

Functional Medicine: An Operating System for Integrative Medicine

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I have been a student of and advocate for molecular medicine the past 40 years. From my experience from 1981 to 1983 at the Linus Pauling Institute of Science and Medicine, I came to better understand how molecular medicine fits together with what was emerging to be called *integrative medicine*.

At first it seemed as if these 2 models were mutually exclusive, with molecular medicine being seen as mechanistic and reductionist in its formalism, and integrative medicine being more experientially and culturally rooted in observation. My experience at the Pauling Institute, where I had the opportunity to interact with some of the best minds in molecular medicine as well as clinical innovators in integrative medicine, led me to recognize that what was missing in bridging the gap between the 2 medical models was an operating system—one that would connect the therapies conscribed by the integrative medicine model with the mechanistic understanding of the origin of noncommunicable, chronic disease that was discovered within the molecular medicine model.

A drive to find a bridging operating system between these 2 systems resulted in 2 meetings in 1989 and 1990 that my wife and I sponsored in Victoria, British Columbia, Canada. We brought together a global group of experts representing both clinical and scientific insight and an interest in exploring the “what if” question of a medical system that incorporated both the molecular and integrative medicine perspectives. Of these 2 meetings came the term *functional medicine*, which the group believed represented the bridge between molecular and integrative medicine. We believed that dysfunction at the physiological, physical, cognitive and psychological levels preceded the onset of the discrete pathology that we term a *disease*, and that a better understanding and quantitation of function from a whole-person, systems approach could provide the operating system for the molecular medicine application to integrative medicine.

For thousands of years, practices have been used in various cultures that promote healing and wellness. These approaches—among them things such as traditional Chinese medicine, ayurvedic medicine, acupuncture, herbal medicine, yoga, homeopathy, meditation, mind/body techniques—are holistic in nature and often look beyond the body to include the mind and spirit as well. Those of us who have focused our careers on wellness know that mindfulness and lifestyle choices are key tools in maintaining health and treating illness. And yet for much of the 20th century, Western medicine maintained a suspicion of—and in some cases even outright disdain for—these practices that fall under the banner of integrative medicine. The emerging science underlying molecular medicine, however, was starting to develop a mechanistic understanding of how these therapies work that would allow them to be applied more successfully to people in need. From this framework came the operational concepts that framed functional medicine in 1990.¹

Two researchers I have been following for many years are Albert László Barabási, PhD; and Joseph Loscalzo, MD, PhD, of the Center for Complex Networks Research and the Department of Physics and the Department of Medicine at Brigham and Women’s Hospital at Harvard University, respectively. In discussing the future of medicine, Drs Loscalzo and Barabási² stated that, historically,

... *disease* is defined on the basis of the principal organ system in which symptoms and signs are manifest, and in which gross anatomic pathology and histopathology are correlated. ... While quite useful in an earlier era, classifying disease in this way vastly overgeneralizes pathophenotypes, does not take into consideration susceptibility states or preclinical disease manifestations, and cannot be used to individualize disease diagnosis or therapy.

They look to the future of medicine as “a move from a field of simple associations rooted in semi-empiric reductionism in search of a ‘cure’ for each disease to one that recognizes the power of molecular networks and systems upon which human biology is based.”²

This model takes medicine from a *disease-centric* focus to that of a *systems biology-centric* focus. The challenge is to develop an operating system for medicine that is robust enough to incorporate the complexity of the

human biological system that derives out of the interaction of a person's genome with their environment. As pointed out by Barabási et al,³ "the potential complexity of this biological network is daunting: with approximately 25 000 protein-encoding genes, about 1000 metabolites, and an as yet undefined number of distinct proteins and functional RNA molecules." In the face of this complexity, however, is the recognition that with the new analytical tools for quantitating functional aspects of human biology coupled with the increasing power of bioinformatics that an integrated understanding of the interactions among the genome, the proteome, the metabolome, and the environment translated through systems biology provides the opportunity to understand the origin of an individual's complex disease and develop treatments for it that would have been unrecognized through application of the traditional disease diagnosis and treatment model.

The functional medicine model was designed to provide a robust operational system that would allow for the application of these network biological concepts to be applied to patient care, and also be flexible enough to accommodate the future evolution of systems biology. The functional medicine model moves away from a histopathological definition of disease that results in a classification of a patient's dysfunction into a limited number of descriptors to that of a postgenomic definition of disease that is based on the unique nature of how the person's genome interacts with their environment and lifestyle in their expression of function. As Loscalzo et al⁴ have stated, "the novelty in this approach rests not simply in nosology, but in defining disease expression on the basis of its molecular and environmental elements in a holistic and fully deterministic way."

Functional medicine represents an operational system that focuses on the underlying causes of disease from a systems biology perspective that engages the patient and practitioner in a therapeutic partnership.⁵ This is complementary to the definition of the goals and philosophy within the integrative medicine model "that focuses on the whole person, is informed by evidence, and makes use of all therapeutic and lifestyle approaches."⁶ It is interesting to note that one definition of *functional* as applied to health care is "medicine involving physiological function rather than anatomical pathology."⁷

In 1999, an article titled "Functional Somatic Syndromes: One or Many?" was published in *Lancet*.⁸ In this article Wessely et al⁸ described a number of disorders they labeled as "functional somatic disorders" in that they were associated with impaired biological function without known organic or structural cause. This list of conditions included chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, interstitial cystitis, benign prostatic hypertrophy, posttraumatic stress syndrome, attention deficit-hyperactivity disorder, autistic spectrum disorder, multiple chemical sensitivity, premenstrual syndrome, polycystic ovary syndrome, metabolic syndrome, essential

hypertension, cognitive decline syndrome, nonulcer dyspepsia, noncardiac chest pain, and atopy. The authors recognized that conventional medical therapy based on a standard pathophysiological-based diagnosis is fairly ineffective for these patients. There is evidence that these functional somatic syndromes represent changes in network biology of the patient due to their unique interaction of their genome with their environment and lifestyle. Sharpe and Bass⁹ report that there are identifiable physiological mechanisms associated with these syndromes and that they are not simply "psychosomatic" and "all in the mind."

In 2007, Henningsen et al¹⁰ authored a paper titled "Management of Functional Somatic Syndromes" in which they argued for a balance between biomedical, organ-oriented, and cognitive interpersonal therapies as most effective. They related the triggers for these multisymptom chronic health problems to the interaction of organic disease, dysfunctional peripheral stimuli, and dysfunctional early and current relationships. Although helpful in bringing a better understanding to the origin of the complexity of these disorders and their multiple etiological factors, they failed to include the concept of network biology and the interaction of a person's unique genome with their environment and lifestyle as a key driver for understanding both the origin of their functional somatic syndrome and the application of this systems biology approach to the development of a personalized intervention program.

A review in 2015 of the National Library of Medicine publications under the search term *functional medicine* identifies 10 000 citations under functional cardiology, 6600 citations under functional endocrinology, 27 000 citations under functional neurology, 71 000 citations under functional immunology, 6500 citations under functional gastroenterology, and 14 000 citations under functional oncology. In 2000, the term *functional genomics* was recognized as the field of molecular biology that applies genomic and transcriptomic data to describe genetic expression and its impact on biological processes. Since its inception as a concept, 27 000 citations have been recorded under the search term *functional genomics*. The rapid increase in the use of the term *functional* as a descriptor in medicine indicates the penetration of the systems biology/gene-environment concept into medicine. It is now clear that alteration in function precedes pathology. The innovations in noninvasive screening of biological function with technologies such as genomic and transcriptomic analysis, magnetic resonance imaging, new biomarkers that assess functional status such as metabolite profiling, and challenge tests that assess functional reserve, such as cardiac nuclear medicine treadmill testing, all provide new insight into network biology. These tools move the clinician from a *snapshot* view of the pathology of the patient to an understanding of the dynamics and resiliency of their biological system and where functional alterations are occurring prior to late-stage pathology.

I recognized in 1989 that we were witnessing a change in the definition of *functional* in medicine, transitioning from that of an association with psychosomatic illnesses to that of an understanding of the impact of a person's environment and lifestyle on their functional genomics/proteomics/metabolomics and their relationship to health or disease. One of the remarkable leaders in the genomics field is Lee Hood, MD, PhD, founder of the prestigious Institute for Systems Biology, who is credited with inventing the instruments that were used in deciphering the human genome. In 2007 he conceived the concept of P4 medicine, which is built on 4 pillars: predictive, preventive, personalized, and participatory.^{11,12} P4 medicine incorporates tools that reside within both integrative and precision medicine.^{13,14} The application of the systems biology-based P4 medicine to that of managing patients with complex, chronic diseases requires an operating system that allows health practitioners to apply these network biology concepts in clinical practice. The functional medicine model incorporates an architecture that allows for the application of the concepts of P4 medicine and the tools that reside within both integrative and precision medicine to make contributions to the improvement in health care and the management of complex chronic disease.

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