

August 2008 Issue | Iris R. Bell, MD, PhD Iris R. Bell Associates LLC

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Welcome to *Functional Medicine Update* for August 2008. This is the age of personalized medicine. How do you implement personalized medicine? What does it really mean? How does it differ from that of pathomnemonically, pathophysiologically-based medicine? What are the tools and the algorithms that might differentiate a personalized medicine from that of a medicine that is focused on disease taxonomy?

That is the topic of this month's *Functional Medicine Update*. This month, our clinician/researcher of the month is one of the real experts in this area: Dr. Iris Bell. You will hear from her later in this edition. Before we get to Dr. Bell, let me set the context of the functional medicine model as it applies to personalized medicine, or individualized medicine, or what Dr. Roger Williams talked about many years ago, "biochemical individualized medicine," or what Linus Pauling called "molecular medicine."

Whatever term we apply to this, we want to understand how it differentiates itself from that of the primacy in present, which is the diagnosis. The diagnosis is the affixation of a name (called a disease) to describe a set of conditions the patient presents with. The person then knows what to do because that disease connotes a specific therapy and it leads to this kind of taxonomic definition-almost Linnean definition-of how we see health and disease, a classification-type of mode

The functional medicine model differentiates itself from the primacy of diagnosis by looking at the assessment of a patient from a different lens that includes antecedents, triggers, and mediators leading to signs and symptoms. You have heard this from me so many times over the years that it is probably *ad nauseum*. For those of you who might be new to this field, let me once again quickly review what I mean about the difference between differential diagnosis and the functional medicine assessment model.

Functional Somatic Systems

The functional medicine assessment model is looking for the unique characteristics that define a patient's signs and symptoms, those things that led them into the healthcare system. Signs and symptoms obviously have differing levels of severity, duration, and frequency. Depending upon what threshold those particular signs and symptoms achieve relative to the patient's own alarm systems (their proprioceptor systems or their noci

ceptive systems), it ultimately triggers a sense of dysfunction in that patient that the patient understands through pain, fatigue, disability, and chronic problems. Often these are what we call functional somatic syndromes, and they exist prior to the onset of a very well-defined, classically articulated disease. These syndromes have names like irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia syndrome,

or essential hypertensive syndrome. The list is very long as it pertains to these things that precede the onset of a clean, histopathologically identifiable diagnosis.

The functional medicine approach is to use the construct of antecedents. What does the patient actually have in their background (their genetic background, their health history, their social environment) that then sets the tone (the soil) for the triggering events that are like the inoculation of that medium with the precipitating factor?

Some people call this the straw that broke the camel's back. While there may have been an underlying reduction (or compromise) in organ reserve that the patient had, they were coping with it. It was only when this trigger (this precipitating factor) was present upon those antecedents that it gave rise to alteration in the web, the network of physiology, the trilogy of 'omics, as we often call it (genomics, proteomics, and metabolomics). This trigger shifts the functional state of that patient into a new state of homeostasis (or homeodynamics) that is then a distorted component of their web of function. Mediators that work on target tissues and cells ultimately produce the signs and symptoms that lead to the dysfunctions that are labeled, at first, "functional somatic syndromes," and then later become, over time, more acute and well-defined diseases.

You'll notice that this model has a kind of sequential staging component to it, starting at low-grade dysfunction that might be just molecular interactions. Maybe it is even at the interaction of energy within the cell, which then has a spreading effect over time: cell to a tissue, to an organ, to an organ system, and ultimately to a whole organism-type level of distortion that we ultimately can see with a measuring lens such as an x-ray, or a CAT scan, or a microscope. We ultimately can see that pathology. Or it may even be through biochemistry that we see pathology, by elevated levels of troponin, for instance, after a myocardial infarction, or elevated levels of protein in the urine with renal failure. These are all examples of the sequence of events that creates the personalization of that individual's own dysfunction. Ultimately, this dysfunction comes to a point where it is called a disease, as if all people with that disease shared common pathways getting to it, and all people who have that disease have the same physiological dysfunction. I think we know that that is not true. From our experiences managing patients in the real world, we recognize that people come to their dysfunction from different mechanisms and they present with their diseases in different ways. This is the patient-centered approach to medicine that is the underpinning of functional medicine and how it relates to personalized medicine.

In the *Journal of the American Medical Association* in December of 2006, a wonderful paper was published titled "A Systems Approach to Patient-Centered Care."¹ I think it is very important that the word "systems" was used in the introduction to this paper because systems biology is the new emerging construct upon which will rest our ability to understand how to deliver personalized medicine. We are looking for distortions in the systems that control biology of the individual. The new biology is looking at biological function within the organism as a system, not as it relates to pathways, but rather networks. I will come back to talk about that later.

Helping Patients Achieve Self-Efficacy

How do we get to a patient-centered care system? I think there is now more and more evidence to indicate that a personalized, patient-centered (or patient-focused) system is one that helps the patient to become self-efficacious. I am taking this term from Alberto Bandura at Stanford University, who has talked about self-efficacy. Ultimately, the objective is to assist the patient in knowing how to manage their own

complex web of physiology. We start with intervention, to manage the specific signs and symptoms that led to the patient seeking out health care, but over time, the objective is to attempt to educate that patient about their own uniqueness in such a way that they become a self-regulator (they become self-efficacious). That is what is discussed in this article in *JAMA*: the attempt to achieve a system for patients to be involved with their own self-care by knowing what to do. It is very important to recognize that this is describing a system that is a distributive medical system. This is in contrast to a focused system that takes broad information and weaves it down into smaller and smaller bits of conclusions until we ultimately have a laser-like understanding of the specific histopathology of that disease in the absence of looking at some of the broader issues that may have led to the occurrence of that disease. What I am really talking about is a different philosophy than that of subspecialty medicine, which is knowing more and more about less and less, assuming that that will help us to better manage the patient.

It is good to have a microscope when we are trying to examine things. Looking through a microscope would be an analogy for specialty medicine (knowing more and more about less and less). But it is also important to have a telescope, and to move back and to look at the whole system. The functional medicine approach towards personalization based on patient-centered care is built on this idea of a collapsing telescope-to-microscope, almost like an accordion. You move from a telescoping vision, looking at the ecology of the illness and the person within it by looking at antecedents, triggers, mediators, signs and symptoms, and then you go to the microscopic level, looking at the cellular pathology into a differential assessment of pathology. Personalized medicine is integrating those views together into a construct of systems biology, and the social network of the individual

We are really talking about the emergence of a systems biology in human health and disease, rather than just the primacy of the disease in isolation. There are some very good articles that have been published recently on this whole construct. One was an editorial published in the *Molecular Systems Biology* in 2007.² This editorial looks at how systems biology relates to human health and disease and what factors influence the functional capability of the individuals. Using new research techniques, the new biology that has been emerging integrates wide and divergent bits of data, everything from patient symptoms and past history, mediators that are analyzed and different fluids, and then ultimately coupling that information together with gene array data, proteomic data, and metabolomic data. Previously, this large, complex data array was too big to manage because we didn't have the computing power, but now, with algorithms and computing power much greater than the past, this can be condensed down into an understanding of that individual system. That is where we are going.

A Systems Biology Approach to Cancer Therapy

I think the first step in this direction is starting to emerge from cancer therapy. In cancer therapy, we are for the first time-starting to look at the unique genomics of the tumors of a patient and individualize the treatment based on mutated kinases, or specific characteristics, of the tissue type that is in the cancer of that patient, recognizing that cancer is really "cancers." There are multiple genotypes and multiple phenotypes that go under one definition of a cancer. Therefore, out of the field of oncology is emerging a systems biology approach towards treatment. Drugs like Gleevec, for instance, which is a kinase-inhibiting drug that is being used for managing certain types of cancers, target a kinase that has become mutated and for which the drug is selective. These are signs of how we are starting to see the emergence of a systems biology approach towards therapeutics.

In the area of pharmacogenomics, we are starting to see significant personalization. In the last ten years, it

has become a requirement that drugs be labeled with the specific cytochrome P450s required for metabolism of those drugs (or how they are metabolized through the body), and also agents that might antagonize or influence the first-pass metabolism of these drugs that share the same cytochrome P450 detoxification pathway.

Individual toxicity to a drug is based upon genetic polymorphisms of the detoxification enzymes, like cytochrome P4501A2, or cytochrome P4502D6, or cytochrome P4503A4, which are three common drug metabolizing phase I enzymes that have polymorphisms for which ultrarapid metabolizers or ultraslow metabolizers may respond in dramatically different ways than the wild type genotypes that have kind of "normal" Gaussian average detoxification first-pass metabolism. If you are an ultrafast metabolizer, obviously the therapeutic dose of a drug may need to be higher in order to get clinical outcome. By the same token, if you are a slow metabolizer, or you have an antagonistic second molecule that that same enzyme is trying to detoxify, then the dose that you are consuming might be producing a toxic body burden of that drug because it is undergoing slow first-pass detoxification and elimination. So we are seeing drugs now that are being tagged to their detoxification pharmacogenomics. I think this is really opening the door for patients to have their genotype of detoxification analyzed (or understood) before they're given certain drugs that might produce a toxic effect if not properly metabolized.

All of this is weaving itself into what has been called a systems biology approach to medicine, which leads to integrative biology and predictive biology. I think these are very important new terms that can be mapped against how we are seeing the etiology of disease and its potential management, particularly in the chronic disease area. With chronic diseases that have a long, latent etiology (going through preclinical into early clinical stages, and then going through different stages of severity), a different model is required than just the differential diagnosis model that we have with an acute disease presentation. The systems biology/integrative biology/predictive biology model leads us to a much better way of managing, early on, chronic complex disease than the differential diagnostic model because it maps itself against things like functional somatic syndromes and allows us to understand and explain, at a mechanistic level, using first principles in the new biology where the origin of that condition or that distortion of the web of life (or the web of function) of that patient came from so that it leads us into tailored, personalized intervention. Not just intervention for the average, but intervention for the individual. Of course, that's the whole basis that we have been talking about (as it relates to functional medicine) for many years.

An example that I think many people would use and is very well understood is methylenetetrahydrofolate reductase polymorphism (MTHFR). This is a key rate-limiting enzyme in the conversion of folic acid, ultimately, in 5-methyltetrahydrofolate, which then serves as part of the homocysteine recycling into the production of S-adenosylmethionine. S-adenosylmethionine (or SAM) is a very important methyl donor that has to do not only with methylation of neurotransmitters, methylation of hormones, methylation of phospholipids to produce myelin, but also with methylation of histone proteins in the genome, and it has to do with methylation of promoter region of genes. The availability of proper levels of S-adenosylmethionine has a very important role to play across a wide range of functions. This is probably why elevated homocysteine has an association with so many different conditions. Homocysteine is a surrogate marker for inappropriate conversion of homocysteine to methionine and the production of S-adenosylmethionine. Therefore, when we start looking at what conditions are associated with elevated homocysteine, it is not just atherosclerosis and cancer, but it is depression. We see it associated with Alzheimer's disease. We see it associated with Down's syndrome. We see it associated with hormone-related dysfunctions-hyperestrogenism and prostatic disorders in males. We see homocysteine elevations

associated with arthritis.

Why are so many diseases connected to one surrogate marker, an elevated level of homocysteine? It is because there are so many metabolic pathways that are dependent upon the availability of S-adenosylmethionine and how it regulates things like gene silencing, or epigenetic effects on the CpG islands of the promoter regions of genes that become methylated and silence those gene expression patterns, or it influences the production of intermediary biomolecules that are very important for cell signaling and cell regulation. So that pathway, which we call the homocysteine-folate pathway is really part of a regulatory network, and that is the point I think that differentiates the old model (which is associated with pathways) from the new model (which is associated with networks and a system that is unique to that person). For many people, the methylenetetrahydrofolate reductase polymorphism (the so-called C677T polymorphism), in which folic acid is not converted as rapidly into 5-methyltetrahydrofolate, may be a regulatory node. It is a weak spot; it is a pressure point; it is a-I've used this term advisedly-a "metabolic acupuncture point." I hope you understand the analogy there. I'm not talking about a real acupuncture point; I'm talking about a point that has hormetic control of overall systems function.

What do I mean by "hormetic" control? Hormesis is a word that refers to something in small amount having a much larger effect on the system than we would have predicted based on the amount. If you have a regulatory node in the web of physiology, and that is a highly sensitive regulatory node to a specific substance (in this case it might be folic acid or 5-methyltetrahydrofolate), it can induce a larger effect on function than we might have predicted, based upon the impact that it has on that critical switching point in physiology. So that's our systems biology/integrative biology/predictive biology model that is emerging as a kind of counterpoint to the differential diagnosis and histopathology model. By the way, I was just describing commentary in the journal *Cell*, volume 121, page 505 in 2005.³

We now recognize that there is evidence of different metabolic phenotypes in humans. This has been discussed for years and years in the field of metabolic typing--trying to understand what differentiates a person, metabolically, from another. We are actually getting the tools now--for the first time--that really quantify metabolic phenotyping. There is a nice paper that was just published in the *Proceedings of the National Academy of Sciences* in 2008 titled "Evidence of Different Metabolic Phenotypes."⁴ This was a study of metabolic responses to drugs, environmental chemicals, and diseases from a metabolomic perspective.

Metabolic Fingerprints

We know that metabolic fingerprints can be obtained by various analytical techniques (high pressure liquid chromatography, mass spectrometry, nuclear resonance, magnetic resonance spectroscopy). By looking at complex data sets of urine or blood, one is able to measure literally thousands of different metabolites. What you then can do is take a person from a baseline kind of evaluation of their metabolites, and you get a signature of their metabolites-kind of a metabolome (it's like their web of metabolites). You stress the patient by giving them something that would challenge their physiology. It could be a glucose load, or it could be a protein load, or it could be a fatty acid load, or it could be a vitamin load. It could be any number of things, or it could be a chemical exposure. And then you examine, post-challenge, how that individual's metabolome (that web) modifies or accommodates that challenge. You start to examine, then, the uniqueness of that person's response to these environmental pressures. If you study that same thing across a wide range of people you can start to understand the

biological variation in what we call metabolic phenotypes.

That is the work that was described in the *Proceedings of the National Academy of Sciences*. Individual metabolic phenotypes exist; numerous studies report differentiation between individuals on the basis of a subject-specific response to particular stimuli, which helps us to better understand how things might categorize themselves in various individual classes. These classes are around the functional nature of the web, of the system, which is really what we have been looking at, and how we then look at the most important controlling parts of the web.

Are there an infinite number of metabolic phenotypes? Theoretically, there are. In actual practice, what I think is more likely, is that they will tend to cluster themselves (or group themselves) into dominant pathways or patterns that are related to specific kinds of ways that genes speak to their environment. Recall, if you would, that we don't get one gene at a time being expressed). They express themselves in families in response to a different environmental perturbation. These cassettes of genes are controlled in such a way that they ultimately influence metabolism, so we get these metabolic types that can emerge from this type of an analysis.

This concept takes us away from the idea of disease being classified in a pathophysiological way into a complex systems biology way. There has been new evidence published in the last year or two on this concept of human disease classification in the post-genomic era moving away from human pathobiology as the classifying term. That is the way that we have basically defined the differential diagnosis that ends up in the ICD-9 codes into a new complex systems approach that looks at distortions of the web at a mechanistic level. In one of the recent papers in *Molecular Systems Biology* that I found fascinating, the authors looked at contemporary classification in terms of the disease and they mapped that against what is being understood in terms of each of those diseases having different mechanistic inputs, so actually, the systems biology approach gives you a finer granularity of understanding.⁵ Let me take this from the abstract to the real. Let's look at cholesterol as an example. I think cholesterol is an interesting example because we are told that it should be minimized in people who have hyper-cholesterolemia, so these people are on dietary cholesterol restricted intakes. In the whole universe of individuals who have elevated blood cholesterol, what percentage of those people has elevated blood cholesterol principally as a consequence of elevated dietary cholesterol? That is a different question than the kind of statistical correlation between elevated dietary cholesterol and elevated blood cholesterol. Now we are going to the individual and asking what percentage of individuals in that set are those for which dietary cholesterol is a major determinant of their elevated blood cholesterol.

It turns out, when you start looking at that and you look at what is called the ABC transporter, which is one of the controlling influences of how people regulate cholesterol biosynthesis in relationship to dietary cholesterol intake, you'll find that about 10 percent of the population (approximately) are dietary cholesterol hyper-responders, meaning these are people for whom dietary cholesterol can really dramatically elevate their blood cholesterol. But for 90 percent of the population, their dietary cholesterol has a marginal and somewhat even insignificant effect upon their blood cholesterol. The elevated cholesterol in their blood is really more a consequence of *de novo* cholesterol biosynthesis, which is more related to other factors: hormones, macronutrients, toxins. The list is quite lengthy now that we have been putting onto it things that we know activate apolipoprotein synthesis and cholesterol *de novo* biosynthesis, which are seen in the blood as elevated cholesterol.

This construct--that all people who have elevated blood cholesterol should be on a cholesterol-restricted diet--doesn't really wash when you get to the personalized level. It is a similar situation with salt. We know that salt (sodium) is associated with hypertension, so it has been said that people who have hypertension should be on a sodium-restricted diet. But again we go back and we ask, how many individuals not in the average, but in the individual person, are those who are hyper-responders to sodium, with regard to sodium transport and the effects that it has on the renin-aldosterone system and ultimately in elevating blood pressure? When you start looking at that literature, again you come to recognize that somewhere between ten and twenty percent of the population who are hypertensive are sodium hyper-responders. The other members of the population (which are obviously the greater percentage) are those for whom sodium (even at average increased levels in the diet) are not the major determinant for their blood pressure. It may constitute a small part of their blood pressure elevation, but it is not the major criterion. Therefore, there are other factors that should be focused on in those individuals in order to personalize their program to improve outcome.

This is the type of logic that is now coming from this systems biology approach: looking at the individual and how they respond to their environment rather than assuming that they are part of the group of averages. This is network biology-understanding the cell's functional organization. Isn't that an interesting title for a paper? "Network Biology: Understanding the Cell's Functional Organization." This is actually the title of a paper that appeared in *Nature Review and Genetics* in 2004.⁶ According to these authors, the key aim in this post-genomic era of research is to systematically categorize all molecules and interactions within a living cell. Ultimately, the goal is to see how the functional organizations of these molecules in the cell regulate (or are involved in the regulation of) the function of that cell, that collection of cells to become a tissue, a tissue to become an organ, an organ to organ system, and then eventually the individual.

Networks Create Function

We are starting to look at this network biology, the interaction of various pathways to form networks. And the networks, then, create the control of function. When you are evaluating a patient and you are looking at a blood test, you ought to be always thinking of that blood test in the context of all other blood tests and all other symptoms and signs, thinking of this as a system (a biological system), and then asking the question, when was the patient last well? Can the patient remember what triggering events might have been associated with the precipitation of whatever led them to come and seek professional health services? These concepts of antecedents and triggers leading to mediators and then ultimately to signs and symptoms gives a medical diagnostician a different way of approaching the detective work. Now what we are looking at is the distortion of the system that leads to the dysfunctional state, which is a steady state, I might add, in that patient, that we call their dysfunction or disease. That steady state is a new state of homeostasis around a new set of presumed markers, and these can become locked in over time. It is not like a bacterial infection that fulfills Cox postulates. In this case, when the patient gets over the precipitating trigger, they still have the residual effects of the dysfunction. It can be locked in for years and years and years until you break the cycle, and how do you break the cycle? You can do so by establishing a new state function for that person's systems biology. You don't do it by just changing one component; you find the regulatory nodes in their web that is creating a locked in feedback control system that produces this dysfunctional state.

Now that is a very easy thing to say, but it may be much more complicated to deliver. How do you deliver it? It is going to be a distributive healthcare system that will allow that to occur because no one molecule,

no one surgery, no one therapy, in and of itself, may free this whole system up. It may be a complex series of variables that modify the environment of that individual so as to send a different signal to their cells, tissues, organs, and organ systems to create a different relaxation of their web of physiology, moving from an alarm state into a state of normalcy. The person will go to a new homeostatic state of regulation, and the new one is the one associated with lowered dysfunction.

I often argue very strongly that the path to deliver personalized medicine is not finding "the" therapy. The path is finding the way to interface multiple therapeutic interventions: diet, lifestyle, physical medicine, structural medicine, energy medicine. All of these things contribute to the inputs that are picked up by cells that create signals that associate themselves with their functional status. That then maps into genomics, proteomics, metabolomics, and ultimately into phenomics.

This is really putting the "systems" back into systems biology. And this is a whole new way of viewing the way people become ill, how to understand the etiology of their illness, and how to work with them collaboratively to turn it the other direction. What we have been doing through the differential diagnosis model is using the diagnosis to find the treatment for that disease. In so doing-because we didn't examine all the functional inputs of the uniqueness of that person's illness-we may be masking, by uncoupling certain warning valves or smoke detectors that that person has. We use drugs that uncouple pain, or inflammation, or neurological function in such a way that the signals don't get there, but the dysfunction of physiology is still present and it still has a trajectory towards increasing degrees of pathology. Putting the systems back into systems biology is to try to understand how we look at the whole-the system of the whole-rather than the system of pathways.

I think what happened for many of us in our education is that we studied physiology and biochemistry on the basis of pathways that were provided on two-dimensional pieces of paper that we memorized and recited on demand. We got the view that somehow this was the way life worked. This view assumed that these pathways worked in isolation, and also that these pathways worked in equilibrium situations, neither of which are true in human physiology. A human is a non-linear, non-steady-state, dynamic system that is constantly responding to a changing environment by changing its physiology. Our whole systems approach has to be non-linear, and it has to be a dynamic system model. What we learned, when we learned our pathways, was a static system that is often unidirectional-A goes to B goes to C-and it is one that seems rigid and fixed in isolation. It gives us this concept of compartmentalized physiology.⁷

Putting the "systems" back into systems biology is a way of thinking as much as it is a way of acting. I believe very strongly that it is the way we think about things that ultimately determines how we act versus the converse, which is we act and then we think. So our perceptions-the lens upon which we sieve information-will determine the therapies that we use, or how we approach that patient, or how we define the etiology of their condition.

With this in mind, there is this whole concept of scale-free networks. How do we view a person as an open-ended dynamic system responding to their environment in such a unique way as to give functional outcome? There is an interesting paper that appeared in *Scientific American* titled "Scale-free Networks" that describes the dendritic nature of physiology.⁸ It almost looks like a nerve map versus a pathway that goes A-to-B-to-C linearly. Feedback processes, both positive and negative, all leading to regulatory control, and we have to start thinking in this way. We have to look at our patients as a network, a biological system.

Is personalized medicine finally arriving? That is the question. I would say, in 2008, the answer is yes. In *Nature Biotechnology* a very interesting paper was published that reviews how select companies are developing or partnering to develop personalized diagnostics.⁹ This list is very long, Companies are developing ways of sequencing or evaluating either genomically, metabolomically, or proteomically individual uniqueness that will then develop new biomarkers for which personalization will ensue. This article actually talks about over 26 different laboratories that are engaged in different types of work, everything from the AmpliChip that is at LabCorp for measuring cytochrome P450s, to looking at the kinase mutations that are associated with various cancers that then lead to specific kinase inhibiting drug applications, to looking at cardiovascular disease risk factor biomarkers that are related to endothelial functional changes like phospholipase A2 (which we discussed in a previous issue of *Functional Medicine Update*). And all of these are tied together into very interesting systems of evaluation, using these biomarkers to look at prognosis and not just diagnosis.

The next step is to map this against genetic variation. There is a lot of variation going on, isn't there? We have two to three million SNPs (single nucleotide polymorphisms). Don't we see everybody as a different person, and how will we ever gain mastery over this complexity? The answer is that some of these SNPs are going to be of little consequence in terms of the outcome to the patient and the phenotype. Others may be very important in modifying regulatory nodes, like the methylenetetrahydrofolate reductase polymorphism I described earlier. As we understand what SNPs have the most important role to play in modulating function, we then can develop biomarkers to assess both the genomics and the phenomics of that individual that then allows personalization of the program and also allows tracking of the success of the program. We are starting to see trials now being done looking at personalized approaches towards cancer therapy, like the HER polymorphism, or looking at BRCA1 and 2 polymorphisms related to breast cancer, and personalizing various types of things that would then allow treatment that is the medicine of the person rather than the medicine of the average.

Let's use an example of leukemia, and there is an interesting example in lymphoma as well. A hundred years ago, leukemia and lymphoma were just said to be diseases of the blood. Eighty years ago, we differentiated those into leukemia and lymphoma. Sixty years ago, they were differentiated into chronic leukemia, acute leukemia, preleukemia, incident lymphoma, and aggressive lymphoma. And now today, as a consequence of better understanding of the differentiation of these conditions, there are 38 different types of leukemia identified, and 51 types of lymphoma, all of which have different personalities and signatures requiring different personalized therapies. So if you can map that concept against what is going on in the whole nature of medicine, we are going from blockbuster medicine to personalized medicine. The age of one-drug-fits all is really going away and personalized medicine is becoming a dominant theme.

In a recent issue of the journal titled *Personalized Medicine*, it was stated that one of the biggest challenges to biotechnology and pharmaceutical companies in the 21st century will be to develop and deliver therapeutics that fit the individual patient's biology based upon this new systems biology approach.¹⁰ Do we have models for the study of whole systems, and what are the appropriate therapies that will personalize and produce better effective outcomes in the chronic disease state? It is that topic that we are going to be discussing with our clinician/researcher of the month, Dr. Iris Bell, who has been a prodigious researcher over many, many years in this area, and has authored an extraordinary paper titled "Models for the Study of Whole Systems" that appeared in *Integrative Cancer Therapies* in 2006.¹¹ In

this article, she and her colleague Mary Koithan said that the growing reliance on complex systems thinking in systems biology for research in the area of chronic disease affords a unique opportunity to bridge the gap between what we have traditionally called alternative or complementary medicine and the conventional medical world. We are going to learn much more from her as to how this actually plays out in the future of the clinic.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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I look forward to this section of Functional Medicine Update with great anticipation every month because it gives me the opportunity to speak personally with someone who I really admire and who has made some extraordinary contributions to the evolution our field, and also to learn from them. Certainly, we have another example this month on Functional Medicine Update because I have the privilege of introducing you to and talking with Dr. Iris Bell, who is a professor of family and community medicine and involved both with psychiatry and psychology in the integrative medical program at the University of Arizona in Tucson.

You probably also know Dr. Bell, whose contributions go back many years in our field, as being a person who is looking at energy systems, looking at non-linear systems theory as it applies to medicine, has also done a tremendous amount of work in the underpinning of homeopathy. She has been very heavily funded by the National Institutes of Health, including a career grant. She has worked in publications to contribute more than 100 different scientific papers; she is highly authored in PubMed. She has done two dozen book chapters on her work. She has really been one of the sentinel contributors to our field over the last 20 years. Her forthcoming book for consumers is titled *Getting Whole, Getting Well: Healing Holistically from Chronic Illness*. It will be published this year.

Dr. Bell, it is just such a privilege to have you as a Functional Medicine Update Clinician/Researcher of the Month. Let me start, first, with the question that I think everyone would like to know something about: how did you get into this field with the extraordinary background you have, both with your MD and PhD? Obviously there were many paths you could have chosen and you chose this path. How did it happen?

IB: Thanks very much Jeff. I have always had a great deal of admiration for the work that you do also, so we'll have a mutual congratulatory discussion here.

When I first got into this field, I actually had the strong sense that that I wanted to study learning and memory in a psychobiology kind of way. I knew that I was very drawn to interdisciplinary work, even as I was starting college. I had to go around in a few different fields before I found a home. I majored in biology, but spent much more of my time in the psychology building learning psychophysiology. So that

was really my background and my baseline. I, very soon in college, got a job in biofeedback research. The person who hired me, the professor there, said "I hope you don't have a bias against the ability to voluntarily control the autonomic nervous system." I said, "No, I don't know anything about either." I think that is one key point about all of this: just having an open mind and taking a look at what you see before you. You certainly have to be informed by what people show you and what the evidence accumulates in saying. But many times the interpretation of the evidence is far from simple.

So after I did college, I knew I wanted to go to graduate school. I got involved in more psychophysiology research as part of a sleep laboratory at Stanford. It was really there that I was first introduced to some of the ideas of Theron Randolph and his groundbreaking work on food and chemical sensitivity. I had the opportunity to really delve into this field for many, many years, and actually made the decision as I was finishing graduate school that if I wanted to study human health (and I was getting plenty of advice) that I needed to go on to medical school. So I said, "Oh well, here's another degree. Okay." So I finished my PhD as I was starting medical school; a feat and trick that I would not recommend to most people. I then began to really look at this whole question.

His [Theron Randolph's] work was really so good at connecting the mind and the body, but also saying that there was a biological thread. There were demonstrable things going on in the background if you looked for them, and that, of course, led me even further into understanding a little bit more about nutrition. So, all of those areas became of interest to me.

As I was starting medical school, I was confident that I was going to go into research on environmental medicine, which I ultimately did. But at the very beginning of the time I started to learn about that, I heard about this very controversial field called homeopathy. That opened up a whole different world of therapy for me, because up until that time I was very focused on understanding mechanisms and trying to explain to the world why low levels of environmental chemicals or common foods could actually make people sick. That continued to be a focus of my work for many years, but the door was opened to this whole notion of homeopathy that there might be ways of using some of the even more controversial therapies that were out there in the world of environmental medicine, such as the provocation/neutralization technique where they were able to turn symptoms on and off in what they called "miniature."

I saw how imperfect that system was when I was working in an allergist's office in the summer between various semesters of school, but I also saw that it had a lot of potential. It [homeopathy] was inappropriately rejected by the mainstream community by using data that actually supported the likelihood that it had a significant effect beyond placebo. It was one of my first lessons in how human biases can get over into science. So in any event, at that point, I learned about homeopathy and I saw tremendous overlaps in the theory and the practice of homeopathy with many of the ideas that had been developed in an entirely different direction by Theron Randolph, who I think was really a very good practical observer, and then someone who put together these ideas into theoretical models.

I never forgot his [Theron Randolph's] bipolar, up-and-down diagram. He showed that when he gave someone a food or a chemical they were sensitive to at a time they were unmasked (by having withdrawn from it for four days) and then rechallenging, that the person could bounce back and forth between what he called stimulatory and depressive (or withdrawal) kinds of symptoms. His work was really seminal in that area of recognizing that reactions were not linear, that what the human being was capable of was very

bipolar. And at the extreme, of course, there was manic depression, which he also reported seeing affected by his clinical diagnostic approach and ultimately by his treatment approach, which was avoidance.

The thing that appealed to me about homeopathy was that it seemed to be a more intensively developed therapeutic system that would change the vulnerability (the inherent vulnerability) of the host to things in the environment. And I realized, after having really gone in depth into environmental medicine, that it could hit a wall where peoples' quality of life was being compromised by having to not eat in any kind of simple way within the culture that they lived in and not be able to be out in the world, working and enjoying their families and their overall environment because of the health problems it brought up whenever they were out there exposed.

And so that was what brought me through the whole thing. But all the way through all of that, I saw this kind of non-linear, up-and-down process that the human being was capable of. I saw that low doses of things, and things that were always being claimed to be nontoxic, and certainly scorned by the skeptics (when you said "Well, corn can make somebody manic," and they would just laugh at you), that those kinds of ideas, that a small, supposedly innocuous dose could be interpreted by a particular individual's body as being toxic for them, were just fascinating. To me, again, that was a non-linear kind of process.

I'll stop, at this moment, to sort of catch a breath and see if you have any questions about that.

JB: Oh boy, you have just opened up so many extraordinary doors in that introduction. Just fascinating. What a panorama. Let's back up just for a second. I find that many people who have come into our field don't probably know, to the extent that they should, about Dr. Theron Randolph and his extraordinary contributions in this whole neutralization/titration concept. Maybe you could help us (for those who are maybe newer to the field) by describing Dr. Randolph-his work in Chicago and what that technique, in terms of patient management, evolved to become.

Research of Dr. Theron Randolph

IB: Sure. Dr. Randolph was very much a fundamentalist. He was part of a group of allergists, actually, who were very well trained in their particular field. He was open to the idea-his patients were really teaching him-that there seemed to be problems with certain foods, and then ultimately with foods that had been sprayed with chemicals. For example, some of his patients reported being able to eat an apple that had been grown organically, but not an apple that had been sprayed with pesticide or waxed.

That expanded into a whole series of discoveries for him. His primary approach was to do what he called "unmasking the addiction to food" or really the habituation to a chemical that you are exposed to all the time. And so he would withdraw people. He actually, at one point, had a hospital unit where he would withdraw people from the usual diet and their environment and then challenge them with this item after 4 or 5 days. Typically they would feel worse at the beginning of this process, and then they would clear up and feel better than they had in a very long time. Then he would challenge them with this item, whether it be a food or a chemical, in a controlled setting, and show that he could produce these very hypersensitive flares of symptoms, acutely, that people would otherwise say didn't happen for them if they were eating the food everyday or breathing the chemical everyday.

Of course, this opened up the whole world of environmental medicine. His contribution was to even build

further on the notion that diet could do this, to look at the entire world of environmental chemicals. As he was doing his work, there were other colleagues who developed even further this idea that you might be able to use allergenic extracts to produce this kind of effect. There was a series of developments, really, but what they did was take the allergenic extracts that were typically used by allergists of the time to inject people with small doses and supposedly produce an immunity. But in this case what they did was really dilutions (low-level dilutions) of these allergens, and certain dilutions would provoke symptoms, and the next dilution might actually shut off the symptoms in a five or ten minute period in the office.

So that enabled Randolph and many of his colleagues to test people without putting them through this very demanding process that sometimes someone who is very debilitated really couldn't undergo with the actual challenge in a hospital setting. They could take someone in an office and turn these symptoms on and off very quickly. Again, certain stronger dilutions would do it and then it was almost like there were harmonics, where the next dilution might remove the symptoms, the next one might provoke them again, and so on and so forth; a very fascinating process. If they were able to find a stable dose that shut off the symptoms, many allergists would then combine what they called neutralizing doses into a treatment bottle and send the people home to take this material, and they would do it either by injecting it under the skin or under the tongue (not injecting it under the tongue, but having them just dilute it under the tongue). They would use that as a treatment just before they would try to eat a food or be exposed to a chemical that they couldn't otherwise avoid.

JB: That's a beautiful explanation. Of course, that leads, then, back to what you were talking about with non-linear systems, that we have this view (from the way we are trained in pharmacology) of this dose-response curve, that with each increasing dose you get an increasing response. It may be not totally linear, but we have this concept that 1, 2, 4, 8, 16, you know, kind of a geometric progression of dose response, and what you are saying here is that different doses may give very different responses, sometimes agonist and sometimes antagonist, which is very different than the traditional pharmacological model of linearity.

IB: Absolutely, and it raises questions about what that can mean because we assume very simple lock-and-key kinds of mechanisms in the body. If that is the case, it means that the interpretation at the cellular level is different depending on exactly how much material is there.

JB: So that leads to a term that we have used in Functional Medicine Update over the years, which you have a better understanding of than anyone that I know, and that's the term "hormesis." It refers to a small amount of something having a bigger biological effect than anticipated. How does this concept of hormesis play a role in explaining, mechanistically, these non-linear reactions?

IB: It is fascinating to see that there have been these different, very well organized disciplines that have identified these concepts. Hormesis has grown up in the field of toxicology, where researchers have actually found--in hundreds of cases, and have published very good reviews of these in all kinds of papers--that the dose-response curves to many things, ranging from radiation to environmental chemicals to common drugs that are used in treatment of conditions. Typically, if you go down the scale of dosing and you get just below the lowest dose that can cause an adverse reaction, which is where you begin to see this phenomenon of hormesis, which is the evidence that there is a non-linear dose-response curve. This appears to be related, in part, with the more recent work that I have read about. The lower dose appears to not be enough to stimulate a toxic reaction in the person or in the animal, but what it does do is stimulate a compensatory, more homeostatic response, if you will, of the organism. So it strengthens the

organism to a future exposure to that same material. Many of the simpler studies have been done. Really that whole phenomenon has not been adequately explored, experimentally, but many of the studies indicate that you might be able to stimulate this protective effect by giving a low dose of something, where the same material in a higher dose will trigger an adverse reaction. This appears not just to be dependent on immune system response, which is very interesting.

JB: So that obviously is a beautiful segue into what, I think, was a seminal paper for our field that you authored with Carol Baldwin and Gary Schwartz back in 2002 in *Alternative Therapies*, which was titled "Translating a Non-linear Systems Theory Model for Homeopathy into Empirical Tests."¹² We then see something related to your interest in homeopathy, obviously, emerging out of this whole construct that you are describing. Maybe you can review for us or summarize for us this kind of next step you took into homeopathy.

Insights on Homeopathy

IB: Homeopathy is an enormous field unto itself. I thought environmental medicine would be controversial, but I was wrong. The world of homeopathy is even more controversial. There are several levels of issues in this field. What was fascinating to me was not continuing to be engaged with this whole argument about how a low dose can actually do something to an individual, which turns out to be interesting in itself, and actually relates to network theory within the non-linear, complex systems, science world. Just the whole notion of what is the human being doing when it heals? I went back to Randolph's model of this bipolar reaction of people being able to go all the way in a stimulatory side. But as they recovered from an acute reaction, or as they recovered from chronic illness, he reported seeing that people, perhaps, might have more emotional or sleep-related problems and they were very severely affected, and then begin to recover through headaches and fatigue, and then ultimately things like runny noses, mucous membrane discharges, the nasal rhinitis kind of thing. And he saw this kind of cycle that people would go through.

Well, homeopaths have seen and reported a very similar thing. They have a phenomenon that they have described for many years called "Hering's Law of Cure," where they say that a human being, in the process of healing naturally, rather than being forced into it by a drug, will actually go through a process of healing from above downward, from the more important organs inside outward, towards the skin, and in reverse order of time of the appearance of the symptoms. That very much fascinated me because it matched up and mapped onto what Randolph had reported and I had seen repeatedly in patients who were food and chemically sensitive: as you were recovering from a reaction you would begin to have these nasal discharges, and that is precisely what the homeopaths were claiming.

So I started there, saying "Well, that's a very interesting phenomenon because now I have people in two different fields observing the human being, and what must be true is that the human being has some truths about him or her that go past whatever discipline, or whatever glasses or lenses we are looking at the person with." So homeopathy claims to be able to give a very low dose of an agent that is really drawn from animal, mineral, or plant materials and prepared in a very interesting way that is similar to allergenic extracts, but a little bit different. It involves serial dilution and what they call succussion of the material. And the succussion is very vigorous shaking, so it is probably even more vigorous and extended than what you might expect with an allergenic extract. And they will take the serial dilution out so far that there are no molecules at the source left, which is the source of the most intense debate about the plausibility of the field.

However, it turns out that the sucussion apparently creates a network effect within the water molecules on the agent itself. Meanwhile, we have the person doing their illness pattern, really a phenomenology of mental, emotional, and physical symptoms. I encourage people to try to go to conferences where they can watch video tapes of patients who have been treated over a period of years, because the changes are truly transformational and there are so many of these cases out there. It seems very implausible that these are the claims of a misguided individual because we are talking about many different individuals worldwide reporting these same kind of phenomena, and actually being supported by a great deal of data that, again, gets overlooked and attacked by the skeptics. But what you see is people doing-living out-Hering's Law of Cure in a most dramatic way. If someone has, for example, skin lesions all over their body, literally you will see a march of the skin lesion down the body and out towards the toes. You can see these video tapes of patients going through the treatment like that.

There are many other even more dramatic situations with people with multiple sclerosis and other kinds of autoimmune diseases, particularly other kinds of allergy, asthma, seizure disorders, and so on, who seem to have this same kind of effect. People alternating between-Randolf observed this-severe depression and skin eruptions. But homeopathy appears to trigger the ability of the body to keep it moving towards the skin and then eventually resolve without pushing it to other parts of the body. One of the most interesting things that you learn from homeopathy is the notion that if you try to treat the body locally, whether you are using an alternative medicine approach or a drug, you could suppress the symptom, and by that they mean they are pushing the symptom from the local area where the manifestation was appearing back into the body, saying "Well sure, the only kind of manifestation the skin could do is a skin eruption." But say you push it back in, the lung is capable of having asthma, or the brain is capable of having depression. So you are saying that there is a disease process that this individual has, which homeopathy recognizes. It is not an entity, by any means, but it recognizes that as a disease that the person has, which simply happens to manifest in all these different local parts, if you suppress illness, you are pushing it into more important organs. If you treat it homeopathically or find other methods of healing naturally, you should see it go the other way, and you should see the thicker organs (the more important organs) that are necessary for survival recovering first during a gradual process of the illness moving out towards the skin and then ultimately resolving.

JB: That's a fantastic explanation. I notice that you are co-author of what I think is a very nice paper in the journal Homeopathy in January 2008 titled "Homeopathy: Quackery or a Key to the Future of Medicine?"¹³ I found that article very insightful because we're all responding, in part, to the Bausell book titled Snake Oil Science, which was published in 2007, in which he basically says there is no scientific support nor clinical justification for anything that is within the domain of complementary and alternative medicine. I presume you probably have an opinion, at least in summary, that you would share about that book?

Facing CAM Skeptics

IB: As a disclaimer, I have not read the book. I have heard about it. I have certainly read many of the arguments that are made from a skeptical perspective about many of these areas. I think that if somebody wants to shut off discussion and say we have what we are comfortable with and we will just stay with that, then it is up to them. But I think we have to really look at the fact that Western medicine has become completely focused on the reliance on pharmaceutical agents as a primary way to treat everything.

One of the things that I have learned, even looking at the mainstream literature, is that people are

beginning to realize that the human being is a complex system. It is a complex living, adaptive system, actually. It is too simple to try and take pharmaceutical research designs, such as randomized controlled trials, and not honor the nature of the alternative medicines being tested, show a negative result, which proves, in fact, that that particular intervention doesn't work like a drug. And I am perfectly willing to accept that conclusion because most of these techniques do not. And then you can go on your way saying, "Well it doesn't work like a drug and drugs are the only important thing," so the important thing to look at is your assumption that mechanisms that are drug-like are the only way to look at the way healing can occur.

We know that the mind and the body speak to each other. We know that you can have profound effects by simply changing the way you perceive a situation. If you get very excited and upset about a particular situation and the person next to you does not, your autonomic nervous system, your hormonal responses...they are all in a different state than the person standing next to you. You are in the same situation, but your response to that situation is different. The way of understanding that and the way of doing research on that is simply different than what you do to come up with a simplistic answer about alternative medicine.

I simply disagree with the completely blanket conclusion that all of the evidence is completely missing or flawed about alternative medicine. I certainly agree that if we really take the material in this area seriously, we have a lot of work to do, and we have to develop rigorous methodological approaches to how to do this work, and we have to think more deeply about what it teaches us. Systems biologists, in the mainstream, are recognizing that they cannot tweak one gene and stop worrying about everything else that may happen, or even look for simply one genetic flaw in a particular phenomenologic condition because we find that there are multiple pathways to get to the same situation. There are multiple factors that take us to the same situation.

What we end up with is really a clash of world views. I don't know that we can easily convince another person who holds a different world view. I think for people who are open-minded you can explain that there are world views and what the implications are if you take a more relativistic point of view of how things interact with each other and how we are all part of networks: we are a network, we are part of larger networks, within our bodies we have microcosmic networks (the biochemical networks of the body). These all interact and communicate with each other to lead to what we call emergent properties of the system. These are the kinds of ideas that you can ignore, if you choose, if you are a skeptic of alternative medicine. But I think in many different areas of alternative medicine, it keeps bringing up this notion of a complex, adaptive system where there is interaction, where there are all sorts of astonishing and hard-to-predict outcomes.

One of the problems, when you think about it, is that a drug can force a body to do a particular thing pretty much every time you give the drug. Many forms of alternative medicine are not even trying to do that; that's not their claim. What they are trying to do is get the body to get back in balance so that the different parts are all communicating in a normal, healthy way, if you will. That is actually not that reproducible unto itself, and that is one of the biggest challenges we have as researchers in this field. We know that science wants reproducible phenomena. And yet, a complex system is never in exactly the same place that it was a few minutes ago, let alone a week ago, and that some things may not be easily reproducible because it is a subtle interaction of whatever stimulus you are giving with a therapy and the state of the individual at that moment in time. That is something that many of the skeptics, including that

book, really keep ignoring. I think it is to their peril because there are so many amazing discoveries we have ahead of us if we open our minds to that possibility.

JB: I think your explanation was absolutely eloquent and thank you. For those of you who want to read a little bit more about this, Dr. Bell and Dr. Mary Koithan have published/authored a paper titled "Models for the Study of Whole Systems" that appeared in Integrative Cancer Therapies in 2006, which kind of reviews exactly what you were talking about in a very nice summary fashion. I think you have set the tone for a whole different thought process about how we look at this interaction of environment with the individual to give rise to health or disease.

Let me ask/go back to a point that you made earlier, which I think is a very critical point and that has to do with mechanisms of action. We have assumed, through our years of study, that there are these interactions that are kind of hard molecular interactions between a ligand and a receptor and they bind with a certain affinity coefficient and you can look at all the molecular interactions, you can model it in silico, and yet there is this concept that you are describing that poses maybe another way that things can interact other than just the dirty dancing of a close contact between a ligand and a receptor. What are your thoughts about these other mechanisms? Are there any hypotheses that you think are interesting?

Computer Model Studies

IB: There are a lot of computer model studies that are done in the field of complex systems science and network science. One of the interesting things, which I think needs to be explored and is beginning to be explored, quite honestly, in the systems biology world, is this idea that the global-this emergent-which is really more than the sum of the parts, basically, of the organism of a whole, appears to be able to communicate back and forth with the parts. We don't always think about that because the parts have their own properties, but what we are saying about the larger system, which is really fairly self-organizing and has emergent properties that the parts don't have, is that that global level of organization can communicate back down, if you will, the organizational scale into all the parts that contribute to it, and vice versa.

In the world of acupuncture research, there are some interesting theories about how that communication could be going on that involves the connective tissue. I think one of the interesting concepts that the world of homeopathy raises is, are there properties of body water that are potentially more electromagnetic in nature that may actually be structured and communicating information at a whole other level than we usually think about at the molecular level? There are papers by people who are looking at the notion that water molecule structure, for example, helps proteins fold in a particular way. What if you were to change the information that those water molecules were providing so that they were actually changing protein configuration at a local level, but the larger signal was some larger piece of information that makes you you?

It is more than just your genetic information per se. There is a lot of interesting evidence about socioeconomic status, even, affecting how we turn certain gene patterns on and off, and actually a low socioeconomic status early in life appears to be retained as a piece of information in the body for years at a time, such that there is a proinflammatory pattern years later. Again, there are studies showing this kind of thing. So we are not talking about something that is just some theory that I have come up with this week. We are talking about the notion that there may be acquired information over a lifetime, and even prenatally, that in fact can be communicated, change the way the genes express themselves and therefore the way the person exists, so they have the genetic potential for whatever. Even in twins we know that in

one year one twin may get a particular illness, and it may take five years for the next twin to get it, and we know that has to be environmental. I think we have to think much more about the interaction between the environment and the organism and the organism and the parts in a flow kind of manner and look for what could possibly carry that information.

JB: I can't believe how the confluence of knowledge tends to run in streams and collect as tributaries, ultimately, to make a river. We were very fortunate to have Sandra Steingraber talking about Living Downstream a few years ago, and then last month we actually talked with Dr. Devra Davis. I'm sure you're familiar with her work on environment and its interrelationships to epigenetics and how that triggers different kinds of physical and physiological changes. Again, going back in both of their examples to how little we really know about low levels of multiple things interacting with complex systems of polygenetic origin and what kind of tags and markers there are in our human genome that make us either receptive or not receptive to certain messages. This is a whole different way of looking at life than looking at it as a series of nodes on a metabolic pathway in two dimensions.

IB: Right, exactly.

JB: So can you leave us, as clinicians, with some thoughts about what would be the way to approach a patient who is sitting in the exam room, based upon this kind of a strategic thinking? How do you train students to even be prepared to be doctors who would be open to this information and filtering it in this way?

IB: Obviously it is a large challenge, really because of the pharmaceutical mindset that we have right now in this country among many mainstream clinicians being trained. But there are many students who are open to these ideas. I think, probably, the main idea is to question the assumptions, because we struggle so hard, especially when we are a student, to learn something so we can excel at the test, showing that we grasp the information being offered. Go back and examine your assumptions. And go back and ask the question, are there other people who have thought in a different way about these assumptions, and starting with a somewhat different set of assumptions, have taken this whole idea of health and disease off in a different direction? What kinds of commonalities flow between the different approaches, be they alternative or conventional? Pay attention to your own observations. If they don't match up with what the textbook says should be happening, then pay attention to what the patient is telling you. Pay attention to what their body is telling you. And try to understand that with fresh eyes instead of trying to impose a particular way of looking at that patient's problems.

JB: That's a beautiful thought. Again, Dr. Iris Bell, I want to thank you for so many years of being a thought leader and also being willing to put yourself at some risk, professionally, and delve into these issues at a much deeper level, knowing that it is not the road easily or often traveled. What you have been able to do is to leave a path behind you that opens up the door for many other emerging practitioners to have some comfort and understanding that there are people like you, with your background, able to look at these things objectively and help guide us so that we have more tools in the tool kit. The functional medicine model that we have been describing for many years is really built around this whole network concept of systems biology, and I think your work is key and fundamental to understanding how this fits into the clinical world. Thank you so much for both sharing with us today and also for your years of contribution.

IB: Thank you very much, Jeff.

I certainly hope that you are as educated and informed by Dr. Bell's comments as I. I think that was a very eloquent and courageous presentation. She covered a tremendous range of topics very eloquently. It really goes back to the functional medicine concept, I believe, of a patient-centered assessment and medicine looking at antecedents, triggers, mediators and how they interrelate to signs and symptoms, which is, as you know, the method of assessment that is described and taught within the functional medicine curriculum, versus the sine qua non being only that of diagnosis.

Obviously Dr. Bell is talking about a non-linear, dynamic, complex system and network approach to looking at physiology that provides a conceptual basis that looks at the whole organism, this patient-centered organism. Complex systems theory then facilitates an understanding of and, hopefully, ability to move beyond the perplexing difficulties of reproducibility of the randomized clinical controlled trial. It allows us to look at this multidimensional world view of whole systems and how the environment interacts with the individual to produce an outcome, versus looking at each thing as piece parts and siloed thinking, one at a time.

If we were to look at the clinical differences that Dr. Bell has described between whole systems, basic biology, and a conventional medicine approach, we might say, how does the evolving life course of a disease differ in these two views? In the concept of systems biology, diagnosis is related to a coherent pattern, really, of interaction of the disturbance of the individual in their environment to produce differing kinds of symptoms that have differing severities, duration, and frequency, versus the conventional medicine approach that each diagnosis, unrelated to and independent of other diagnoses. We look at systems patterns in this systems biology approach as expressions of global disturbances in the organism's web of physiology. In a traditional model we might look at symptoms as local expressions of local disturbances versus this global disturbance. The outcomes that would be expected in a global well-being, energy and pattern model related to systems biology would be this whole organism treatment, versus, in a conventional medicine, more siloed thinking with differential diagnosis and elimination of the chief complaint and associated symptoms. As Dr. Bell said, maybe these would even drive those symptoms deeper by blocking them at certain levels. So there is a different philosophy, psychology, formalism, and basis of thinking. The old model, which is treating one thing one at a time, is not really consistent with human physiology nor biology. We need to move to a biologically based medicine, which I like to think is the functional medicine model.

Thank you, Dr. Bell, so much for your extraordinary contributions to our education in this area.

We'll look forward to being with you next month.

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