July 2006 Issue | Wayne Jonas, MD Director, Samueli Institute for Information Biology

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Welcome to the July issue of *Functional Medicine Update*. Thank you for being with us. I think this will be an epic issue, focused on a topic that is long overdue: healing environments.

Over the last 25 years of *Functional Medicine Update*, we have talked about topics related to therapy, intervention, diagnosis, and assessment, and also how one looks, early on, at altering function. But we have never focused a whole issue on the nature of the healing environment: the context surrounding patients and their conditions, and how this ultimately relates to the ability to recover, repair, and restore function.

This month, we are privileged to have Dr. Wayne Jonas as our clinician/researcher of the month who, as many of you know, is a very important member of our community. He is the former director of the National Institutes of Health Center on Complementary and Alternative Medicine, and now is the director of the Samueli Institute of Information Biology. You will hear more from Dr. Jonas later in this issue about the work they are doing on establishing the context of the optimal healing environment. Before we get to his eloquent discussion, I thought it might be useful to set the tone and provide an overview of this topic.

The concept of the optimal healing environment is so timely; it is an important part of the algorithm that is incorporated within the context of functional medicine and the functional medicine matrix. Functional medicine attempts to understand the interactions of the complex processes that connect the individual to the environment. This gene interaction and epigenetic connection to function is what ultimately gives rise to health and disease patterns. The trajectory of living arrives at an outcome called our health or our disease. Understanding these interactions ultimately supports our ability to use the functional medicine model effectively in clinical practice. The concept that underlies functional medicine is the assessment of antecedents, triggers, mediators, signs, and symptoms; this concept contrasts with the sine qua non of traditional medicine, which is a differential diagnosis. Rather than just provide a description (in the way of a diagnosis for the outcome), functional medicine attempts to understand processes that underlie dysfunction.

The Environment of the 21st Century

What is the environment into which we are interjecting this model? The environment is one that is fraught with conflicts about what we say compared to what we do. This cognitive dissonance can set up challenges in the exam room with a patient because what a patient may believe and what he or she is

doing can translate into dysfunction that ultimately may lead to disease. A part of what we would define as an optimal healing environment is helping to make the perspective of what a patient believes the same-or as close to the same-as what he or she does. Hopefully, as functional medicine providers, we can guide the patient into a functional congruence between the beliefs he or she has and what he or she is actually doing.

The Traditional Office Visit

Let's do a quick review of the domain that defines the way patients are traditionally treated today. The patient arrives with signs and symptoms that are evaluated, often using a SOAP (Subjective, Objective, Analysis, Plan) process. Ultimately, through some kind of diagnostic criteria or classification, a diagnosis is generated with an ICD descriptor code. This sets in motion a specific therapy designed for that specific diagnosis. Although the patient may present with multiple signs and symptoms that cut across many diagnoses, they are codified into very specific, independent classifications that we call disease classifications.

Different disease codes and classifications are 'owned' by different medical specialties. The presentation of a patient with symptoms that reflect multiple symptomatologies across multiple organ systems (therefore transgressing across multiple subspecialties of medical areas of expertise) begs the question: Who is the shop boss who will oversees the whole organism rather than just the individual management of piece parts, as if each of the diagnoses were independent each other? Without this coordination, the patient may end up with appropriate medical therapy for each of their diagnoses by different practitioners, each treating him or her independently, ultimately arriving at polyintervention. None of these therapies is evaluated with respect to how they interact with each other, or how the multiple signs and symptoms with which the patient presented may point toward a common theme in a mechanistic (or functional) disability.

Pharmacotherapy

The treatments generally employed (for both efficiency and presumed effectiveness) are pharmacotherapy and surgery. Pharmacotherapy is a convenient way of introducing therapy because of its speed. Once the diagnosis has been made, a simple annotation on a prescription pad can lead the patient out of the exam room, out of the office, and into remedial care. The prescription becomes a psychological and socially acceptable way of terminating the relationship patients in the exam room, allowing them to move on with their life, presumably with a more positive outcome. The prescription pad provides a mechanism for high-throughput efficiency (the six-minute office visit; the turnover of tens of patients in a day). In six minutes, the trained and skilled provider can ask a few salient questions, check vital signs, review some laboratory analysis, come to a conclusion as to what the most appropriate diagnosis is, write the prescription; and the patient can be on his or her way. When medicine is structured with an assembly line-type of efficiency, it is more cost effective.

Over the last ten years, various scholars have written about the difficulties with this approach. The concept of differential diagnosis leading to independent disease diagnoses-separated one from the other-is a fallacious concept. Patients generally do not present with one independent, isolated disease. They have multiple signs and symptoms that relate to different levels of dysfunction. There may be an Occam's Razor-a connector-that relates their apparently different dysfunctions through a root mechanism. It is this construct that frames the foundation of functional medicine: looking at the underlying mechanism(s) that connect genes and environment together in a patient to result in either function or dysfunction, either health or disease.

The pharmacotherapy generally employed today is a recipe designed to manage independent symptoms. If a patient has a specific type of dysfunction-for example, hypertension-there is a family of medications that work by different mechanisms to produce the desired effect, which is to lower blood pressure. You could consider using a diuretic; you could consider using a beta-blocker; you could consider using an angiotensin receptor inhibitor or an angiotensin receptor blocker. You could use a number of different types of calcium channel blockers. For the management of the endpoint called high blood pressure, all of these prescription options would be at the disposal of the practitioner. These medications-these new-to-nature molecules-will have different impacts in different individuals; the functional change within a person's vasculature may be dramatically different from one patient to the next, requiring a very different intervention for the improvement of function.

The drugs may be treating the signs and the endpoint of the symptoms downstream rather than managing a mechanism (or ultimate cause) of a condition that was initiated upstream. This leads into some very interesting difficulties relative to the safety and effectiveness of pharmacotherapy. The actual functional disability of the patient is not understood, but an empirical approach based upon a presumed mechanism for managing his or her problem is employed. The interesting part of this empirical approach to pharmacotherapy is that it can result in unexpected adverse effects.

Potential Adverse Effects of Pharmacotherapy
Practitioners who are experts in pharmacotherapy understand early-stage adverse effects and monitor their patients closely for signs. They modulate the patient's dose and their scheduling of administration, and even the class of drugs that are being used to try to avoid adverse effects. Even so, practitioners do not know on the front-end how a patient will respond to a particular drug; they can only look at the back-end and how the patient responded post hoc.

Often, we are told that this form of medicine-this pharmacotherapy-is based on scientific principles, and people who use it are doing scientific medicine. If you really listened to what I just said, though, about an empirical approach toward the application of pharmacotherapy, it is ironic, because we are doing a kind of medi-science (or proto-science). It is not predictive in its nature; it is post hoc (evaluative on the outcome side). We have presumed mechanisms, but we do not know if the mechanism of a particular drug applies to an individual patient. After the drug is applied to the patient, we try to monitor and manage any potential less-than-desirable outcome, which can be either ineffectiveness or adverse drug reactions.

Chronic pain from inflammation is a specific example of a need for pharmacotherapy. There are many drugs that can be applied to this particular concern. You can look at the nonsteroidal anti-inflammatory drugs (NSAIDs). You can look at agents that are steroidal in nature. You can look at the new class of selective cyclooxygenase-2 type of inhibitor drugs like the celecoxibs. Each one of these drugs works by a different mechanism, has a different pharmacodynamics and pharmacokinetics, and influences the inflammatory process indifferent ways. Yet, they are often all viewed in a similar vein, and administered to a patient on the basis of some body- surface-area argument or body-size argument, as if the metabolism of different patients is going to be similar, and the mode of action of the drug is going to be similar. After marketing, a clinical trial on rofecoxib (Vioxx) showed that after 18 months of treatment, some individuals have unexpected serious adverse outcomes from the drug, which included cerebral vascular accident or a cardiovascular accident leading to death. How could this happen with a medication that had gone through rigorous front-end testing and had been proven scientifically valuable, in addition to being

validated by the Food and Drug Administration (FDA) and approved for insurance reimbursement for the management of pain? It can happen because the patient's uniqueness is not understood when that particular drug is administered. For drugs that are used chronically-possibly for many years-the adverse effects may not be fully seen until after many months or more of post-marketing experience, when the full effects on physiological function get to a point of dramatic enough intensity (or severity) that they can be recognized. Sudden cardiac death is a pretty dramatic outcome, and there may be many other subtle functional changes that occur well before that that are not easily picked up as post-market drug surveillance data. Ultimately, it requires (as in the case of rofecoxib) 18 or more months before these outcomes become assembled in a large enough data set that the company voluntarily removes the product from the market.

Pharmacotherapy and Chronic Disease

When pharmacotherapy is applied to the management of chronic disease, there are a number of potential challenges that should be considered. The management of chronic disease entails the application of pharmacotherapies for extended periods of time, but medications are only being studied for a fairly short period of time in clinical trials prior to approval by the FDA. The first group of study subjects to understand how a newly-approved drug of that type works long-term in the management of chronic disease is the first group of patients who take it for a long period of time. This understanding is not going to come out of the clinical trial because clinical trials don't go on for years with a large and diverse patient population. Pre-market clinical trials generally don't go on for 3, 5, or 10 years. As more and more products to manage chronic illness (the dominant form of healthcare challenge that we have today, constituting 78 percent of healthcare expenditures) come onto the market, we start asking questions. Eventually, we can examine stratified data sets and look at unique genotypes in individuals and how these different risk factors exist in different people. We may become wiser downstream, but only after individuals may have been injured on the front end due to the lack of understanding.

The pronounced inhibition of cyclooxygenase-2 (COX-2) seen with the COX-2-specific inhibitors can have effects on blood pressure, reduction of heart rate, increased vascular endothelial injury, and increased platelet adhesiveness causing thrombi formation. These effects can differ from person to person. This has been well documented in the literature, including in a recent paper in the journal Arthritis & Rheumatism that talked about the differences among the different classes of these drugs and how they interact with the vasculature in different ways in different people.1 It is much more complex than we may have been led to believe by the simple statement that these are new, specific drugs selected for COX-2 isozyme that have a significant advantage over the nonspecific NSAIDs.

Multiple Medications

What happens if you use multiple medications, all taken at the same time? I am often asked about why I talk about areas in Functional Medicine Update that have not been totally subjected to double-blind, randomized, placebo-controlled trials (like diet and lifestyle intervention), and suggest that these things should be used in clinical practice, even in the absence of large clinical intervention trials. My response to this question comes out of the type of thinking that was described in a recent paper in Nature Genetics, which talks about a recipe for looking at drug interaction networks.2 It is hard just to prove how one drug works at a time in a patient over a long period of administration in terms of efficacy and safety, and when you start looking at two drugs at a time, three drugs at a time, or more, the problem becomes exponentially more challenging. In fact, there are very few (if any) combinations of medications that have been studied in randomized, clinically controlled trials. Therefore, my response to people who ask me the

question about discussing, in Functional Medicine Update, things that have not been subjected to randomized, clinical controlled trials, is a query: Do you, as a physician, ever prescribe more than one drug at a time to a patient? If you do, you are not doing science; you are not using randomized, clinically controlled, placebo-crossover trial data to understand how those multiple medications work in that patient over time. You are using suggestive evidence, along with your belief that it is going to be successful based upon commentaries or editorials. That is not true science; that is proto-science.

The point I am trying to make is that clinical decisions about how to manage patients are often made from imperfect data. I'm not casting aspersions at the use of polypharmacy in the absence of randomized, double-blind, placebo-controlled trials because I understand the complexity and challenge. What I am trying to point out is that medicine derives its origin from clinical decision-making using the best information that we can find for management of the complex problems that patients present with. One of the differences, however, in our discussions in Functional Medicine Update is that often the molecules we suggest are those derived from nature. These often have a long history of safe use and have arrived, through natural selection and evolution, as having some biological compatibility with our function. This is in contrast to the new-to-nature molecules that may have only been on the scene since bench chemists synthesized them within the last 30 or so years; we don't have that same kind of history with these molecules and how they incorporate into our physiology. I want to make sure we are all operating from the same theme when we are talking about a healing environment. As we use new-to-nature molecules and pharmacological therapy that is not individualized or personalized, and on the back-end we examine adverse signs and symptoms, we are not always setting up a healing environment. We have not yet talked about the context of the administration of medication. If medication isn't administered-as we'll learn from Dr. Jonas later-in an environment that is actually conducive to healing, the efficacy of the medication may be limited just by the nature of the belief of efficacy. We get into a whole interesting conundrum here relative to how to establish, within a functional medicine context, the healing environment.

Adverse Drug Effects: Gatifloxacin and Glycemic Control

I have talked a lot about medications, but let me say something about adverse drug reactions (ADRs) because these are becoming even more concerning. The medical community and the public have seen a steady stream of reports linking the use of widely prescribed medications to serious health risks. An article appeared in the Journal of the American Medical Association in the 90's that talked about over 1 million adverse responses in hospitals and 100,000-plus deaths due to adverse drug reaction to the appropriate drug, administered by trained health professionals in the hospital under proper monitoring.3 That was a wake-up call, and many people started to look more intensively at the risk-benefit relationship of some of these medications. I found a recent article in The New England Journal of Medicine that presents one such story. This article, authored by Jerry H. Gurwitz, MD, was titled, 'Serious adverse drug effects: seeing the trees through the forest.'4 The author discussed a paper in the same issue of The New England Journal of Medicine about an antibiotic-gatifloxacin. This was Park-Wyllie's work, titled 'Outpatient gatifloxacin therapy and dysglycemia in older adults.'5 This paper was very interesting because this drug has been on the market for six years and is used commonly as a third-generation antibiotic. In studying the drug over several years, adverse effects on glycemic control that included severe hypoglycemia in some patients and hyperglycemia in others were found. This is a 180-degree different response in different patients to the same molecule. Once again, this indicates that an extraordinarily different response can occur in different individuals, leading to very different types of patient outcome. In this case, both outcomes can be potentially life-threatening. The analysis of risk of hypoglycemia in the patients associated with the use of gatifloxacin was higher than similar molecules

within its class, so there is something very interesting about this particular molecule. The relative risk of hyperglycemia (as contrasted to hypo) was 16 times as high (compared against other macrolide antibiotics). Use of gatifloxacin is now linked to both an increased risk to hypoglycemia in some patients (leading to emergency room medicine), and hyperglycemia in others (leading, again, to emergency room medicine).

According to Gurwitz, gatifloxacin was first marketed in 1999, and reports of dysglycemic effects appeared soon after the drug was approved. Health Canada, the Canadian FDA, published a report about the drug that was very critical in 2003. Gurwitz poses the question: is six years too long to wait for a high-quality, controlled, epidemiological study quantifying such important drug related risks? In other words, how long does it take before we start to understand these potentially adverse side effects that occur from these new molecules? The author says that gatifloxacin now takes its place among an ever-growing list of medications that have been associated with very serious adverse effects.

The Changing Face of Teenage Drug Abuse

If you couple this example together with another interesting and important trend-the changing face of teenage drug abuse-it raises a bigger question about what our medical world is becoming. There is a trend (as you may be aware) in teenage drug abuse, toward the use of prescription drugs. One of the most commonly prescribed drugs in America is hydrocodone-acetaminophen (trade name: Vicodin). Where does some end up being used? Some is being used illicitly, particularly in teenage drug abuse situations. For some teenagers, street drugs have been replaced by prescription drugs, and it is a very interesting trend. The number of high school students who are abusing prescription pain relievers, such as hydrocodone or oxycodone, is on the rise as we see a decline in some of the traditional street drugs. A total of 7.2 percent of high school seniors reported non-medical uses of sedatives in 2005, up from 2.8 percent in 1992. The similar reported use of oxycodone in this group increased from 4 percent in 2002 to 5.5 percent just three years later in 2005. These findings are reported in The New England Journal of Medicine in an article by Dr. Richard Friedman titled, 'The changing face of teenage drug abuse-the trend toward prescription drugs.'6 This is a dramatic trend. Why is this happening? It is happening because some teenagers see prescription drugs as being safer than illicit street drugs, but yet the prescription drugs produce the desired pharmacological effect: to medicate them to be able to manage their lives. This is in a culture where our watchword, a few years ago, was 'just say no.' It seems paradoxical that the medications that have been used to manage disease are now starting to be used for the management of chronic complaints of maladjustment to living.

In the article by Friedman, some teenagers who were abusing prescription drugs were interviewed. One of them wrote, in an email message, 'We're living in a time that seems decidedly more apocalyptic. Maybe we need something to slow us down.' He or she is apparently referring to medications that will make life more manageable. These are dangerous trends that speak against the whole concept of functionality and a healing environment.

The Perception that Prescription Drugs Are Safe

We know that kids can get prescription drugs from parents, friends, or even on the internet. A 2004 survey of physicians (also mentioned in Dr. Friedman's article) found that 43 percent of physicians did not ask about prescription drug abuse when taking a patient history, and one-third of these physicians did not regularly call or obtain records from patients' previous physicians before prescribing potentially addictive drugs. Even those medications that we might consider to be some of the more dangerous drugs

are now becoming available to our youth as ways of managing life. This is driven, to some extent, by the facetious belief that these medications are safe because of direct-to-consumer advertising. Dollars spent on direct-to-consumer drug advertising rose from 1.8 billion dollars in 1999 to 4.2 billion dollars just five years later, in 2004. The author of The New England Journal of Medicine article says, and I quote,

'physicians play an important role in this problem, given their apparent laxness in prescribing controlled drugs. Physicians should routinely assess their patients for substance abuse and psychiatric illness before they put pen on a prescription pad'

The perception that prescription drugs are largely safe seems to justify, in the minds of our teenagers, the attitude that occasional use poses little risk.'

These are very dramatic trends that are painting a picture of relative risk.

Black-box Warning on ADHD Drugs

If we look at the drugs used to treat attention deficit hyperactivity disorder (ADHD), it is a very interesting constellation. On February 9, 2006, the Drug Safety and Risk Management Advisory Committee of the FDA voted, by a narrow margin (8 votes to 7), to recommend a black-box warning description (for cardiovascular risk) be placed on stimulant drugs used to treat ADHD.7 This decision came more than a decade and a half after these drugs were first prescribed for our youth. The drugs under review were primarily amphetamines (Adderall and other brands) and methylphenidate. (Ritalin, Concerta, and other brands). These drugs are broadly classified as sympathomimetic amines and have very active effects, not only on the central nervous system, but also the cardiovascular system. They substantially increase heart rate and blood pressure, and in placebo-controlled trials (when administered to adults) they increase systolic blood pressure by 5 mmHg.

Similar effects were found across all the drugs in these families. The FDA advisory committee heard testimony indicating that 2.5 million children now take these stimulant drugs for ADHD, including nearly 10 percent (or 1 out of every 10) of ten-year-old boys in the United States. Did you hear what I just said? One out of every ten 10-year-old boys in the United States is on a stimulant drug for the management of ADHD. Do you remember the quote from the eighteen-year-old mentioned above? 'We're living in a time that seems decidedly more apocalyptic. Maybe we need something to slow down.' These drugs for ADHD are the opposite of 'slow down;' these are 'speed up' drugs.

The Connection between ADHD, Insulin Resistance, Hyperinsulinemia, and Obesity

What are the alternatives? What is the functional medicine approach? What would lead to a healing environment for these concerns? Those are big questions. There is a strong connection between the mechanism associated with ADHD and obesity, metabolic syndrome, and insulin resistance. In a recent paper in Medical Hypotheses, the authors talked about the model for revealing mechanistic overlap among cognitive metabolic and inflammatory disorders that connect ADHD to insulin resistance, hyperinsulinemia, and obesity.8 These are not unconnected problems; the central nervous system (CNS) is connected to the liver, which is connected to the pancreas, which is connected to the adipocyte, which is connected to the muscle, which is connected to the gut signaling process. We have fed disinformation to our children and put them in a very complex environment, thereby creating less optimal network signaling and producing dysfunction for which the empirical clinical intervention is to use sympathomimetic stimulant drugs to manage what appears to be a hyperactivity disorder. When one

considers it from a rational perspective, it appears crazy, as well as antithetical to the context of a healing environment.

Years ago, we learned, from the work of investigators at the University of Colorado School of Pediatrics, that low-quality diets in children can alter brain chemical function, change learning abilities and the ability to thrive, and alter immune function. Zinc is one of the many nutrients implicated in this effect. We know that zinc is an important nutrient for cognitive performance, immune function, muscular development, and growth and development in children. Zinc is obtained in the diet; it is not fortified, like iron. Snack or convenience foods (highly processed, shelf-stable foods) generally contain low amounts of zinc. Furthermore, low serum zinc levels have been linked to major depression, and zinc treatment has been shown to have an anti-depressive effect. Therefore, it is possible that we should be looking at trace minerals like zinc in situations involving neurocognitive performance problems.

The concept of zinc as a nutrient important for mood is discussed in a review paper that recently appeared in *Nutrition Review*s.[9] Zinc is found in high-quality, muscle-made foods and whole grains (such as organically grown). Zinc is also very important for taste and olfaction. People with a poor sense of taste (often the case with children who have poor-quality diets), may have impaired discrimination for sweetness and saltiness, and require high stimulation with salty and sweet foods in order to get the same level of sensation as a person who is not impaired. We often use the zinc tally test to measure this. Some of you may be familiar with this. A dilute oral zinc sulfate solution is put on the tongue, and if a person has a very bitter feeling from that-an astringent effect-then they are presumed to have high zinc status. If, however, they can't taste the zinc sulfate solution (even if quite a bit of the liquid is administered), this is presumptive evidence for zinc insufficiency. Supplementation with zinc to help restore their taste and olfaction may be desirable. This is seen not only in children, but also in older-age individuals.

Mercury is an environmental substance that can modify neurocognitive performance. Last month on *Functional Medicine Update*, we were privileged to have Dr. Herbert Needleman tell us about the pioneering work he has been doing with lead and intelligence quotient in children over the past 30 years. Mercury is a problematic neurotoxicant. Recently, in the *Journal of the American Medical Association*, there were two papers published on neuropsychological and renal effects of dental amalgam in children.[10,11] The first of these papers was principally authored by Dr. David Bellinger, who was a presenter at the 13thInternational Symposium on Functional Medicine (on biotransformation and detoxification) in Tampa. The same week Dr. Bellinger presented at the Tampa Symposium, the article he authored appeared in the *Journal of the American Medical Association*, and it was very fortuitous for the attendees to have the principal author of this work there to discuss the implications. He pointed out that although statistically the studies did not indicate that amalgams had any adverse effect on neuropsychological performance in children, there were children within the study group that seemed to have adverse effects. Therefore, one might ask: Are there some genotypes that are more at risk than others? This gets into the bigger issue of how we look at averages; sometimes we wash out any specificity for individuals who have unique genotypes and susceptibility factors.

In Bellinger's study, an increased urinary output of mercury was seen in the children who had dental amalgams. If you believe that mercury is not really a desirable element to have in the body, then the appearance of mercury in the urine at least suggests that there is some kind of a release into body fluids and tissues, and this could potentially have adverse effects in some children. Certainly this is the same type of battle that Dr. Needleman has been fighting with the lead question over many years. These are

difficult issues to resolve and relate to how to establish a personalized, optimal healing environment for an individual.

Before the development of insulin, (at least from 1914 to 1922) diabetes was managed with diet. There were extraordinarily effective diets for the management of diabetes that were reminiscent of what we are relearning today: low-glycemic-load diets that were low in sugar, high in unrefined carbohydrate (such as fiber), modest lean-animal protein, and essential fatty acids. Many different dietary variables had been used during this period, well before insulin was developed. What is interesting is that the drug eventually made it so seemingly easy to manage diabetes that people no longer had to worry about their diet or lifestyle. Now, however, we are recognizing that type 2 diabetes (the predominant form of diabetes in our culture), is associated with an altered lifestyle gene-environment interaction, and is probably best managed not by drugs, such as metformin or peroxisome proliferator activated receptor (PPAR) agonists, but rather by diet and lifestyle intervention. We are going back to the future, learning about what worked for many people prior to the development of medications. For those of you who are interested in reading about the history of the dietary treatment of diabetes in the pre-insulin era, you might want to look at the winter 2006 issue of*Perspectives in Biology and Medicine*.[12]

The context has been set for the question: what is a healing environment? Is there something about the relationship between the provider and the patient-and the patient's condition-that can lead to differing types of outcomes? With these questions t in mind, we are fortunate to have the most interesting person to bring this topic to our perspective and help guide us in integrating it more effectively within our functional medicine model-Dr. Wayne Jonas.

INTERVIEW TRANSCRIPT

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JB: Once again we are at that place in Functional Medicine Update that we all look forward to-our clinician or researcher of the month. This month's discussion has been 20 years in the making. Dr. Wayne Jonas and I have known one another for more than 20 years. I have watched, with great admiration and respect, what Wayne has done in the field that we have shared over the past two decades. It has been quite remarkable. Many of you are familiar with Dr. Wayne Jonas because he has made a tremendous contribution and is one of the leaders in our field.

Dr. Jonas is a medical doctor who, after training at Wake Forest University School of Medicine, went into service in the Army and had a family medicine internship at Dewitt Hospital in Fort Belvoir in Virginia. Through many different theaters of activity and places to gain greater skill and experience, his seeking mind and his background (both in humanities and biomedicine), brought him to a position in which he was looking at ways to improve the efficacy and safety of therapies. He opened his mind to things that work across wide ranges. He expanded his universe for thinking and a lot of other peoples' universes for

thinking in the process. Eventually, he became the director of the office of the Alternative Medicine/National Center for Complementary and Alternative Medicine. The center had an annual research budget of 50 million dollars and, during the time he was there, established 13 major research centers around the country, supported over 50 other research projects and four multi-center clinical trials, and started to codify the nature of research methods applied to complementary and alternative medicine. Dr Jonas asked the 'get real' questions about what works and what doesn't and how we can define what works and what doesn't. From there, Dr. Jonas went into the Uniformed Services University of Health Sciences in Bethesda as an Associate Professor and Brigade Surgeon.

A major transition occurred in his career in 2001, which has had a very strong, positive impact on our field. Dr. Jonas helped found the Samueli Institute for Information Biology in Alexandria, Virginia and Corona del Mar, California, and now serves as its director. Over the past five years, Wayne has brought this Institute to a place of international prominence, and we are going to hear much more about it.

Wayne, I want to welcome you to Functional Medicine Update and thank you for being available for us today. It is a real pleasure to finally have you as one of our clinicians after two decades.

WJ: Thank you, Jeff. It's an honor to be on Functional Medicine Update. You know, the first tapes that came out when you started doing this many, many years ago had a profound influence on me as a resident, because I was looking for ways to connect my training in biochemistry in medical school with actual practical application and nutrition. When I came across some of your educational tapes and seminars, I thought, 'Here is somebody who is finally doing it.' I've really enjoyed learning from you and being inspired by you over the years, so it's a great pleasure to be on FMU now.

JB: Thank you. It's a mutual admiration society that I share with you and what you have helped me to understand. Let's talk a little bit about the Samueli Institute. Many of our listeners are probably well aware of it, but it might be useful (in that this goes out to people around the world) for you to tell us a little about the Institute and its origin.

The Samueli Institute

WJ: The Samueli Institute was started in 2001. It was founded by a couple out in California by the name of Susan and Henry Samueli. Henry Samueli was a UCLA engineer who invented some very useful electronic information that allowed broadband communication. He started a company right at the age of broadband communication, and it is now one of the leading companies in that area. Susan is a trained mathematician. She practiced the use of a variety of natural medicines, first for her family and friends, and then her community. She looked at homeopathy and herbal medicine and these types of things. They were both interested in science and they were interested in healing and complementary and alternative medicine's role in facilitating healing. In 2001, we got together and discussed what was needed in the field. We decided a nonprofit independent organization was needed that could ask fundamental questions and then develop partnerships with groups and individuals to help answer those questions about how to move medicine forward in the direction of healing approaches. And so the Samueli Institute was founded as a nonprofit research institute in 2001. We are now coming up on our five-year anniversary, and the goal of the Institute is really to transform medicine through science. Our research is especially focused on learning how to better apply the science of healing: how do we recover, how do we repair, how do we restore? We focus on that, and then look at the relationship between that and disease treatment and how they can best be integrated.

JB: I have followed the work you have been doing at the Institute very closely with regard to the definition and codification of the optimal healing environment. I think this is such a tremendous concept because no matter what a person's background is in the health sciences, I believe their objective would be to try to assist in the development of an optimal healing environment for a patient. Whether it be a surgeon, an oncologist, a natural medicine specialist, or a body work practitioner or psychologist, all of these people would be trying to define an optimal healing environment. Your group has done the best job of any I've seen in codifying what that kind of environment might look like. Can you take us through its evolution and what you've learned? I think it's transferable, in principle, to many of our listeners.

The Healing Environment: A Concept in Evolution

WJ: Yes, I'll be happy to talk a little bit about where we are, and let me just say that this is a concept in evolution. By no means have we come up with definitive definitions or measurements or understanding about the components that go into an optimal healing environment, but the goal of our optimal healing environments program is to try to look at the processes of healing and the components that support and stimulate healing processes from a scientific point of view, so that we can begin to develop a science that allows us to maximize those components in any environment. I think the thing that originally inspired us in this area was my exposure to healing practices in different places in the world. I was stationed in Germany, for example. I lived in Asia for a number of years. It dawned on me that there were a variety of healing approaches that were quite diverse, both in their assumptions and in their practices, and yet most of them claim that they were getting good effects, especially in the management of chronic disease and mind/body areas (pain, and that type of thing). If you look back through the history of medicine, even in the west, there are two main philosophical thrusts that have paralleled each other in medicine. One is the idea that if you facilitate healing processes that are innate, this brings about recovery and is a useful approach to the treatment of illness, suffering, and disease. The other is what I call the disease-specific approach, in which you try to identify an isolated cause for a disease and then you interfere with, or somehow break, that causal chain. Both of these concepts, obviously, are very useful at different times, and in recent times (meaning the last 100 years), with the explosion of science and technology, and detailed understanding of specific causal change around particular diseases, modern biomedicine has really revolutionized health care by focusing on isolating those particular chains of cause and effect around disease and then developing treatments (drugs, surgery, etc.) to interfere with those.

But along with this (and in parallel), science has also revealed the complex web of interactions that facilitate healing. There is an emerging understanding that the healing approach can be understood on a scientific basis, and that by doing so we can facilitate healing. It provides us with a whole new perspective and a whole new set of approaches in these areas. What we have been attempting to do at the Samueli Institute over the last few years is, first of all, try to start with a description of the broad domains of components that facilitate and stimulate healing, and then begin to understand how they are being delivered in healthcare systems: how we can define them, how we can measure them, how we can begin to then (from that) investigate the optimal way in which they may be applied in health care. That is really the perspective of why we have gone about trying to formulate the idea of an optimal healing environment.

JB: I know you have put together a very nice model-a grid-that describes some of these domains of healing and the interface among them. Could you describe that for our listeners?

The Five Domains

WJ: Sure. This process has come out of several years of bringing together experts from diverse areas in

health care, getting their input, synthesizing it, providing feedback, and then getting into larger groups. We started with a series of small meetings of clinicians, patients, and scientists who are interested in this area, and then developed a grid. We have had a series of meetings since then with larger groups, getting their input and attempting to refine these ideas. What has emerged is that there are basically five main areas if you look at healing systems from around the world, including those that are being developed in hospitals and in clinics in conventional medicine. There are five areas that we think-and our consultants feel-need to be addressed if we are going to optimize the process.

When we talk about healing environments, we have a broader concept than just the physical environment; we are talking about both the internal and the external environment. Some of the components in the internal environment involve the proper management of our own mind/body aspects (the inner aspect of our intention, our belief, and what we pay attention to). We know, for example, that belief, expectation, and the control of our stress is really an inner management issue; it's management/control of the mind and the mind/body. The whole area of intention is one domain.

A second domain involves the concept of holism, and this is the idea that the mind and the body are, in fact, a unit. The mind/body spirit is a unit, and so experiencing that connectivity and that holism, and engaging in activities that help to complete that sense and experience of holism, then brings the mental aspects into the body in a functional way. There are a variety of ways of doing this: mind/body practices, bioenergy practices, psychological/psychotherapy types of practices, and even things like yoga and acupuncture (which are really mind/body practices). Within standard psychotherapy there is also the concept of healing the past and healing the future. So, for example, being able to address past traumas appears to be an important aspect of attaining a sense of wellness and well-being. Having a sense of meaning and purpose in the future is also an important aspect of survival and of improved function. This area of experiencing wholeness and practices that do that is the second domain.

The third domain, which is really at the center of much of this, is the social relationships that we are involved in. There is now extensive research showing that social support, social interaction, altruistic behavior, and social service have a significant impact on our health. They are salutogenic; they are health protective, and preventive. And so, the proper engagement in healing relationships then becomes the third domain.

The last two domains are things that are more well known in medicine because they focus on some of the behavioral and external environmental components. For example, lifestyle and proper behavior-behavioral medicine and lifestyle medicine-are key aspects to both maintaining health and recovering health once it's lost. This includes appropriate nutrition, exercise, stress management, life balance, and addiction management, which is a major issue in our culture. Smoking, alcohol, and other types of addictions are part of lifestyle approaches, and many of your listeners, I know, have developed effective ways of delivering lifestyle medicine and behavioral medicine within their own practices.

Finally, the fifth domain is something we call collaborative medicine, and this is the idea that one individualizes, or personalizes, the therapies for individual patients, from the perspective of, first of all, supporting and stimulating healing processes and then moving on, when necessary, to remove or interfere with the disease. Each of these can be delivered in conjunction with each other. They need to be properly integrated. They need to use good evidence-based aspects when that information is available, but it also has to be individualized to the particular patient-to their cultural background, the use of complementary

medicine, as well as conventional medicine when necessary.

These five components have to be nurtured, they have to be planted in a garden that is supportive, and so the leadership-the culture, if you will-has to support that. The organization in which one works, be it at a hospitable or a clinic, needs to explicitly say, 'We are about healing;' needs to outline that, needs to provide the structure and the support to do that, and then, of course, we know that the physical environment, itself, can either detract or enhance all of these processes. Proper air, proper light, proper clean water, and organization of the work sites so that one can facilitate communication-these types of things are important. Those are the primary domains this group has come up with that we think are elements of an optimal healing environment.

The Institute is now in the process of working with partners, both in hospitals and clinics, and at work sites and elsewhere, in order to try to begin to understand how these kinds of domains are being applied in medicine. There are many programs that are already applying these, and I know a number of your listeners have been focused on these areas for a long time. They themselves have probably developed some ideal healing environments for the interaction with their own patients and clients.

JB: Wayne, thank you. That was a very eloquent description/summary of what I know has been thousands of hours of collaborative work on your part and your group's part. It strikes me, when I hear you go through those domains, that the majority of the first part (intention, holism, relationships) could be categorized as a state of being, but often in western medicine all of our training is a state of doing, and so there seems to be a juxtaposition between this being and doing duality. How have you rationalized, resolved, or communicated this dialectic in the field of medicine, in which the training that docs undergo seems to be all about doing, intervening, fighting a battle, and winning the war-all of this versus this sense of being that you just described?

WJ: The first two components I described are bringing in one of the unique aspects that I think the Institute can bring to this field, which is a focus on the crucial role of the inner environment. We are always being and doing; you can't separate them. Even when you are doing, you exist in some way, and so it is a matter of focus, intention, and training in those areas. If you look at other traditional healing systems-Ayurveda, Chinese medicine, or even many practice swithin western medicine that are not necessarily focused on new technologies or techniques in their application-the idea of the role of being and the healing presence is predominant. For example, in nursing practice, there is extensive discussion, literature, and theoretical models that have been developed around the idea of caring, and the role of being and caring in the facilitation of healing. Within Ayurvedic medicine, consciousness is a core aspect of how you maximize being. Actually, physicians have also discussed this extensively-maybe not extensively enough-but they've discussed it over the years when they talk about the therapeutic alliance and the healing presence. You see this in the literature, and-everybody's probably experienced this-where you go into a medical encounter, and in some cases you come out and you feel like whatever you needed in there you didn't get. There was no connection. And there may be other medical encounters where you go in and you immediately feel a sense of connection and you feel, essentially, a healing presence. We have all known individuals who are natural healers, and no matter what their background, training, technology, and what they're actually doing, they do it in a way in which you get a sense of increased wholeness, of focus, of presence, that facilitates your own sense of well being, and then facilitates healing. What are these components? How does this get maximized? There are training programs. We know now, for example, that skills in empathy, communication, and compassion are things that can be

learned and are an important part of healing. We also know from the placebo literature that the manner in which you deliver a therapy, and the context in which you deliver the therapy, can have profound effects on the outcomes. For example, there have been studies showing that simply changing the tone of voice and delivering a placebo in a warm, caring, and confident manner can almost double the rate of recovery, compared to providing things in a neutral or negative way. This is especially true in functional illnesses where there is no major organic problem, which actually comprises the majority of things dealt with in the average family doc's office, We know that the culture and the context in which a therapy is delivered (the belief of that culture in a particular therapy) is important. For example, in the west, we believe a lot in technology, and so lasers and surgery and those types of procedures have a very powerful cultural therapeutic expectation attached to them. There have been studies showing that that expectation-that environment, that relationship, and communication issues that develop along with delivery of the technology-in many cases is the major contributor to the outcomes, even more so than what is actually done in the technology itself. These components have been undervalued in recent times, and certainly underevaluated when it comes to doing rigorous science to try to understand the mechanisms and understand how they can be applied. The Institute is focused on those areas (realizing that the areas of nutrition, for example, are extremely important), and we support and do some of that research, but there are actually a number of groups already doing research in those areas, and we hope what we are doing will both help facilitate that and complement that kind of research.
JB: That obviously leads to a very interesting question. You have 135 or more publications that I could find on PubMed that have pioneered this field of interfacing science with these healing environments and healing methods. How do you use research to study complementary and alternative medical concepts? I know one of the many areas you have been looking at is the area of homeopathy, which is certainly a very historically interesting area that has been difficult for people to get their hands on from a research basis. Can you give us a structure as to how you start down this road of evidenced-based science underpinning these concepts?

Is Homeopathy Evidence-Based?
WJ: Yes. First of all, I am often asked this question (at NIH and other places, it was one of the main questions that came up). Can you use standard, reductionistic, conventional, scientific approaches to investigate complementary medicine, which tend to be more holistic and multi-component in their application? The answer I give, that I've come to over the years, is that you have to use good scientific methods in these areas. If there is anything we've learned over the last 100 years in the application of science, it is that without science we can easily get led astray. We can easily begin to believe (or provide attribution to) areas that turn out not to be beneficial or, in some cases, may be harmful. So you have to apply high quality research methods in these areas. That being said, the question comes up: if there is a whole system-one that has evolved out of a culture involving these complex interactions of the dynamics of the delivery, as well as the components-how do you understand that? To understand that using scientific methods, we need a multi-modal approach; we need a multi-methodology approach. There is no one single research design that is going to answer these questions. I have written extensively on this area and propose that we need to look at evidence as building an evidence house, rather than a hierarchy. There are various types of evidence, all of which provide us with important information to understand what's going on in the areas of medicine and healing, and this includes randomized controlled trials, observational research, quantitative biological biomarker data (laboratory-type of research), and qualitative interviews to look at what is relevant to patients. Each of these things has its own set of methodologies, but has to be applied in an expert and high-quality way. To do qualitative research well is a very complex process. Within each of those methodologies-building this evidence house-good quality

methods need to be used. In some cases, we have to look at whole systems, and the goal there is to ask pragmatic questions. How useful are these systems? The answer comes from observational and health services types of research. In some cases, we want to identify and isolate a component: does this contribute on its own and, if so, how much does it contribute? When you do that, of course, you always risk pulling out the component that is not the most crucial one, or, if by disentangling them, you undermine the synergistic components, then that also can lead you astray. A multi-modal/multi-method approach is needed in these areas.

The area of homeopathy illustrates this. Homeopathy, if you look at how it was developed classically by Samuel Hahnemann and how it is applied in its original classical form, involves a detailed interview (hour to an hour-and-a-half) with a patient in which small aspects of their general health and their mental health, as well as the modalities and the pros and cons of their illness, are taken. There is a deep relationship-or interaction-that is developed. All of the symptoms the individual has are valued; they aren't discounted, so there is a context in which it is delivered. If you look at it from the mind/body and the healing relationship perspective, it is expected to have a profound effect. If you then want to ask the question of whether the pills, themselves, have an additional effect on that, you have to look at it within the context of that delivery system. You have to look at not only the traditional aspects of quality research (internal validity and external validity), but you have to look at model validity, that is, has this been applied in an appropriate way? We need research that looks at the entire practice, as well as the individual components, to see what contributes to this. I'm not saying anything new in terms of research methodology. In conventional medicine, we do research on whole systems all the time. For example, studies that compare medical treatment to surgical treatment of coronary artery disease, two systems that couldn't be more different; going in and getting bypass surgery versus maximizing medical therapy are completely different systems of therapy. One can't set up double-blind designs in those areas, but one can do (and there have been) good, pragmatic, randomized, comparison studies to see what the relative contribution of each of those is. Those are the kinds of whole-system methodologies that I think need to be looked at. The other thing that is arising now on the cutting edge of mainstream medicine and science that needs to be applied in the area of healing, is the area of the cellular and systems functions. This, of course, Jeff, is an area that you've been working on, talking about, and demonstrating for decades, and I think finally the time has come where your cutting edge work and the mainstream science are going to merge in the area of functional medicine. What used to be identified as isolated and individual diseases, we are now realizing are contributions of multiple functional components, and they may be different for different individuals. By looking at the functional components, there is a new way emerging of approaching health and disease that is not based on simply the medical diagnosis (as was developed over the last 200 years). Those kinds of categories are eventually going to disappear as we look more and more at the fundamental functional aspects of how our bodies work.
JB: You've said, obviously, some tremendously important things with a high degree of insight. I know in the minds of many of our listeners for whom this may be a new thought process, they are probably trying to connect together your description of placebo and also the concepts of homeopathy. Can we say from the research methods that homeopathy is more than placebo, at this point? Is there data to support that?

WJ: I don't think we can say that for sure. There was a recent meta-analysis published in the Lancet in which the authors looked at clinical trials in homeopathy, and then did a whole series of selections based on quality issues to try to see if there was evidence from the clinical research within homeopathy as to whether it worked better than placebo. The findings of that article, which was published, I think, last year by Shang and Egger, reported that there was no evidence that it worked any better than placebo. The

curious thing is that about eight years ago, a colleague of mine, Klaus Linde, and I, used almost identical methods to look at almost the same data set in these areas and, in fact, the recent article in the Lancet used our data set as a basis for doing their research. They went through almost the same methodologies, and yet we came out with different conclusions. We found that we could not eliminate the effect of homeopathy greater than placebo in the clinical research. The problem with both of these studies is that clinical research is a messy business. If you look at the details of these studies, they are all set up differently. The quality is quite different. The outcome measures are different. The remedies are different. Even the systems of applications of homeopathy are different. Some of them are small studies. Some of them are large studies. Some of them are properly managed and some of them are not. You get a real heterogeneous group, and you end up easily coming to a conclusion of, 'yes, it works,' or 'no, it doesn't work,' based on which set of studies you think are good or which set of studies you think are not good. And even with that, it is very difficult to use clinical research to ask this question. For example, we probably wouldn't ask the question, 'Does surgery work-' as a general question. We would want to know, does surgery work for what? In the homeopathic studies-the ones that we did and the ones that were recently published-they aren't asking that question; they are just asking, does homeopathy work in general? That doesn't make a lot of sense. What should be asked is if there is an effect from the specific remedies, and if there is a different effect from the remedy versus the social interaction (or the history) that I described before. Then you would expect, in certain types of conditions, that you would be able to see more of an effect or less of an effect. And yet, there is not enough research, not enough independent, replicated, clinical research in the area of homeopathy to answer that question.

I published a critical overview of homeopathy in the Annals of Internal Medicine a couple of years ago, in which we took the standard approaches that are currently used within groups like the Cochran Collaboration, which is an international group that does high quality, randomized, controlled trial analyses of clinical research. I looked at whether there were independent replicated studies on individual conditions within homeopathy. In other words, is there evidence that some areas (clinical conditions) work better with homeopathy, and some that do not work? And we found a handful on each side. For your readers-if they are more interested in the details of how you go about this and what the conclusions of that are-I'd be happy to put the reference on your disk for them to look up; it was in the Annals of Internal Medicine last year. It also talked about whether we can use basic science research to help understand some of these fundamental questions. Part of what the Institute is doing is trying to support and conduct high-quality research in these and other areas and try to disentangle these questions.

Useful References

JB: Yes. For our listeners, your article in Annals of Internal Medicine in 2003 was titled, 'A critical overview of homeopathy.'13 And, for our listeners, you also wrote a very nice article titled, 'Research on homeopathy: state of the art,' that appeared in the Journal of Alternative and Complementary Medicine in 2005.14 And then, this article that you were referring to in the Lancet-this meta-analysis-that appeared in volume 366 in 2005.15 And then you and Dr. Linde wrote a very nice response that appeared in the Lancet in 2005 in the December issue,16 and that was replying on your original Lancet article that appeared in 1999 in which they chose to use some of your data.17 Obviously, there is a very nice lineage of intellectual contribution here for people interested in homeopathy, and also the inter-relationship that it has to the work you have published over the years on the placebo effect. I think it is a very good study of both of these areas of extraordinary importance, and I think we both agree that placebo has been stigmatized negatively, but it is an extraordinarily important tool in medicine. Your work has really helped us to understand that as well.

WJ: Thank you, Jeff. And thank you, as usual, for, having all the literature at your fingertips, even some of the stuff that I've published. I think we've got a problem with the term 'placebo' because it is being used in different ways, but we use the same term. It has been given a negative connotation over the years. Part of the problem is that we use the term 'placebo' for two completely different things. In some cases, we use 'placebo' to mean the use of an inert substance in medicine, which, of course, you wouldn't want to do in medicine; if you knew it was inert, you wouldn't intentionally use it. On the other hand, people use the term placebo to indicate that it is all in your mind, and we know that a lot of things occur because of expectation, belief, and tension-things that are in the mind-and those things we want to enhance; we want to maximize our relationship, our communication, our expectation with our patients in a therapeutic encounter within the culture because we want to support our treatment interventions as much as possible. Those are completely different things, one we want to avoid and one we want to encourage.

Several years ago, Dan Moerman and I wrote a piece-also published in the Annals of Internal Medicine-on placebo, titled 'Deconstructing placebo and finding the meaning response.'18 It was our suggestion that we start using the term 'context and meaning effects' rather than 'placebo effects' because 'placebo effects' is a confusing term. What we really want to know is how you can use communication, the context, and the facilitation of meaning-these components that also go into the optimal healing environment-in a way to facilitate healing. I should add, not to detract from it, the so-called 'nocebo' effect. Negative communication, for example, can have profound negative effects on individuals and individual outcomes, especially when it is delivered within a context of great authority, like many physicians hold. These are things that produce very real effects in actual practice. We need to train, attend, and pay attention to those, as well as investigate them, so that we understand how they work and how to best use them for our patients' benefit.

JB: Well, Dr. Jonas, I want to thank you. This has been a very important missing link, I think, in our 25 years of Functional Medicine Update, to really dig deeper into this question of what healing is and what the variables are that connect an individual to their healing process. I think you have done an eloquent job in a very short period of time in helping to guide us. I know that people can go to the Samueli Institute website. You've got an extraordinary amount of in-depth information and content there that they can follow-up on. Your work will continue, I think, in the publications that you are instrumental in getting into our literature and guiding us. Wayne, thanks a million. It has been a pleasure, sharing this field over the last 20 years . I look forward to the years to come. I think we are going to see some interesting things in synthesizing a better healing environment in the western medical model.

WJ: Thank you, Jeff. It's been a pleasure and an honor to be on Functional Medicine Update.

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