

# THE EVOLUTION OF RESEARCH, PART 2: THE CLINICIAN'S DILEMMA—TREATING SYSTEMS, NOT DISEASES

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*Studying the interaction and interplay of many levels of biological information, systems biology will enable us to not only cure complex disease but to predict an individual's health and extend the human body's natural lifespan by preventing diseases. The new era of predictive, preventive and personalized medicine—made possible by application of systems biology—represents a profound shift in the practice of medicine and will reach into many corners of our lives.*

—Leroy Hood, MD, PhD

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Like most clinicians, every day I am confronted with patients who present with a whole list of complaints and who are trying to figure out why they feel sick and how they can feel better. Most patients know intuitively that their various complaints must be related in some fashion. Many understand that a healthcare system that is focused on specialization and pharmacologic treatments of specific “diseases” often misses the underlying story of the origins and the reasons for their suffering.

I was trained to be a clinical pharmacologist, not a clinical physiologist, biochemist, or practitioner of systems biology and medicine. When I apply the model of differential diagnosis in which I was trained, I am often lost when addressing the complex patient with multiple conditions and seemingly unrelated symptoms. It is only by engaging in a different thought process, a different method of inquiry into illness, that I have a hope of helping a patient unravel complex illness and find a way back to health. Unfortunately, evidence-based medicine rooted in randomized controlled trials (RCTs) leaves me with only peripheral signposts in the very thick forest of disease in which I find myself every day. It is the ecosystem of human health, and studying 1 flower, mammal, or insect helps me understand very little of the whole unless I unravel the very nature of that flower's, mammal's, or insect's relationship to and interaction with the whole.

It is a difficult dilemma because as scientists, we seek to do that which is based on valid evidence, to practice “scientific” medicine, which has been proven in rigorous clinical trials. Yet as heal-

ers, we do not see clean and sterile patients with single diseases, in which all variables are neat and controlled, and we cannot count on specific outcomes. Rather, we are faced with finding a way to relieve suffering and promote healing in the face of a thousand variables forming the tapestry of the patient seeking our help, a person whose biology is a system of complex networks of genes and molecules interacting within an even more complex social, psychological, and environmental context. In short, our system of research leaves us in uncharted territory in nearly every clinical encounter. We will never see the statistical patient. Most of us confront this daily, when we practice poly-pharmacy for complex illnesses that have never been studied together in the unique patient in front of us.

My intention, in the rich new era of systems biology, is to include every variable, to think differently based on function, processes, and networks of physiological and biochemical relationships that influence the symptoms and diseases in the patients I treat. With each patient I now navigate not by differential diagnosis, seeking to match the disease to the presenting symptoms and signs, but by basic principles common to all disease. These unifying concepts allow me to understand the relationship of varied symptoms to each other and the ecosystem of health.

This new roadmap guides me via the immune system, digestive function, the creation of energy in the body in the mitochondria, the hormonal and neurochemical milieu that changes every moment, the capacity for biotransformation and metabolism of toxins, the redox system, and the function and integrity of cell membranes. How are these systems affected by inputs from the environment, including diet, stress, and toxins, and what is the influence on each person's unique genome and gene expression? That is my context for each clinical encounter, and from that general framework I create a treatment plan that is not reproducible in groups, but must be created anew for each patient. What I do is actually quite simple. I identify what is wrong in the system (or systems) and fix the things that create imbalance in each of those systems without treating disease specifically. The results are often surprising because the methods are vastly different from those of my core training and contradict my classical notions of disease.

My question, for which I have no ready answer, is how can we study clinical medicine without uniform patients or treatments? Just as the RCT is the best tool to study a single intervention in a

single disease in controlled patients, what is the best tool to study systems medicine in the era of genomics and biochemical individuality? At the very least, we can filter existing and emerging research in the context of understanding complex systems and not so quickly dismiss contradictory or negative findings if we understand the limitations of specific interventions. This is particularly true of interventions that support or normalize biologic function, such as nutrients and herbs, or dietary and lifestyle interventions that have more subtle effects—effects often dependent on interactions with genes and molecules and complex cybernetic physiologic networks of cell signaling and function. Physiology is the result of a web of molecules working in concert to produce essential functions. Providing 1 molecule, such as folate, vitamin E, omega-3 fatty acids, calcium, or vitamin D alone likely will prove to have little benefit until all the factors that interfere with function and those that enhance or normalize function are accounted for and systematically addressed. Studying interventions that are customized to individuals based on correcting core imbalances in biologic systems irrespective of the disease entity is a challenging but important step in clinical science meeting the needs of systems medicine. It is only by doing this that clinicians will have a more robust roadmap for helping the patient with multiple related chronic illnesses.

#### A NEW GENERAL THEORY OF DISEASE

In *The Fabric of Reality*, David Deutsch presents a new framework for clinical medicine. “More general concepts are replacing more specific ones as common, underlying molecular mechanisms are found for dissimilar diseases in different parts of the body. Physicians . . . may be able to apply a general theory to work out required treatment, and expect it to be effective even if it has never been used before.”<sup>1</sup>

What follows is a story that illustrates the limitations of our current model of care and reductionistic inquiry into disease. This patient suffered for decades with multiple diseases that resulted from a very few unifying causes leading to the varied clinical symptoms that led her to consultation with numerous specialists and treatment with 14 different medications. According to our current method of diagnosis and treatment, each “disease” was presumed to be a different entity and mandated a different therapy. At no point in her more than 20 years of seeking help were the context, origin, and treatment of the imbalanced ecosystem that contained her illnesses explained to her. Her chronic sinusitis mandated frequent antibiotics; depression required multiple anti-depressants; the migraines, migraine prophylaxis and abortive therapies; dysmenorrhea, NSAIDs; and sleep apnea, continuous positive airway pressure (CPAP); dyslipidemia, statins; gastroesophageal reflux disease (GERD), H<sup>+</sup> pump inhibitors; and irritable bowel syndrome, Metamucil. The questions that had been asked were, what disease (or diseases) does this patient have, and what is the best evidence-based (ie, pharmacological) treatment for this problem?

Rather than ask again what diseases the patient suffered from, I looked for unifying themes, for insults and stresses that derailed her biological integrity, altered her internal milieu, and disturbed

the core interlocking systems of the body that support and create health. The clues were many—chronic infections, gut dysfunction, immune dysregulation, hormonal imbalance, and more. I started by removing allergens in her diet; reducing molds in her house; treating chronic fungal sinusitis; improving the quality of her diet; promoting gut health with enzymes, probiotics, and essential fatty acids; using adaptogens to enhance her resistance to infection and stress; correcting nutritional deficiencies and supporting mitochondrial function with nutrient cofactors such as coenzyme Q10, D-ribose, magnesium, and acetyl-L-carnitine. I was not treating a particular disease or symptom, but helping to unburden her system from dietary, infectious, allergic, and toxic stresses and replenishing it with the raw materials needed for biological networks of function to regain balance. The body’s innate healing mechanisms then facilitated recovery. Her story is not unique, but the treatment was. The challenge is to find a way to research and document a new method of assessment and treatment based on a new theory of medicine and biology—systems theory and genetic uniqueness. Here is her story in her words.

*The first time I walked into the doctor’s office I was at my wit’s end. I was on 14 different medications and so fatigued that I couldn’t stay awake for more than 3 to 4 hours before I had to nap for another 3 hours (at least). I was experiencing daily migraines and was desperate to understand why I couldn’t break out of a constant cycle of illness that had been getting worse and worse. In the year leading up to that day, I had been on 18 different courses of antibiotics and steroids for sinus and respiratory infections that just wouldn’t stop. I was missing a lot of work and any time I wasn’t at work, I was sleeping. I wasn’t physically present for my life, including my marriage or my children. It was horrible.*

*For years I had struggled with health issues that included everything from hair loss (alopecia areata) to blood clots in my lungs and even brain surgery! I realized that all of these things must have a cause and intuitively I felt they must be related somehow. I literally pleaded with my doctors to help me figure out what was happening to me. I was clearly desperate and depressed. Having long ago been placed on anti-depressants to help me deal with severe PMS (part of having PCOS), my doctor upped the dose and layered in another anti-depressant in an effort to help me feel better.*

*I was starting to feel crazy, and with good reason. I have learned that when you are sick, it’s VERY hard to advocate for yourself and it’s very easy for physicians to marginalize your complaints, particularly when they don’t have any answers for you.*

*So, by the time I showed up in the doctor’s office I was desperate to say the least. As I sat with him and started to recall a long a long and difficult medical history that really began in my 20s (I’m now 43), he patiently listened and encouraged me to tell him everything. This was a far cry from the “I can only deal with one thing at a time!” response I had received from other doctors. This doctor thankfully did not respond by getting a look on his face that said, “This woman is crazy.” He had a look of recognition. After an hour and a half, he told me he was completely confident that he could help me. He ordered several lab tests and started me on an elimination diet, along with some nutritional support in the form of a rice protein shake and some supplements.*

Three weeks later I went back for the test results but I was already feeling so much better that I couldn't believe it. My weight had dropped more than 10 pounds and I had stopped wheezing; the swelling in my wrists, ankles and feet had disappeared and the joint pain that came along with it was almost completely gone.

As the doctor reviewed my test results and explained what everything meant, I was dumbfounded that no other physician had been able to identify what was causing me to be so desperately ill. I had never been to a doctor who embraced the concept of functional medicine, which looks to the underlying cause of wellness or disease. He was picking up the pieces of the puzzle and one by one explaining to me how we were going to put things back where they belonged. Ever single piece. Not just 1 or 2 of them.

When I returned to his office 3 months later, I felt like a completely different person. I was off all of my prior medications; including the anti-depressants that I was told I would need the rest of my life. I was able to go back to work, after having been out on disability (which I hated). I was able to make it though the entire day without falling asleep and the brain fog I had been living with had cleared away. There is a shift in my thinking that has taken place [that] lets me view my life in terms of potential instead of thinking about restrictions.

I suggest that complexity theory is a more robust model for the clinician than reductionism, which is necessary to construct the elements that comprise the whole. Scientific illumination of the underlying mechanisms of disease has advanced faster than clinical research. In the article, "The biopsychosocial model 25 years later: principles, practice and scientific inquiry,"<sup>2</sup> the authors provide an alternate framework for clinical medicine. "Complexity science is an attempt to understand these complex recursive and emergent properties of systems and to find interrelated proximal causes that might be changed with the right set of interventions."<sup>3</sup>

## THE 20TH CENTURY DISEASE-BASED DIAGNOSTIC PARADIGM

At a recent dinner for Research! America, an advocacy group for research and dissemination of research, in Washington, DC, discussion focused on the limitations of reductionism in science, exemplified by the RCT's difficulties in providing solutions to the chronic complex, multi-factorial diseases of today. Discussion focused on the importance of breaking down artificial disease constructs, medical specialties and disciplines that, increasingly, do not reflect biologic laws. The Director of the National Institutes of Mental Health, Thomas Insel, MD, proposed a new model of psychiatry called "clinical neuroscience." He lamented that the DSM-IV (Diagnostic and Statistical Manual IV), on which all psychiatric research and clinical diagnosis and practice are based, has 100% accuracy, but 0% validity. It perfectly describes a nomenclature that has no correlation to underlying biology or causal mechanisms and is an imprecise tool for guiding research and therapy. What is necessary is a shift in our research orientation from studying groups and individual interventions to studying systems, causes, and mechanisms; from orienting diagnosis around pathology to focusing on function. Then we can

bridge the chasm that exists between systems medicine and clinical medicine. Then we can effectively address the chronic illnesses that affect 125 million Americans.<sup>4</sup>

Improved research design is needed to address the new diagnostic and therapeutic paradigm based on systems medicine. The current limited anatomical model of differential diagnosis and International Classification of Diseases (ICD-10) no longer reflect our understanding of functional physiology and biology. Randomizing treatment and designing studies for diseases based on this classification is becoming less useful. The example of studying functional interventions for "cardiovascular disease" based on this system highlights a number of inherent problems in research methods that do not address the needs of systems medicine and personalized, patient-centered diagnosis and treatment.

## Cardiovascular Disease: Understanding the Failure of Vitamin Therapy

*Reductionism is the primary and essential activity of science. Also crucial are synthesis and integration, tempered by philosophical reflection on significance and value. . . . To make any progress [researchers] must meditate on the hidden design and forces of the networks of causation.*<sup>5</sup>

—E.O. Wilson, *Consilience: The Unity of Knowledge*

Two new negative interventional trials of B vitamins to lower homocysteine for secondary prevention of cardiovascular disease contradict earlier research showing benefit. The conclusions of the investigators, the media, and many doctors and patients are that B vitamins don't work to prevent cardiovascular disease; they might even harm and should not be used. The Norwegian Vitamin trial (NORVIT)<sup>6</sup> and the Heart Outcomes Prevention Evaluation (HOPE) 2 trial<sup>7</sup> are examples of well-designed randomized trials that confuse rather than clarify because of the nature of the intervention—the use of a single intervention in a controlled group to prevent a multi-factorial disease.

Consider the study groups—patients with existing advanced vascular disease. Also consider the known causes of vascular disease: endothelial dysfunction caused by insulin resistance, inflammation, lipoprotein oxidation, platelet activation, lipid and cell permeability, sympathetic nervous system activation, and activation of the renin-angiotensin system. All of these physiologic dysfunctions have multiple causes. For example, consider that occult infection, periodontal disease, autoimmunity, allergy, insulin resistance, and environmental toxins all trigger inflammation, which then promotes cardiovascular disease. Consider further the multiple genomic polymorphisms that influence functional physiological alterations related to inflammation. Add to this all the single nucleotide polymorphisms (SNPs) and environmental inputs that affect each of the other proximal causes of cardiovascular disease. Also consider the environmental factors, including diet, lifestyle, and stress that influence gene expression and epigenetic biology.

More specifically, consider the SNPs that regulate methylation (and sulfation) and can influence cardiovascular risk, includ-

ing methylene tetrahydrofolate reductase, cystathionine b-synthase, methionine synthase, and betaine-homocysteine methyltransferase. Consider the secondary effects of ineffective methylation, including impaired glutathione synthesis and control of oxidative stress. Add to this the variations in diet, activity, and stress level (all with clear influences on cardiovascular disease) of the study participants, and the limitations of the randomized “controlled” trial can be better understood. The conclusion that vitamin therapy is not effective as a single intervention in patients who have advanced vascular disease, multiple co-morbid diseases, and who are on multiple medications is not surprising. As my colleague Sidney Baker, MD, has taught, if you are standing on 2 tacks, taking 1 out does not make you 50% better. Relief comes only from removing both tacks, from addressing all the underlying problems. This fundamental principle is not emphasized enough in most clinical research.

Given the very nature of systems biology and the complex interaction between genes, lifestyle, and environment, it is nearly impossible to find answers to the questions we are asking about the effects of a single biologic agent to treat any particular “disease.” In fact, the nearly 9,000 patients in the HOPE 2 and NORVIT trials with “cardiovascular disease” may have had many “diseases.”

The notion that cardiovascular disease is one disease is fundamentally flawed. It is often a combination of “diseases” with variable causes resulting in the same clinical manifestation. The causes may be polymorphisms and lifestyle behaviors that promote insulin resistance; impaired methylation; oxidative stress from environmental toxins; systemic inflammation from an autoimmune disease; altered lipid metabolism related to specific SNPs, such as Apo E 4, CETP (cholesterol ester transfer protein); or others. Unless we incorporate assessment based on underlying biologic function and study systems of diagnosis and treatment based on patient-centered diagnosis, we will never know if a particular intervention or set of interventions is effective.

The overwhelming influence of diet, exercise, and stress on cardiovascular disease must be accounted for in study designs. I would not expect a vitamin supplement to produce a relevant outcome if the treatment group consumed a high-glycemic-load, trans fat-rich, nutrient-poor diet, didn't exercise, and experienced psychic or physical stressors that chronically activated their sympathetic nervous system. Overcoming those underlying causal factors with vitamins is neither reasonable nor scientific, and the negative outcome is predictable. In fact, in the HOPE 2 trial, members of the treatment group had hypertriglyceridemia (178 mg/dL), low high-density lipoprotein (46 mg/dL), hypertension (138/77 mmHg), central obesity (waist-to-hip ratio 0.95, body mass index 29.6), and diabetes (fasting blood sugar 128 mg/dL), and their diet was already fortified with folate. How could one expect to reduce cardiovascular disease with B vitamins without addressing the dyslipidemia, diabetes, obesity, and hypertension? It is never 1 thing in health and disease; it is always everything—“biological pathways and networks” that form a web of function or dysfunction.

Various other mechanisms may explain the null outcome of the studies, including the role of folate in cell proliferation and

hypermethylation, which may facilitate the development of atherosclerotic plaque and the methylation of l-arginine to asymmetric dimethylarginine (ADMA), inhibiting nitric oxide synthase, reducing nitric oxide levels, and promoting vascular disease. Equally valid mechanisms and studies demonstrate impaired endothelial function, inflammation, and oxidant stress resulting from elevated homocysteine and folate deficiency. These studies, combined with prospective observational studies showing reduction of first events with reduction in serum homocysteine, support the homocysteine hypothesis.<sup>8</sup> The recent Centers for Disease Control and Prevention report in *Circulation* shows a reduction in stroke mortality in the United States and Canada following folic acid fortification of refined grain products without any change in other known risk factors, whereas stroke mortality increased in the United Kingdom, where there is no folic acid fortification of food.<sup>9</sup> Subgroups in the clinical trials did show benefit but were not stratified according to SNPs and biologic function, only by pathology. The confusing results, therefore, are not unexpected. Pathology-based interventions may no longer represent current science.

What might be the impact of a study that comprehensively assessed and addressed biomarkers of inflammation, oxidative stress, platelet activation, perturbations in the sympathetic nervous system and renin-angiotensin system, glucose and lipid metabolism, and endothelial function, as well as primary endpoints such as cardiovascular events and death? What if a study was designed that used multiple interventions including diet; exercise; stress management; and specific nutritional, herbal, or pharmaceutical therapies that “restore disturbed pathways to their normal functions”?<sup>10</sup> These questions can be answered by science. We simply have to reconsider how we ask them. Science is an indifferent tool, but we now have new instruments to use to discover the solutions for health, new lenses through which to view the current puzzle of complex chronic diseases.

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