ВОПРОСЫ МЕДИЦИНСКОГО ОБРАЗОВАНИЯ

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З. Ковач

ПРЕПОДАВАНИЕ И ИЗУЧЕНИЕ ПАТОФИЗИОЛОГИИ КАК НАДЕЖНЫЙ ПУТЬ К ИНТЕГРАТИВНОМУ КЛИНИЧЕСКОМУ МЫШЛЕНИЮ

Медицинский факультет Загребского университета, кафедра патофизиологии. Загреб, Хорватия

Изучение патофизиологии в медицине является сложной задачей с научной, гносеологической и практической врачебной точек зрения. Сложность реактивности человеческого организма накладывает отпечаток на требования к соответствующей методологии преподавания/обучения. Объем постгеномных данных, нелинейность и избыточность природных физиологических реакций, изменчивость и множественность молекулярных взаимодействий, природные изменения реактивности и реактивной надежности, естественного возобновления, репарации и процессов регенерации и т. п. — все это служит настоящей патобиологической основой сложности медицины. Кроме того, методы, которыми мы добываем патофизиологические знания, добавляют сложности. Ряд аспектов критичен для освоения патофизиологии. Во-первых, в макромасштабе уровень клинического рассмотрения болезненных процессов требует соединить воедино, интегрировать качественные и количественные типы понятий. Во-вторых, клиническая работа исходит из ценностей щажения объекта, ориентирована на достижение пользы и выполнение практической миссии, в то время как наука подчиняется правилам контролируемого экспериментального подхода, ориентированного на достижение истины. В-третьих, практическая медицина имеет тенденцию к сведению объема знаний к узким специализированным областям, представляющим прикладной интерес, в то время как естественные процессы и пути развития не обязательно разобщены. В-четвертых, мозг взрослого человека имеет когнитивные механизмы и внутренние закономерности обучения, навязывающие «невидимые внутренние правила», которые служат самыми важными регуляторами в осуществлении различных патофизиологических подходов (в частности, общих, специальных, молекулярных и т. д.). Алгоритмический, базирующийся на матрицах, клинически ориентированный подход и основанная на нем методология обеспечивают мост через уровни гносеологической иерархии, подключая нано- и макромасштабный мир к каждому исследуемому клиническому случаю. Клинико-патофизиологические задачи при этом построены таким образом, чтобы стимулировать активное использование студентами предоставленных элементов и реконструкцию этиопатогенетических связей. После аналитического повторения соответствующих знаний, непосредственно связанных с данным клиническим случаем, студентов просят сделать свои собственные графические интерпретации связи элементов в изучаемых процессах. Через развитие алгоритмов, количественный учет и систематизацию студент представляет собственное видение проблемы. Этот метод успешно интегрирует различные уровни информации, преодолевает различия в степени «детализации» знаний и соединяет научные и клинические данные в твердых патофизиологических рамках. Понятие об этиопатогенетических кластерах появилось при изучении множественности патогенетических путей заболеваний и их тенденции к соединению и развитию по новым направлениям. Этиопатогенетические кластеры можно рассматривать как пересечение и интеграционные точки естественного развития болезненных процессов. Таким образом, они могут стать координационными центрами интересов для преподавания/изучения патофизиологии. Мы ссылаемся на новый объемный учебник, в котором 1165 исследований клинических тематических случаев были преобразованы согласно алгоритмическому подходу. Они функционально классифицированы в 91 этиопатогенетический кластер, которые имеют тенденцию к выстраиванию сети и межкластерных соединений. Оба метода: этиопатогенетические кластеры и алгоритмические матрицы интенсивно способствуют интегративному клиническому мышлению, взращивают

его. Они питают интерес к возможно более полному рассмотрению проблем с учетом интересов студентов. Таким образом, эти методы могут рассматриваться в качестве мощных подходов к преодолению медико-биологических сложностей постгеномной эры. Библиогр. 18 назв. Ил. 2. Табл. 3. 2 блока с примерами.

Ключевые слова: патофизиология, общая патофизиология, частная патофизиология, типы патофизиологии, интегративная патофизиология, алгоритмический метод обучения, этиопатогенетические кластеры, клиническое мышление, медицинский учебный план, Загребская модель курса патофизиологии, постгеномная эра.

PATHOPHYSIOLOGY TEACHING/LEARNING AS RELIABLE PATHWAY TOWARDS INTEGRATIVE CLINICAL REASONING

Kovač Zdenko

University of Zagreb Medical School, Department of Pathophysiology, KBC Rebro, Zagreb, Croatia

Study of medical pathophysiology is challenging issue from scientific, epistemological, and practical medicine standpoint. The complexity of human body reactivity imposes the demands for an appropriate teaching/learning methodology. Postgenomic quantities of data, nonlinearity and redundancy of natural physiological responses, variability and multiplicity of molecular interactions, natural alterations of reactivity and reactive robustness, natural regeneration, repair and renewal processes (etc.) are the real pathobiological foundations of complexity in medicine. In addition, the ways we gain pathophysiological knowledge adds to the complexity. Several aspects seem to be relevant for mastering the pathophysiology. Firstly, macro-scale level of clinical consideration of disease processes tries to fuse and integrate the qualitative and quantitative types understanding. Secondly, the clinical work is patient-benefit-mission oriented, whereas, the science follows the rules of controlled experimental approach. Thirdly, the practical medicine tends to reduce its scope to the narrow specialized areas of interest, whereas, the natural processes and pathways are not necessarily compartmentalized. Fourthly, adult human brain cognitive mechanisms and intrinsic learning mechanisms impose „invisible internal rules", which are important regulation itself in dealing with variety of pathophysiological approaches (like general, special, molecular, etc.). Algorhythmic matrix-guided clinical-case based methodology provides a bridge over the gnoseological hierarchy, by connecting the nano- and macro-scale world in each study case. The problems are constructed in a way to stimulate active student's usage of provided elements and redesign of etiopathogenetic pathways. Following analytical repetitions of relevant knowledge, which are directly referred to exposed case study problem, students are asked to make their own graphical interpretations of the processes. Through development of algorhythms, quantitative consideration and systematization student presents his/her vision of the problem. This method successfully puts together various levels of information, differences of „granularity"of knowledge and connects scientific and clinical data into a solid pathophysiological framework. Etiopathogenetic clusters have emerged out of study of multiple disease pathways and their tendency to join, and to branch into new directions. Etiopathogenetic clusters can be considered as the crossing and integrative points of natural development of disease processes. Thus, they may become the focal point of interest for pathophysiology teaching/learning. We refer to a new voluminous textbook in which 1165 clinical case studies have been written in algorhythmic style. They are functionally arranged into the 91 etiopathogenetic cluster, which have tendency to build the network and inter-cluster connections. Both etiopathogenetic-cluster method and algorhythmic-matrix-guided method strongly induce and foster the integrative clinical reasoning. They nurture and lead towards as-complete-as-possible consideration of problem in a student friendly mode. Thus, these methods may be considered as powerful approaches to deal with biomedical complexities of postgenomic era. Refs 18. Figs 2. Tables 3. 2 boxes with examples.

Keywords: pathophysiology, general pathophysiology, special pathophysiology, types of pathophysiology, integrative pathophysiology, algorhythmic education method, etiopathogenetic clusters, clinical reasoning, medical curriculum, Zagreb model of pathophysiology course, postgenomic era.

1. Introductory epistemological remarks

Scientific study of the integral complex systems, like study of human physiology, imposes methodological, gnoseological and conceptual problem. Classical scientific methods are reductionistic quantitative approaches. The simplified models provide manageable rela-

tions that are testable, reproducible, ethically approvable, easy to control, and thus suitable for extensive quantitative analysis. Our knowledge of "more and more about less and less" is driven by introduction of new methods and growing sophistication of existing methods. The power of biomedical sciences is built by imported methods coming from chemistry, physics, biology, information technologies (etc.) [1, 2]. All those approaches have inherent problem of simplification and methodological "ignorance" of complexities. In general, they tend to ignore parallel pathways, regulatory loops, biological redundancy, inter-dependence on physiological gradients, chronobiological alterations (etc.) that are functional in the integral body system.

On the other side, clinical reality and physician' knowledge and interventions into the patient' problem are based on macro-scale knowledge and diagnostics. The phenomena of disease and disorders are often considered on qualitative interpretation and perception. Thus vast majority of clinical books are written in narrative and descriptive manner. They try to crystallize certain taxonomic orders, distribution of phenomena and dynamics of processes. Quantitative consideration and analysis in recent decades is growingly present and used, but still it is far beyond qualitative type of knowledge in medicine. In addition, clinical practice teleology is different than scientific one (a benefit of a patient's health, versus, a nature of the mechanism, respectively). Such target-difference imposes a permanent conflict in physician's practical vs scientific consideration of the same issue. In order to avoid and prevent potential epistemological skewing, double blind randomized clinical studies have been designed, institutionalized and practiced in clinical research.

Present pathophysiological interpretations of clinical manifestations and natural history of diseases and disorders are faced with of an exponential growth of information, non-linear behaviour of pathobiological system and comprehensibility demands of educational systems. Evidence based medicine movement has been struggling with the issues and semantic differences related to qualitative and quantitative approaches. On the other side, students and practicing doctors, very much like scientists, are inclined to limit their scope to the given narrow area of interest. They rush down into the limits of given branch medicine and thus solidify the system of compartmentalized medicine. Such narrowing of the specific area of interest comes from a natural tendency to reduce the complexity. It is believed that compartmentalisation enables and increases the expertise level for the problems of the selected field. Such approach is relevant to the practical dealing with daily clinical problems of the patient.

However, pathophysiological processes are complex, often redundant, and not always predictable. They tend to manifest a high variability, mutual interdependence and both self-propagation and self-inhibitory phenomena. Genomic, transcriptomic and proteomic data have been revealing an amazing multiplicity of molecular interactions and regulatory loops. This plethora of information is pending for a new interpretations schemes and their integration into the classical phenomenology. Integrative pathophysiology should be able to cope with complexities and to enable the student of medicine to master the problem comprehensively. Proper pathophysiological framework should integrate vertical, horizontal and longitudinal dimensions of the problem [2–4].

Rapid expansion of molecular knowledge of genomic and postgenomic era has been generating a profound impact and resourceful expansion of the basis for physiological and pathophysiological integration. Powerful computing machines, throughput scale of scientific research, as well as advancements in diagnostic methodologies, have been challeng-

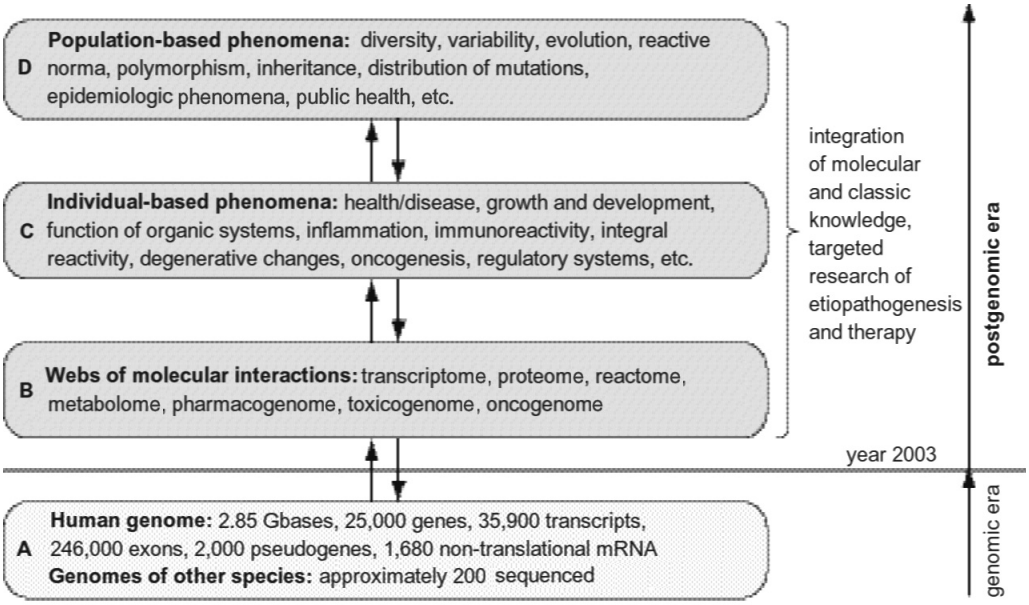


Figure 1. Complexity of biomedical information imposes a unique demand on teaching/learning techniques. A through D levels of methodological approaches generate an important facets of knowledge which are relevant sources of studying the medicine. Both genomic and postgenomic eras are faced with throughput quantities of scientifically relevant facts, which should be integrated and used as a pretext of medical education

ing our concepts and visions. Four disparate types of methodologies, scientific and clinical concepts can be envisioned as main players at the educational agenda in medicine (Fig. 1). Classical medical knowledge, mainly qualitative in its nature (depicted as level C in figure 1), is enriched and challenged by molecular and biophysical measurable and quantifiable data (levels A and B) as well as population-based information (level D). Relevance, hierarchy and potential importance for therapy usage of myriads of facets of knowledge are to be interpreted within the contemporary education.

2. Types of pathophysiology teaching/learning methods and courses in medical curricula

General pathophysiology may be defined as an integrative branch of medicine which deals with the causative (etiological) and processual (pathogenetic) aspects of disease. Since many diseases follow common pathobiological patterns (e.g. inflammatory, neoplastic, degenerative, etc.) general pathophysiology is targeted towards study of common etiopathogentic pathways. Both quantitative scientific knowledge and qualitative descriptive knowledge are stemming foundations for development of comprehensive concepts and visions. Generic pathobiological groups of processes in medicine very often behave nonlinearly. General pathophysiology should provide a reliable frame of reference of pathobiological processes which underlay the clinical problem. It should facilitate a rational usage of the information plethora and mastering professional demands.

General pathophysiology reduces pathobiological phenomena to several groups of processes (eg. inflammation, immune disorders, acid-base-, water- and osmotic- macromolecular disorders, neoplastic processes, disorders of hemodynamics, disorders of bioenergetics and thermoregulation, etc.) whose elements and, more often, combinations of elements are involved in the individual diseases. At the University of Zagreb those generic groups are listed in Table 1. Study of those strata provides a synthetic and synoptic view of etipathogenetic processes, which are relevant of various branches of specialized medicine [5, 6]. It is aimed to create the background and bridge between the usable knowledge in practical medicine and basic sciences advancements. In such a curriculum pathophysiology crosses boundaries of scientific and clinical disciplines and integrates various sources and heterogeneous nature of information. As depicted in Figure 2, a study of inflammatory disease processes stems from A through D types of data. Similarly in clinical settings, with compartmentalized reality of specialized medicine, pathophysiology serves as a unifying and conceptual approach, common to a majority. Therefore, general pathophysiology provides a frame of reference to clinical knowledge and practice, and reliable scenario for the evidence based medicine. It aims to develop and to design of comprehensive views of generic pathobiological groups of processes.

Table 1. **Structure of the pathophysiology course of 135 contact hours for medical students — the University of Zagreb Medical School model ***

1. Introduction to pathophysiology	General pathophysiology
2. Health and disease: Concepts, definitions, homeostatic/homodynamic regulation, natural course, decompensation/compensation, reactivity, functional reserve and constitutive features, terminal and vegetative states, death and resuscitation	
3. Disorders of macromolecular structure and functions	
4. Disorders of subcellular structures	
5. Disorders of energy metabolism	
6. Disorders of basic metabolic compounds	
7. Disorders of specific metabolic compounds	
8. Disorders of body fluids, osmolality and electrolytes	
9. Disorders of acid-base equilibrium	
10. Endocrinopathies	
11. Endogenous biologically active compounds	
12. Etiopathogenesis of the neurovegetative system	
13. Etiopathogenesis of pain	
14. Etiopathogenesis of thermoregulation	
15. Immunopathophysiology	
16. Inflammation	
17. Integral body reaction to noxious stimuli	
18. Etiopathogenesis of hemodynamic shock syndromes	
19. Disorders of consciousness	
20. Etiopathogenesis of conception, development, growth and aging	
21. Etiopathogenesis of neoplasia	
22. Physical etiological factors	
23. Chemical etiological factors	
24. Biological etiological factors	

25. Disorders of structure and function of connective and bone tissue
26. Pathophysiology of the hemopoietic system and blood
27. Pathophysiology of the heart
28. Pathophysiology of blood pressure and blood flow
29. Pathophysiology of respiration
30. Pathophysiology of the kidney and urinary tract
31. Pathophysiology of the gastrointestinal system
32. Pathophysiology of the hepatobiliary system
33. Pathophysiology of the skin
34. Pathophysiology of sensory and motor functions of nervous system
35. Pathophysiology of brain functions

} Functional- and organ-system pathophysiology

* The model of pathophysiology curriculum for which the accompaning textbook of pathophysiology is published both in Croatian [8] and English translation [9].

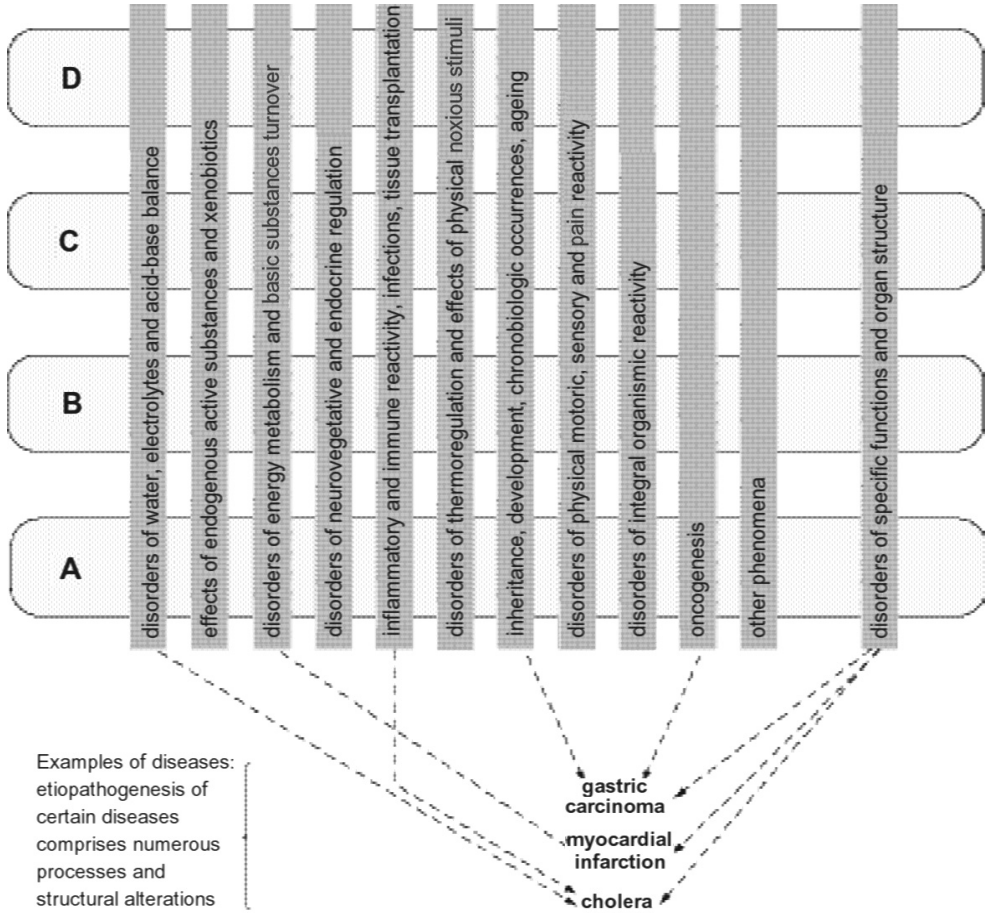


Figure 2. General pathophysiology course is designed to bridge and to integrate heterogeneous types of information into synoptic, clinically relevant interpretation. In each of vertically assigned group of problem data and principles are drown from the A through D sources (as in Figure 1). Pathophysiology course in Zagreb contains 35 groups of etiopathogenesis relevant focuses (compare Table 1)

Disease processes, natural dynamics, regulation and outcomes are complex phenomena. Our understanding of underlying etiology and pathogenesis is highly dependent on quantity of elements taken into consideration. Interconnectivity of parallel and branching of processes impose a demand of horizontal and vertical integration in pathophysiological teaching/learning. Longitudinal aspects of natural course of secondary, tertiary (etc.) etiopathogenetic processes enables a comprehensive integration and understanding of a self healing, or progressive deterioration, etc. General pathophysiology enables a synthetic view of heterogeneous types of information and stimulates an integrative study process. Stemming from nanomolecular and macromolecular level, general pathophysiology makes bridges towards inheritance, subcellular, cellular and tissue as well as organism level. Etiological factors (chemical, physical, live agents, inherited genomic polymorphisms) induce a variable set of body reactions, which differ both in a quantity and in a quality [6, 7].

Table 2. **Types of pathophysiological teaching/learning and basic academic constituents of the discipline of pathophysiology**

Types of pathophysiology present in medical education and curricula

General pathophysiology — Integrative study of disease/disorder processes that includes systematization and classification of phenomena, principles of etiology and pathogenesis. It is top-down approach, that gives a comprehensive vision of human body dysfunction, and describes general pathological processes common to a number of diseases. It often referrs to information coming from animal studies and other experimental models. It deals with the nature of diseases, types of reactions, dysregularoty phenomena and interactive pathogenetic networks integrating disorders on consecutive hierarchical levels (from macromolecular up to integral organismic level).

Functional-system pathophysiology* — Integrative study of disease/disorder processes pertinent to dysfunctions of functional systems (e.g., hemodynamcs, respiration, immunopathophysiology, inflammation etc.). Along with systematisation and classification of phenomena, it deals with principles of relevant etiology and pathogenesis.

Pathophysiology of organ-system* — Integrative study of disease/disorder processes bellonging to dysfunction of particular organs (e.g., heart, kidney, liver, muscle, etc.). Along with systematization and classification of disease and disorders, it deals with principles of specific etiology and pathogenesis.

Nosology* — Individual disease and disorder pathophysiology, it always contains given specific etiology and pathogenesis. Theoretically, presently there are 32000 nosologies belonging to 32000 diseases. Nosology is often referred as „mechanism of the disease", especially in English speaking literature. It is usually studied as constituent part of individual branches of medicine (e.g., urology, nephrology, neurology, etc.).

Basic constituents of pathophysiology

Etiology — Study of causes, causative agents and starting points of the diseases and disorders. The main contents of study are their classification, interactions and interference with the host structures, functions and sensors. Physical, chemical and biological etiological groups of factors may induce processes in virtually any body system and at any hierarchical level or organization.

Pathogenesis — Study of processes induced in a host by etiological agents. These reactive processes are self-regulated, genomically orchestrated and mainly protective. They may become harmful due to an excessive quantity of response, or due to triggering of *de novo* pathologic processes (like, autoimmunity, tumor conversion, etc.).

Etiopathogenetic clusters — Study of natural crossing points of etiopathogenetic pathways in which various processes come together. Clusters are integrating points of many entering pathways, and triggers and starting points of some other pathways. They are formed in diseases triggered by heterogeneous etiology and show natural tendency to connect into the networks of clusters.

* The term „**special pathophysiology**" refers to contents of „functional-system pathophysiology", „pathophysiology of organ-system" and „nosology". All special pathophysiologies deal with general pathophysiological principles and processes applied to a given subsystem in the body with their broad diversity of dysfunctions and manifestations.

Special pathophysiology includes three types of pathophysiological organization and concept (Table 2). All three types deal with unique aspects of pathophysiology in specific subsystems of the body. Functional-system pathophysiology is an integrated study and interpretation of diseases processes focused on isolated physiological systems like hemodynamics, etc. Pathophysiology of organ-system is focused on individual organ dysfunctions. Part of education in Zagreb model of pathophysiology follows this two types of special pathophysiology (please compare Table 1). Pathophysiology of individual disease entities (also synonymously called nosology or cause and mechanism of disease) deals with a unique set of etiopathogenetic processes that are given behind dysfunctions, symptoms and signs. Understanding nosology of individual diseases enables a design of rational pharmacological therapy and other therapeutical procedures. Dealing with redundant and ever growing information related to roughly 32 000 diseases/disorders becomes manageable with adoption of general pathophysiology systematization, classifications and elaboration of generic etiopathogenetic processes. In Croatian curricula of medicine majority of nosology is studied within the individual branches of medicine (e.g. internal medicine, neurology, dermatology, etc.), and integrated modules. Part of nosology in our model is done through teaching/learning worksheets.

3. How to deal with the complexities and confusing plethora of medical information — the power of algorhythm construction of knowledge

Many educators would agree that it is less important what we know than our capacity to learn more with understanding the context. It appears that learning and teaching capacity and skills have become a crucial for advancements in medicine. Even more, teaching/learning issue been considered a critical key for a progress. Thus it was stated "Pathophysiology as a science and curriculum discipline stands in front of biggest challenge in its history" [4].

Educational methodology, pro-learning attitudes and skills are adopted much earlier in the development of student, within primary and secondary education. Both teachers and students are aware (may be not always on declarative level) of tensions, advantages and shortages in learning/teaching procedure, which come from cognitive, methodological and practical pathways of previous academic experience.

Medical student education in Croatia follows a chimerical model of a traditional curriculum and several integrated courses. European framework regulation of MD education imposes the six years program (>5500 hours of "theoretical practical instruction given in university"). Such concept is built in the reforms according to the Bologna Declaration. Following secondary gymnasium (of equivalents) education, students have university program of preclinical and clinical subjects. General pathophysiology is given as an independent subject (135 hours) within the third year (Table 1) [8, 9]. The course of pathophysiology is given following the completion of physiology, immunology and biochemistry courses, and in parallel with anatomic pathology, microbiology and pharmacology. The fourth through sixth years are dedicated to clinical and public health education.

In order to make pathophysiology teaching/learning workable from teachers point of view, as well as attractive and friendly to students, we established educational model with four steps [10, 11]. Problem based pathophysiology education is guided via matrices, an

example of which is given in Box 1. Each task is based on four following segments. The first part is ***the exposition of problem***, which provides short presentation of "raw data" derived from patient records, selected publications with experimental data, etc. It gives realistic examples, a description of the problem seen from the clinical point of view. The second part is ***the repetition of relevant knowledge***, which is a multiple choice test, whose statements are related to the exposition and referred other teaching materials (textbooks, websites, etc.). Multiple reinterpretations of various facets of the problem enrich student's understanding and re-enforces revitalisation of previous knowledge, and its consideration within the selected problem. 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-consequence sequence of events, with positive and negative feedback loops, and parallel and contextual events. This part is very inductive and inducing a fruitful discussions and very vivid class atmosphere. In terms of didactics it represents a synthesis, catalysed and controlled rounding-up of knowledge. The fourth part is ***the feedback integration of the problem*** which deals with additional relations, systematization and quantitative aspects of the same problem. One example of complete problem with solutions is outlined in the Box 1.

This four-step approach clearly outlines etiopathogenetic pathways and networks of interconnected elements within the hierarchy of the system. Some interconnecting nodes (e.g., processes, structural alterations, concentration abnormalities, etc.) form clusters, with multiple entries and outputs. Focusing to such clustering points may become a reliable approach to master complexities in medicine.

Four reiterative steps seem to be the efficient way to deal with complexities. Both students and teachers describe this model as inciting and powerful tool, and, 2,3 times more efficient method in comparison to others (according to the institutional yearly survey data). It leads to integrative comprehension and follows didactic principles of natural acquisition of knowledge. It nurtures vertical, horizontal and longitudinal conceptualization of the problem. It has practical versatility and enables easy upgrading of information. Students have shown better and longer lasting declarative knowledge and understanding of study matter. We think that horizontal, vertical and longitudinal dimension of the processes being reconstructed within the tasks contribute to better conceptualisation and knowledge. Sometimes, they tend to apply this mode of learning to the subjects which are given via classical approaches.

4. Significance and experience of matrix guided algorhythmic methodology

Etiopathogenetic clustering of natural development of diseases processes justifies this approach. Several aspects of this educational model can be outlined as advantages in the study of contemporary biomedicine. Firstly, the four levels of problem elaboration provide both analysis and synthesis of the pathophysiological events, the matrix of which covers a broad spectrum of elements spanning from molecules and genes to symptoms/signs and natural course of disease. Secondly, each task-matrix is designed in a way to bridge basic and clinical sciences and are always kept within the clinical reality of reported study cases. Thirdly, student tacitly adopts horizontal, vertical and longitudinal reasoning in appreciation of etiopathogenetic mechanisms and clustering, their branching, hierarchy, parallelism, as well as nonlinear homeodynamic nature of self regulation. Fourthly, this methodology

ignites students' enthusiasm, gives studying incentive that generates vivid discussions and declarative versatility of knowledge. Through anonymous questionnaire students ascribe better quality to this method in comparison to others. Fifthly, this methodology provides an open system; it easily implements relevant new aspects, and points towards „un-finishness" of knowledge. The usage of „lego" mode of algorhythm development induces didactically positive response and facilitates natural acquisition of knowledge. Sixthly, it integrates and reduces the pathobiological complexity and biomedical information redundancy towards manageable/usable levels, appropriate to medical curricula, and gives the comprehensive frame of reference as the scientific foundation for clinical reasoning and practice. It therefore fully complies with the International Society for Pathophysiology Declaration on Education [6]. Seventhly, it imposes integrative and systemic approach to the etiopathogenesis of disease/disorder, thus promoting a synthetic view of the pathophysiological nature of underlying processes and regulation. It catalyses an evidence-based-medicine approach by putting together heterogeneous facets of understanding into the unified/metaanalytical interpretation. Eighthly, teachers are given a powerful tool in form of elaborated teaching matrix, which puts a teaching/learning procedure into active analytical and synthetic reasoning.

5. Etiopathogenetic clusters — a new points of interest in study of pathophysiology

In algorhythmic elaborations of etiopathogenesis of various disease states we noticed an important regularity. There is general natural tendency to form the common crossing points of reactivity. Very often many unrelated etiopathogenetic pathways converge to the common units of pathogenesis. It appears that pathways belonging to heterogeneous types of diseases tend to group together, spontaneously, around certain etiopathogenetic element. Such common units are formed at certain deviation of electrolyte concentration (like hyponatraemia, hyperphosphatemia, 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 we named the etiopathogenetic clusters (EPC). We consider them as important integrators of natural pathophysiological processes, and, thus, the EPCs are outlined as one of the three basic constituents of pathophysiology (see Table 2). Such clusters integrate multiple inputs and multiple exits in the natural development of various diseases and altered conditions in 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. For example, the EPC of acute renal failure leads to the EPC of the metabolic acidosis, and to the EPC of the hyperkalaemia, anf to the EPC of the consciousness disorder, and so on. One could speculate that such EPC networking reflects the inherent capacity of human body to react. EPC networking thus follows the general patterns of natural body reactivity.

Following such findings and vision, 51 authors contributed to the writings of manuscript of the new texbook which is organized around the EPC as the central points of pathophysiological development [12]. The book was published in Croatian in four volumes [9] and general structure of one out of 1165 study cases is outlined in Box 2. The 91 EPCs are clinically identifiable events and their estimated relative importance for the clinical practice is outlined in Table 3. Through multiple study cases, the EPC approach keeps the learning/

teaching procedure close to the practical every day reasoning and activities of the physician. Thus, it seems to fulfill the need of integral pathophysiologic interpretation based on real clinical situations and real patient cases. By doing that way theoretical concepts and referral scinetific frameworks are put together with the available clinical information in daily doctors practice.

Table 3. **Etiopathogenetic clusters are elaborated through 12,8 study cases each in the book [9]**

1. Pain	32. Respiratory alkalosis	61. Hypoosmolality
2. Arterial hypertension	33. Urolithiasis	62. Obstructive uropathy
3. Atherosclerosis	34. Hyperthermia	63. Immunodeficiency
4. Hyperglycemia	35. Hypovolemic shock	64. Seizures
5. Vomiting	36. Thrombotic diathesis	65. Hypercalcaemia
6. Edema	37. Hypoglycemia	66. Neutropenia
7. Heart ischemia	38. Bleeding diathesis	67. Hypocalcaemia
8. Leukocytosis	39. Autoimmunity	68. Intestinal ischemia
9. Anaemia	40. Arterial hypotension	69. Pathological fracture
10. Heart failure	41. Chronic liver failure	70. Fibrosis
11. Diarrhoea	42. Hypoxemic respiratory	71. Malnutrition
12. Obesity	insufficiency	72. Acute liver failure
13. Arrythmia	43. Acute renal failure	73. Hyperhydration
14. Dyslipidemia	44. Abdominal compartment	74. Hypocapnia
15. Hypohydration	syndrome	75. Hypermetabolism
16. Hypovolemia	45. Leg ischemia	76. Intracranial hypertonia
17. Tissue healing	46. Multiple organ failure	77. Blood hyperviscosity
18. Disorders of	47. Cholelithiasis	78. Hypersplenism
consciousness	48. Thrombocytopenia	79. Eosinophilia
19. Metabolic acidosis	49. Hypoproteinemia	80. Cardiac tamponade
20. Brain ischemia	50. Vasohypotonic shock	81. Hypothermia
21. Metabolic syndrome	51. Hypoventilation	82. Transfusion reactions
22. Jaundice	52. Hyperventilation	83. Hyperphosphatemia
23. Chronic renal failure	53. Nephrotic syndrome	84. Graft tissue rejection
24. Cardiogenic shock	54. Hyponatraemia	85. Hypochloremia
25. Sepsis	55. Respiratory alkalosis	86. Hyperchloremia
26. Hypercapnia	56. Ileus	87. Hypophosphatemia
27. Ascites	57. Metabolic alkalosis	88. Hypomagnesiemia
28. Hypokalaemia	58. Hypernatraemia	89. Graft versus host reaction
29. Immune hypersensitivity	59. Hypercapnic respiratory	90. Hypermagnesiemia
30. Hyperosmolality	insufficiency	91. Amyloidosis
31. Hyperkalaemia	60. Cachexia	

* Ordinary numbers associated with the EPC indicate its relative frequency in clinical practice, according to survey 200 physicians and 50 demonstrators (advanced student-teachers). The number 1 means the most frequent cluster, whereas the number 91 means the least frequent cluster.

These 91 EPCs are formed on various levels of physiological hierarchy, spanning from the EPCs of electrolytes disorders up to the EPC of multiple organ failure [12, 13]. The initiation of the disease process by etiological factor can be turn on by any EPC-level as the primary etiopathogenetic event. For example, mechanical trauma due to car accident may cause organ damage like bone fracure or liver rupture, and thus turning on the EPCs at that levels. Secondary, EPCs on other hierarchy levels may develop due to primary dysfunction (e.g., hypovolemia, arterial hypotension, hypovolemic shock, disorder of consciousness, etc.).

6. The clinical advantages of the EPC-strategy and usage

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. For example, infusion of glucose solution will correct the hypoglycemia and prompt recovery from hypoglycemic coma (or related consciousness disorders). Similarly, timely conversion of ventricular fibrillation to physiological rhythm will cause a fast recovery from cardiogenic shock having the effect on the entire body and not only the heart. Similar principle applies to the majority of EPCs [13, 14].

EPCs give the quick guidelines how to deal with clinical complexities and nonlinearity of pathophysiological responses within the real working-time framework. They are of special importance in life threatening emergencies. Immediate interventions based on corrective EPC-effects leads to patients stabilization, and leaves enough time to doctor's reconsideration of condition and designing diagnostic and therapeutic strategy. Thus, practicing physician may gain through EPC-concept a valuable professional attitude and subroutine.

The ECP-strategy of organizing medical knowledge and understanding helps in reducing the information noise. They provide identifiable and simple, but critically important, landmarks in clinical work. In addition, they help to dig out main etiopathogenetic pathway, contextual and parallel pathways, branching points and their mutual interaction. Thus, networking of processes, in which EPCs are connecting nodes, builds a new horizon and vision on interconnectivity of pathophysiological pathways.

The EPCs as teaching/learning tool may be considered as proper response to the challenging demands of contemporary medicine. With increasingly in-depth study and knowledge of myriads of facets of given disease, the growing quantities of details may be confusing. Thus EPC-skeleton and networks may keep a reliable framework of dominant pathophysiological trends. This may help medical students, curricular reforms and academic police makers in their attempts updating teaching contents and its linking to clinical practice.

In an attempt to relate patient's condition to a database of 32,000 diseases, physician looks for patterns of clinical manifestations, laboratory findings and other diagnostic tests. She or he seeks for the etiology of the disease in a broad spectrum of potential causes, the progression and the potential outcomes in relation to given therapy. The EPC-skeleton points towards the branching points and simultaneous consideration of multiple pathways.

The EPC focuses primary attention to a patient's condition, both local and systemic manifestations of underlying pathophysiology. EPC-networking of natural etiopathogenetic interconnections shows a self-directed propagation, spreading and pathways. Thus the EPC-approach has no medical specialty limitation. It simply imposes the inductive attitude to follow a vertical, horizontal and longitudinal dimension in considering the given condition [14, 15].

The unraveling of pathophysiological mechanisms underlying patient clinical conditions may be considered as the most reliable foundation for contemporary medicine. In general, pathophysiology provides integrative views of disease/disorder processes. It studies etiological stemming elements, regulatory pathways (both positive and negative ones) and identifies branching points in the pathway. The EPC-approach may be useful in systemic consideration of disease processes.

7. Prospective of integrative algorhythmic reasoning and EPC-vision in teaching/ learning and position of pathophysiology in biomedical curricula

Medical education strategy and methodology should follow the most efficient approach. Example-base learning is traditionally considered as the most efficient method of learning, in general. In medicine case-based learning enriches 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.

Plasticity of human body reactivity seems to stem from multiplicity and redundancy of pathways, robustness of body reactivity and clustering of responses. Both genomic end enviriomental factors contribute to the reactive complexity. Polygenic diseases' inheritance, non-Mendelian patterns of inheritance, imprinting, de novo germ line mutations, epigenetic mechanisms cannot be reduced to classical genetics. It seems their mechanisms function at various levels of etiopathogenetic development, including various EPC-like strata of body reactivity. The advent of omics-tehnologies and multidimensional measurements and increasingly diagnostic upgradings is about to set a stage for a new era in medicine, which demands appropriate teaching/learning methodologies, as well.

On the other side, human intellect does not deal with plethora at the individual data points. It masters copious amounts of data though 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.

Adult brain learning procedures include a necessity of repetition, spontaneous associative brain maps formation and both holistic and reductionistic consideration. All three aspects contribute to intellectual powers of understanding anf integration of scientific and clinical information and processes. They nurture the gain and retain relevant knowledge and subroutine reasoning and compentencies. Both algorhythms and EPC-strategy are structured in a way to bust these three groups of processes of adult learning.

Both algorhythms and EPC-strategy enforce the studying of both local body reactions and systemic responses, at the same time. Since this EPC-model is not medical specialty limited, it may be applied in many areas, as a useful studying methodology. Both methods have opened up a new horizon in dealing with complexity of human pathobiology within the real study-time framework.

Pathophysiologists are faced with challenging issue of with a chasm between the increased specialization in medical practice and knowledge, and, quick growth of the body of scientific knowledge about the same problem. The situation is sometime confusing. These methods provide a simultaneous consideration of multiple pathways. Therefore it may be considered as useful tools in contemporary post genomic era and exponential accumulation of data and information.

Some papers report that pathophysiology as the subject, its mission, vision, approach and education, as well as its discipline framework in medical study curricula are enriched by these approaches [16, 17]. They provide the robust methods to deal with plethora of potentionally relevant information and way how to manage the complex issue.They give a scheme that is able to manage postgenomic molecular data quantities and use information computing machines and human fuzzy logic.

Curricular and institutional position of pathophysiology (departmental, educational and curricular requirements) and clinical/preclinical relations are recommended by international guidelines [1, 2]. Regardless of types and scopes of various curricular position of the discipline (general principles, nosology, organ-related pathophysiology, etc., see Table 1), all of them may find these two approaches applicable. Their modular nature and case based style provides the active inductive mode of study that brings together and fuses the clinical and basic knowledge.

Progressive compartmentalization of medical practice, education and research has a tendency to reduce the integrative reasoning in the physicians' education and practice. This phenomenon may be considered as serious source of traps and pitfalls. Study of network of etiopathogenetic pathways and crossing points leads and imposes an opposite scenario of teaching/learning. Both methods are designed as matrix guided integrative approaches and problems solvers, and thus may be useful to reduce the chasm between science and clinical medicine.

Teaching/learning of pathophysiology by these methods can be characterized as practice-based education through multiple study cases keep the learning process close to the practical every day activities of the physician [18]. A comprehensive holistic approach and vision, as well as building the skeleton of etiopathogenesis in EPC-network, upgrades the way of clinical consideration. It additionally boosts the rational diagnostics and therapy, as well as the personalized approaches in medicine.

Box 1. An example of matrix guided algorhythmic problem task which is used as template for study of integrative pathophysiology. It contains the exposition of problem, the repetition section (exercize A), the algorhythm construction (exercise B) and feedback integration (exercise C). Parts A, B and C are tasks to be sovled by student. The Book Two (11) contains solutions of all tasks and it is a convenient problem solver.

Study problem 86. Pathophysiology of the carbon monoxide poisoning

(The problem was based on data from: Winter PM et al. Carbon monoxide poisoning. JAMA 1976; 236:1502–4, Ernst A et al. Carbon monoxide poisoning. New Engl J Med 1998; 339:1603–8 and Cobb N et al. Unintentional carbon monoxide — related deaths in the United States, 1979 through 1988. JAMA 1991; 266: 639–63).

Carbon monoxide is a colorless, tasteless, nonirritating gas. When inhaled, it easily absorbs into the blood and directly binds to hemoglobin thereby producing carboxyhemoglobin (COHb). Table 1 indicates the approximate ratio between the relative portion of CO in the inspired air, COHb in blood as well as consequential signs and symptoms of the intoxication. Figure 1B depicts a 10-year epidemiological study of the death rates in the USA, with 6552 (57%) out of 11547 total deaths occuring due to a motor vehicle exhaust inhalation, accumulated in a closed space. The rest is comprised of the victims of heating with technically faulty domestic heaters using coal, gas or liquid fuels, together with other unintentional carbon monoxide exposures. Figure 1A shows that COHb increases the oxygen affinity of the remaining hemoglobin, which shifts hemoglobin dissociation curve to the left and changes its shape. Figure 2A indicates a reduction in blood oxygen binding capacity consequential to the COHb level in the blood. During treatment of CO intoxication, clinically safe interval (approximate COHb content <20%) is achieved more rapidly if the hyperbaric oxygen treatment is administered. During this

process, the competitive displacement of carbon monoxide by «excessive» oxygen occurs in the certain molecules that have bound CO (e.g. hemoglobin, myoglobin).

Table 1. Approximate relationship between CO concentration in inspired air and the signs and symptoms of the intoxication

CO in inspired air (%)[a]	COHb[b], hemoglobin %	Pathophysiologic signs and symptoms of the intoxicated patients
0,007	10	- shortness of breath on heavy exertions - sensation of "pressure" around forehead and head - dilatation of the skin blood vessels
0,012	20	- shortness of breath on moderate exertions - temporal "pulsating" headaches
0,022	30	- not defined sensations and mild headaches - irritability - easy fatigability - impaired judgment - impaired balance and visual deterioration
0,035–0,052	40–50	- headache, confusion, hemodynamic shock, lightheadedness on exertion
0,08–0,122	60–70	- coma - intermittent convulsions - respiratory failure - possible death on prolonged exposure
0,195	80	- abrupt, immediate death

[a] CO concentration in CO-nontoxic air is <0.001%; city air usually contains higher CO concentrations than the rural air does.
[b] Healthy non smokers that inhale CO-nontoxic air have 1-3% COHb in blood, while smokers have 10-15%

Problem 84. Pathophysiology of the carbon monoxide poisoning

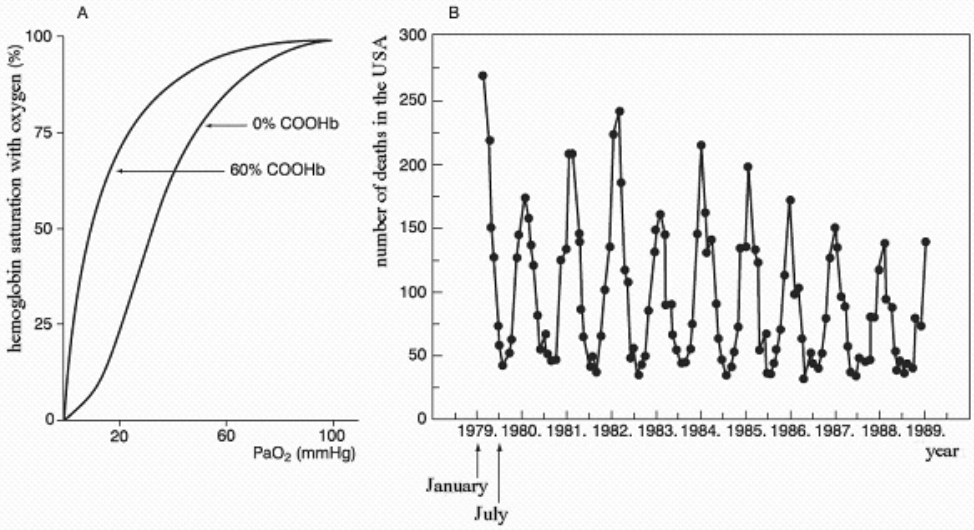


Fig 1.A Sigmoid dissociation curve for oxyhemoglobin under COHb influence shifts to the left and acquires hyperbolic shape
B Incidence of CO-related deathsin the US from 1979.-1989.

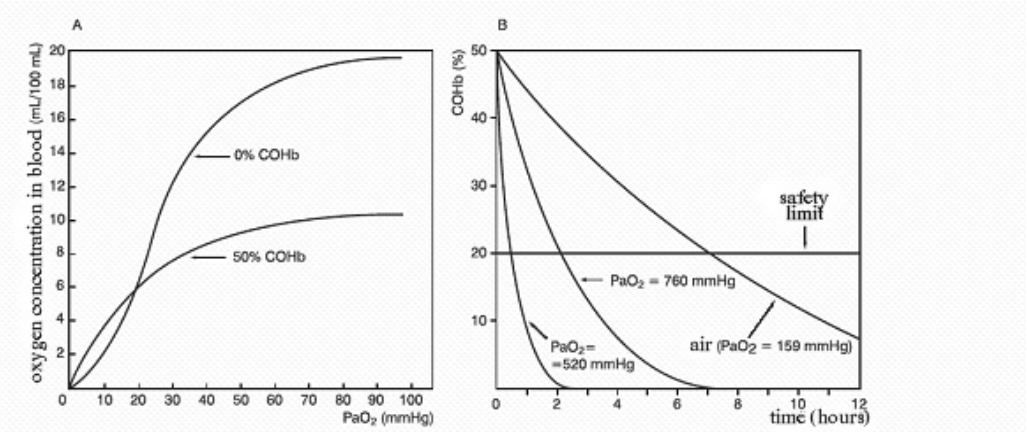


Fig.2 A Effect of carboxyhemoglobin on the oxygen saturation. B The rate of CO elimination from the intoxicated organism depends on partial oxygen pressure that a patient inhales. Hyperbaric treatment enhances CO elimination from the organism.

EXERCISE A: Repetitions of relevant knowledge — TYPE I

1) Signs and symptoms of the carbon monoxide poisoning are based on all of the following pathogenetic mechanisms, except:
   a) Coma, central nervous system vital center (respiratory, vasomotor) failure and the death of a patient occur due the decreased oxygen delivery, tissue hypoenergosis and consequential fundamental cellular dysfunction.
   b) In patients with preexisting chronic ischemic diseases (vascular insufficiency, coronary artery disease), CO intoxication manifests even at lower blood COHb concentrations, along with the more severe clinical features.
   c) The severity of clinical features is approximately directly proportional to the carboxyhemoglobin content in blood (see Table 1) since the concentration of oxygenated hemoglobin decreases significantly.
   d) "Shortness of breath", as a symptom, can be interpreted as impaired oxygen binding to the hemoglobin due to COHb concentration in the erythrocytes, which causes reduced contents of total bound oxygen in the arterial blood.
   e) Clinical term "pink death" reflects possible features of a dying patient, originating from a skin blush, due to increased skin blood flow caused by vasodilatation.

2) Energy metabolism dysfunction in CO-intoxicated organism is characterized by all of the following mechanisms, except:
   a) Hyperlactacidemia in patients occurs as a compensatory metabolic response to a decreased tissue oxygen supply, during which ATP production efficiency in relation to the mol of substrate, is significantly lower than in the aerobic metabolism.
   b) Tissue hypoenergosis is classified as an acquired hemoglobinopathic/hemopathic disorder of the energy metabolism; while CO in the organism, by inhibiting myoglobin function as well as function of some hem-enzymes (like cytochrome-c oxidase) contributes to the impairment.
   c) Tissue CO excess reduces the substrates and causes severe metabolic acidosis which increases anion gap and, at the same time, reduces free proton quantity in the mitochondria.
   d) Since the compensatory energy producing processes are not sufficient, tissues develop energy depletion, which causes the cells to become dysfunctional, thereby contributing to the symptom manifestation (e.g. patient's confusion, impaired vision, convulsions — see Table 1).
   e) Hypoxic hypoenergosis occurs as a consequence of electron acceptor deficiency in oxidative phosphorylation which is caused by hemoglobin occupancy with CO (COHb), increased oxygen affinity of the remaining free hemoglobin, consequential reduction in blood oxygen concentration as well as decreased oxygen delivery to the tissues.

3) According to data in Fig. 1A and 2A, all the following statements are true, except:
   a) Altered shape of the oxyhemoglobin dissociation curve from sigmoid to hyperbolic shape, is a consequence of COHb inhibition of the positive cooperative effect of the oxyhemoglobin molecules to the hemoglobin molecules ready to bind oxygen.
   b) At 50% COHb concentration in blood, total oxygen binding is about 50% less in comparison to the physiologic binding state, since at the time, only about half of the hemoglobin is available for oxygen binding.
   c) Due to reduced oxygen concentration in blood during CO intoxication, accelerated blood flow can only partially compensate for the altered tissue energy metabolism.
   d) Since CO has a 200–250 times higher affinity for hemoglobin, during PaO_2 increase from 60 to 100 mmHg (passing through the pulmonary capillaries) oxygen saturation of the arterial blood increases only slightly in comparison to the venous blood.
   e) COHb in contact with oxygen turns into CO_2 and hemoglobin, during which CO_2 acts as an endogenous CO_2 thereby increasing bicarbonate puffer capacity.

4) In a CO-poisoning syndrome, all of the following pathogenetic mechanisms occur, except:
   a) Hemoglobin dissociation curve shifts to the left (see Fig. 1A) which indicates that the remaining molecules in oxyhemoglobin difficultly release oxygen into the tissues, thereby contributing to the reduced oxygen delivery to the tissues.
   b) Both tachycardia and tachypnea are indicators of the compensatory cardiovascular and respiratory system response, induced by activation of chemoreceptors, baroreceptors and direct activation of the brain stem regulatory centers.
   c) High CO affinity for the hemoglobin, rapid diffusion through respiratory membrane (almost equal as CO_2 diffusibility) cause the intoxication to occur despite the fact that gas concentration in the inhaled air is less then the oxygen concentration (see Table 1).
   d) Since the CO concentration in the inhaled air >0,1% rapidly increases carboxyhemoglobin concentration above 60%; makes hemodynamic, hemoglobin and metabolic compensatory systems to become insufficient, which causes rapid coma and death of a patient (see Table 1).
   e) Easy fatigability of the intoxicated patients occurs due to increased energy expenditure for carbon monoxide extraction from carboxyhemoglobin, which physiologically occurs in the spleen and liver.

5) Specific aspects of the CO-intoxication pathogenesis are accurately described by all of the following statements, except:
   a) During CO-intoxication treatment with hyperbaric oxygen, CO displacement from carboxyhemoglobin increases, which can clinically be traced as its share decrement in blood (see Fig. 2B); at the same time soluble oxygen contributes to the energy deficiency repair.
   b) Retinal hemorrhage, myoglobinuria and hyperamylasemia are CO-intoxication signs, with pathogenetic implication of specific cell death which can pathogenetically be classified as a cytoplasmatic cell death.
   c) Tooth-shaped curve (Fig. 1B) annually indicates seasonal variations; incidence is 3–6 times higher during winter than in summer, caused by the use of heating appliances and predominate staying indoors during winter.
   d) Incidence of the nonspecific symptoms related to dysfunction of the central nervous system, such as headache 91%, dizziness 77%, weakness 53%, nausea 47%, indicate high cerebral sensitivity to the energy metabolism alterations.
   e) Based on Fig. 1B, it can be said that decreased epidemiological incidence of the CO poisoning during summer, is a consequence of decreased seasonal cerebral sensitivity to the hypoenergosis due to increased physical activity.

EXERCISE B: Algorhythmic workout of the pathogenesis

Arrange the following items in a causative order:

1. Oxyhemoglobin dissociation curve shift to the left
2. Incomplete combustion in a confined space
3. Headache, orthostatic instability, nausea
4. Peripheral vasodilatation

5. Decreased blood oxyphority
6. Mean arterial pressure decrease
7. Vasomotor center activation
8. Inhalation of gas mixture containing increased amount of carbon monoxide
9. Increased hemoglobin affinity to the oxygen
10. Increased contents of carbon monoxide in the air
11. Cerebral hypoxic hypoenergosis
12. Increased carboxyhemoglobin concentration in the blood
13. Increased venous return
14. Tachycardia
15. Decreased oxygen release from the erythrocytes
16. Hypoxia
17. Tachypnea
18. Skin hypoenergosis
19. Hyperlactacidemia
20. Anaerobic pathway metabolic shift
21. Decreased oxygen concentration in the blood
22. Cyanosis like color of the skin and mucous membranes
23. Hyperdynamic blood flow
24. Electrolyte disbalance and impaired cerebral biosynthetic processes
25. Metabolic acidosis
26. Respiratory center activation

EXERCISE C: Feedback integration of the problem — TYPE V

1. Toxic CO effects in the organism are based on reduced availability of the hemoglobin due to carboxyhemoglobin synthesis, increased hemoglobin affinity for the oxygen (sigmoid to hyperbolic curve transformation combined with a leftward shift), decreased oxygen delivery to the tissues, decreased oxygen release form the myoglobin and partially by inhibiting cytochrome-c oxydase (compare claims 3a, 3b, 3d and 4a)

because

hypoenergosis, which biochemically represents decreased ATP concentration, in CO intoxication is primary dysenzymatic.

a b c d e

2. Although the smokers are either asymptomatic or oligosymptomatic, they even when inhaling air without CO intoxication, have 10–15% COHb levels in blood (see Table1) which limits their maximal functional capacity

because

due to decreased functional reserve during increased body and mental strains, they show significantly easier fatigability, reduced maximal oxygen consumption in comparison to the non-smokers, which can contribute to the increased specific morbidity of the smokers.

a b c d e

3. Since the gas presence in the air cannot be detected with one's senses, CO-poisonings represent diagnostic problem and hardly predictable danger

because

headache, dizziness, shortness of breath, nausea, irritability and other symptoms (see Table 1 and claim 5d) can be a presenting symptom of the infectious syndromes, and do not directly reflect COHb concentration in blood during intoxication.

a b c d e

additional questions

4. With hemoglobin concentration in blood measuring 150 g/L, erythrocyte count $5x10^{12}$/L and 50% COHb concentration in blood, calculate the number of COHb molecules contained in 1 mL of blood (hemoglobin molecular mass is 66500 daltons).

5. With arterial PaO_2=100 mmHg and arteriovenous pressure difference ΔpO_2=60 mmHg, determine how many times is oxygen release from hemoglobin decreased, in relation to a 50% COHb concentration in blood, according to data from Fig. 2A.

The Book Two (11) contains solutions which are located at the end of the book.

Problem 86.

Exercise A: 1d, 2c, 3e, 4e, 5e.

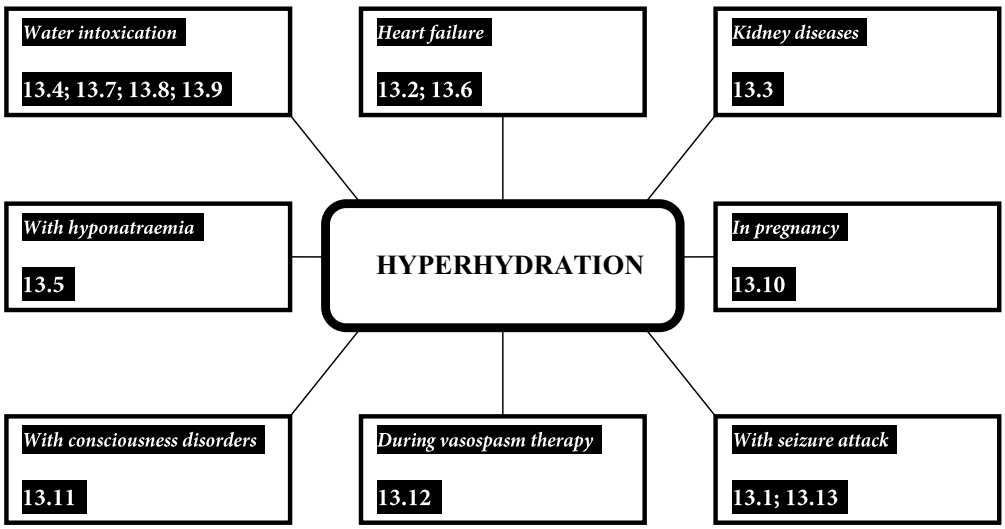
Exercise B: 2→ 10; 4→ 3,6,13; 5→ 21,24; 6→ 7; 7→ 13,14,23; 8→ 12; 9→ 1,5,15; 10→ 8; 11→ 3; 12→ 5,9,21; 13→ 23; 13⊣6; 14→ 23; 15→ 5; 16→ 4,6,7,11,18,20,26; 17⊣16,25; 18→ 4; 19→ 25; 20→ 19; 21→ 22,24; 24→ 16; 25→ 4,17,22; 26→ 7,17.

Exercise C: 1c, 2a, 3b.

4. Approximately 6,79 x 1017 CoHb molecules.
5. In these conditions at 0% COHb approximately 5 mL of oxygen per 100 mL of blood is released, and at 50% COHb <1mL/100mL of blood is released (according to direct reading from curve on image 2A).

Box 2. An example of etiopathogenetic cluster: Cluster 13. Hyperhydration with Case study 13.10. Each cluster starts with orientation diagram and contains 12.8 case studies in the Book Three. Each study case contains the exposition of problem (part I) in form of medical history and additional insight, short algorhythm (part II) and systematization task (part III). Book is a problem solver and contains solutions of all case study tasks (12).

Cluster 13 HYPERHYDRATION



Case study 13.10. HYPERHYDRATION — WITH SEVERE HYPONATRAEMIA IN MOTHER AND NEWBORN AS A RESULT OF PRIMARY POLYDIPSIA DURING LABOR

The case study has been adopted from the article of Graham K. et al. Severe hyponatremia as a result of primary polydipsia in labour. Aust N Z J Obstet Gynaecol. 2004; 44: 586–7.

I. Medical history. A 33-year-old primipara was admitted to delivery room for labor in the 38th week of gestation. She was given an epidural analgesia due to progressive agitation and uncontrolled behavior, assuming that her behavior was altered due to pain. Because of the termination of cervical dilation 9 cm, Syntocinon (synthetic oxytocin) infusion was started, but was interrupted an hour later due to excessive sleepiness and inappropriate verbal response in the patient. The patient drank more than 7 liters of water within 12 hours from admission.

She was afebrile, normotensive, with normal oxygen saturation of hemoglobin, had symmetric and reactive pupils, followed simple commands without focal asymmetry. The patient had hyponatremia (118 mmol/L, normal range 135–145). Urine specific weight dropped from 1.030 to 1.010 (normal range 1.005–1.030), but urine volume was not measured.

Female child was born with emergency caesarean section under epidural anesthesia. Child weighted 3,500 g with Apgar score of 9 in the first and the fifth minute (<3 implies severe asphyxia, 4–6 moderately depressed vital functions, 7–9 implies ease depression, 10 is the optimal value). The newborn had hyponatremia (119 mmol/L, normal range 133–146). After birth mother also had hyponatremia (118 mmol/L, normal range 135–145) and normokalemia (4.5 mmol/L, normal range 3.5–5.3), hypoosmolal plasma (248 mOsm/kg, normal range 270–300) and hypoosmolal urine (356 mOsm/kg, normal range 400–1200). Short ACTH test, thyroid function tests and blood glucose levels were normal.

The mother was moved to the intensive care unit (ICU) for limiting fluid intake and monitoring serum electrolytes with the possibility to quickly correct natremia because of the risk of central pontine myelinolysis. Serum sodium concentration was normalized after 24 hours that was followed by complete recovery of neurological function.

ADDITIONAL INSIGHT: Hyponatremia is a rare, but potentially fatal consequence of primary polydipsia due to exceeded excretory capacity of free water of kidneys (1500 mL/h). Fluid overload more easily occurs during pregnancy due to physiological reduction of the osmotic threshold for the release of antidiuretic hormone (ADH) from 280 to 272 mOsm/kg, increased secretion of oxytocin that has vasopressin effect, recommendations for increased fluid intake during labor and medical intervention (Sintocinon). Hyponatremia is initially asymptomatic (> 125 mmol/L), but as hyponatremia increases progressive neurological dysfunction develops due to cerebral edema. Symptoms include headache, nausea, vomiting, lethargy, muscle cramps and disorientation, with progression to seizures, coma, respiratory failure and death. Fetal hyponatremia is a result of transplacental flow of hypoosmolal fluid in combination with immaturity of fetal kidneys.

Apgar scoring is a quick method of estimating the state of the newborn immediately after the birth. It is based on evaluation of skin color, heart rate, reflex irritability, muscle tone and breathing-with points rating from 0 to 2. It is usually determined at the first and the fifth minute after the birth, but if necessary it may be repeated later. Oxytocin is a nurohypituitary peptide hormone, structurally very similar to vasopressin, with mild vasopressin and natriuretic effect. It has a role in lactation, uterine contraction and cervical dilatation and affects adrenal axis. Vasopressin (ADH) increases the permeability of the distal and collecting tubule of kidney for water by inserting aquaporine channels, and it also has moderate vasoconstrictictive effect.

Central pontine myelinolysis denotes osmotic demyelisation of pons caused by too rapid correction of hyponatremia (>1 mmol/L/h). It is manifested with quadriparesis, dysphagia, dysarthria, diplopia, loss of consciousness, or locked-in syndrome. The damage is often permanent.

II. Etiopathogenesis of the disease. (Using the given elements compose an etiopathogenetic algorhythm of the disease)

1. Pregnancy
2. Hyponatremia
3. Increased secretion of endogenous oxytocine with the addition of synthetic oxytocine with vasopressive and natriuretic effect
4. Reduced threshold for ADH secretion
5. Polydipsia exceeds renal free water clearance capacity
6. Fluid shift from the extracellular to intracellular space accompanied by edema of the brain

7. Plasma hypoosmolality
8. Increased water reabsorption in distal and collecting tubules of the kidney in response to vasopressin and oxytocine

III. Classification, etiopathogenetic nature and features of disease/syndrome progression

According to information in this study case please list a) 13 features of etiology; b) 11 features of pathogenesis; c) 18 features belonging to chronobiology and processes distribution in the body and d) 10 features of clinical elaboration (diagnosis, treatment). The classification should be done by using the features specified on pages 661–2 of this book.

The Book Three (12) contains solutions which are located at the end of the book.

II. Etiopathogenesis of the disease. 1–>3,4,5; 2–>7; 3–>2,8; 4–>8; 5–>2,7; 6–> 2,7; 7–>6; 7–> 5, 8; 8–>2,7

III. Classification etiopathogenetic nature and features of disease/syndrome progression
a) ***Features of etiology***:
1.13; 2.3; 2.5; 2.16; 2.21; 3.1; 4.1; 4.2; 4.3; 4.4; 4.14; 4.15; 4.17.

b) ***Features of pathogenesis***:
5.14; 5.27; 5.44; 6.2; 6.5; 6.10; 7.2; 7.4; 7.5; 7.10; 7.11.

c) ***Features belonging to chronobiology and processes distribution in the body***
8.4; 8.5; 8.6; 8.7; 8.8; 8.9; 8.28; 8.30; 8.33; 8.38; 10.1; 10.5; 10.7; 10.10; 10.14; 11.2; 11.3; 11.7.

d) ***Features of clinical elaboration (diagnosis, treatment):***
12.1; 12.2; 12.3; 12.15; 12.16; 12.17; 12.19; 12.21; 12.25; 12.33.

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Профессор Зденко Ковач — доктор медицины, доктор философии, зав. кафедрой патофизиологии. KBC Rebro, Zagreb, Croatia; zkovac@mef.hr

Professor Zdenko Kovac — MD, PhD, pathophysiologist, internist, Head of the Department. KBC Rebro, Zagreb, Croatia; zkovac@mef.hr