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ИНТЕГРАТИВНЫЕ АЛГОРИТМЫ И ЭТИОПАТОГЕНЕТИЧЕСКИЕ КЛАСТЕРЫ В МЕТОДОЛОГИЯХ ОБУЧЕНИЯ, ОРИЕНТИРОВАННОГО НА СВЯЗЬ ФУНДАМЕНТАЛЬНОЙ НАУКИ И ПРАКТИЧЕСКОЙ МЕДИЦИНЫ

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Преподавание в медицине уже столкнулось с проблемой взаимоотношений между фундаментальными науками и клиническими дисциплинами. В постгеномную эпоху вопросы методики преподавания связаны и с выбором содержания и с объемом материала, предлагаемого для освоения. Качественная и количественная природа информации и заслуживающие доверия методологии исследований создают дополнительные проблемы в медицине. Возникает необходимость выбора между реальной и потенциальной клинической релевантностью (точностью и надежностью), сложностью регуляции на молекулярном уровне, разработкой концепций иерархического структурирования, адекватности и нелинейности реактивности и методики преподавания/обучения и т.д.

Изучение патофизиологии должно обеспечить надежные интегральные подходы и создать возможность для того, чтобы скомпоновать этиологические и патофизиологические компоненты. В этой статье вкратце обсуждаются общие особенности комплексных алгоритмов и этиопатогенетических кластеров. Эти 2 подхода обеспечивают пошаговые методики, которые от индивидуального уровня (клинические примеры, специфические этиологические и патогенетические проблемы) переходят на релевантное вертикальное, горизонтальное и лонгитудинальное интегральное представление о природе заболевания. Оба подхода создают структурно организованную систему и побуждают читателя к сотрудничеству и интеграции знаний. Обе методики представлены в монографиях, в которых рассматриваются подходы к решению проблем. Такие пособия широко используются в ряде университетов с поразительным успехом. Они подходят и для самообразования. Оба подхода основаны на аналитической и ресинтетической системе решения проблемы. Когнитивные механизмы (распознавания) мозга человека, по-видимому, способны реализовать такой синоптический (всеобъемлющий) подход, и поэтому такие методы нашли признание и получили высокую оценку многих поколений студентов. Обучение в аудиториях и время реального общения студента с преподавателем конвертировались во взаимовыгодное сотрудничество. Обе стороны выигрывают в процессе преподавания и обучения, основанном на этих 2 подходах. Истинная ценность разработки алгоритмов, а также этиопатогенетических кластеров состоит в их одновременном комплексном подходе к локальным и системным аспектам заболевания. Такие подходы, по-видимому, позволяют преодолеть некоторую предвзятость в компартментализированной медицине и упрощенной природе исследования. Они могут помочь в ликвидации пробелов в общих представлениях в области медицины благодаря комплексности достижений фундаментальных и прикладных клинических исследований. Не вызывает сомнений, что профессиональное сотрудничество клиницистов с исследователями будет способствовать повышению эффективности их усилий, направленных на сохранение здоровья будущих поколений.

Ключевые слова: *алгоритмическое обучение, междисциплинарый подход, этиопатогенетические кластеры, медицинский тезаурус, патофизиология, проектно-ориентированное обучение, системный подход*

INTEGRATIVE ALGORHYTHMS AND ETIOPATOGENETIC CLUSTERS AS STUDY METHODS TO BRIDGE THE CHASM BETWEEN THE BASIC SCIENCE AND PRACTICAL MEDICINE

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Education in medicine has been facing a challenging problem of relations between basic biomedical sciences and clinical medicine. In postgenomic era emerging didactic issue is related both to contents and quantity of knowledge to be studied. Qualitative and quantitative nature of information and respective methodologies of research impose additional cognitive problem in medicine. The challenges are related to a real versus potential clinical relevance, molecular regulatory complexities, conceptualization of subsidiarity, robustness and nonlinearity of reactivity, and methodologies of teaching/learning (etc).

Study of pathophysiology should provide reliable and integrative pathways and networking of etiological and pathogenetic components. In this paper general features of integrative algorhythms and etiopathogenetic clusters are shortly discussed. These two approaches provide step-by-step methodologies, which from the individual level (case reports, specific etiopathogenetic problem) expand into relevant vertical, horizontal and longitudinal integration of disease phenomena.

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, which are used in several universities with impressive success. They are convenient for self-education, as well. Both of them are using analytical and re-synthetical system of problem consideration. Human brain cognitive mechanisms seem to be akin to such synoptic approach and thus these 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 an advantage of teaching/learning procedure based on these approaches. The real power of both algorhythmic workout and etiopathogenetic clusters is in their simultaneous integral consideration of local and systemic processes of the disease. These methodologies seem to resolve and circumvent some biases of compartmentalized medicine and reductionistic nature of the research. They may contribute to reduction of collective cognitive chasm in medicine by bringing together basic and clinical knowledge. It seems that professional activities of both physicians and researches may be facilitated towards more fruitful efficiency in their efforts for tomorrow's heath.

Key words: *algorhythmic learning, interdisciplinary teaching, etiopathogenetic clusters, medical thesaurus, pathophysiology, pathology, project-oriented learning, systemic approach*

INTRODUCTION – THE PRESENT STATUS OF RESEARCH AND EDUCATION IN MEDICINE AND RELATED FIELDS

Biomedical sciences and medical practice started the 21-st century with the exciting driving forces, which come both from basic discoveries and new clinical applied methods. This essay is a short overview of landmark discoveries, methodological breakthroughs, new medical paradigms and «cutting-edge» interest of medicine, and educational issues, as well. Contemporary understanding of general features of the scene can be summarized as follows.

Postgenomic era of medicine started with the completion of human genome sequencing in the year 2003. Along with the factual contents of chemical basis of genetic information, the new powerful methods have been developed. Those methods are often able to generate the throughput quantities of measurable and verifiable data [16]. The real macromolecular communications have become the major players in the interpretation of physiological phenomena. The horizons of molecular insight into the living processes are unprecedented in the history of science. Beyond DNA-codifying machinery, genetic and epigenetic regulation (transcriptomics) has become a challenging issue. Together with proteomics, reactomics (and other omics-scientific strategies) molecular orchestration of life processes has become a central theme [20, 21]. Bioinformatics helps in converting the raw molecular data extracted from patient samples into interpretable, accessible and statistically meaningful information. The power of quantitative molecular consideration of living phenomena has brought new insight and vision. The triumph of **molecular medicine** sets a stage for a reinterpretation of classical framework of knowledge. Biology as science (including science of human life processes) has gone through a **positivistic scientific revolution**.

In parallel with molecular medicine, a new prospective of medicine has been opened by discoveries of cellular unique ontogeny and tissue dynamics during the lifetime. **Stem cells biology, renewal and somatic cell reprogramming** shed new light on human body regeneration potential, life span concepts, and chronobiological alterations, etc [17]. The pluripotency of stem cells has become the second paradigm of medicine. Stem cells can transform into a dazzling array of specialized tissue cells. Disorders of their physiology and body trafficking may be responsible for various serious medical conditions (such as cancer and birth defects, etc). Presently, they are seen a sort of internal repair system, dividing essentially without limits [2, 13]. The concept of replenishment of cells in damaged or functionally failing tissues/organs comes as «materialized wishful thinking» of practicing physicians. Application of pluripotent stem cells have been approaching to the clinical arena. Methodology offers the possibility of a renewable source of replacement cells and tissues to treat a myriad of diseases (like, Parkinson's disease, amyotrophic lateral sclerosis, postischaemic conditions, spinal cord injury, burns, heart disease, diabetes, arthritis, etc). Along with upcoming strategies of **stem cells – based therapies** and **regenerative medicine**, stem cell natural physiology itself represents the landmark advancement of knowledge in human biology.

The complexity and functionality in human health and disease states should be considered as physiological continuum. The same functional units of body reactivity are active in both groups of states, but with altered homeostatic regulatory features. Two fundamental characteristics of the complex systems are a system robustness and subsidiarity of elemental functional units. **Robustness** is defined as ‘a property that allows a system to maintain its functions against internal and external perturbations’ [9]. It is considered as the fundamental characteristics of biological systems in general. The organism’s phenotype remains constant within the broad limits of reactivity (i.e., a «reactive norm» of the system). It is so due to biological reserve, hormetic adaptative response, genomic adaptative response, mutual balancing of antagonistic responses, redundancy of pathways and units’ structure (i.e., multiple components performing similar functions), etc [12]. Robustness as the capacity of a system to function despite perturbations is fueled by a functional **subsidiarity**. Namely, human physiology may be considered as a self-regulating system, with internal subsystems. Those subsystems contain a given level of autonomy of reactivity and they have bidirectional communication lines with the central regulatory unit. Such «distributed authority» of subsystems (like, organs, cells, genome regulation etc) contributes to adaptive efficiency, a selection of recruitment of appropriate mechanisms, safe-guarding an alarming of the entire system, etc. A robust power grid of the body stems from safeguarding and synchronizing all subsystems.

Translational medicine policy shifts an academic strategy towards the defined ultimate goal of practical patient’s benefit [1, 6]. Pragmatic vision fosters both clinical and basic research towards the improvement in health of population. Policy makers have established a broad front that synchronizes regulatory forces (pertaining to scientific, healthcare, financial, ethical, legislative and broader social aspects), to bring about efficiency of complex undertaking. Academic centers, research programs, foundations, industry, disease-related organizations, and health-care systems are involved. The aim of optimizing patient care and preventive measures is considered as a natural progression from **evidence-based medicine strategy**. The strategy of «explicit, consciousness and judicious use of current best evidence» is now enriched and enforced towards the active generation of a new knowledge and procedures, to be usable directly at the heath-care level.

Compartmentalization of practical medicine and dominant reductionistic nature of scientific research impose a limitation on cognitive processes and conceptualization of integral physiology and pathophysiology [3, 4, 14]. In simple terms, it may be stated that due to a narrowing down the scope of consideration, the ignorance of parallel processes (within the other parts of the same body) is increased. Professional compartmentalization into specialties and subspecialties contributes to the focusing and gaining greater expertise for given type of the disease. Structure of hospitals, education system and curricula are organized according to such conceptual scheme. However, natural development of disease processes often shows a tendency to spread away from the primary locus into surrounding and remote tissues and functional systems. Compartmentalized medicine faces the problem how to deal with complex states of diseases, whose patterns are not necessarily «compartmentalized». Similar objections and weaknesses can be raised with respect of reductionistic nature of scientific research. Natural reactivity and disease development are thus sometimes described as «non-linear», chaotic, «deterministic chaos – driven etc. Integrative understanding of physiology and pathophysiology should not ignore any side of the coin. In both holistic terms and in individual parts the integrative view should constitute the main pillar of medical intervention.

Societal demands of **personalized medicine** adds important stamp to the health-care system demands in 21-st century. Instead of administration of a standard scheme of optimal therapy (validated for the group as a whole), individual variability of body reactivity should be taken into clinical consideration [8, 11]. The most efficient treatment and individual healing procedure is sought, and each person own reactivity should be diagnostically evaluated and taken into decision making process. Tailored therapy is to be designed according to the quality and quantity of individual patterns of reactivity. Since clinical evaluation is costly procedure, a degree of personalization of heath-care system heavily is conditioned by the level financial availability.

In the best scenario **medical education strategy and methodology** would follow the most efficient approach. In optimal scheme appropriate time, quantity of theoretical and practical knowledge and competencies should be allocated to the newcomer to master the profession requirements [5, 15]. Presently European administrative directives set a lower limit of basic medical education to be >5500 hours, or six year curriculum. However, stake holders and academic policy-makers tend to impose contracted time limits on teaching contact hours. It is a paradox of demanded reduction in spite of the knowledge expansion. Various recommendations and recommended procedures have been proposed [7, 10]. Heterogeneity of approaches and extensive variability of curricular schemata and methods are due to a lack of real progress in methodology of teaching/learning concepts. Example-based learning is traditionally considered as the most efficient method of learning. In medicine case-based learning enriches the clinical experience in diagnostics, therapy and abstract knowledge, as well. Theoretical considerations encompass taxonomic classifications, information technologies and referent knowledge (physics, chemistry, molecular biology, omics-sciences etc) as useful supplementary ways. Quantity of potentially medically-relevant information, and technical nature of information impose additional limitation on the progression of medical education.

Understanding of **nature of human brain cognitive functioning** may help in developing more efficient ways of studying. Cognitive powers of adults, including scientific reasoning, are tightly connected to a motivation, logical reasoning and previous experiences. Human intellect does not deal with plethora at the individual data points [18, 19]. It masters copious amounts of data through generalization, statistical averaging and extracting the common principles to be valid for majority, etc. Adult human brain grasps the plethora of perception and molds it into internal concepts, stratifications and visions. Gain and retain of declarative knowledge and practical subroutine competencies are repetition-based processes. The study procedure of adult human brain includes a construction of knowledge in self directed, autonomous and previous – experience – related manner. Adults try to apply a new comprehension and specific mechanisms directly to his/her problem solving tasks. Through evaluation and active re-synthesis of patient's data students of medicine and doctors facilitate a gain and retain of medical knowledge. It is a sort of intellectual reinforcement of knowledge construction. Reiterative inquiries into the same or like-problems enable the proper professional grasp, elaboration and solution of any practical problem.

MATRIX DRIVEN ACTIVE ALGORHYTHMIC ELABORATION OF THE PROBLEM – A POWERFUL METHOD

Medical information has been grown and it continues to grow, with a fast pace. How to reduce the information noise and dig out main etiopathogenetic pathways, contextual and parallel pathways, branching points and their mutual interaction has become the burning issue. Not all information is relevant (at least at the present time). The context of inquiry, experimental design, the levels of control and appropriate conclusions are factors of relevance. Proper pathophysiological interpretation of natural history aims to integrate **vertical dimension** (from the molecule to symptom), **horizontal dimension** (simultaneous involvement of multiple systems), as well as **longitudinal dimension** (natural course) of the problem. Such framework of integration was used as a systemic approach in the concept and narrative of the textbooks of pathophysiology, which are in use in last three decades (Figure 1).

Although, pathophysiology education has been following many pathways, including concepts of general principles, nosology, organ-related pathophysiology, etc, all teaching/learning configurations have a common idea – one should follow the nature of pathobiological development considered in three dimensions. Natural history of disease and disorder should be the principal foundation and the frame of reference. In the following two approaches those three dimensions of pathobiology have been systematically applied and enforced throughout individual tasks.

In order to make pathophysiology teaching/learning workable from teacher's point of view, as well as attractive and friendly to students, we established educational matrix-guided model of **problem based seminars (PBS)**, with four steps. The first step is **exposition of problem** that gives short presentation of «raw data» derived from patient records, selected publications with experimental data, etc. Narrative presentation uses natural language in medicine. Each case study is derived from published reports concerning a certain problem. Scientifically it is primarily qualitative type of information mixed with qualitative data whenever it was possible and appropriate. The exposition part gives a study context for the upcoming elaborations within the 2 thought 4 step of the matrix. The second step is the **repetition of relevant knowledge**. It is a multiple choice test, that includes statements related to the exposition and referred teaching materials. Questions and the tasks are designed in a special way to be the most informative and instructive. Namely, the correct answers are the wrong statements, whereas all other statements are essentially truthful descriptions of pathophysiological pathways of the study case from exposition. Such matrix guides a reader towards new facets and through additional layers of considered etiopathogenesis. It is a tacit strategy to provide the solid foundation of declarative knowledge and deeper understanding. In the third step, **the algorhythmic workout of the pathogenesis** student's task is to build-up the cause-consequence sequence of events out of given 25–30 units of etiopathogenesis. Student discovers a positive and negative feedback loops, and parallel and contextual events, as well. The active re-construction of etiopathogenesis out of fragmented elements may be considered as a formal integration of knowledge. Visual graphic re-design (Figure 2) helps developing habit of systemic elaboration though stepwise procedure, which are close to the practical every day activities of the physician. The fourth step, the **feedback integration of the problem** deals with additional relations, systematization and quantitative aspects of the same problem. All four levels of PBS are focused on the central theme given in the exposition and each new level adds up important facets and aspects. Thus, the integrated take-home message is generated. The method is 2.3 times more efficient in comparison to classical teaching. It nurtures vertical, horizontal and longitudinal conceptualization of the problem. So far >9000 students of medicine at Croatian universities have been successfully educated via this methodology and appropriate textbooks were published (Figure 3). They often claim to have been practicing the same scheme of thinking, later on, in their daily elaboration of individual patient's health problems. They find 4-step matrix exercise of PBS as challenging frame of reference useful in many branches of medicine.

Figure 1. *Seven editions of the textbook Pathophysiology (in Croatian) in which a synthesis of general etiopathogenesis is outlined in 35 chapters. The book has become the referal text and it is the best selling book of medicine in Croatia*

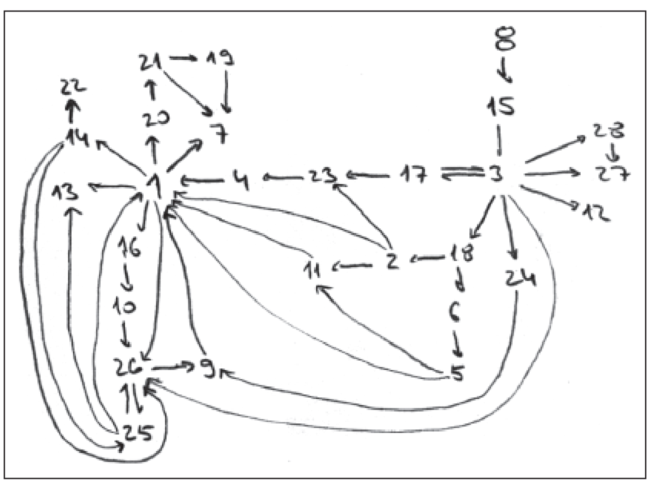

Figure 2. *An example of students solution of etiopathogenetic algorhythm. Each number is a code name for given etiopathogenetic element which are used as the unit blocks. The construction of algorhythm is formal representation of synthetic interpretation of decribed etiopathogenesis*

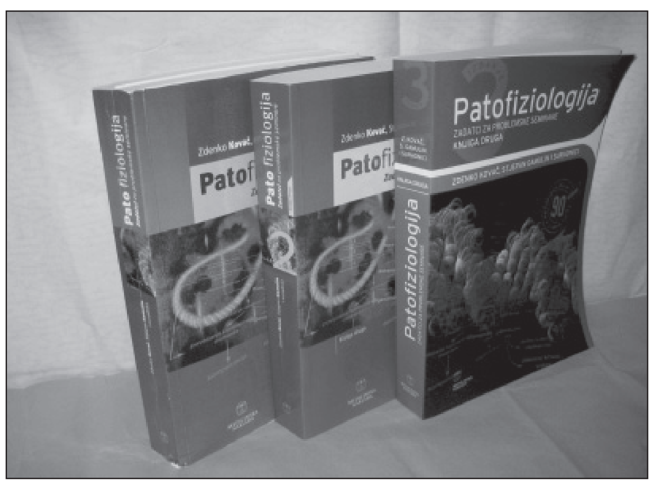

Figure 3. *Three editions of Pathophysiology – Problem Based Seminars (in Croatian) introduced an algorhythmic workout of the problem. It became the standard methodology in education of medicine. It has been described as a student friendly approach*

ETIOPATHOGENETIC CLUSTERING AROUND THE NODES OF NATURAL NETWORKING OF REACTIVITY

During disease development there is a natural tendency of individual etiopathogenetic pathways to join together and to form networks. The inter-connective elements serve as building blocks within the hierarchy of the system. We named those interconnecting nodes the **etiopathogenetic clusters (EPC)**. The EPCs may be considered as crossing points of the natural reactivity. They are formed at various levels (e.g. electrolyte concentration abnormalities, pH-alteration, energy disorders, cellular quantity-alteration, whole organ dysfunctions etc) (Figure 4). In terms of homeostatic regulatory relations, the EPCs have multiple entries and outputs. They are branching and integration point of reactivity. The EPCs are systematically elaborated and all tasks solutions in the published book are provided (Figure 5).

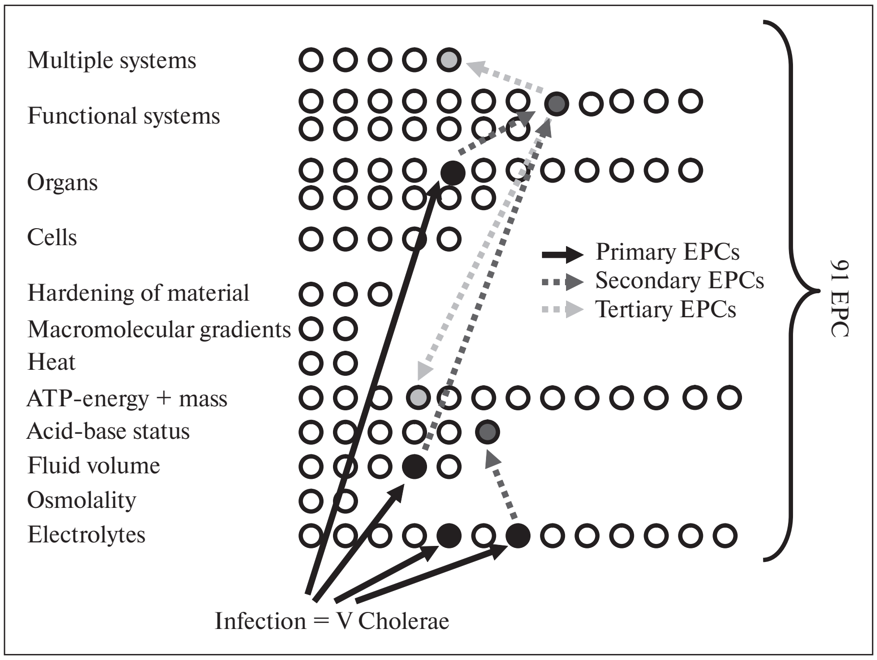

Figure 4. *The 91 etiopathogenetic clusters (EPC) are formed at various levels of functional hierarchy of the body. Primary EPC induced by etiological factor often triggers secondary, tertiary (and n-th) EPCs and contributes to the networking of processes*

Even more, therapeutic corrections of such cluster values may lead to a clinical improvement. For example, correction of arrhythmia of ventricular fibrillation leads to a fast recovery from cardiogenic hemodynamic shock and saves the life. Therapeutic correction of hyperglycemia that causes the hyperosmolar syndrome leads to improvement of consciousness disorders and fluid derangement in the body. In addition to direct practical importance, teaching/studying of EPCs may become a reliable approach to master complexities in medicine. All tasks are designed in a way to bridge basic and clinical sciences and are always kept within the clinical reality of reported study cases. There are 91 principal clusters within the 30000 diseases. General assumption predicts that interconnection of those 91 EPCs creates the basic network of body's «skeleton» of reactivity. Their interconnections would be the principal pathways according to which the system work. Variability of clinical symptoms and signs of the same disease in various individual patients would come from genomic, chronobiological and personal history variability (and others). However all conditions will have the basic EPC-interconnections behind the course of the disease. In other words, this concept and vision claim that the vast majority of human pathology may be reduced to a basic network of EPC-system.

We designed 1165 case studies (based on the published case reports) clustered within the 91 EPC. These case studies are directly usable as illustrative examples in daily clinical practice. In order to facilitate the usage of the book, the graphic introductory diagram in each chapter serves as schematic orientation within the multiple causes and consequences related to the given etiopatogenetic cluster (Figure 6). Such «mille-stoning» and visual networking helps in better conceptualization and comprehension of complex processes.

On the other hand, the concept of clusters helps to grasp a nonlinearity and complexity of pathobiology within the real study-time framework. The EPC-approach facilitates a rational usage of the information plethora and mastering professional demands. They provide a reliable frame of reference of pathobiological processes which underlay the clinical problem. It seems that EPC-approach facilitates

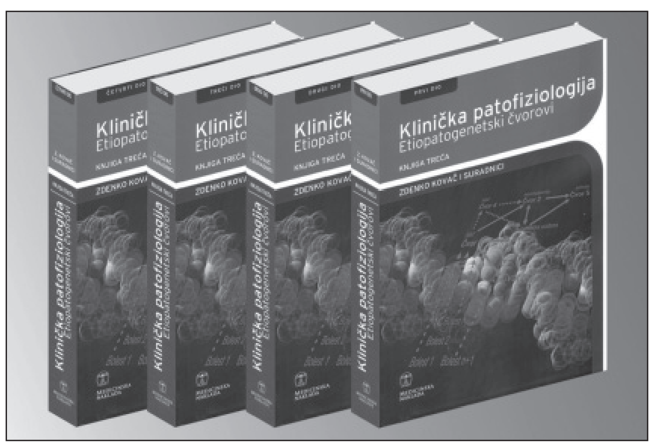

Figure 5. *The book of Clinical Pathophysiology – Etiopathogenetic clusters (in Croatian) is four volume edition in which 91 etiopathogenetic clusters are elaborated in form of case studies. The clusters are considered as central integrative parts of natural networking of processes*

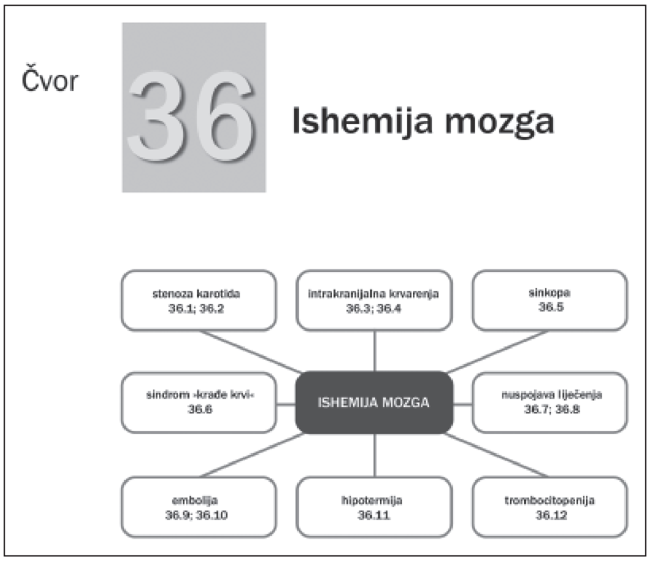

Figure 6. *Copy of EPC introductory page shows that each cluster has an introductory diagram that connects the central clustering event with the individual cases elaborated in that chapter. The cluster 36 «BRAIN ISHEMIA» is one out of 12 clusters described within the dysfunctions and disorders related to «ATP-energy and body mass level» of functional hierarchy (please compare Figure 4)*

medical reasoning towards integrative vision, and bridging the chasm of compartmentalized medicine education and research.

CONCLUDING REMARKS

Both PBS and EPC together form a useful methodology for teaching/learning of pathophysiology and medicine in general. Both of approaches challenge student to take active role, facilitate a lot of student-teacher interactions, enforce a multiple repetitions and re-interpretations of etiopathogenesis, and always tend to integrate the basic sciences with clinical knowledge.

Conceptually, these two approaches represent a practice oriented pathophysiology that presents a contemporary state-of-the-art pathophysiology at individual patient cases. It seems that this approach brings about a better gain and retain of pathophysiological knowledge. Written materials are in form of problem solver (all solutions of the numerous tasks are given in the accompanying materials) which makes them suitable for a self education, as well.

The EPC-model offers etiopathogenetic network of crossing points. Elaboration of those clusters through multiple study cases keeps the learning process close to the practical every day activities of physician. Since it is following natural etiopathogenesis, it is not limited to the specific branch of medicine. Thus, the EPC-approach crosses the boundaries of professional compartments in medicine.

Both PBS and EPC approaches are open systems into which the new upcoming discoveries could be easily built in as contributing units. The authors of the book and methodology consider this as important feature. Since present knowledge naturally is partial one, the new relevant discoveries and insights will deepen our understanding of EPC-networking.

Both PBS and EPC may be useful for researchers and other professionals with non-medical background. With usage of this scheme they may find a reliable way to deal with the complexity of human clinical pathophysiology.

Both PBS and EPC are bringing together clinical and basic science knowledge (molecular, cellular, etc). Both methods tend to fuse reductionistic knowledge and holistic view into the clinically workable scenario. One may say the two methods have made a solid bridge between the basic and clinical sciences and practice.

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