

PERSPECTIVE

Making sense out of the world: Expanding our mental model of health and disease

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Abstract

We make sense of the world through our mental representations or models. They allow us to identify and categorize objects and ideas and shape our views of the world determining what we consider relevant and valid. Mental models enable reasoning, including clinical reasoning in regard to diagnosis and therapy. Scientific advances in understanding of biologic processes in health and disease have begun to reveal their complexity. Systems biology has embraced this complexity and is recognized as complementary to the reductionist approach to science. The mental models educators impart in their students create the boundaries for what is deemed relevant scientifically and clinically. The successes emanating from the prevailing Western mental model of health and disease focusing on the individual and the reductionist approach to scientific inquiry is unquestioned. However, as our understanding of biologic processes has grown, the necessity of a new mental model that encompasses factors external to the individual is evident. The author proposes that a mental model, akin to an ecosystem, with the individual residing at the confluence of their genetic, behavioral, environmental, and microbiota factors be consciously developed in students. Embracing the complexity and interactions of biologic processes within and external to the individual is necessary to continue to advance science and medicine.

KEYWORDS

behavior, ecosystem, environment, genome, mental models, microbiota, social determinants of health

1 | INTRODUCTION

Our understanding of human biology, its normal functioning in health and disruptions thereof resulting in disease, is continually evolving. From a historical perspective, as chronicled by Porter,¹ Western biomedicine has its roots in the ancient Greek approach of focusing on the human body and its workings in health and disease. This is in distinction to other ancient traditions, such as Chinese and Indian, that included

associations with the physical and social environment in their understanding of health and disease.

In the ensuing millennia, paradigm-changing breakthroughs in the conceptualization of biomedical processes, often facilitated in the last two centuries by technologic advances, heralded periods of great progress and major advances in the understanding of normal human functioning and disease. For example, in the mid-1800s advances in microscope design and optics enabled the discovery of cells and the advancement of the cell theory, and the discovery of

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bacteria and the development of Koch's postulates. Indeed, the mid-1800s with its advances in technology, chemistry, and physics ushered in the era of “modern medicine” based on the scientific understanding of human biology. Probing ever deeper from organ-level physiology to molecular biology, scientific discovery has allowed us to explore and understand biologic functions at evermore granular levels. The resulting advances in knowledge emanating from this scientific approach to the study of biologic processes and their perturbations have transformed not only the depth of our biomedical understanding but also our clinical options for the diagnosis and treatment of disease.

While resulting in great advances, this reductionist approach to bioscience has its limitations. As our understanding has grown, we have continually been faced with the realization that biologic systems are far more complex than initially envisioned. As we entered the 21st century, systems biology, seen as the antithesis of reductionism, which embraces an integrative approach to comprehending the complexity of biologic systems has been gaining recognition as a valued scientific research complement to the dominant reductionist approach. While a singular definition of systems biology remains elusive, the NIH defines it as “an approach in biomedical research to understanding the larger picture—be it at the level of the organism, tissue, or cell by putting its pieces together. It is in stark contrast to decades of reductionist biology, which involves taking the pieces apart.”²

For the past century, the practice of clinical medicine has followed a similar “reductionist” approach to the treatment of disease. Frequently referred to as the “infectious disease” approach, a single putative causal “agent” is sought for a particular disease. While proving invaluable for problems such as pneumococcal pneumonia in an otherwise healthy individual, where identifying the offending pathogen and treating with appropriate antibiotics results in dramatic salutary effects and a return to health, many modern maladies have shown to be intractable to this approach. In parallel to the march of science and its dramatic increase in understanding at progressively more granular levels, there has been a proliferation of specialty and subspecialty physicians with deep expertise in increasingly narrow clinical domains. This leads to the all too frequent lament that “I have multiple physicians treating my different parts but no one is treating me!”

But, as in biomedical science, astute physicians observing the course of patients' diseases have repeatedly voiced concerns about the limitations of the prevailing “scientific approach” to clinical medicine. As early as 1927 Francis Peabody in a famous lecture at Harvard Medical School opined “What is spoken of as a “clinical picture” is not just a photograph of a man sick in bed; it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes, and fears. Now, all of this background of sickness which bear so strongly on

the symptomatology is liable to be lost sight of in the hospital.”³ Half a century later George Engel advocated for what he termed the biopsychosocial approach to medicine which encompassed the biologic, psychological, and social cultural aspects of the patient.⁴ He argued that an individual's biologic functioning, including disease states, was inexorably linked with psychological and social concerns that must be considered by physicians when providing patient care. And most recently the social determinants of health have been shown to play an important role in the health of an individual as well as in the health of populations and are major contributors to observed health disparities. As defined in the CDC's Healthy People 2020 report “Social determinants of health are conditions in the environments in which people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks. Conditions (e.g., social, economic, and physical) in these various environments and settings (e.g., school, church, workplace, and neighborhood) have been referred to as “place.” In addition to the more material attributes of “place,” the patterns of social engagement and sense of security and well-being are also affected by where people live. Resources that enhance quality of life can have a significant influence on population health outcomes. Examples of these resources include safe and affordable housing, access to education, public safety, availability of healthy foods, local emergency/health services, and environments free of life-threatening toxins.”⁵ Despite a century of calls for attention to external factors recognized as influencing the course and development of disease, we are only beginning to understand the complexity of these relationships and decipher causal linkages.

It is now clear that factors often considered external to the individual and therefore not relevant, are essential contributors to understanding biologic processes that play significant roles in health and disease. While recognizing the enormous value of the Western biomedical tradition focusing on the human body, we must consider the value of the ancient traditions that embraced the physical and social environment as playing important roles in health and disease. It is time for a paradigmatic change in our conceptualization of biologic processes.

If one accepts that there is value in a broadened consideration of factors worthy of study as relevant to human health and disease, one must consider a multitude of barriers. All too often there is almost no communication and collaboration between basic science researchers and researchers investigating the contributions of the array of “social determinants of health.” Generally, the focus of scientists investigating human biology is the individual or model organism in a controlled laboratory setting. Researchers studying the social determinants of health emphasize communities and populations in real-world settings. Different research methodologies, different approaches for determining what are considered

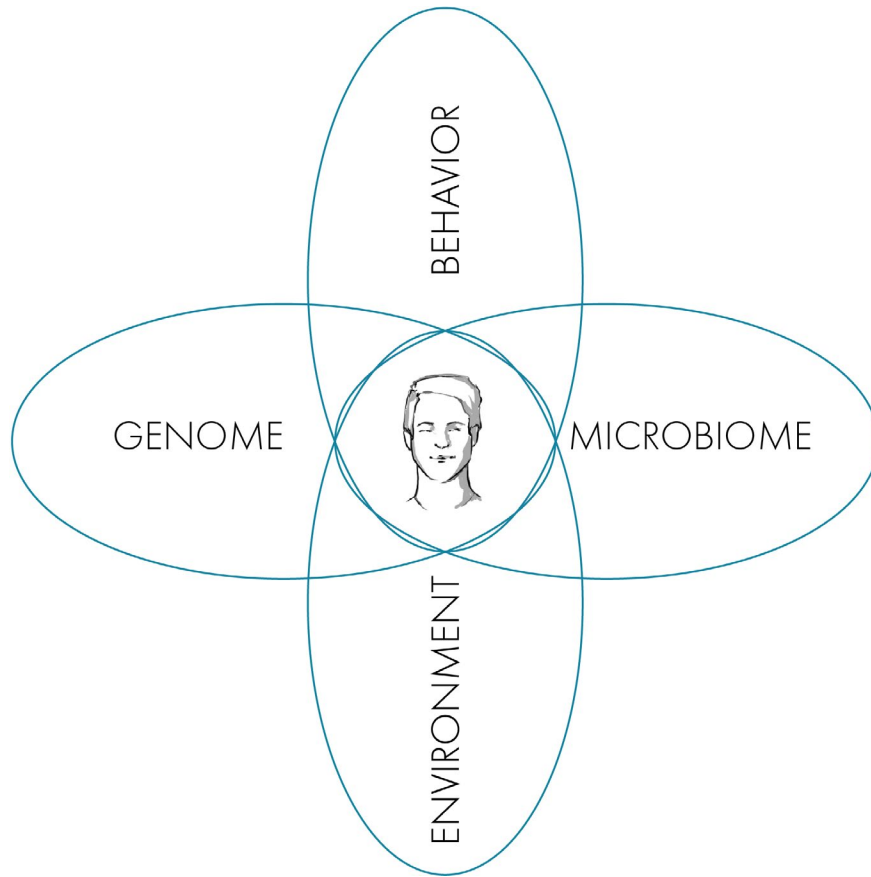


FIGURE 1 Each individual can be conceptualized as an ecosystem determined by the confluence of their genomic, behavioral, environmental, and microbiota factors. ©2019 Victoria Bornstein [Colour figure can be viewed at wileyonlinelibrary.com]

significant findings, different professional organizations, and different journals for the dissemination of the research, all contribute to the seeming lack of progress.

Potentially the greatest barrier is our worldview or mental model of what is considered “true science” and the appropriate questions for biologic researchers to study. As individuals, we make sense of the world through our mental representations or models. These mental conceptualizations pervade our daily lives. They allow us to identify and categorize objects, ideas, and more. But these mental models also shape our views of the world and determine what we consider relevant and valid. This is true not only for daily functioning but also for our professional lives. Mental models enable reasoning, including clinical reasoning in regard to diagnosis and therapy. Therefore, theoretical and empirical work regarding their development has been studied for decades.⁶ Importantly, the mental constructs which form the foundation for reasoning are shared among members of a discipline. “We become acculturated into societies that provide us with a cognitive toolkit of knowledge and ways of using such knowledge. Professional education and training are primarily about socializing students into particular ways of knowing and thinking about the world of practice.”⁷ The mental models we consciously or unconsciously impart to our students set

boundaries as to what is “in scope” and what is not. For life science educators laying the foundation for the development of robust mental models is an essential educational outcome, one that is unfortunately very rarely communicated clearly.

It is time for educators to explicitly convey an expanded model that encompasses the seemingly disparate factors that are external to the body, but pertain to human health and disease. While not minimizing the importance of in-depth study of isolated processes, we must inculcate in our students the centrality of understanding how these processes function in an organism and the complex web of interactions in which they exist. Our tendency is to simplify concepts to enhance understanding, but we are doing our students a disservice. The complexity of biologic systems must be embraced. Major advances in science, and subsequently in clinical medicine, will be made when the full panoply of inputs including the genome, proteome, and other -omes, the external physical, social, and psychological environments and behaviors are investigated and facilitated by the use of modern tools such as machine learning. We must provide our students, a mental scaffold on which to build their understanding that embraces both the complexity of biological processes and the myriad behavioral factors and external relationships that either directly or indirectly impact biologic systems.

A potentially helpful analogy is that of an ecosystem. An ecosystem is the physical environment and the living species that inhabit it. Ecosystems such as a tidal pool can be small or expansive like the Great Lakes. As indicated in Figure 1, each of us, as human beings, can be thought of as an ecosystem existing at the intersection of our genomic, behavioral, environmental, and microbiota elements.⁸ While recognizing that a single factor may be deterministic, such as a dominant genetic disease with 100% penetrance, generally these elements act in concert to influence health and disease.

What is the evidence that this is a timely consideration?

The dramatic increases in our understanding of basic pathophysiology and mechanisms of disease have raised new issues, one being that the body has only a limited number of responses to a multitude of insults. Even our current disease taxonomy needs revision as mechanisms and interactions are elucidated. Let us consider the example of myocardial infarctions (MI), a leading cause of death in the US and increasingly so in developing nations. Due to the morbidity and mortality associated with MIs they have been a focus of study for decades. However, investigations have shown that different underlying pathophysiologic mechanisms can result in MIs. Seeking a clinical definition consistent with the pathologic definition, the Task Force for the Universal Definition of Myocardial Infarction in 2000 first published a consensus statement providing definitions for different types of myocardial infarctions incorporating the pathologic mechanism. Subsequently, three revisions have been published, the most recent the Fourth Universal Definition of Myocardial Infarction (2018).⁹ Modified with each revision, five different definitions for myocardial injury and infarction exist. They range from MI type 1, presenting with symptoms of myocardial ischemia, new ECG changes consistent with ischemia including the development of pathologic Q waves, and imaging evidence of new loss of viable myocardium or wall motion abnormality consistent with ischemia and an acute coronary atherothrombosis to type 5 which is a MI after coronary artery bypass grafting.

Now let us focus only on MI type I which is due to an acute coronary atherothrombosis. While the proximate cause for the MI is the atherothrombosis, if progress is to be made in reducing the morbidity and mortality from type I MIs we need to move upstream to address the problem of atherosclerosis. For over a century, the lipid hypothesis of atherosclerosis emphasized the central role of cholesterol¹⁰ and based on clinical studies, led to the development of recommendations to lower cholesterol.¹¹ In addition to the focus on dietary cholesterol and pharmacologic manipulations (statins) to lower cholesterol levels, it was recognized that other factors also play a role in the development of coronary artery atherosclerosis. Familial hyperlipidemia has long been recognized as leading to premature atherosclerosis and MIs and recent studies have expanded our understanding of dyslipidemia and

the importance of apolipoproteinB₁₀₀.¹² Similarly, a genetic predisposition to higher serum calcium levels has been associated with an increased risk for coronary artery disease and MI.¹³

Epidemiologic studies have shown a correlation between the intake of red meat and the development of atherosclerosis even though the causal mechanisms remained elusive. Recent studies have shown that dietary choline and l-carnitine (found in red meats) are metabolized by intestinal bacteria to produce trimethyl amine, which is absorbed into the bloodstream and oxidized in the liver by the enzyme flavin monooxygenase 3 to trimethylamine N-oxide (TMAO) which plays a causal role in the development of coronary artery disease.¹⁴ Interestingly, a long-term study in initially healthy women showed that increases in TMAO, attributed to changing dietary patterns, led to an increased risk for coronary heart disease irrespective of the absolute level.¹⁵

Environmental factors, such as air pollution, have also been implicated in epidemiologic studies of coronary artery disease. A study of Chinese individuals with long-term exposures to fine particulate matter with aerodynamic diameter less than 2.5 μm and nitrogen dioxide due to living in proximity to major roads were both independently associated with elevated coronary artery calcium scores (a measure of atherosclerosis). It is hypothesized that these pollutants, or others not yet measured, react with airway and lung cellular membranes and generate oxidative reaction products which in turn may have an atherogenic effect.¹⁶

Intriguing, but as yet unexplainable, are findings such as the inverse relationship between adult coronary artery calcium scores and favorable psychosocial scores in childhood when adjusted for other known risk factors. The childhood psychosocial factors that are included in the score include social-economic status, home emotional environment, health behaviors of parents, stressful events that might threaten a child's sense of stability and continuity, the child's self-regulatory behavior or self-control, and the child's general level of social adjustment.¹⁷ A related finding is that subjective social status as reported by an adult individual is similarly inversely related to coronary artery disease.¹⁸ Subjective social status is an individual's self-perception of their position in the social and social-economic hierarchy. It is related to but has been shown to be independent of traditional social-economic status determinations.

What does all this mean? Is there common pathophysiologic mechanisms such as inflammation that is responsible for the initiation and progression of atheroma and atherosclerotic coronary artery disease or are there are a multitude of mechanisms that must be considered? How important are interactions among an individual's environment, behavior, genome, and microbiota? We know that genetic and behavioral factors are independent, but additive in their effect on the risk of developing coronary artery disease.¹⁹ We also know

that epigenetic patterns are modulated by environmental and behavioral factors and that epigenetics may play an important role in the development of coronary artery disease.²⁰ These are but a few examples of the complex interrelationships being explored. The questions are many even in this exceedingly well-studied “disease.” Interventions based on scientific studies that focus on one or just a few factors may well have only a modest or even inconsequential effect on coronary artery disease when applied broadly to individuals.

The literature is replete with examples of effects observed under controlled experimental conditions that are not replicable in wild type settings. Lack of attention or inability to account for behavioral, environmental, genetic, and even microbiota factors may be responsible for some of the irreproducibility. Perhaps, such myopia is also responsible for the number of pharmacologic agents that showed great promise in experimental laboratory conditions, but failed in human clinical trials. And even drugs that have been approved based upon controlled clinical trials, but were subsequently withdrawn due to untoward effects observed in post-release follow-up. With the benefit of hindsight often these failures are explainable. An ecosystem model that consciously incorporates not only the intrinsic biologic factors but also external factors that directly or indirectly impact the biology will enable investigators to better anticipate and account for important variables.

It is sometimes argued that a simplistic model is superior to an overly complex one. I would argue that advances in our understanding of the complexities of biologic processes and the factors that influence or determine them necessitate embracing this complexity in our educational endeavors. However, how best to develop desired mental models remains to be determined. One approach is to build on work depicting complex systems that characterize multiple components at multiple levels interacting with one another, as proposed by Singh et al.²¹ Their model consists of a three-level hierarchical tree composed of organs, tissues, and cells with their interactions within and across levels. The complexity of biologic systems and diseases becomes readily apparent with such a depiction. While it further increases the complexity, we need to add to the causal model the effects of interactions with the environment, one's behaviors, and their microbiota. It is only through such a model, an ecosystem model, that the “in scope” boundaries will be broadened.

As scientific paradigms continue to evolve so to our educational paradigms must evolve. Given the rapidity of change in the life sciences and their implications for clinical medicine, the challenge for educators is great. For decades the focus has been teaching our students “what to think.” Given the ubiquitous access to factual information educators must now pivot to teaching our learners “how to think.” An important part of this transformation is inculcating appropriate mental models on which current and future knowledge may

be built. To best enable our students and trainees to study and unravel the complexities of biologic systems and enhance our collective understanding of health and disease, we must instill an appreciation for system biology and lay the foundations for a mental model that includes genomic, environmental, and behavioral factors as well as the microbiota. Similarly, our future clinicians must be trained to understand the central role played by these factors in the maintenance of health and development of disease in their patients. While not diminishing the advances enabled by the ancient Greek tradition of focusing on the body, there is a great deal of wisdom in embracing the Chinese and Indian traditions that recognize the importance of the environment and behaviors.

AUTHOR CONTRIBUTIONS

The entirety of the manuscript was conceived by and written by James Woolliscroft.

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