consequences of the materialization of the clinical concept of pathophysiology. In order to achieve the noble goal of merging the science and clinical practice he was ready to stand those difficulties as a price to be paid. He was convinced that proper development of a medical school and medicine in general should in parallel follow two major sources of biomedical knowledge, the clinical practice and scientific results obtained in various experimental systems. They are inseparable and should be practiced in parallel, in order to grasp properly the knowledge of the problem studied. The working experience of both is a prerequisite for proper understanding. University mission usually encompasses the triple activity areas as the unity: the research, the education and the application. Such mission is worldwide considered as self-generating principle and proper pathway for development of the academic institution. The achievement of professor Sokolić with his concept and department of clinical pathophysiology can be considered as real fulfillment of the triple university mission. In his hands, the science in direct service of health promotion at hand of students, the future physician-biologist became a working reality.

![Figure 5. A) Pavao Sokolić – the legendary physician-pathophysiologist, who was referred to as „The Teacher“ by many generations of students; B) One prodigy student inspired by erudition, charisma and approach of the Teacher - drew benign caricature of „dear flying professor“ focused on his visions of disease processes.](image-url)
Professor Sokolić was the *spiritus movens* of generations, and the central figure to whom one may refer when perplexed with the complexity of patient conditions. Literally, his clinical department became the *ultimum refugium* for complicated health issues where patients gathered for help from all parts of Croatia, and from other countries, as well. Many of those longstanding medical problems were resolved, and patients had been discharged healed or in an improved condition. He became the living legend, the reliable person always ready to act to the betterment of a person in a need. His colleagues, his students, his nurses, and, even his enemies, respected his insights, diagnostic skills, and obeyed his therapy prescriptions. In academic community he has been remembered for his insights and far reaching projects. Two examples will illustrate his broader contributions to the other branches of medicine. Firstly, in the year of 1954 he proposed to Dean of the Medical School a foundation of separate unit which would deal with the problems related to diabetes mellitus. His concept of „The Infirmary for diabetes and endocrine diseases – to be named Vuk Vrhovac“ was taken as the national health system policy agenda. Through the time it developed into the specialized University Hospital Vuk Vrhovac, presently adjoined to the Clinical Hospital Merkur in Zagreb. Secondly, professor Sokolić was an expert and the one who contributed to deeper understanding of electrocardiography. His chapter on principles of electrophysiology of the heart was considered as the classical referral text, second to none, for many generations, equally valid in present days as it was more than half a century ago when it was written.

Personal life of professor Sokolić was described as „unique, rich and inspirational“. He played violin, sometimes as source of subsistence during rainy days of his student life (Gamulin 2010). From his family roots in Lika, where conditions of life had always been harsh and not-easy-going, he carried on a deep humanistic devotion and feeling of responsibility. He had a refined sense of justice, persistence in his conviction and believes and natural sense of measure of things. Those character features made him a likeable person. Following completion of medical studies in Zagreb, he enrolled in Bern into scientific training in the group of Alexander von Muralt (1903-1990), physiologist and physicist, whose group was one of the European leaders in research in biomedicine. Sokolić was inspired by the theoretical work in biology of Ludwig von Bertalanffy (1901-1972), who was trying to identify common patterns in any system (biology, chemistry, information system etc) (Gamulin 2017). Some of those ideas were present in Sokolić’s lectures on etiology and pathogenesis, which were highly valued by his students and colleagues. In his lectures he used to outline the nine principles according to which body physiology processes take place in health and disease (Table 1). Opposite to a prevailing tendency of direct reduction of physiology to moulds of chemical and physical laws, Sokolić added a new dimension into interpretation and understanding of pathobiological phenomena. He spoke of open system principles, biopotentials, reactivity alterations, proactive and reactive principle, etc. In his ninth principle he tackles the limits of knowledge generated via simplified models, and relations of holistic versus fragmented understanding of physiology of health and disease. In a complex system Sokolić turns attention to a self-maintenance principle (principle six in Table 1), in which mutual interdependence of functional systems provides necessary conditions for differentiation and development. Such conceptualizations were very inspirational to his students, and remained equally important today. His demonstrators, who advanced to high academic positions in various branches of medicine, often referred to Sokolić’s lectures as the „critical events which made change to the better in their lives“. Many students rushed very early in the morning to catch a good position in the crowded auditorium (Šoštarko 2017). Some student described that he had an impression of „seeing blinking stars in the sky“ in clarifications presented in the lecture (Narančić-Gurović 2017). Students wrote and published booklets according to the notes taken during the lectures. Many of them remained life-long admirers of their unique „teacher“ or made drawings of „Pavao“- which had something prophetic in his academic utterances. Professor Damjanov, the world reknown pathologist in Kansas University, recalled his students days at the Pathophysiology in Zagreb - a half of century ago, that he even today „...can clearly see him (Sokolić) in the auditorium at Rebro, in his maestral moves during lecture, like Moses, in front of us, trying to grasp his visions...“ (Damjanov 2012). Damjanov says that Sokolić made a huge impact on student reasoning, which can be compared with cathedral architects and builders. He even quoted the famous Gaudí3 that “…there is no reason to regret that I cannot finish the cathedral. I will grow old, but the others will come after me. What must always be conserved is the spirit of the work, but its life has to depend on the generations it is handed down to, and with whom it lives and is incarnated...“ (Damjanov 2012). Sokolić had “…the charisma that became the permanent inspiration in medicine...”, recalls a student, later on professor of gynecology (Grubišić 2017). With no doubt professor Sokolić belonged to „the upper class“ of educators in Medical School of Zagreb.

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2 Vuk Vrhovac (1903-1952), endocrinologist, Professor of Internal medicine, Medical School University of Zagreb. The proposed name in Croatian is „Vrhovčev dispanzer za diabetičare i endokrinološke bolesti“.

3 Antoni Gaudi (1852-1926) was the architect of Sagrada Familia, the world heritage catholic cathedral of Barcelona.
Table 1. Lectures of Professor Sokolić have been inspiring intellectual challenge. They had an impressive attractive power, to which many of his students used to refer to many decades late in their professional lives. The recalled core points of his integrative vision of etiopathogenesis could be summed up on several principles and unique definitions*

Human body is an open, reactive-proactive polyvalent biological system

**The system contains following built-in principles:**

I. Basic features of life are 1. individuality, 2. reactivity, 3. autoregulation, 4. metabolism, 5. adaptability and 6. reproduction

II. Progressive transformation of mater and energy in time and body space, i.e. 4-dimensional flow through and in the system

III. Dynamic carry on (regeneration) of functional structure, including the reproduction

IV. Expansive tendecy of living entities

V. The chain reaction principle

VI. The principle that only function can preserve function, and stimulate and upgrade the structure, which thereby brings about the quality of new function, and so on…

VII. Life out of life, ie., a higher differentiated organism can live only on living material of less differentiated ones

VIII. The principle of genomic continuity

IX. The integrity (the whole system) is more than the sum of values of individual parts

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*Prepared and translated from S Gamulin. Pogled Pavla Sokolića na patofiziologiju, u Z Kovačiću sur, Pavlovo poslanje (in press), with permission of the author, editor and publisher

Some aspects of Sokolić’s professional life gave a vivid picture of social relations and conditions of his time. He was elected into the Assistant Professor of Internal Medicine in the year 1943. When communist system came in power he was degraded (compare timeline in Figure 1). They did not obey the principle of institutional autonomy, or university tenure track principle. In Medical School of Zagreb he remained in the status of assistant teacher (the lowest academic position) until retirement in the year 1977, despite his leading role in the field. Sokolić became the victim of the totalitarian system, the innocent bystander silently punished for no real reason. It was said that „his intellectual and professional dominance might have been a disturbing factor in minds of some communist puppeteers and policy makers“*. The irony goes even further. Not rarely, when prominent political persons of the system were faced with health problem themselves, or in their families, they would not hesitate to consult Professor Sokolić, the direct victim of their own totalitarian system. That academic injustice was partially repaired in the year 1971, when Sokolić became the full professor of pathophysiology at the newly established Faculty of Dentistry.

Molecular pathophysiology in direct health service at Rebro - the contributions of Professor Gamulin

Stjepan Gamulin (born 1934) and his collaborators followed guidelines and general trends of Mikuličić's and Sokolić’s era of Croatian pathophysiology (Figure 6). They deepened molecular understanding and facilitated closer positioning of science and clinical medicine. The new trend was added in development of pathophysiology. Molecular research became daily practice at the Department and applicative avenues of science were opened. Professor Gamulin in his working years (1967-2001) struggled with a prevailing zeitgeist of symptomatic studies, a phenomenological syndrome analysis, a dominant role of „authorities“ in diagnostic and therapy procedures and paradigmatic reliance on clinical empirical observation as a principal source of medical knowledge. In tradition of clinical education and practice, such pattern and mode medical thinking was handed down from generation to generation of physicians. Professor Gamulin clearly saw a need for change. Macromolecular perspective became his challenge, the operative agenda. New molecular approaches which came out of scientific horizons as a useful possibility were to be tested in clinical settings for their real applicability. Research of protein and DNA molecular level of pathophysiological pathways has come of age. The advent of macromolecular quantitative methods and research data enabled a deeper understanding of classical etiology and pathogenesis concepts and interpretations of disease/disorder states. In addition, molecular approaches were about to introduce a new diagnostic and therapeutic era into the practical medicine.
Professor Gamulin established a molecular laboratory and collective energy of his group was forwarded towards applicative problems. His clinical research projects added important facets in nature of disease. His group investigated several themes, including a role of electrolyte transport systems in essential hypertension pathophysiology, estrogen and progesterone receptor expression in etiopathogenesis of breast carcinoma, role of androgen and some other tumors, etc. Their efforts were tuned with current epidemiological problem, and some solutions were generated. Diagnostic value of tissue receptor expression and clinical correlations with breast carcinoma therapy and outcomes became the national health standard. Department of pathophysiology became referral and internationally certificated laboratory for estrogen and progesterone receptor diagnostics. That diagnostic procedure conducted at Rebro for many years has been used by all breast carcinoma departments in hospitals in Croatia and some in Slovenia and Bosnia and Herzegovina. In total, >30000 determinations have been done. The value of the receptor expression is important for therapy modes of adjuvant therapy (quantity, duration) and it has prognostic and predictive significance. In addition to applied research professor Gamulin pursued research projects with a broader pathophysiological impact. Energy metabolism has been a lasting Gamulin's inspiration and scientific call. Investigation of disorders of energy metabolism in animal models of hypoglycemia, ischemia (etc) at the subcellular level of polyribosome structure, showed very fast kinetics (the scale range of minutes) and high sensitivity of polysome disaggregation. Since uninterrupted protein synthesis is a prerequisite for cellular life that research has had importance for understanding the etiopathogenesis of clinical conditions like infarction, cerebro-vascular insult, etc. Body hypothermia effects on electrophysiology and its arrhythmic correlates in a mouse model are important research projects and discoveries for understanding clinical arrhythmogenic phenomena.

During his tenure a shortage of pathophysiology teaching materials became the burning issue. Students felt the importance of the subject for their understanding of medicine and relative insufficiency of available literature, in Croatian and other languages. Therefore, they encouraged and demanded a contemporary textbook at the academic level comparable to that one given at pathophysiology lectures and seminars. The idea and the project turned out to be a great success. Professor Gamulin embarked to the project with 88 authors and two co-editors – Matko Marušić and Slavko Kravivci. Along with Croatian pathophysiologists authors were recruited from other branches of medicine. It contained 35 chapters, 3 of them deal with the etiology, 19 describe general pathogenesis, 11 are summarizing the pathophysiology of organ systems and two chapters are introduction into principles of disease development (Figure 7). The first edition was published in the year 1988, and it quickly became the bestseller in medicine. So far seven revised editions of the textbook were published (the eight editions are in preparation). It was translated and published in Albanian (two editions) and English language. The fourth edition of textbook was awarded the HAZU-prize Josip Juraj Strossmayer in the year 1999. There are estimates that at least 18000 students in in last three decades have studied and deepened their knowledge of pathophysiology with textbook contents, as a principal source of information.
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Figure 7. Pathophysiology teaching/learning program comprises the general and functional/organ system pathophysiology. Nosologies of individual disease states are the constitutive parts of various branches of medicine (e.g., dermatology, neurology, pediatrics, etc). Gamulin's textbook is organized in a way to follow and support this concept

Following the retirement, Professor Gamulin has continued honorary teaching and research activities within the doctoral studies at several universities. Out of those activities he published, in the year 2015, the book Clinical investigation – Clinical epidemiology. Retrospective and prospective analysis of clinical efficiency done via tools of scientific treatment of clinimetric data represents, by large, a missing brick in the objective evaluation in medicine. Epidemiology of clinical outcomes, done with mathematical rigor of double blinded data, is advocated as the most reliable way towards non-biased claims of clinical efficiency. Since physicians, in general, are not strong in mathematical reasoning, Gamulin presents the same methodology in narrative descriptive ways in order to increase receptivity of the book by physicians. This is important thematic in any branch of medicine and should be applied to drug efficiency/toxicity, clinical procedures, diagnostic efficiency, outcomes, etc. Since the clinical knowledge and data are one of the two critical sources of information on pathobiology of the complex system, the increase in clinical certainty is important for reliable understanding of the nature of disease. Gamulin insists on analysis of pathophysiological pathways in the background of symptoms and syndromes. Each facet of information should be considered within the context of the system analyzed. He warns that uncritical translation of concepts and patterns is a source of error in the interpretation and understanding of etiopathogenetic relations.
Croatian academic community recognized and appropriately rewarded the academic and practical contributions of professor Gamulin. He was elected professor emeritus of Pathophysiology at the University of Zagreb in the year 2000, and became the full member of the National Academy of Science and Art (HAZU) in the year 2002. In the year 2010 he received the State of Croatia Award for Life Academic Achievement.

**New methods and medical reasoning: algorithmic analysis / resynthesis and etiopathogenetic clusters (EPCs)**

Understanding of medicine and biology in the post-genomic era has been, step by step, converted into the system of knowledge comparable to the fields of physics and chemistry. One may say that medicine has become a “more mature science”, both in theoretical and practical aspects and sense. Despite physiological complexities of the human body, the growing certainty and quality of analytical approaches have set a stage for a new perspective in clinical medicine. New avenues of practical perspective in medicine have become the urgent challenge to scientists and physicians. Translational medicine movement has enforced a synthetic orientation in undertakings, with global target of improvement of health. Along with the evidence based medicine, the translational movement has been focused on the efforts towards upgrading the clinical benefit based on new insights. Bridging the basic science – clinical application gap has become the central agenda and intellectual challenge. Integrative teaching/learning includes activation of multiple facets of human brain physiology and maximal insight into the subject studied. Such integrative processes heavily relay on information technologies (including diagnostic information technologies), cognitive mental processes of gaining and retaining of knowledge, epistemological problems of scientific methodology, as well as differences between scientific and clinical approaches.

Pathophysiology is the integrative branch of medicine. It is focused on horizontal, vertical and longitudinal integration of knowledge of human body function in disease. The mission of general pathophysiology studies is to enable a synthetic view of heterogeneous types of information and to stimulate an integrative study process. Stemming from nanomolecular and macromolecular level, general pathophysiology makes bridges towards inheritance, subcellular, cellular and tissue as well as organismic level. It aims towards study of common etiopathogenetic pathways. It tries to figure out a reliable frame of reference of pathobiological processes responsible for a given clinical problem. Synthetic pathophysiology outlines and crystallizes pathways, taxonomic orders, and distribution of disease phenomena and describes dynamics of processes. Thus it takes into consideration local and systemic processes, their dynamics, interferences, and regulatory loops (etc).

Pathophysiology has a tendency to reduce pathobiological phenomena to several groups of processes (e.g., inflammation, immune disorders, acid-base-, water- and osmotic- macromolecular- disorders, neoplastic processes, disorders of hemodynamics, disorders of bioenergetics and thermoregulation, etc). Such useful simplification imposes, however, a skewed attitude to consider the given problem as a “pure event”. Such skewing is present both in physician’s and scientist’s mind, as well. On the other side, in natural development of disease, various processes are very often combined with the elements belonging to other classes of processes. Thus, disease processes, natural dynamics, regulation and outcomes (etc) as complex phenomenology seek for a new frame of reference and methods to be used. Etiological factors (chemical, physical, live agents, inherited genomic polymorphisms) induce a variable set of body reactions, which differ both in quantity and in quality. Pathophysiology uses clinical and basic data and knowledge and applies new methods, with a growing sophistication of existing methods - imported methods coming from chemistry, physics, biology, and information technologies (etc).

We developed two methods, integrative algorithmic elaboration and etiopathogenetic clusters, both of which include a stepwise approach. Clinical problem (case report, specific etiopathogenetic problem) is studied within the framework of vertical, horizontal and longitudinal integration of disease phenomena. Both methods are using analytical and re-synthetic system of problem consideration. Both approaches impose active matrix-driven system and enforce reader’s participation and integration of knowledge. Both methodologies are elaborated in respective problem solver books. They are convenient for self-education, as well. The methods have been accepted and praised as a student friendly by dozens of generations. Class teaching and real contact time has been converted into student-teacher bidirectional tutorship. Both sides have gained the advantage of teaching/learning procedure based on these two approaches. One may say that the real power of both algorithmic workout and etiopathogenetic clusters is in their simultaneous integral consideration of local and systemic processes of the disease. The study of etiopathogenesis leads a newcomer in the field towards a critical appreciation of various strata of medical data. These methodologies seem to resolve and circumvent some biases of compartmentalized medicine and reductionistic nature of research. They may be considered as a solid introduction into the evidence based medicine that may facilitate translational medicine advancements.

Proper pathophysiological framework should facilitate a rational usage of both quantitative scientific knowledge and qualitative descriptive knowledge information plethora and mastering professional demands. In order to improve the efficacy of teaching/learning approach we developed the algorithmic analysis/ synthesis method, which became attractive and friendly to students,
as well as from teachers’ point of view. The method is a matrix-guided educational model with four steps. The first part is exposition of a problem, which provides short presentation of “raw data” derived from patient records, selected publications with experimental data, etc. The second part is repetition of relevant knowledge, which is a multiple choice test, whose statements are related to the exposition and refer to other teaching materials (textbooks, websites etc). The third part is algorhythmic workout of the pathogenesis, a task in which students, out of given 25-30 units of etiopathogenesis, build-up the cause-effect sequence of events, with positive and negative feedback loops, and parallel and contextual events (Figure 8A). The fourth part is feedback integration of the problem which deals with additional relations, systematization and quantitative aspects of the same problem (For detailed method description please see Kovač 2014, 2015).

We also wrote the problem solver textbook, which contains 128 study cases, each based on real clinical data. Three editions of the textbook were published (2002, 2006, 2011), the fourth edition is in preparation. The approach has been considered student friendly and 2.3 times better approach in comparison with classical approaches (Kovač 2014). The four layers of problem elaboration guide the reader to multiple repetitions with consideration of various additional facets of knowledge. Consistent with the ways how the brain deals with new information those reiterated and enriched repetitions help fixing and adopting the learning contents. The graphic representation of algorhythmic resynthesis, it was said, “… gives sense of mathematization of medicine (…) and medical knowledge is systematized and integrated along the logical pathways (the algorhythms)...” (Švagelj 2016). Matrix algorhythmic approach, as apposite to classical textbooks “… starts from real data and leads to understanding of individual patient case within the context of general knowledge. (…) Algorhythmic elaboration of etiopathogenesis is a purposeful type of interconnecting of basic knowledge of genomic, proteomics, metabolomics and other –omicses and understanding of phenomena which includes the manifestation of disease…” (Gamulin 2016). Several reviewers gave their feedback opinions on this approach. This strategy appears as “… original insight into pathobiology processes…” (Miličić 2014). The power of this approach is in “… integrative relations of macro-world and nano-world of molecules and forces…” (Rukavina 2014).

Figure 8. A) Student’s solution of complex etiopathogenesis presented as the graphic network; B) Etiopathogenetic clusters (EPC) spontaneously form a network; C) The four volume book of Clinical Pathophysiology published in 2013, 91 EPC is elaborate via 1165 patient study cases, D) the EPC rosette of „Leukocytosis“ connects many diseases elaborated in the chapter to follow the introductory rosette.
There is general natural tendency of etiopathogenetic pathways to form common crossing points of reactivity. Etiopathogenetic clusters are the points where, very often, many unrelated pathways converge to the common units of pathogenesis. It appears that pathways belonging to heterogeneous types of diseases tend to group together, spontaneously, around the certain etiopathogenetic element (Figure 8D). Such common units are formed at certain deviation of electrolyte concentration (like hyponatraemia, hypophosphatemia, hyperchloremia, etc), macromolecular alterations (e.g., hypoproteinemia, dyslipidemias, etc), and than on cellular and organ functional levels (e.g., acute renal failure, seizures), as well. Such common „hubs“ of the response were named the etiopathogenetic clusters (EPCs). We consider them as important integrators of natural pathophysiological processes. Such clusters integrate multiple inputs and multiple exits in the natural development of various diseases and altered conditions in the human body. Thus, EPC may have both theoretical and practical importance in study of medical pathophysiology. The EPCs have tendency to form a network, with connecting pathways among them (Figure 8B). For example, the EPC of acute renal failure leads to the EPC of the metabolic acidosis, and to the EPC of the hyperkaemia, and to the EPC of the consciousness disorder, and so on. One could speculate that such EPC networking reflects the inherent capacity of the human body to react. EPC networking thus follows the general patterns of natural body reactivity. In Figure 9 EPCs are depicted along the structure/function hierarchy of human body physiology constitution. Networking of EPCs is outlined. The example of Vibrio Cholerae infection is presented. The infection triggers processes which naturally progress toward hypovolemic shock, multiple organ failure and death due to excessive secretory diarrhea. The EPC networking behind the clinical presentation includes 4 primary EPCs, three secondary and two tertiary EPCs (please follow arrows in Figure 9). Symptoms, signs, dysfunctions and outcomes are contributed by at least 9 EPCs. The EPCs have importance in clinical reasoning and clinical interventions. These clusters are often targets of therapeutic interventions. Correction of EPC deviation from reference value leads to immediate clinical improvement, both locally and generally.

We published the 4-volume textbook (in the year 2013), in form of practical clinical manual with 1165 study cases, which has a form of problem solver (Figure 8C). Each study case leads the reader to a short algorithmic elaboration and systematization and has the solutions. Each case is interconnected with the appropriate EPC, and the books are based on 91 EPCs.

**Big data and information plethora – the critical role of pathophysiology in postgenomic era**

From a broader prospective, the living human body may be viewed as an open system with the permanent import and export of mater/energy and information with the environment. Living body is fully dependent on oxygen, macronutrient and some micronutrient import. Daily produced and used biological energy enables structural and functional channeling of informational exchanges between the genome and environmental demands. In addition, some categories of macromolecules, generated within the body subsystems, serve as the information-containing and conveying units. The information and energy interplay serves as a driving principle that maintains the basic structure and physiology of the body. From the conception of zygote onwards, throughout development, growth, maturation and body involution, the bi-directional open system is governed by a set of internal rules. Quantity and quality of human body responses are guided within the limits of life compatibility. At the level of clinical phenomenology body physiology shows a highly reactive variability, adaptive and chronobiological plasticity. Genome provides basic biological information pool which is used and maintained during the individual life span. Transcriptomic, proteomic and reactomic genome expression is guided by permanent physiological demands. Self-maintenance and functional performance from cellular to whole-body level may be analyzed as a response to the environmental conditions. For example, antigens, mechanical trauma and body exercise do turn on complex patterns of inflammation/immune, repair/ regeneration and reactivity build-up, respectively. Components of those challenges are recognized by human body as unique sets of information to which adaptive responses are generated.

Body adaptive responses are usually thought to follow nonlinear patterns. Nonlinearity stems from several levels of body functional organization. They include macromolecular functional features (e.g., enzyme kinetics, molecular turn-over), cellular level (e.g., integration of multiple signals, triggering division versus death pathways), tissues levels (e.g., remote effect of hormones/ cytokines) and regulatory levels (e.g., endocrine/neural homeostasis, mirror-j physiology), etc (Sedlić & Kovač 2017). Nonlinearity contributes to complexity patterns of natural responses in health and disease. The complexity of human body physiology, additionally, stems from parallel pathways, multiplicity of regulatory homeostatic/homeodynamic loops (feedback and feedforward), biological redundancy, genomic variability, inter-dependence on physiological gradients, chronobiological alterations of reactivity robustness and plasticity of function/structure maintenance.

Postgenomic era has shed a new light into the nature of diseases. Enhanced advances in methodology and theoretical concepts have opened new avenues of practical perspective in medicine. Contemporary databases are flooded with copious amounts of verifiable point data and myriads of nanoscale relations. Classical mission of biomedical education system has been facing challenges and necessity of redesigning and upgrading.
of curricular contents and structure. Established pathophysiological concepts and pathways are enriched with new facets of potentially relevant insights. Understanding of etiopathogenesis is burdened with a vast variability, nonlinearity, redundancy and complexity of disease pathways and networking. Comprehensive vision should take into consideration parallel, contextual, secondary, tertiary (etc) pathways along with the dominant primary sequence of events. In consideration to 32,000 diseases/disorders in human pathology there are newly emerging patterns of common tendencies in body reactivity.

The nature of scientific method in biomedicine is a dominantly reductionistic quantitative approach. Tacit scientific reasoning implies that knowledge of the elements will necessarily tell us the story of the whole system. Understanding biomedical life phenomena is thought to be reducible to the levels of chemistry, physics and information. Simplified models are developed and widely used. Those models provide testable, reproducible, and ethically approvable condition. They are easily controlled, and thus suitable for extensive quantitative analysis. In dept knowledge gain is facilitated by sophisticated methods and their growing refinements. We learn and reason in a way of “more and more about less and less”. Out of methodological simplification the whole body reactivity has been envisioned as the sum of elementary mechanisms. Integrative physiology of the organism as a whole has tacitly been derived from elements, with rarely proper testing of integral reactivity. All these approaches have inherent problem of simplification and methodological “ignorance” of complexities. In general, they tend to ignore parallel pathways, regulatory loops, biological redundancy, interdependence on physiological gradients, chronobiological alterations (etc) that are functional in the integral body system. It is obvious especially with the big data of omics-methodologies, which are pending for new interpretation schemes and their integration into the classical phenomenology.

International Society for Pathophysiology (ISP) promoted and published in Beijing Declaration, to define the role and targets of the pathophysiology (Figure 10). The document has been addressed to academic policy makers, stakeholders, professional societies and public demands with clear messages related to pending advancements in teaching/learning methodology, profiles of pathophysiology teachers as well as curricular and institutional position of the pathophysiology. Those demands are based, among other reasons, on quantity of available data which may have relevance to understanding of the whole system functioning and potentially for clinical application. On the other side, those ISP-societal recommendations, including >8% teaching hours, visibility of pathophysiology subjects in curricular designs, university appreciation and support (etc) are not fully present in all medical schools around the globe. The power of pathophysiology in dealing with complexities of human body reactivity has been accepted both by academia and clinical health providing system. They agree that pathophysiology brings a more profound understanding of patient’s condition. It remains an issue to fully implement the pathophysiological approach, institutionally and within the biomedical curricula.

Figure 9. Natural networking of the EPCs. EPCs are aligned according to the hierarchy of growing function/structure complexity on y-axis, with identified numbers of EPCs in each category. Etiological factors trigger a complex network response. The example of infection with the bacteria *Vibrio cholerae* is outlined. Arrows indicate a direction of pathobiological information flow within the network during disease.
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With reference to:
1. enhanced advances in the field of pathophysiology and related subjects, methodologies and concepts that bring a new light into the nature of diseases
2. emerging theoretical concepts and practical perspectives that form a new frame of reference related to molecular biology and medicine
3. the rapidly changing lifestyles in the developed world and the overuse of its increasingly sedentary population to a growing burden of chemicals due to over prescription of drugs as well as the ever more frequent use of electromagnetic and ionising radiation for diagnosis and treatment.
4. the growing pressure of contemporary society and public demands for reconsideration of the scope, quantity and quality of medical education
5. the necessity of providing pathophysiologically relevant information which will help academic policy makers in redesigning and upgrading curricular structures and guidelines
6. the specific mission of biomedical education system to advance and restore health, and to secure a better quality of life for the chronically ill and disabled

The ISP during its Fifth International Congress of Pathophysiology ISP 2006 held at Beijing, China (June 28 - July 1 2006) adopted the following

ISP DECLARATION CONCERNING THE ROLE AND POSITION OF PATHOPHYSIOLOGICAL TEACHING/LEARNING IN BIOMEDICAL CURRICULA

1. The sequencing of the human genome and related molecular frontline research (proteomics, metabolomics, pharmacogenomics etc) and progress in biophysics as well as in computing has underlined the importance of horizontal and vertical teaching/learning in health sciences. Integrative pathophysiology is a powerful tool in the quest to comprehend the pathobiological nature as foundation of clinical reasoning and a proper appreciation of disease.
2. 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.
3. The rapid expansion of scientific knowledge related to multiple facets of a complex pathobiological phenomenon increasingly enables a quantitative estimation of relevant processes within an integral body system. Recognition of primary, secondary and less immediate pathogenic mechanisms leads towards internal consistency of the natural course of disease.
4. Integrative pathophysiological teaching/learning increases the student’s drive to obtain and retain theoretical, practical and usable knowledge/competence. Integration leads to a better understanding, retention of knowledge, as well as an appreciation of the hierarchy of disease mechanisms (molecular, biophysical, subcellular, cellular, organ, systemic, epidemiological), and a synthetic view of morphological, biochemical, genetic, and clinical knowledge.
5. Sustainable reforms of biomedical curricula should observe and implement proper pathophysiological teaching/learning strategies. The ISP recommends that 8% or more of the total teaching/learning hours should be dedicated to the pathophysiological consideration of disease and preclinical states and conditions. Optimally, a half of these hours should consist of general pathophysiology, dealing with common concepts, principles and patterns of etiology and pathogenesis.
6. The understanding of complex phenomena involves synthesis of information derived from many sources (maximal insight). Further understanding is achieved by doing, reinforcement, repetition and continuing referral to diverse sources, thus leading to an increasing refinement and depth of perception (consensual validation). In pathophysiology this refinement of insight involves recognition of both feedback and feed-forward loops in the processes of etiopathogenesis.
7. The methods used in the teaching/learning of pathophysiology should not ignore parallel and contextual mechanisms and potential etiopathogenetic points of branching within consideration of a basic/dominant pathogenetic mechanism. Implementation of such etiopathogenetic reasoning is an essential and reliable foundation for diagnostic and therapeutic interventions as well as prevention.
8. Adoption of an integrative approach to thinking and acquiring knowledge makes it possible to synthesise coherent structures from heterogeneous data. This approach is equally relevant to the study of general and specialized pathophysiology (nosology), and should be applied within various teaching/learning forms, such as classical seminars, problem-based-learning modules, practicals, clinical rounds etc.

Figure 10. The Beijing declaration on Pathophysiology role in education curricula
To cope with the growing plethora of information Department of Pathophysiology at Rebro has institutionalized the Colloquia pathophysiologica, the series of seminars, which has been continuously held weekly, (Figure 11). Those seminars are in depth reading and discussions of updated sources of selected published materials.

Zagreb Pathophysiology in English

Etiology and pathogenesis constitute the physiology of disease/disorder condition of the human body. Pathophysiology has been considered the most reliable foundation for rational diagnostics and therapy (Gamulin 2003). It reveals a pathobiological skeleton of etiopathogenesis. Understanding the etiopathogenetic foundations of patient’s condition and general reactivity patterns is a complex cognitive step. It should respect regulation, homeostasis, kinetics, process branching, natural development and outcomes of the disease. University authorities have approved the scheme of 135 teaching contact hours, out of total 5700 hours in the 6-year program. International Society for Pathophysiology recommends that >8% of teaching hours should be devoted to pathophysiology studies. That level remains a desideratum (a wishful thinking) for future policy makes. Department of pathophysiology condensed the expected program into the given framework. Presently, study program covers general pathophysiology and functional organ system pathophysiology (Figure 7). It is aimed to enable integration of morphological, biochemical, physiological and propedeutical knowledge into plausible etiopathogenetic mechanisms which incorporate and develop a synthetic view of pathobiological basis of the disease. Methodology and study contents nurture and stimulate vertical (from gene/molecule to symptom), horizontal (simultaneous cross-interactive relation of organ systems) and longitudinal (though the time) reasoning and consideration of disease processes, with emphasis on both quantitative and qualitative aspects. Learning outcomes have been specified as follows:

- Student identifies, integrates, analyses and comprehends pathophysiological events characteristic for individual functional system and the entire organism to unravel and construct the course of clinical events in a patient during clinical practicals and physician’s practice later on. Through the analysis of etiology and pathogenesis student develops the skill of systematical integration, from the molecular, nanoscale level up to the macro-world of clinical manifestation of disease etiopathogenesis;
Through the analysis of etiological and pathogenetic mechanisms and regulatory loops, student composes general patterns of body reactivity; Student combines the up-to-date knowledge and concepts and gradually develops skills and competencies to integrate clinical problems, and identify the pathophysiological basis of rational therapy and diagnostics;

In classes student integrates pathophysiological foundations of patient's condition in simplified models (in vitro, in silico, etc), simulations and animal models. Student integrates etiopathogenetic and branching pathophysiological processes in organismic responses according to vertical, horizontal and longitudinal dimensions of the disease/disorder;

The Pathophysiology course contents is structured and composed of lectures, seminars practicals and self-guided casuistic problem elaboration. It consists of 35 educational units and 2 groups of skills and competencies. Student actively composes and discriminates the etiopathogenetic pathways and dynamics out of elements organized in matrices;

In lectures student systematically distinguishes and synthesizes causes, processes and regulatory relations within the various groups of diseases/disorders. Student compiles and summarizes pathophysiological principles which include physical, chemical and biological foundations as well as taxonomy, hierarchy and statistical analyses. Student formulates and reconstructs natural pathways. Student makes conclusions and comparisons based on general principles of etiopathogenesis, always following the approach from the general (abstract) down to specific levels of understanding (i.e. applies top-down approach);

Through multi-layered approach in seminars student re-constructs, defends and compares relevant knowledge by developing etiopathogenetic algorithms (i.e. applies the contextual benchmark approach). Out of the given elements, student re-arranges, concludes and distinguishes the parallel pathways, branching points and positive and negative feedback homeostatic loops. Student appraises the corresponding symptoms, signs and degrees of dysfunction.

In practicals, comprised of self-guided solving of the Workbook and work in clinical wards, student identifies, analyses and combines relevant elements and assesses condition of the individual (i.e., applies the case-study bottom-up casuistic and inductive approach). By integrating clinical, laboratory, animal and quantitative exercises student combines, outlines and concludes on pathophysiological nature of patient's reactivity.

Student combines the three cognitive-educational levels, which mutually complement each other in Pathophysiology education. Student extracts the unique pattern and competence of integrative comprehension of etiopathogenetic triggers, dynamics, reactivity alterations and outcomes of the disease/disorder. Through theoretical and practical contents, methodology, and analysis-synthesis skills, student builds up the basic competencies and attitudes to analyze and to re-construct, the nosology of any disease/disorder in any branch of the medicine.

These outcomes, although not formulated out in that way, were already practiced from Sokolić’s time on. The advent of big data in the postgenomic era has given additional demand on integration of knowledge and reinterpretation of classical physiological understanding. To facilitate and stimulate active participation students elaborate and construct graphic representation of natural course of diseases. In order to nurture a proper clinical reasoning students work with etiopathogenetic clusters as branching points of reactivity.

In academic year 2005./2006. Department of Pathophysiology started Pathophysiology course teaching in English. It was a challenge. Our concept of pathophysiology teaching/learning could not directly use the available written materials, due to a quite different approach in studies of pathophysiology contents in English speaking tradition (UK, USA, and others). We could not find available ready-to-use materials written in English, to be compatible and to directly support our program (as official textbooks/materials) of pathophysiology teaching/learning (outlined in Figure 7). Those books could have been used only as a broad basis of referenced literature. Namely, that language speaking areas do study pathophysiology as a separate discipline, usually not under “pathophysiology” name. They use terms “clinical physiology”, “correlations of basic sciences and clinical medicine”, “mechanisms of disease” and sometimes “general pathology” or “investigative pathology”. Their approach is closer to nosology, the specific pathophysiology (etiopathogenesis) of individual diseases (Kovač 2014). They rarely organize a department of Pathophysiology, as a university unit, and they do not always consider pathophysiology as the separate branch of medicine. Therefore their pathophysiology has just ancillary role within other subjects (like internal medicine, surgery, neurology etc). Their textbooks are written in similar fashion and conceptual organization. The critics of such approach argue that by keeping pathophysiology reasoning within the contents of any specialization limits, the „enemy from within” is embarked in the process. The understanding of pathobiology framework tends to be confined to the same limits. Already, in the 19th century, pathologist Rudolf Ludwig Karl Virchow (1821–1902) warned against this kind of problem (Virchow 1858, Churilov 2015). He spoke that pathophysiology should mean the whole really scientific theoretical medicine, bearing in mind that theoretical does not mean hypothetical: it is sourced out of evidence…” The evidence is, according to Virchow, based on „...two
pathways: clinical observations and experiment...“ in sense broader than limits of any singular branch of medicine. Therefore, he says, "...that's why Pathological Physiology does not flow out of Anatomic Pathology. (...) It is great autonomous and extremely important science...“ (Virchow 1858). In similar way, famous Russian physiologist, the Nobelist, Ivan Petrovich Pavlov (1849–1936) makes the argument that "...pathophysiology can not and should not be just a supplement to Anatomic Pathology. Nowadays it would be unforgivably anachronistic...“ (Churilov 2015). Despite the Virchow's and Pavlov's critique of such „singularization“ concept, the British and the American tradition have ignored it, by a large, and they proceeded with a fragmented approach and supplementary role of pathophysiology, till present days. Therefore, presently available textbooks of pathophysiology in English are written in organ-system fashion (e.g., cardiovascular, gastrointestinal, etc) with elaboration of nosologies of individual diseases of the system. They strongly insist on reductionist interpretation of underlying processes, as a foundation of understanding. This holds true for university textbooks of Smith-Their-Wygaaarden group, of Sodeman-Sodeman group, Frolich group as well as of McPhee/Ganon group. Interestingly, nursing education English textbooks of pathophysiology take a different approach. They have taken the semiological strategy. Namely, they try to interpret symptoms, signs and syndromes. Since they are aimed to nursing and related health services, those textbooks do not insist heavily on pathways, interconnections of systemic and local processes, etc. This is true for textbooks written by Hansen-group, Porth-group, Bullock-Rosendahl group, McC-chance-Hueter group, Price-Wilson group and Nowak-Handford group.

Department of Pathophysiology applied the established Mikulić-Sokolić-Gamulin integrative clinical concept, algorithmic methodology and clustering analysis in the English program. We wanted to implement the Croatian-like program (Figure 7), and to fulfill those outcomes as well as basic requirement and recommendations of the ISP (Figure 10). Quantity and quality of English education were to be equal to the Croatian one. The adoption of integrative skills, competencies and ways of thinking required the textbook in English, that will follow such strategy. Above mentioned textbooks were used just as supplementary materials. Department translated and published the 7th Edition of Gamulin's textbook, The Basic Mechanisms of Disease is the integral translation from Croatian of the 7th edition of Gamulin's textbook, The Book One. Study Guide Algorhythms – Problem Solver is the translation of the 3rd Edition of the Book Two – a companion textbook used as working matrices for problem seminars.

Figure 12. English translations of textbooks was published in 2014 by Medicinska Naklada in Zagreb. Basic Mechanisms of Disease is the integral translation from Croatian of the 7th edition of Gamulin's textbook, The Book One. Study Guide Algorhythms – Problem Solver is the translation of the 3rd Edition of the Book Two — a companion textbook used as working matrices for problem seminars.

Figure 13. The workbook for Practicas is reedited each year. It contains practical tasks and examples as a study guide of clinical exercises and 20 most common etiopathogenetic clusters (EPC) with 4 study cases each.
Figure 14. Three levels of knowledge construction in teaching/learning are interconnected in contemporary teaching/learning approach which stemmed out of the Mikulić-Sokolić-Gamulin integrative clinical concept of Pathophysiology. Some features of reasoning and knowledge processing are described, and aligned in parallel with three levels of our educative materials and methods.

possible the integration of real clinical casuistic data and patterns with a broad academic, theoretic and universal principles, present in the problem. Such exercise puts student into integrating reasoning pathways and develops a subroutine attitude to deal with each case in a similar way. The power of approach, we think, stems from enforcement of three directions of consideration in parallel. Those are a “top-down”, “contextual bench marking” and “bottom up” directionality in dealing with heterogeneous facets of information. Construction of pathways and clustering points of disease development interchangeable uses those directions in designing the synthetic presentation of the case. These methods enable both quantitative and qualitative data and descriptive facets of information and construction of local and systemic networking of disease processes.

In academic years 2016./17. we introduced complementary 3-7 minutes movie as illustrations of selected etiopathogenetic issues. Both in the Croatian and the English program this has been well received. The vivid visual/acoustic movie media seems to have easier communicative pathways and keep better attention in present generations of students. Since those media are available to students for 24 hours, 7 days a week, they may be an important component in adoption of integrative skills, competencies when dealing with medical problems.

Zagreb pathophysiology outside of academia and echoes abroad

University of Zagreb is the state university with 348 years of tradition in academic activities. It is a classical universitas studiorum European type of a higher education institution with 33 units, one of which is the Medical School of Zagreb. The main stake holder of the University is the Government. Due to turbulences in general history, Croatia in the 20th century rarely reached a reasonable stability. Multiple geopolitical, often radical alterations in Croatia are marked in the lower part of Figure 1. She was exposed to 3 wars each lasting for 5 years (the First and the Second World War, the Homeland War 1991-95), followed by long postwar recovery times. She was oppressed by a significant foreign domination and two non-democratic governmental systems (1941-45 and 1945-1990). In such historical framework, university budgeting and investments into academic development were not high on priority list of government budgetary agenda.

Despite the unfavorable context in 95 years of academic and practical activities in the Department of Pathophysiology has made visible achievements. Leading authorities have managed and directed their groups’ activities towards new areas of interest and a permanent
quest on underlying mechanisms and their common patterns. Such inquiry attitude has been exercised in parallel in all three aspects of pathophysiology, the scientific research, the clinical service to the patient’s needs and the education at various levels (graduate, postgraduate, doctoral). The cutting edge attitude and innovative approaches have been a challenge and attractive for a broader biomedical community in Croatia. The Editor-in-Chief of Croatian Medical Chamber monthly journal, Ž. Poljak, even went to name those first 95 years of pathophysiology activities and achievements as the Zagreb School of Pathophysiology (Poljak 2014) The title of „school“ implies and/or refers to a unique position and a unique professional academic way. He reasoned that in contemporary medicine „…there has been a continues excessive growth of copious amounts of point-data. Those data are technically-marked and not always self-understandable to physicians. Those big data in medicine appear, from time to time, to be contradictory to each other. Sometimes they cause confusion. On the other side medicine needs the integrative approach. Zagreb Pathophysiology School has established (...) methods of etiopathogenetic clustering and algorhythmic problem elaboration – which successfully put together contemporary understanding of both basic and clinical sciences' data. Those methods facilitate physicians' integration and make a bridge over the gap in contemporary medicine. They provide a reliable foundations for rational diagnostics and therapy...“. Impressed by the pathophysiology timely proactive introduction of new steps which turned out, later on, to be productive/useful and/or far-reaching undertakings,

Table 2. Introductory papers (1-3) and thematics’ papers (4-9) within the serial of **Integrative Lessons in Clinical Pathophysiology**

1. Kovač Z: Integrative algorhythmic and etiopathogenetic clusters as study methods to bridge the chasms between the basic science and practical medicine. *Mol Med* 2014; 2:51-6

Figure 15. The blank graphic matrix of etiopathogenetic networking used in the Test of Liječničke novine. Each circle should be filled with the appropriate number - the code of the given element of pathophysiological pathways within the problem considered.
Figure 16. Russian journal Clinical Pathophysiology. A) The detail from headline page of the journal; B) Introductory part of Integrative Lessons in Clinical Pathophysiology serial. The problems are written in English, with the abstract in Russian added.

the Editor emphasized that “... Sokolić’s legacy (...) in clinical pathophysiology has reached the appropriate place in practical education of physicians...” (Poljak 2014) Therefore he invited Department of Pathophysiology to extend its algorithmic and clustering approach to broader physician’s community. The serial of problem solving - permanent education thematic was initiated in Physicis Bulletin (in Croatian - Lijecnickie Novine), in the year 2014. Dozens of published elaborated problems within the Column The Zagreb Insights into Etiopathogenesis induced vivid readers' responses, critiques and discussions. Many of them expressed the recognition of a novelty in the approach. Later on, in the year 2016, the Column was converted into The Chamber Credits Test, used as a component for doctors' professional licensing procedure. The example of test graphic representation of etiopathogenetic pathways and clustering is outlined in Figure 15.

Throughout 95 years, Department of Pathophysiology practiced, since the very beginning, international exchanges, interactions and collaborations. Started with Mikulić, through Sokolić's and Gamulin's era it has become the standard of performance. There are many facets of international interactions practiced through years, including postdoctoral training, doctoral degree studies, scientific research projects, clinical research projects, conference organizations, journal editorial participations, reviewing the manuscripts, invited lectures, participation in professional society boards, etc. Special international attention has been aroused by novelty of
teaching/learning methods in the last two decades. Etiopathogenetic clusters and algorhythmic elaboration have been presented at many conferences, including Beijing 2006; Hyderabad 2008; Shanghai 2009; Sankt Petersburg 2009; Montreal, 2010; Washington, 2011; New Orleans 2012; Iasi 2013; Rabat, 2014; Iguassu Falls, 2014; Kuala Lumpur 2014; Boston 2015; Plzen, 2015; Zaghdazor 2015, San Diego, 2016; Chicago, 2017; Cluj Napoca, 2017; and Rio de Janeiro, 2017 - presented in various formats. There were 5 plenary lectures, 3 keynote lecture, 4 short symposia lectures, etc. The summer school “A bird's Eye View to Pathophysiology“ in Armenia, held July 2015, paid a special attention to our methods. First few presentations of two methods in Russian journals have induced an interesting feedback request. The Journal Editorial Board of Clinical Pathophysiology invited us to systematically familiarize their readers with our approach in form of Integrative Lessons in Clinical Pathophysiology. Six themata groups of problems have been so far treated in the form of problem solver in journal issues of 2015-2017 (see Table 2). All contributions are published in English, with summaries in Russian language (Figure 16). Curricular tradition of pathophysiology teaching/learning in Russia and consistency with goals and recommendations with the Beijing Declaration on Pathophysiology (Figure 10) seems to be recognized by the Lessons’ readers. LC Churilov in analysis of historical trends in pathophysiology recognizes that “…algorhythmic 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 (…) They have a multiple redundant inputs and multiple equifinal exits, so they demonstrate some targets of therapeutic interventions. (…). Additionally, he concluded that there are “…around 100 of mosaic blocks, interplaying in all nosological forms, like elements of Mendelejev’s table adjoined in any substance, so they give strong impetus to systemic autonomous analysis of clinical and pathophysiological problems by students…” (Churilov 2015).

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References

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