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Evidence-based Medicine in the Clinical Setting: Uses and Limitations

The scientific method disciplines the creative process of human inquiry. In the applied biological sciences (e.g., clinical medicine) prior to World War II, evaluation of emerging therapeutics was mainly the purview of recognized leaders in the medical profession, based primarily on their clinical experience and reputations, and without the rigor of systematic controls or external standards.[208] To improve the quality of evidence and render a more accurate judgment with less personal bias, postwar researchers developed the randomized controlled trial (RCT) protocol. The major characteristics of this method include blinded assessment (of subjects, investigators, or both), often in the presence of a placebo control; random assignment to comparable groups; and inferential statistics as a surrogate for establishing causation.[209]

The reliance on the expert gave way to reliance on results from RCTs. Clinicians could no longer reduce uncertainty by following the lead of a confident expert, but they increasingly appreciated the power of the double-blind, randomized, placebo-controlled clinical trial—a step up in certitude.[210, 211] Putting aside, for the moment, the many problems inherent in the RCT model, not the least of which is the bias introduced by the influence of big Pharma,[212, 213, 214, 215] let's briefly explore EBM—the offspring of the RCT model—as understood and used by clinicians to reduce uncertainty.

Proponents of the RCT as the gold standard for unbiased research results have fostered its preeminence in the applied medical fields, both in primary and specialty care. They have argued for and developed algorithms for grading recommendations based on a research quality scale that ranks methodologies in descending order of accepted best evidence:[216, 217]

- Systematic reviews and meta-analyses of RCT studies
- RCTs
- Nonrandomized intervention studies
- Nonexperimental studies
- Expert opinion

Amid the early excitement generated by this new schema, certain assumptions were posited as foundational:

> A new paradigm for medical practice is emerging. *Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making* and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature.[218] [Italics added.]
>
> —Evidence-based Medicine Working Group, JAMA, 1992

The application of EBM in the clinical setting is described as following this general scenario:[219, 220]

- Select specific clinical questions from the patient's problem(s)
- Search the literature or databases for relevant clinical information
- Appraise the evidence for:
  - validity against the hierarchy of evidence as described above, and
  - usefulness to the patient and practice
- Implement useful findings in everyday practice

Arguments in favor of EBM infusion into both medical education and clinical practice are based on the following facts and inferences:[221, 222]

- Available new evidence can and should lead to major changes in patient care
- Practicing physicians often fail to obtain available newer relevant evidence
- Medical knowledge and clinical performance deteriorate over time without the leavening of newer evidence influencing clinical decisions
- Traditional continuing medical education (CME) alone is inefficient and generally does not improve clinical performance without significant follow-up and evaluation measures
- The discipline of using evidence-based medicine can keep clinicians up-to-date

In a cogent paper in *The Lancet* in 1999, van Weel and Knottnerus responded to the proddings of many eminent medical thought leaders to move ahead quickly and comprehensively with the integration of EBM into the clinical setting by pointing out the many difficulties of using this schema to manage the care of individual patients with complex, chronic illness:[223]

- EBM tends to concentrate on research methodology and reduces clinical practice to the technical implementation of research findings. In a more colloquial view, it is the tail wagging the dog. Rather than using clinical judgment to guide the choice of relevant evidence, EBM is structured with a hierarchy of evidence as the driver of clinical judgment.

- The structure of RCT methodology assumes the consequences of individual variability in response to treatment will "wash out" if the subject pool is large enough and the statistical analyses sophisticated enough. *While this may be true for populations, it seriously limits the applicability of the research in primary care, where therapy is delivered one unique patient at a time.*
- Co-morbid conditions are the usual justified reason for the exclusion of many patients from RCTs, *so the very patients most in need of usable evidence (e.g., those with complex, chronic conditions) are often not in the cohorts of patients being studied,* making the findings from the research trials very limited in their applicability.
- In primary care, treatment usually involves several interventions, sometimes delivered concurrently and sometimes sequentially. Unfortunately, combinations of evidence-based interventions do not sum to a treatment plan that is evidence-based. Interactions between single interventions may increase or decrease their efficacy (even under ideal trial conditions), when blended into a comprehensive plan. Adverse interactions among treatments may, and often do, occur.
- Clinical research does not focus on the overall outcome of composite interventions because of the complexity of such studies and the absence of well-developed tools for studying such whole systems approaches.
- Drug interventions have been studied more extensively than nonpharmacological interventions, in part due to the technical and methodological difficulties in the design of RCTs for nondrug interventions (and, in part, because of the nonpatentable nature of most lifestyle interventions). This situation creates a significant problem in primary care, where the use of educational, dietary, and lifestyle interventions is attractive because of their resonance with the principle of "maximum effect using minimum resources."

In marked contrast to the assertions of the EBM Working Group cited earlier, van Weel and Knottnerus suggest that the driving force behind EBM should be a coherent system of fundamental research in *pathophysiology and the humanities,* combined with careful clinical observations, on which systematic (RCT-based) evidence of effectiveness is superimposed. Existing clinical practice should be supported or, if erroneous, corrected on the basis of this coherent system. They go on to propose that "two complementary approaches are needed to strengthen the evidence base of nonpharmacological interventions and complex multifaceted strategies. First, the generic characteristics of complex interventions must be acknowledged as essential for its evaluation. Second, a methodology to allow the assessment of complex effects should be further developed."

Dr. David Mant in his seminal 1999 paper, "Can randomized trials inform clinical decisions about individual patients?" takes a slightly different tack in exploring the irony that the RCT combines strength of concept for the population being studied with weakness of specific application to the individual patient:[224]

> 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 and not patients. In clinical trials, patients are randomized to allow a comparison of intervention efficacy unbiased by the individuality of patient. This methodological approach provides society with powerful protection against witch-doctoring, and helps us eliminate the inefficiencies in the provision of medical care described by Cochrane. *But the methodological minimization of information on effectiveness in relation to the individual patient leaves an evidence gap for clinicians.* [Italics added.]

Dr. Alan Feinstein, from the Department of Medicine at Yale University, echoes similar reservations in his article, "Problems in the evidence of evidence-based medicine."[225] Larry Culpepper and Thomas Gilbert, in their Lancet commentary, "Evidence and ethics," focus on this same difficulty in the primary-care arena.[226] Although the debate has continued over the past decade, these reasoned arguments have been heard less frequently as the push toward EBM has gained momentum. However, the problems described above have not been solved. Rather, with the advent of personalized medicine and systems biology, it is even more clear that the reductionist simplicity of the RCT frequently does not work to address the significant questions now facing 21st century practitioners in their struggle to cope with the epidemic of complex, chronic disease.[227, 228, 229, 230, 231]

We can now begin to understand why the effect of research findings on clinical practice has been weaker than the early proponents of EBM postulated. The first problem that has impeded the successful application of EBM to patient care is the complex nature of the translation of research studies to the individual patient's unique clinical problem(s)—what Larry Weed called knowledge coupling.[232, 233] John Hampton, Professor of Cardiology, University Hospital, Nottingham, England, in a review titled "Evidence-based medicine, opinion-based medicine, and real-world medicine," reasons: *"Clinical trials will tell us what treatments are effective, but not necessarily which patients should receive them…Treatment must always be tailored to the individual patient."*[234] (We would add to that statement that RCTs can only tell us what treatments are effective *from among those studied*. The decision about what to investigate introduces so much bias into the evidence base that it would be difficult to overstate its impact.)

Added to this methodological conundrum are the real-world exigencies of daily clinical practice that make it virtually impossible to acquire, collate, and filter all relevant evidence prior to direct application to the unique needs of the patient. Imagine a clinic where, after each therapeutic encounter—involving both appropriate history taking and physical examination procedures—a problem list is developed and then carefully subjected to a medical literature search and analysis. The pace of clinical practice will not tolerate the inertia of such a process,[235] even to improve the care of patients who may be in desperate need of new interventions based on emerging evidence.

A second major issue is even more complex. If medical care were as simple as making a diagnosis and then prescribing an appropriate pharmacologic agent (or agents), then the EBM system, as presently configured and applied, might work—but only if appropriate *Problem Oriented Evidence that Matters* (POEMs) [xiii, 236] were available for each medical problem (and disregarding, for the moment, that

[xiii] To assist the practicing physician's effective inclusion of new evidence into daily practice, both government-sponsored and commercially affiliated organizations have moved EBM forward with a collation of filtered studies called: *Problem Oriented Evidence that Matters* (POEMs). Most POEMs and most studies in the Cochrane Collection are research trials of pharmacologic therapeutic interventions. It is now possible to search these specific databases, or self-developed relevant databases that review groups of studies that directly link research findings with specific clinical problems.

most chronic disease is complicated by multiple comorbidities that are rarely addressed by POEMs). Unfortunately, the "better living through chemistry" dream that fueled half a century of research has not, in fact, created a healthier population (see Chapter 2).[237] Although many acute medical problems do appear to respond consistently as envisioned by the EBM model, more than 70% of health problems presenting to clinicians today are both chronic and complex[238] (Chapter 2), and they require a different approach. "Treating only known biological components of disease minimizes the ability of the practitioner to tailor therapeutic interventions to individual patients."[239]

Despite these sobering facts, physician education, training, and reimbursement, as well as research designs for clinical studies that physicians depend upon for effective decision making, continue to be focused primarily on an acute-care model that emphasizes pharmacologic solutions for complex, chronic problems, leaving the discerning clinician without the evidence and tools needed for addressing their patients' complex needs.

It's not enough, of course, for us to understand what's wrong. We must also seek better solutions for these urgent problems, regardless of the difficulty of the task and the elusiveness of the answers. The RCT tool was developed during a specific period in our medical history and worked well to differentiate the traditionalists, who claimed that clinical experience trumped bench science, from the scientists, who perceived the value in systematic inquiry. Major strides in treatment have occurred in the intervening 50 to 60 years as a result of the shift toward the use of RCT methodology. But we are now at another nodal decision point, unique to our cultural and medical evolution. We need more sophisticated tools to shed light on the nature of the web-like interweaving of mechanisms at work in complex, chronic illness.[240, 241, 242] While alternate study designs and statistical methodologies are being developed for analyzing complex data sets,[243, 244, 245] we must return the practice of EBM to its original mission of using evidence to inform clinical experience and to expand the understanding of basic mechanisms of health and disease.[246, 247] This will help to reverse the decade-long plunge toward "... reducing clinical practice to the technical implementation of research findings."[248, 249]

In sum, we are now facing another major transition in how we perceive and utilize evidence in clinical medicine. Thomas Kuhn offers this insightful analysis:

> When defects in an existing paradigm accumulate to the extent that the paradigm is no longer tenable, the paradigm is challenged and replaced by a new way of looking at the world. Medical practice is changing, and the change, which involves using the medical literature more effectively in guiding medical practice, is profound enough that it can appropriately be called a paradigm shift.[250]

A Science-Using Profession

Given the serious limitations of applying the EBM model in clinical practice, we must ask two questions central to the future of medicine:

- How do we develop an effective therapeutic relationship based upon (1) efficacious, reproducible, and personalized clinical applications that are solidly anchored in science, (2) emerging knowledge about the multifactorial causes of chronic disease, and (3) an expanded awareness of the nature of clinical/critical thinking?

- How do we transition from an EBM-based, guideline-driven, prescriptive clinical practice to an individualized, patient-centered approach that captures both the science and the art of medicine?

First, we must recognize that most clinicians, by professional training and inclination, are not scientists. ***Clinical medicine is a science-using profession***. It is true that diagnosis and treatment have become intensely science-using activities, but these activities have a distinctly different process and endpoint than those of the professional scientist.[251] "Physicians start from the demands of the patient's condition and not from the demand for generalizable knowledge, and their goal is just as particular: to treat the patient's illness, not to test the therapy."[252] The evidence needs of clinical medicine are also distinctly different. The focus on application and usefulness centers on how the evidence informs the assessment and treatment process for each individual patient, given that patient's unique genetic propensities and unique environmental influences.

At a number of points in this paper, we have documented how most clinical evidence based on RCTs informs about cohorts of patients with similar signs and symptoms (the basis of diagnosis and diagnostic groups), but not does not necessarily provide decision support for an individual patient. The primary responsibility of the attending clinician is to ferret out meaningful evidence for each patient, knowing that unique genomic specificities may predispose that patient to unanticipated results. From this perspective, evidence often serves to qualify *insight*, but when applied in a simplistic or statistically linear way, can create unintended mischief.[253] From this perspective, every maneuver, either further assessment or therapeutic intervention, becomes a clinical probe that must be assessed in partnership with the client as the shared journey of investigation and healing proceeds.

Dr. Sackett, founder and advocate for EBM, was quite clear about this in the early development of EBM: "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research…. *Good doctors use both individual clinical expertise and the best available external evidence and neither alone is enough.*"[254] [Italics added.]

The combining of these elements can be viewed as a Venn diagram, where the best outcomes occur when all three elements are represented (Figure 9).

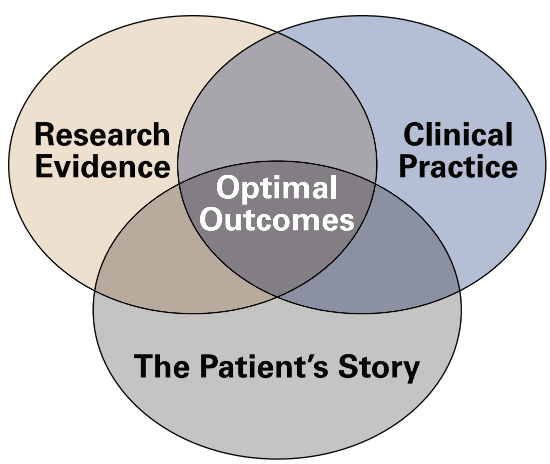

Figure 9:
Optimal Outcomes: Applying Evidence-based Medicine to the Real World

Another Perspective on the Biomedical Model

The complexity of the developing explanatory models has been serially addressed in the *Annals of Family Medicine,* a peer-reviewed medical journal "dedicated to advancing knowledge essential to understanding and improving health and primary care," including the development of methodology and theory for addressing this conundrum. In the article, "The biopsychosocial model 25 years later: Principles, practice, and scientific inquiry,"[255] the authors critique the limitations of the conventional biomedical model and the research methodologies that evolve from this model and preview the evolving model of complexity and causality and the nested model of structural causality:

> Few morbid conditions could be interpreted as being of the nature "one microbe, one illness"; rather, there are usually multiple interacting causes and contributing factors. Thus, obesity leads to both diabetes and arthritis; both obesity and arthritis limit exercise capacity, adversely affecting blood pressure and cholesterol levels; and all of the above, except perhaps arthritis, contribute to both stroke and coronary artery disease. Some effects (depression after a heart attack or stroke) can then become causal (greater likelihood of a second similar event)….These observations set the stage for models of circular causality that describe how a series of feedback loops sustain a specific pattern of behavior over time.[256, 257, 258] Complexity science is an attempt to understand these complex recursive and emergent properties of systems[259, 260] and to find interrelated proximal causes that might be changed with the right set of interventions.[261]

David Deutsch, in *The Fabric of Reality,* describes the need for a next step in using the science of underlying pathophysiological mechanisms of disease in the clinical setting of medicine:

> The science of medicine is perhaps the most frequently cited case of increasing specialization seeming to follow inevitably from increasing knowledge, as new cures and better treatments for more diseases are discovered. But as medical and biochemical research comes up with deeper explanations of disease processes (and healthy processes) in the body, understanding is also on the increase. More general concepts are replacing more specific ones as common, underlying molecular mechanisms are found for dissimilar diseases in different parts of the body. Once a disease can be understood as fitting into a general framework, the role of the specialist diminishes.... Physicians… can look up such facts as are known. But [more importantly] they may be able to apply a general theory to work out the required treatment, and expect it to be effective even if it has never been used before.[262]

The real question now facing every discerning, informed clinician[263] is how to bring relevant, graded, emerging scientific evidence to the complex list of problems made unique by the patient's genetic susceptibilities and potentialities that, in turn, communicate constantly with the ever-changing environment within which the patient lives. No RCT can inform, *in a specific way,* the appropriate clinical roadmap for assessment and planning for therapeutic interventions in this complex environment.[264] Clinicians must use science; it is a powerful tool. But they should be in charge of how and when to use it, not dominated and intimidated by it.

The Heuristics that Guide Doctors' Thinking

We believe it is fair to say that the fear of uncertainty has led us to narrow our field of vision far too soon. "Science has not one method, but many. These include observation in the natural world, experimentation in the laboratory, mathematical proof, computer simulation with real data, analysis of surveys and demographical statistics, and thought experiments for the great geniuses, such as Galileo and Einstein. In the social sciences, a climate of anxious identification with a sub-discipline goes hand in hand with methodological rituals … methodological uniformity and discipline-oriented research are two sides of the same coin...." A shift is needed to "free us from the straightjacket of methodological rituals, allowing us to consider and choose proper methodologies for the problem at hand and to verify a result obtained with one method by using other methods."[265]

Has broad-based and open-minded scientific inquiry been skewed by EBM and its hierarchy of evidence codification and ranking?[266, 267, 268, 269, 270, 271] Is the hegemony of EBM in contemporary medicine, as exemplified by Drs. Montori and Guyatt,[272] closing the door on the reintegration of the science and art of medicine?[xiv] We need to ask what we have surrendered by de-emphasizing "unsystematic clinical experience and pathophysiologic rationale." What is the irreplaceable loss in patient outcomes with the dismissing of experience, intuition, and wisdom? What must we do to develop skills and methodologies appropriate to clinical decision making in a context of uncertainty?

There is a robust literature that explores the actual methodologies used by clinicians who must make decisions when time and information are limited and the outcome is uncertain. It is clear from brain research that there is an important difference between the human brain and other features of the universe. The brain is a complicated, nonlinear, living system capable of self-organization. The brain does not respond to incoming stimuli in a direct, reflex-like action but continuously changes, constructing its own neural activity patterns in order to adapt to and synchronize with external stimuli. Genetic makeup and continuous stimuli from the environment are the only factors that create individual differences; the twin magnets of chaos and self-organization shape the constant interplay of those factors. The human mind is highly capable of dual processing; in fact, the continuous and virtually seamless integration of reason to test intuition and of intuition to generate the creative thinking that fuels rational inquiry is what advances insight and knowledge.

We usually represent problems in a linear fashion despite the convincing evidence that this type of modeling is not appropriate or adequate for studying the nervous system or human behavior.[273, 274] This naturally leads to some interesting conclusions about the interrelationship of brain and mind when faced with decision making in a sea of uncertainty.[275, 276, 277, 278, 279] The mind is an adaptive toolbox with genetically, culturally, and individually created and transmitted rules of thumb. These rules of thumb are called heuristics and are foundational to daily function, intuition, or inspiration.[280] *The study of judgment under uncertainty is the study of heuristics.* The human species' response to uncertainty is to rely upon experience, coupled with knowledge, data, and applied wisdom through processes such as heuristics and insight.

[xiv] In their 2008 review of the progress in EBM, VM Montori and GH Guyatt reiterate a basic principle of EBM cited earlier in this chapter: "Evidence-based medicine *de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale* (italics added) as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research," ignoring the significant push back from the international scientific and clinical community regarding the hobbling effects of EBM on both research and translational medicine.

Heuristics and "rules of thumb" are synonymous terms. It is important to distinguish between heuristic and analytic thinking. For instance, heuristic thinking is indispensable for discovering a mathematical proof, whereas analytic thinking is necessary for checking the steps of the proof.[281] A limited number of simplifying heuristics rather than more formal and extensive algorithmic processing is the rule.[282] The classic example of a heuristic that most people have experienced is the "rule of thumb" (gaze heuristic) used for catching a ball, as illustrated in Figure 10.

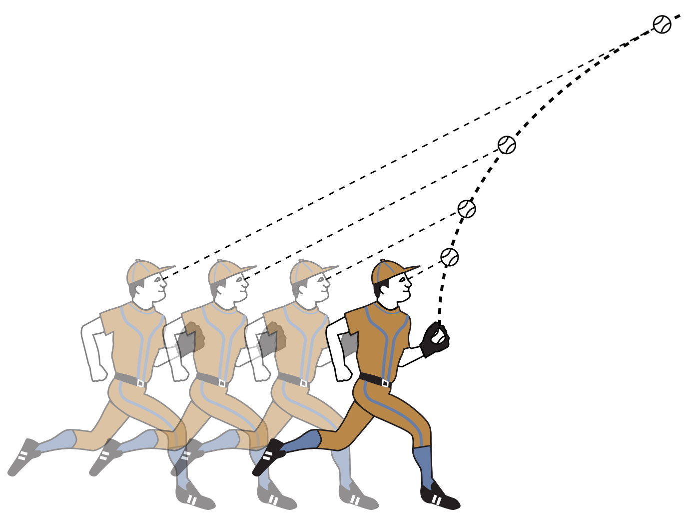

Figure 10:
How to Catch a Fly Ball: Players rely on unconscious rules of thumb. When a ball comes in high, a player fixates his gaze on the ball, starts running, and adjusts his speed so that the angle of the gaze remains constant.

From page 22 of the essay Rationality for Mortals, originally published in Blackwell Handbook of Judgement and Decision Making. Copyright Oxford University Press/UK Blackwell, 2004.

The angle of gaze is the angle between the eye and the ball, relative to the ground. For years, brain scientists assumed that a complex process of computations was required for tasks like catching a ball. The artificial intelligence (AI) groups attempted to duplicate these tasks with robotic technologies. However, research by the 'heuristics' groups showed a very different process at work.[283] It turns out that a player who uses the *gaze* rule does not need to measure wind, air resistance, spin, or the other complex, causal variables. "All the relevant facts are contained in one variable: the angle of gaze. Note that a player using the *gaze heuristic* is not able to compute the point at which the ball will land. Yet the heuristic leads the player to the landing point...most fielders are blithely unaware of the gaze heuristic, despite it simplicity. Once the rationale underlying an intuitive feeling is made conscious, however, it can be taught."[284]

Elwyn et al., in their well reasoned paper, "Decision analysis in patient care,"[285] demonstrate the efficacy and comprehensiveness of this methodology. Naylor summarizes in his editorial comments on their paper (published in the *Lancet*):

> The process of individualized decision analysis might best be viewed as a way of enhancing communication with patients, rather than as a "black box" from which directives emerge. But if that is the ultimate aim, it seems more useful to develop simple decision aids aimed at helping patients and doctors share information and work through tough choices in the clinical setting. To that end, Elwyn and colleagues call on clinicians and patients to communicate better while embracing fast and frugal rules of thumb [heuristics]. In so doing they have arguably drawn their

> readers full circle—*from clinical art to bedside science and back again*. It is ironic, moreover, that the best lessons in *fast and frugal rules of thumb* may well come from understanding the cognitive processes of those master clinicians who consistently make superb decisions without obvious recourse to the canon of evidence-based medicine.[286] [Italics added.]

If we are to develop both a clinical methodology and a curriculum that will approximate the best characteristics of successful clinicians, we must compare what is usually done with what could be done. A very pertinent example of how we might transform medical care affects the primary heuristic of contemporary medicine—the patient history and physical exam reporting structure (the H&P heuristic)—that dominates all communication among healthcare practitioners today. We will then compare it to the new heuristic developed by IFM to achieve a more comprehensive communication tool.

Every healthcare provider recognizes this formal construct for medical information and communication. It both describes and dictates the process of the patient visit. The story that emerges from a clinical encounter is typically organized around the following elements:

From Patient Encounter to the Diagnosis:
The Conventional Medical Heuristic

- **Chief Complaint (CC)***
- **History of Present Illness (HPI)***
- **Past Medical History (PMH)***
- **Review of Organ Systems (ROS)***
- **Medication and Supplement History***
- **Dietary History***
- **Social, Lifestyle, Exercise History****
- **Physical Examination (PE)***
- **Laboratory and Imaging Evaluations***
- **Assessment and Diagnosis***
- **Treatment Interventions (usually pharmaceutical and/or procedure -based)***

*** = STANDARD PRACTICE**
**** = EXPANDED MODEL**

It is not always recognized that this construct facilitates the "fast and frugal processing" needed to efficiently collect, collate, and use patient information. The conventional H&P heuristic propels all information headlong toward the diagnosis, with the intention of identifying and prescribing the pharmaceutical or procedural therapy associated with that diagnosis. Each individual diagnosis is viewed as a distinct entity unto itself—often investigated during separate office calls and/or by different practitioners. There is no place in the conventional H&P heuristic to tie together multiple diagnoses into a consistent and coherent patient narrative. There is no identification of the antecedent conditions that may predispose the patient to the triggering of dysfunctional adaptive responses, nor of the mediators that may perpetuate the dysfunction. Thus, patients filtered through this conventional heuristic never have a chance to be fully heard and understood in the context of their whole life experience. Instead, their stories are reduced to a series of diagnoses, treated by different specialists, often in isolation from one another.

The H&P heuristic was shaped by, and thus reinforces, the organ-system model of disease, with its distinct and separate information silos, rather than a systems-medicine perspective that encourages the search for common underlying mechanisms of, and pathways to, disease.

IFM's functional medicine heuristic (FM heuristic) expands upon the same basic structure we are all familiar with, but organizes the information to integrate the patient's genetic and developmental susceptibilities (*antecedents*), historical *triggers*, and ongoing *mediators* of disease. Thus, the patient's story emerges with greater detail, a broader context, and a different focus and ultimate goal:

The Functional Medicine Heuristic

- **Chief Complaint (CC)**
- **History of Present Illness (HPI)**
- **Past Medical History (PMH)**
  —Explore antecedents, triggers, and mediators of CC, HPI, and PMH
- **Review of Organ Systems (ROS)**
  —Genetic predispositions?
- **Medication and Supplement History**
- **Dietary History**
- **Social, Lifestyle, Exercise History**
- **Physical Examination (PE)**
- **Laboratory and Imaging Evaluations:**
  —Immune/inflammatory imbalance
  —Energy imbalance/mitochondrial dysfunction
  —Digestive/absorptive and microbiological imbalance
  —Detoxification/biotransformation/ excretory imbalance
  —Imbalance in structural, boundary, and membrane integrity
  —Hormonal and neurostransmitter imbalances
  —Imbalance in mind - body - spirit integration
- **Initial Assessment:**
  —Enter data on Matrix form; look for common themes
  —Review underlying mechanisms of disease
  —Recapitulate patient's story
  —Organ system-based diagnosis
  —Functional medicine assessment: underlying mechanisms of disease; genetic and environmental influences
- **Treatment Plan:**
  —Individualized
  —Dietary, lifestyle, environmental
  —Nutritional, botanical, psychosocial, energetic, spiritual
  —May include pharmaceuticals and/or procedures

As can be seen in the FM heuristic, the diagnosis is one factor among many that help the clinician and patient explore why and how a condition was triggered and why and how the dysfunction is being mediated. From a disciplined filtering of the patient information through the Functional Medicine Matrix Model™ (see Chapter 5), patterns emerge that illuminate both the underlying causes of dysfunction as well as plausible (and multiple) points of leverage where individualized treatment can create improved function. The potential interventions reflect a broader array of health vectors than just pharmaceutical and procedural interventions because the FM heuristic elicits a pattern that helps the clinician and patient identify where lifestyle and environmental interventions can be applied.

Because clinical reasoning is very often grounded in heuristics (simplified models that guide evaluation and treatment at an unconscious level of awareness), we argue that to change the outcome, we must change the model. The ability to utilize heuristics when time and information are limited and outcomes are uncertain is a very special cognitive trait—an evolutionary breakthrough in adaptive cognition. To understand and refine clinical reasoning and clinical practice—to ultimately improve outcome—a deeper understanding of these adaptive skills must be understood and consciously applied.

Insight

If we are to develop an effective model for the healing partnership, we must also explore the research that illuminates the emergence of insight as a reproducible phenomenon.[xv] Brain research has illuminated very different functions of the left and right brain that explicate the objective neural correlates of a brain that produces insight. Among the most important features of this emerging view of brain function are the following:

- Solving computational questions is primarily a left-brain function. Asking a computational question triggers left-brain activity at the expense of right-brain function. (This has tremendous relevance to the interactions between doctor and patient. When a patient is interrupted with a computational question in the midst of an attempt to describe a pattern of dysfunction, the patient's own opportunity for insight may be lost.)
- If the left hemisphere excels at denotation—storing the primary meaning of a word—the right hemisphere deals with connotation, everything that gets left out of a dictionary definition, such as the emotional charge in a sentence or a metaphor. Language is so complex that the brain has to process it in two different ways at the same time. As humans, we need to see both the forest and the trees. The right hemisphere is what helps you see the forest.[287, 288]
- Much of the research into the adaptive unconscious (aka unconscious cognition) suggests that pattern recognition capacity resides in the right brain, but is not specifically localized.[289, 290] Solving questions requiring insight generates activity that starts in the prefrontal cortex and eventually extends throughout the cortex and deeper structures,

[xv] "What is insight? The term 'insight' is used to designate the clear and sudden understanding of how to solve a problem. Insight is thought to arise when a solver breaks free of unwarranted assumptions, or forms novel, task-related connections between existing concepts or skills." (Bowden EM. New approaches to demystifying insight. TRENDS in Cognitive Sciences. 2005;9(7):322-28.)

> searching for possible experiential information that contributes to the emergence of a pattern. It is the appearance of that pattern that sparks the "aha" or "Eureka!" experience in the connotative language centers of the right brain.

In brief, left-brain function helps us with the denotative, computational, linear functions of life and thought, whereas the right brain provides the connotative shadings that give depth and character and color to meaning. Right-brain function is the source of pattern recognition and moments of insight.

The researchers in this field have produced a robust and credible body of research about pattern recognition from experiments that delineate and substantiate the functions of unconscious cognition (the adaptive unconscious) that shape moments and expressions of insight.[291, 292, 293] Reproducible patterns of brain activity correlate with the experience of insight.[294] The prefrontal cortex does not simply function as an aggregator of information. Instead, like the conductor of an orchestra, brain wave activity and energy expenditure are coordinated as if instructed by the prefrontal cortex maestro, waving its baton and directing the players.

This is known as top-down processing, since the prefrontal cortex (the top of the brain) is directly modulating the activity of other areas. Studies show that cells in the right hemisphere are more broadly tuned than cells in the left hemisphere, with longer branches and more dendritic spines. As a consequence, neurons in the right hemisphere are collecting information from a larger area of cortical space. They are less precise but better connected. When the brain is searching for an insight, these are the cells that are most likely to produce it. A small fold of tissue on the surface of the right hemisphere, the anterior superior temporal gyrus (aSTG), becomes unusually active in the second before the insight. The activation is described as sudden and intense, a surge of electricity leading to a rush of blood.[295, 296]

One of the unusual aspects of insight is not the revelation itself but what happens afterward. The adult brain is an infinite library of associations, a cacophony of competing ideas, and yet, as soon as the right association appears, we *know*. The new thought, which is represented by that rush of gamma waves in the right hemisphere, immediately grabs our attention. As soon as the insight happens, it seems so obvious. People can't believe they didn't see it before.[297, 298, 299]

Insight researchers call the "aha" experience the *moment of categorical insight*. This moment of epiphany registers as a new pattern of neural activity in the prefrontal cortex. The brain cells have been altered by the breakthrough. An insight is a restructuring of information—it's seeing the same old thing in a completely new way. Once that restructuring occurs, you never go back.[300]

Insight and the Healing Partnership

"While it's commonly assumed that the best way to solve a difficult problem is to focus, minimize distractions, and pay attention only to the relevant details, this clenched state of mind may inhibit the sort of creative connections that lead to sudden breakthroughs. We suppress the very type of brain activity that we should be encouraging. Jonathan Schooler has recently demonstrated that making people focus on the details of a visual scene, as opposed to the big picture, can significantly disrupt the insight process. 'It doesn't take much to shift the brain into left-hemisphere mode,' he said."[301] We can extrapolate that, as clinicians, although we don't ignore evidence, when we want insight about a patient's condition, we are clearly better off not turning to left-brain analysis of the most recent RCTs. And, when we want the patient's insight, we must learn to elicit the patient's story (pattern) and really listen to it.

Research focused on the typical, clinical therapeutic encounter has noted that clinicians interrupt the patient's flow of conversation within the first 12 to 18 seconds (or less) of the patient's response to a question.[302, 303] This reproducible phenomenon in the conventional clinical setting makes sense if you compare the heuristic for contemporary medicine to the functional medicine heuristic. The heuristic of conventional medicine (rule of thumb) achieves the stated goal in an expeditious manner: clinicians use it to identify the primary organ system domain of the presenting problem and then focus on the differential diagnosis within that domain, marching resolutely to the final diagnosis. This is a computational process, without need for a partnership that can produce insight into the underlying causes and mechanisms of the medical problem.

The functional medicine heuristic, on the other hand, requires a carefully nurtured and protected partnership between the clinician and the patient to illuminate the underlying mechanisms of the patient's illness(es). The FM heuristic requires an iterative, cooperative process that yields a more complete narrative story. From a thorough investigation of the antecedents, triggers and mediators of the patient's condition, emerge information and insights that can help to shape a deeper and more comprehensive therapeutic response.

Summary

We have devoted this chapter to achieving a better understanding of an urgent problem facing clinicians today: how to combine both science and art, evidence and insight, into an individualized, patient-centered approach to complex, chronic disease. We do not claim to have *the* (sole or definitive) answer. But we do offer a new focus for both education and practice that can be described and substantiated, taught and practiced. We have presented findings that suggest that the management of uncertainty—the inherent context of clinical medicine—requires a change in the therapeutic relationship on the part of both clinician and patient and a change in how we view and use evidence. The technical therapeutic encounter that has characterized a great deal of patient care for the last few decades must be transformed into a healing partnership through appropriate applications of scientific understanding, evidence from clinical trials, and a new understanding of brain function.

The Institute for Functional Medicine's model of comprehensive care and primary prevention for complex, chronic illnesses (described further in Chapter 5) is grounded in both science (the Functional Medicine Matrix Model; evidence about common underlying mechanisms and pathways of disease; evidence about effective approaches to the environmental and lifestyle sources of disease) and art (the healing partnership and the search for insight in the therapeutic encounter). These two cornerstones of clinical medicine must be integrated into our teaching and practice in order to achieve what we owe to our patients and ourselves—a more effective response to the epidemic of chronic disease. We assert that this can be done.