

THE EVOLUTION OF RESEARCH: MEETING THE NEEDS OF SYSTEMS MEDICINE, PART I

Mark A. Hyman, MD

Mark A. Hyman, MD, is the editor-in-chief of *Alternative Therapies in Health and Medicine*. (*Altern Ther Health Med*. 2006; 12(3):10-11.)

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Reality is merely an illusion, albeit a very persistent one.
—Albert Einstein

Medicine stands at the edge of a quantum leap in understanding human biology, function, and illness. New research methodologies must help researchers address and clinicians implement medicine's shift from pathology to function, from the focus on diseases to the perspective of systems. In the light of complex cybernetic informational networks and systems that represent human biology, the limitations of randomized controlled trials (RCTs) and evidence-based medicine (EBM) founded on reductionism can be understood and placed in context.

The director of the National Institutes of Health, Elias Zerhouni, MD, created a Roadmap Initiative¹ for scientific cross-disciplinary collaboration based on functional biological principles, which can be extended beyond the basic to the clinical sciences to solve the "puzzle of complex diseases."² Research efforts, he suggests, should focus on the "building blocks, biological pathways and networks" that determine health and disease.¹ Initiatives in basic science and molecular biology that are based on genomics, proteomics, metabolomics, and nutrigenomics need to be translated into new clinical research methodologies. Improving research design can help medicine shift from a disease-focused to a patient-centered paradigm. New clinical diagnostic and therapeutic tools are the natural outgrowth of this effort.

RESEARCH AT A CROSSROADS

The Chinese character for crisis is comprised of 2 individual characters—danger and opportunity. Clinical research stands at the crossroads of danger and opportunity. Healthcare practitioners stand at the intersection of the basic sciences, clinical research, and the complex individual patient seeking relief from suffering. New opportunities exist for designing and applying research to the individual, who often presents with multiple chronic, complex diseases. Currently, clinical research is designed to study groups, not individuals; to study single diseases and single drugs, not real people who present with unique and varied genetic, environmental,

and lifestyle characteristics. Until medicine catches up with other fields of inquiry in the biologic, physical, and social sciences, the innovative architecture of clinical decision-making cannot reach the practitioner or patient.

The evolution and importance of RCTs in clinical medicine grew from a desire to bring critical evaluation to unproven therapies in the early part of the 20th century.³ The concept of EBM attempts to orient clinical practice around clinical evidence from RCTs. The current bias in research infrastructure, funding, pharmaceutical orientation, and attempts to study single interventions in identical groups in RCTs, however useful for evaluating the effectiveness of treatment in populations with a single condition, has limitations in addressing complex chronic diseases. Applied complexity and systems theory represent a more accurate and relevant model for the diseases we currently face. New instruments of clinical research and decision-making are now available through models of artificial intelligence and analysis of complex clinical data (from historical assessment, laboratory data, and advanced imaging) using applied bioinformatics in clinical medicine.

RANDOMIZED CLINICAL TRIALS: LIMITATIONS IN SYSTEMS MEDICINE

The recent spate of large RCTs on nutritional interventions showing negative results is understandable when considered in the light of systems medicine, functional genomics, metabolomics, and patient-centered medicine. Practitioners and patients are left wondering how to interpret the findings that calcium and vitamin D offer no benefit in osteoporosis prevention; that low-fat diets are ineffective for cardiovascular disease prevention; that glucosamine is ineffective for osteoarthritis, etc. Should we abandon research into these functional interventions for the prevention and treatment of chronic disease? Or are we asking the wrong questions?

Is there a problem with using the concept of "disease" as an organizing principle for research? It will not be easy to address the research dilemma of finding an alternative to using reductionism in science to address thousands of variables that affect biologic function in health and disease. Clinical research and practice tools assess the balance of individual single nucleotide polymorphisms intersecting with diet, lifestyle, and environment and illuminating patterns of connection and interaction. This will speed the application of basic research to clinical medicine. Practitioners will soon have enhanced methods to measure clinical outcomes through assessment of gene expression patterns and functional biomarkers of health and disease.

THE LIMITATIONS OF EVIDENCE-BASED MEDICINE

Van Weel and Knottnerus provide a coherent criticism of the value of EBM in their *Lancet* article, "Evidence-based interventions and comprehensive treatment."⁴ EBM falls short, they argue, in the clinical context of patients with chronic complex illnesses. They put forth the following concerns about the limitations of EBM in clinical practice.

- EBM tends to concentrate on research methodology and reduces clinical practice to the technical implementation of research findings.
- The exclusion of patients with co-morbid conditions from clinical trials makes their findings least useful to those most in need of clear evidence: those with chronic, complex, and multiple illnesses.
- Clinical practice most often employs multiple interventions that do not add up to an evidence-based approach based on single interventions.
- Clinical research fails to focus on the combined outcome of multiple interventions because of the complexity, cost, and absence of effective tools for studying such approaches.
- Non-drug interventions are not studied because of the limitations of RCTs to assess functional, not pharmacologic, treatments.
- The potentially most useful clinical approaches, involving comprehensive educational, dietary, and lifestyle interventions, are the least studied even though they are the most likely to have the "maximum effect using minimum resources."

THE SIMPLICITY OF BIOLOGIC LAWS: A NEW PARADIGM FOR MEDICINE

The simplicity of nature is not to be measured by that of our conceptions. Infinitely varied in its effects, nature is simple only in its causes, and its economy consists in producing a great number of phenomena, often very complicated, by means of a small number of general laws.

—Pierre-Simon Laplace

New research methods must be developed to identify effective therapies for chronic disease. Blending the best of scientific reductionism and analysis with systems medicine may be more relevant to clinical practice. This model would study the effects of treatments that normalize function across the spectrum of known causes for each condition. Tailoring treatment based on individuals' genetics, environmental triggers, and lifestyle patterns can help determine the optimal intervention using the underlying principles and foundations of systems biology.⁵ We simply have to reconsider which questions to ask. Science is an indifferent tool; however, we have been using imprecise instruments to discover the solutions for health, and cloudy lenses to view the puzzle of complex chronic diseases.

In his *Lancet* article, "Can randomized trials inform clinical decisions about individual patients?" Dr David Mant discusses the

dilemma of the value of RCTs for studying populations and their limitations for the individual patient.

The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but is arguably the worst way to assess who will benefit from it. . . . However, the nub of the argument for me is that randomized controlled trials are primarily about medical interventions not patients. In clinical trials, patients are randomized to allow a comparison of intervention efficacy unbiased by the individuality of the patient. . . . But the methodological minimization of information on effectiveness in relation to the individual patient leaves an evidence gap.⁶

To close that evidence gap, new lines of inquiry and research methods can explore complex interventions based on theoretical principles of systems medicine that more closely represent biological reality and clinical care for patients. For example, deriving from basic research an understanding of biologic pathways, networks, and intervention assessment, treatment protocols for cardiovascular disease could be designed to normalize lipid metabolism, improve insulin sensitivity, control inflammation and oxidative stress, eliminate toxins, optimize methylation and platelet function, and address chronic sympathetic nervous system activation with lifestyle and dietary interventions, supplements, and drugs. The focus of treatment is not on a particular disease, but on optimizing disturbed functional systems by assessing causes and designing treatments unique to the patient. The study would not be on a particular drug or molecule, nor even on a uniform array of interventions, but on a diagnostic and therapeutic system that orients therapy to the dysfunction specific to the individual. That will be the beginning of truly patient-centered medicine.

This requires a re-orientation of our current scientific agenda so that we can complement the RCT with research methods to evaluate chronic complex diseases and sets of interventions. It requires patient-centered medicine—focusing on the individual not just from a psychosocial perspective, but also from a genetic and molecular perspective. Treatments in this framework would evolve from first principles. While the success of any one of the interventions studied may never be proven or disproved, the system of assessment and treatment as a whole can be validated. As every clinician knows, the power of multi-interventional approaches for chronic complex disease is far greater than that of any single intervention. Today's healthcare crisis presents us with the opportunity to reframe the research agenda and advocate for practice based on systems medicine and for more clarity in communicating the research to practitioners and patients.

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