



Editorial

Health in medicine: The lost graal



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1. Introduction

Because of the difficulty in predicting which basic research areas would yield information of greatest diagnostic or therapeutic value, biomedical and biopsychosocial sciences including psychosomatic medicine historically were opted to use the well-balanced interdisciplinary, rather than disease-oriented studies of the interactions between environment and human mind, brain, and body to determine multiple (molecular, neurobiological, physiological, emotional, cognitive, behavioral, spiritual, and social) factors influencing health and behavior (as exemplified by the organization of basic and clinical research programs by Seymour Kety and Robert Cohen in the National Institutes of Health). This approach in psychosomatic research, as in other biomedical studies, was captured in the World Health Organization (WHO) definition of health, formulated in 1948, describing health as ‘a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity’.

However, the economic climate later influenced the sciences through a disproportional allocation of money based on lobby-determined investment priorities, resulting in a more disease-oriented bias in both basic and clinical research [1]. Moreover, regulatory authorities (e.g., US Food and Drug Administration), most companies of the biopharmaceutical and device/diagnostic industries, and top-ranked biomedical journals have been inclined to dismiss a health-oriented approach for disease-focused studies and products [2]. Subsequently, the WHO definition of health has been criticized by some scientists as an unachievable goal. They consider this conceptualization of health to be an elusive idea and have proposed to downgrade the definition by reformulating it into a more disease-centric, event-reactive, or disability-coping one, describing health as ‘the ability to adapt and self-manage in the face of social, physical, and emotional challenges’ in people living with chronic diseases or after disasters [3,4]. Authors argued for this reformulation of the meaning of health based on progress from disease-focused studies. However, proponents of the revised definition ignore the fact that this approach might

contribute to modern big challenges with over-diagnosis, multi-morbidity and overmedication, including the recent opioid abuse epidemic and national healthcare crises.

2. Disease-centric approaches in biomedical sciences

To date, most biomedical and psychosocial researches including psychosomatic studies have concentrated their efforts on discovering which psychological mechanisms, biological processes, or specific genes cause specific diseases. In biomedical sciences, this “disease-phenotype homogeneity” (i.e., an accurate phenotyping of patients) methodology has been developed with relative success and mainly for very specific genetic, orphan, and rare traits and diseases [5]. Subsequently, the latest large-scale genetic and molecular studies yielded that the most common disorders (e.g., depression and type 2 diabetes) have polygenic or heterogenous architecture of risk and cannot unequivocally be predicted by individual genotypes or *endo*-phenotypes [6,7]. Moreover, these variations are complicated by high epigenetic-related genome diversity across individuals during genotype-environment (e.g., genome-stressor) interactions [8]. Indeed, evidence-based medicine and physiological studies have shown that people with a similar disease (e.g., hypertension, type 2 diabetes, or major depression) or related phenotypic trait (e.g., high blood pressure, increased blood glucose, negative affect) may have different underlying causal mechanisms [9–13]. After a half century of disease-centric studies, the psychosomatic research faced the similar challenge [14]. It was found that the causal relationships between the same psychological and somatic domains of the psychosomatic disorders could be more complex with multistage within- or between-subject feed-forward and -backward causal pathways. For example, in some cases high blood pressure (hypertension) has been found to be associated with pathological mechanisms increasing depression and chronic pain severity, but in other cases high blood pressure was found to be related to protection mechanisms reducing depression and chronic pain severity [11,15–21]. This variety in mechanisms should correspond with diverse treatments

within the same nosological units: e.g., incorrect (too aggressive) antihypertensive treatment in some cases may provoke depression and chronic pain relapse or antidepressants and analgesics may increase hypertension risk [11,16,19,22]. To resolve the problem, an alternative ‘disease genotype or *endo*-phenotype homogeneity’ (i.e., an accurate genotyping or *endo*-phenotyping of patients) methodology was recently suggested for somatic disorders. In parallel, psychiatric researchers established the Research Domain Criteria (RDoC) to cope with the same phenomenological heterogeneity of the disorders spanning their units of vulnerability-oriented analysis from risk genes to measures of bio-behavioral impairments. Some researchers from the psychosomatic community also suggest to modify the traditional psychosomatic paradigm and to direct attention to a more comprehensive *endo*-phenotyping of patients (e.g., with hypertension), to associate them then with psychological and behavioral phenotypes [14]. However, to be clinically valuable, this “new” approach will also face the same challenge of comprehensive and detailed analysis of clinically recognizable risk phenotypes after assembling the study population based on genotype or *endo*-phenotype [23].

While the big multi-omic data approach with comprehensive pathway analysis methods is considered to resolve the challenge with the accurate prediction of risk phenotypes and diseases [24], a practical application of these genetic, molecular, and biological discoveries cannot yet satisfy physicians and patients [25]. Thus, all the traditional disease-centric methods in biomedical sciences have presented ambiguous interpretations and failed in translating most genetic and biological findings to the clinic. It is considered that the main challenge of these traditional methods is a lack of accurate or correct phenotyping of the disorders (i.e., the misuse of the disorder or risk trait incorporating its different clinical [symptom quality, number, and severity] presentations for homogenic phenotype grouping), but not in the methods of analyses. However, extensive risk phenotyping, whether categorical or dimensional, may be disadvantageous without necessarily improving the homogeneity of samples due to needed time, resources, and costs. Indeed, a fast, simple, and inexpensive phenotyping that would help illuminate biological pathways from genetics to disease and suggest correct therapeutics is widely sought in biomedical sciences. Thus, multiple risks are difficult to precisely genotype and phenotype in each complex clinical case to assess and control its treatment and outcomes. To be beneficial, biomedicine and other components of health industry need a really alternative approach that maps genome and phenome relationships more readily onto individual health (longer life-span and prolonged health-span) and brings a real health-related perspective to the current dominant disease-centric approach. This calls for the rehabilitation of the original WHO definition of health claimed by general practitioners [26].

3. A health-centric ‘resiliency’ approach as a game-changer

Such a potential alternative approach in explaining, predicting, and manipulating the person's health has been suggested due to the evidence that risk of multiple diseases is preserved by a fewer number of resiliency mechanisms or factors protecting and promoting health that are cheaper and easier to assess, predict, monitor, and manipulate. This proposal is supported by findings of a few common genetic variants ($N \approx 10$) in ethnically heterogenic groups of centenarians that together with healthy environmental factors and lifestyles probably counter the effect of a large number ($N \approx 1000$) of some disease-specific risk variants associated with most common pathologies, compressing morbidity and/or disability towards the end of very long lives [27–29]. Thus, it is not fewer ‘bad’ variants that makes centenarians survive longer in healthy condition, as disease-orienting investigators have suspected, but the presence of a few protective variants in combination with environmental resiliency factors that buffer the effect of any disease-associated variants and deleterious environmental factors [29,30].

The ‘resiliency’ topic has been widely discussed for the last decade

in biomedical, clinical, and psychosocial literature, but the related studies were not sufficiently conclusive to transfer the main clinical viewpoint on health from the disease-centric to the resiliency-centric mechanisms [31,32]. To date, the main problem in resiliency or resilience research is related to its broad conceptualization [33]. Most researchers mix the concepts of ‘resilience’ and ‘adaptation’ combining them in searching for integrative biomarkers of the same explicit, positive ‘resiliency’ outcomes (e.g., successful coping with stress and adversity without the development of disorders) [32,34]. However, two fundamentally different ‘covert’ processes, regulating resources for flexibility and stability of the living organism, lay in the background of its ‘overt’ resilient (health protection, promotion, and recovery) response in the face of adversity [35]. To distinguish the categories, its explicit health-related manifestation is labeled ‘resiliency’, but a covert resource regulating stability is named ‘resilience’, in contrast to ‘adaptation’ resources regulating flexibility.

Resilience mechanisms contribute to survival and mental and physical fitness by maintaining proactive biological or psychosocial stability in response to potential risks. They counteract to adaptation mechanisms that contribute to survival and fitness by maintaining reactive biological or psychosocial flexibility in response to imposed conditions [35]. Due to genetic or epigenetic mechanisms individuals may be predisposed to overly flexible adaptation or to excessively rigid resilience (high resistance) in response to challenges. These two counteracting responses determine behavior at different stages through regulating perception, central processing, and effector responses.

4. A theoretical background for health-centric ‘resiliency’ approach

During human development, brain systems mature under genetic and environmental control to form central surviving-support mechanisms keeping the balance between whole-body resilience (stability protection) and adaptation (flexibility maintenance). These two main attractors or basins of attraction (using the dynamical systems’ and Chaos theory’s terminology) function to arrange the activity of biological structures to produce, use, dissipate, and store metabolic energy for favorable functioning in different environmental conditions. This balance is associated with a range of individual physiological steady states with minimized total rate of entropy production and heat dissipation to the surroundings (using the terms of Ilia Prigogine, a Nobel Laureate best known for his discoveries in thermodynamics). Such steady states with time-dependent reversal symmetry between adaptation and resilience aiming maximum metabolic energy economy are well-known in human physiology. For example, it is evident in the baroreflex regulation of blood pressure steady states in response to external and internal challenges (i) with the response-recovery symmetry in the good-health condition with the least work consuming the minimum amount of total metabolic energy (e.g., when a high gravity- or g-resiliency effectively absorbs the orthostatic blood pressure perturbations; see Fig. 1A) and (ii) with the response-recovery asymmetry in ill-health conditions with extra metabolic energy consumed for extra work to pay this cost for either response or recovery (e.g., when a low gravity- or g-resiliency ineffectively absorbs the orthostatic blood pressure perturbations; Fig. 1B and C) [15,35,36]. This physiological ‘energy economy’ mechanism seems to determine the rate of function of a large number of genes with related post-translational modifications and allosteric control of proteins working synergistically in circadian, standing-lying, moving-relaxing, and eating-fasting symmetrical rhythm modulating the balanced status in anabolic and catabolic metabolisms [21,37–41].

A direct positive relationship is considered between the extra energy expended for the work support at a steady state and the durability, chronicity, or severity of the ill-health condition consuming and dissipating this extra energy (Fig. 1). This extra energy consumption or ‘dissipative’ adaptation leaves the sick organism without sufficient

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