PATHOPHYSIOLOGICAL FOUNDATIONS OF PERSONALIZED MEDICINE

ETIOPATHOGENETIC CLUSTERS AS INTEGRATING UNITS OF CLINICAL PATHOPHYSIOLOGICAL PATHWAYS AND NETWORKS

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The hallmarks of human body reactivity are complexity, biological nonlinearity and variability of reaction patterns. Thus, the understanding of physiology and pathophysiology remains a challenging issue in clinical medicine. In order to understand a complex phenomenon a maximal insight is required. It relies on synthesis of information derived from many sources. The broader insight into these processes is leads to the more powerful synthetic view and higher level of certainty of interpretation. Even those data that do not fit into the current concepts should not be ignored. On the contrary, such data urge for further scientific investigations and search for improved concepts. An advent of new data and newly discovered mechanisms (or classes of mechanisms) contributes to refinement and reinforcement of interpretations and visions. In addition, a working concepts and interpretations are daily rechecked and reevaluated in clinical practice. Such practical application of knowledge contributes to understanding and may through many steps lead to consensual validation of given interpretation. Such reiterative testing and reevaluation leads gradually to reconfirmation of established mechanisms and concepts. A proper organ-system reactivity and whole-body reactivity heavily relay on maintenance health-bearing genotype and phenotype that allows continuity of substrate/energy turnover. Regulatory hierarchy is based on cybernetic mutual subsidiarity of individual functional systems in human body (e.g. cardiovascular system is under control of sympathetic nervous system, kidneys, etc – and vice versa). Both ways interdependence of coupled reactions and mechanisms feeds into the network. Compensatory homeostatic pathways are often converted from negative into positive feedback mode of action.

Natural initiation, development, termination and outcomes of disease/disorder states constitute a biological continuum of interaction between the body and noxious stimuli. That continuum of life processes represents a driving force of the biological system and

provides natural self-healing processes. Often, the very same responses unique to an individual (molecular, celullar, organ-related) participate within the general („normal") physiological as well as pathophysiological patterns of reaction, giving a specific clinical presentation that can be explained by biological variability. Those individual responses may be considered as elements of higher strata of functional organization. For example, maintenance of sodium/potassium transmembrane gradients is basic electrophysiological prerequisite. A failure in the maintenance of that gradient may cause catastrophic secondary dysfunctions. Quality and quantity of individual reactions contributes to a functional-unit-specific performance, including dysfunction within the specific disease context. Optimal pathophysiological consideration of disease processes includes vertical, horizontal and longitudinal integration of relevant data. Vertical dimension of pathophysiology analysis refers to establishing causal relationships among broad spectrum of clinical, macroscale signs, symptoms and dysfunctions down to the nano-scale of genomic expression, biochemical reactions and cell physiology. Horizontal analysis includes parallel processes that take place in adjacent and remote organs that are not directly involved in the disease. It provides a background to a dominant etiopathogenetic pathway in affected organ. Longitudinal consideration refers to the temporal aspects of the disease that may have distinct manifestations depending on the time elapsed, including a changing a nature of processes. For example, infectious disease (e.g. *Campylobacter jejuni*) can trigger autoimmune reactivity (e.g. *Myasthenia-like syndrome*) and thus lead to a new disease due to critical cross- reactivity of antigenic determinants.

In dealing with etiopathogenesis we tried to have establish a comprehensive approach that successfully deals with complexities and bridges the basic and clinical aspects of the diseases. We noticed a general natural tendency of pathophysiological pathways that belong to heterogeneous types of diseases, to form common units of reaction. Many pathways converge to more or less identical points. Such common units are formed at certain deviation of electrolyte concentration (like hypernatremia, hypophosphatemia, etc), macromolecular alterations (hypoproteinemia, dyslipidemias etc), and than on cellular and organ functional levels, as well. We named them the etiopathogenetic clusters (EPC). Such clusters seem to act as cross-roads for multiple inputs and multiple exits in the natural development of various diseases and altered conditions in human body. In Table 1, 91 EPCs are listed with rough estimate of their relative importance for the clinical practice. 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. These 91 EPCs and possible new ones that are yet to be identified could be considered as elementary units („common hubs of the response") within the natural pathophysiological network of interactions. Schematic diagram outlines a potential interplay of EPC-relations in Figure 1, etiology and physician brain mapping of disease processes during a diagnostic procedure. 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. A simultaneous consideration of multiple pathways

Table 1. Frequency of etiopathogenetic clusters in clinical practice according to quantitative survey of 30 professors of various branches of medicine and 30 student-peer-teachers

RP * Intensity **Etiopathogentic cluster **** of support #		RP * Intensity **Etiopathogentic cluster** of support	
1. Pain	**11,34**	47 Cholelithiasis	**7,05**
2. Arterial hypertension	**10,80**	48 Thrombocytopenia	**7,02**
3. Atherosclerosis	**10,63**	49 Hypoproteinemia	**7,00**
4. Hyperglycemia	**10,27**	50 Vasohypotonic shock	**7,00**
5. Vomiting	**10,08**	51 Hypoventilation	**6,97**
6. Edema	**10,05**	52 Hyperventilation	**6,91**
7. Heart ischemia	**10,00**	53 Nephrotic syndrome	**6,84**
8. Leukocytosis	**9,80**	54 Hyponatraemia	**6,83**
9. Anaemia	**9,78**	55 Respiratory alkalosis	**6,78**
10. Heart failure	**9,75**	56 Ileus	**6,78**
11. Diarrhoea	**9,73**	57 Metabolic alkalosis	**6,77**
12. Obesity	**9,73**	58 Hypernatraemia	**6,71**
13. Arrythmia	**9,63**	59 Hypecapnic respiratory insufficiency	**6,64**
14. Dyslipidemia	**9,46**		
15. Hypohydration	**9,30**	60. Cachexia	**6,63**
16. Hypovolemia	**9,08**	61 Hypoosmolality	**6,61**
17. Tissue healing	**9,07**	62 Obstructive uropathy	**6,61**
18. Disorders of consciousness	**8,97**	63 Immunodeficiency	**6,59**
19. Metabolic acidosis	**8,87**	64 Seisures	**6,54**
20. Brain ischemia	**8,85**	65 Hypercalcaemia	**6,47**
21. Metabolic syndrome	**8,78**	66 Neutropenia	**6,25**
22. Jaundice	**8,67**	67 Hypocalcaemia	**6,20**
23. Chronic renal failure	**8,46**	68 Intestinal ischemia	**6,17**
24. Cardiogenic shock	**8,38**	69 Pathological fracture	**6,15**
25. Sepsis	**8,30**	70 Fibrosis	**6,13**
26. Hypercapnia	**8,18**	71 Malnutrition	**6,12**
27. Ascites	**8,15**	72 Acute liver failure	**5,81**
28. Hypokalaemia	**8,12**	73 Hyperhydration	**5,78**
29. Immune hypersensitivity	**8,12**	74 Hypocapnia	**5,78**
30. Hyperosmolaltity	**7,94**	75 Hypermetabolism	**5,68**
31. Hyperkalaemia	**7,90**	76 Intracranial hypertonia	**5,66**
32. Respiratory alkalosis	**7,91**	77 Blood hyperviscosity	**5,35**
33. Urolithiasis	**7,81**	78 Hypersplenism	**5,03**
34. Hyperthermia	**7,80**	79 Eosinophilia	**4,95**
35. Hypovolemic shock	**7,75**	80 Cardiac tamponade	**4,95**
36. Thrombotic diathesis	**7,72**	81 Hypothermia	**4,83**
37. Hypoglycemia	**7,71**	82 Transfusion reactions	**4,71**
38. Bleeding diathesis	**7,68**	83 Hyperphosphatemia	**4,68**
39. Autoimmunity	**7,66**	84 Graft tissue rejection	**4,53**
40. Arterial hypotension	**7,32**	85 Hypochloremia	**4,41**
41. Chronic liver failure	**7,30**	86 Hyperchloremia	**4,37**
42. Hypoxemic respiratory insufficiency	**7,20**	87 Hypophosphatemia	**4,15**
		88 Hypomagnesiemia	**3,98**
43. Acute renal failure	**7,19**	89 Graft versus host reaction	**3,91**
44. Abdominal compartment syndrome	**7,18**	90 Hypermagnesiemia	**3,39**
45. Leg ischemia	**7,17**	91 Amyloidosis	**3,10**
46. Multiple organ failure	**7,05**		

RP* Relative prevalence of etiopatogenetic cluster in clinical practice.

** Etipathogenetic clusters are in the book Clinical Pathophysiology –Etiopathogenetic clusters (in Croatian) Medicinska naklada, Zagreb (2012, in press).

Intensity of support is avaraged value of individual quantitative estimate within the 1-12 scale, where 12 represents the most frequent event and 1 represents the least frequent appearance of individual cluster

and their cross-talk is likely to generate a more complete understanding of the disease that can lead to better adjustment of therapeutic approach to a patient as an individual with unique reactivity. The EPC-network may be considered a „skeleton" of body's reactivity to multitude of diseases.

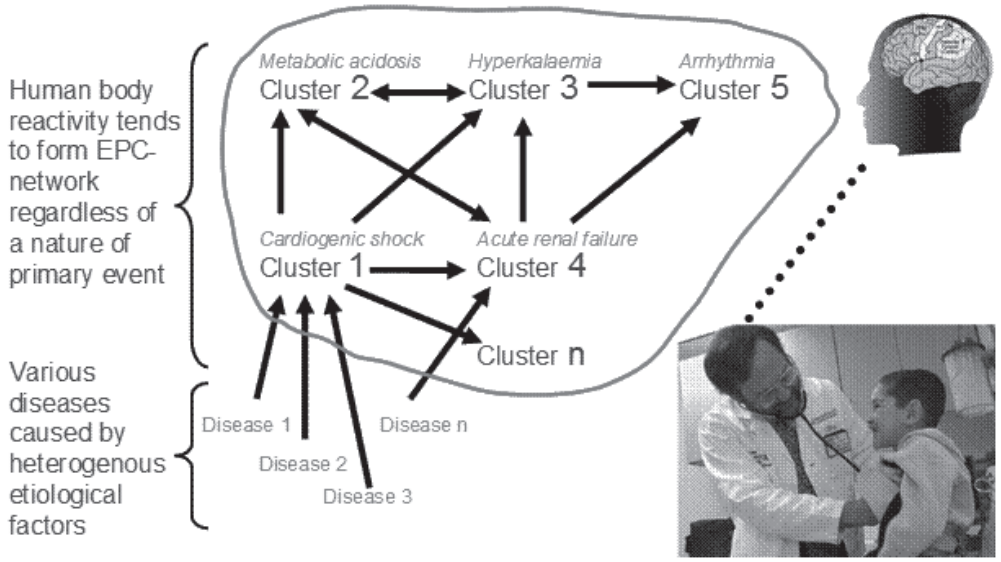

Figure 1. **General pathophysiology framework of interactions may have an importance to personalized medicine. Human body reactivity in disease tends to create etiopathogenetic clusters (EPC) network regradless of primary etiological factors and diseases. Induction of individual EPCs and their quantitative aspects contribute to variability, progression, therapy-reaction, and outcomes of the disease. Diagnostic procedure is directed towards identification of primary disease pathway and secondarilly triggered EPCs.**

An example of a specific case of reactivity is given by the terms written in italic-red which indicate the flowchart of EPCs triggered by ventricular fibrillation.

OMICS-METHODOLOGIES, BIOINFORMATICS AND PERSONALIZED MEDICINE – THE STAGE IS SET

According to National Cancer Institute (NCI) guidelines personalized medicine is *„a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose and treat disease*". Personalized medicine paradigm reinforces the evidence-based-medicine approach in the individual patient care. However, the *„explicit, consciousness and judicious use of current best evidence*" should not ignore the fact that knowledge and data considered in medicine are based on very heterogeneous methodologies and thus reflecting a specific research context. Numerous relevant pitfalls can be identified within medical reasoning. Firstly, statistical analysis of data is a powerful tool that describes probabilistic relations between selected parameters, but it is less reliable in determining cause-reaction relations. Statistics identifies chance, but not a necessarily the causal relation. Very often statistical outliers, usually considered as a nuisance in data analysis, contain valuable information about biological variability and disease manifestation under extreme conditions. Unfortunately, some physicians tend to consider association and causative relation as the same thing. Secondly, copious amounts of data and reactive patterns in medicine are generated in simplified experimental, including animal models. Those interpretations should be carefully considered when trying to apply to the complex human body reactivity. Thirdly, due to analytical nature of scientific and diagnostic methodologies and external pressure (lack of time, resources, etc) on researchers and clinicians, the observed phenomena are often interpreted without serious intention of organization and integration. Fourthly, systematization into categories has its own limits. Biological continuum of body reactions is often ignored. Phenomena are considered

as category-limited and almost isolated from the rest of the system. Fifthly, categories themselves tend to function as mental frame of reference. Thus, consideration of given aspects (molecular, or genomic level) tends sometimes to limit a comprehensive view of the disease and the patient, as a whole. Nevertheless, despite such shortcomings in medical reasoning, medicine has gradually advanced and procured the high quality of evidence. Randomized controlled, double blind, trials and meta-analysis of systemic reviews have paved the way for individualization of medical care. Medical history has witnessed numerous examples of personalized approaches, much earlier before the era of molecular medicine. The fact that 2400 years ago Hippocrates had used to prescribe a „cold food to a phlegmatic patient" indicates a long standing primordial sense of personalized approach. The advent of medical genetics added a deeper foundation in personalization concept. For example, euphenic diet with reduced quantity of phenylalanine prevented mental retardation, epilepsy, myelin disorders and small bran size in patients with phenylketonuria. Such personalized preventive approach became a standard procedure. Many other examples could be singled out in oncology (e.g. BRCA1/2 in breast carcinoma, steroid receptor expression), haematology (e.g. beta thalassemia, *BCR-ABL* gene fusion), etc.

In genomic era, the field of classical genetics (study of single genes) has been enriched by the field of genomics (simultaneous study of large number of genes). Human genome and high-throughput technologies have made a strong tide towards translations into personalized applications of knowledge and methodology. Those technologies are advancing to clinical arena at a rapid pace and with declining costs. Many distinguished laboratory and clinical scientists speak about „personal genome" and its implications to medicine (preventive, diagnostic, prognostic, ethical, pre-symptom risk assessment, and therapeutical aspects). Technological breakthroughs and bioinformatics-bases methodologies have expanded our knowledge on molecular composition and dynamics of disease processes. Bioinformatics help in converting the raw molecular data extracted from patient samples into interpretable, accessible and statistically meaningful information. The clinical context and natural pathophysiology of diseases/disorders has been enriched with copious facets of underlying processes. Thus a re-interpretation and sometimes re-conceptualization are required. Quantitative aspects of genomic expression (transcriptomics) have recently become available. Transcriptomics and related fields of proteomics, metabolomics, pharmacogenomics (and other omics-approaches) seems to be in an early stage of exponential growth. The molecular information that emerged from these approaches (both qualitative and quantitative aspects) is becoming a major tool in understanding medical etiopathogenesis and patient management.

The unraveling of pathophysiological mechanisms underlying patient clinical conditions may be considered as the most reliable foundation for personalized medicine. 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. Personalized medicine may benefit from the EPC-network especially because of its comprehensive holistic approach and vision. Plasticity of human body reactivity seems to stem from multiplicity and clustering of responses. 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 extensive personalization in medicine.

THE ISSUE OF MEDICAL CURRICULUM FOR PERSONALIZED MEDICINE

There are two mutually opposing tendencies in medicine. One is professional compartmentalization into specialties and subspecialties for the purpose of focusing and gaining greater expertise for given type of the disease. Structure of hospitals, education system and curriculum are organized according to such conceptual scheme. On the other side, available molecular data have shed a new light into the nature of disease. Natural developments of localized diseases, however, are not strictly localized processes. They often show a tendency to spread away from the primary locus into surrounding and remote tissues and functional systems. For example, local inflammatory response can be readily converted into a systemic inflammatory response (SIRS) affecting multiple organs systems. It appears that delicate balance of many factors (like, genetic variations, chronobiology-related conditions, quantity of reactive components, etc) governs etiopathogenetic relations. Imbalance in various mutually antagonistic forces may lead to development of a dominant disease pathway in quite different directions. Therefore, compartmentalized medicine faces problem in dealing with complex states of diseases and „non-compartmentalized" patterns of natural reactivity and disease development. Academic policy makers and professional societies strategy plans agree that scientific understanding of physiology and pathophysiology in both holistic terms and in individual parts constitute the main pillar of the medical intervention. Both sides of the coin should be taken into consideration for integrated comprehension. That fundamental principle remains equally relevant for personalized medicine.

Behind the scene there is a hidden reality. Standard classifications of diseases claim 30,000-32,000 of nosological entities to constitute a diseasome, the encyclopedia of all human diseases and disorders. These individual diseases/syndromes and disorders are classified into numerous taxonomic strata, like, organ-system-directed pattern of organization, etc. That quantity may stem, however, from the underestimated reality by one or two orders of magnitude. Namely, should the molecular variants of nosogenic alleles be taken into account as principal unity of an etiopathogenetic pathway quite larger disease base should be envisaged. In addition, due to sophistication of diagnostic methodology disease processes are more precisely indentified and quantified in living patients. 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. Methodology of teaching should not ignore a robust plethora of potentionally relevant information, neither the way how human brain manages the complex issue.

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 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. The EPC-model offers an 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 the physician. It can be characterized as *practice-based education*. Primarily, attention is

focused to the patient's condition, its development and the effects of therapeutic strategies. At the same time it channels a studying process towards considering integral and local body reactions. Since this EPC-model is not medical specialty limited, it may be applied in many areas as a useful studying methodology.

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