

March 2005 Issue | Daniel G. Amen, MD

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Orthomolecular Medicine and Functional Neurology - Back to the Future

Welcome to Functional Medicine Update for March 2005. We are going "Back to the Future" in this issue. That phrase has been used many times in our culture recently. Our past sometimes resides in the future. That is certainly the case as it relates to the prescience of Dr. Linus Pauling, two-time Nobel Prize winner, and the work he and his colleagues pioneered in the birth of what he termed "orthomolecular medicine," later to be called "orthomolecular psychiatry." This edition of FMU will focus on a retrospective review of the birth of this remarkable concept that evolved from molecular medicine into orthomolecular medicine, and then into orthomolecular psychiatry. At the Institute of Functional Medicine (IFM), we call it "functional neurology." Linus Pauling's concept has become a component of functional neurology and the intellectual wellspring from which we derive much of our formalism at IFM.

Whether a psychiatrist or neurologist thinks he practices any form of orthomolecular medicine today probably does not matter. Over the last 30 or 40 years, this concept, because of its power, insight, and ability to provide answers to complex questions that, in its absence, would be unanswerable, has inculcated physicians through an osmosis effect. This issue of FMU will pay homage to and give credit to the intellectual origin of this idea and look at how it has evolved into our practices in different ways. When we talk with our Clinician of the Month, Dr. Daniel Amen, truly a functional neurologist/psychiatrist, he will explain how he is putting these concepts into practice by using various imaging technologies as assessment tools.

Functional Medicine on the Internet

It is interesting to go to Medline or PubMed on the Internet, do a search on "functional medicine," and observe where the term forms clusters in the tens of thousands of hits received. Many of them are focused in the areas of radiology and imaging. Radiology used to be principally focused on diseased tissue, but with the advent of new scanning and imaging technologies, it is now a discipline that examines dynamic changes in tissue. Nuclear magnetic resonance, PET, and SPECT scans provide information about the changing physiological function of tissue. These techniques have changed the whole field of radiology and it is now more aligned with functional medicine. You see the terms, "functional radiology," "functional endocrinology," and "functional gynecology." These are starting to emerge as disciplines that look at the changing patterns of physiology.

Let's go back to the future and ask some questions about what was going on in the middle 1950s that led to the birthing of the concept of orthomolecular medicine by Dr. Pauling and his colleagues. Let us be reminded that ideas do not generally occur in a vacuum. New ideas are born out of the incubator of other people's great thinking and the advancement of an idea until it gets, as Thomas Kuhn said, to a point

where it undergoes a paradigm shift, or the structure of a true revolution. Kuhn, in his classic book, *The Structure of Scientific Revolution*, introduced the term "paradigm shift." Using that terminology, he tried to demonstrate that cultural changes and ideas do not occur smoothly. They occur abruptly as the critical mass of an idea is reached. Then, it shifts over very rapidly. That is the "paradigm shift." That would be true for virtually every great discovery, be it the classic physics of Newton, the relative quantum physics of Einstein, or information science. Great paradigm shifts come about abruptly in the way they are incorporated into culture-the "tipping point," to use another phrase to describe it. One day, no one is talking about it, and in a short period of time, everyone is talking about it, as if it is "old hat." Suddenly, everyone believes in it. Over the last 40 years, that has been the story of the evolution of ideas about orthomolecular medicine.

The origin of the idea goes back to the turn of the last century, when genetic metabolism diseases of infancy were discovered, the first one being alcaptonuria. Alcaptonuria was considered to be a disorder based on an autosomal recessive gene characteristic passed on from parents to children. From that paradigm shift, it was discovered that many other infant metabolism diseases were passed on genetically. As they were discovered, questions were asked, and the answers gradually came forth. This is similar to what happened with the vitamin revolution. Eijkman discovered thiamine in the early 1920s. Not long after that, we had "the age of vitamin discovery." Within 10 to 15 years, virtually all of the traditional vitamins, such as the B vitamins and vitamin C, were discovered. People finally knew what to look for.

The concept of inborn errors of metabolism resulting in serious and often life-threatening infant diseases was associated with things like dementia and various types of neurodegenerative conditions. Similarly, there was a confluence of ideas about vitamin deficiency diseases, such as niacin deficiency, or pellagra. Recall that the "three Ds" include symptoms we often associate with an acute deficiency of niacin-diarrhea, dermatitis, and dementia-which include adverse effects on brain chemistry. Even beriberi has a dementia-related component because of the vascular effects vitamin B1 and B2 have on perfusion of the brain.

There was an interesting connection between the discovery of genetic metabolism disorders of infancy and vitamin deficiency disorders relating to chemical changes in the brain. That raised the question of whether certain people are born with specific genes that may make them more susceptible to vitamin deficiency-related disorders that appear clinically as altered brain chemistry or dementia. It is easy to look with 20/20 hindsight today, but those were the types of questions many were asking during the early 1900s.

In 1949, Dr. Linus Pauling, then at Cal Tech, and his post-doctoral student, Dr. Charles Itano, were studying sickle cell anemia. Sickle cell anemia is clearly a genetic-related disorder, the etiology of which was unknown at the time. Dr. Pauling had a broad-based background and he thought across disciplines. He did not think of himself as only a chemist or only an inorganic, crystal metallochemist. He saw himself in the broadest concept of using science and reasoning to try to address broad questions, including things like the nature of anesthetic drugs and the origin of the immune system. Those are things he had explored in that period of time.

In terms of sickle cell anemia, an interesting observation was made. Cells from individuals who were genetically inclined toward sickle cell anemia were put in a tube. The tube was degassed by taking oxygen out of the environment and putting it in a magnetic field. The result was a certain kind of

deflection of the needle, indicating that the cells were paramagnetic in a certain way. Normal red cells that were not sickled resulted in a different type of effect. The magnetic field from the iron contained in the porphyrin balanced differently than in the sickle cells. By oxygenating the cells and doing the experiment again, a greater difference was found. Most of us would find this observation interesting, but we would want to know what it meant. For Dr. Pauling, this became an area of significant interest. Because his span of interests was so broadcovering everything from inorganic chemistry to biochemistry and cell physiology he was eventually able to discern that this difference was related to a phase shift transition occurring in the packing of the hemoglobin molecules in the heme from sickled cells, versus the heme from normal cells. That led to a different kind of packing, or a different kind of crystallization, changing the way the magnetic field and light interacted with the red cell. He began to think about structure/function and what would cause the sickle cells to pack more closely, stick together, and demonstrate this unique sickle effect under the microscope. He believed that the sickle conformation was the effect of something going on within the cell. Knowing that more than 50 percent of the volume of the erythrocyte is hemoglobin, he thought that it had something to do with the packing of the hemoglobin molecules. That, in turn, had something to do with the unusual thing he saw with regard to the iron component of the porphyrin and how they all lay on one another, forming a crystalline-like structure within the erythrocyte of the sickled individual.

Eventually, Dr. Pauling wanted to find out what controlled the structure of the way the hemoglobin, or the heme portion, could crystallize the iron-containing component. He thought it must be the globin portion, the protein portion, of the hemoglobin molecule. The large chains of polypeptides wrap themselves around and maintain the conformation of the hemoglobin molecule and ultimately present the heme portion of the molecule (the iron-containing portion) in different configurations, based on the altered tertiary structure of the protein. Dr. Pauling surmised that must be where the genetic differences start in the globin portion of the molecule. Protein sequencing was coming into its own, looking at the exacting kind of chemistry required to do amino acid analysis. Noting the difference in the polypeptide chain of the sickled individual versus the non-sickled individual, Dr. Pauling found that the difference between the globin chains was only one amino acid substituted in the chain. In the chain of hundreds of amino acids, there was only *one* difference between sickled hemoglobin and normal hemoglobin. That one difference occurred at a very critical point for the conformational integrity of the globin molecule. By substituting a single amino acid for another in someone with that genetic difference, it changed the shape of the globin molecule which, in turn, changed the shape of the way that the heme portion was presented. That changed the packing arrangement of the hemoglobin in the red cell causing it to crystallize, which changed the shape of the red cell. It stretches the red cell, resulting in a sickled appearance, which causes deformation. It cannot go through the capillaries as well and it results in injury. Just as a sickle would slice grain, it slices the vasculature, producing injury and damage.

That was Dr. Pauling's model and it was presented in 1949 in *Science* magazine in an article, titled "Sickle Cell Anemia: A Molecular Disease".¹ It was the first use of that term that I could find in the literature. It followed beautifully in the definition of a new kind of disease that makes a connection between genes and the environment and how that relates to structure/function relationships and the pathogenesis, or pathology, of a disease. Dr. Pauling proposed that there might be ways of changing the environment. There was no way to change the genes of an individual, but perhaps the environment in which the red cell was bathed could be changed, or the way the genes were influenced could be changed, altering the potential for red cells to pack together and engage in what we call a "sickling crisis." That was the theme of the 1949 article on sickle cell anemia.

The Role of the Environment in Modulating Protein Structure and Function

In the 1960s, investigations were conducted by many different groups looking at the role that environment plays in modulating protein structure and function. Dr. Pauling and his group were certainly at the forefront of these investigations. He was very interested in what the origin and lineage of vitamins had to do with physiological function, as that area tended to converge with the origin and function of protein and, ultimately, the regulation of cellular function. Today, that seems like a very obvious connection. It seems, in retrospect, almost simplistic, but at the time, in the late 1940s and early 1950s, just on the heels of understanding the physiology and biochemistry of vitamins, this was quite a remarkable concept-that somehow, there was a convergence of vitamin physiology and genetic function.

To have those concepts linked together into a single theory, or theme, led to a remarkable change in people's beliefs. Before that, it had been felt that beriberi, pellagra, rickets, xerophthalmia, scurvy, kwashiorkor, and marasmus, were conditions that all people would get with equal prevalence if they were deficient in certain nutrients. They were not based on individual differences related to genetic variations. In retrospect, the observation that different individuals would respond in different ways to a deficiency had some support. Recall the concentration camp victims during World War I and II. There was a wide variety in mortality among different individuals that could never be explained, based on the fact that they were all getting similarly deficient diets. People would ask why some would wither and die so quickly when placed on deficient diets and others could seemingly survive for a long period of time. Admittedly, their physiology was injured, but they would survive.

The Concept of Biochemical Individuality

That leads to Roger Williams' concept of biochemical individuality. He was pioneering this concept at the University of Texas in the early 1950s, at the same time Dr. Pauling was pursuing his concept of molecular medicine. These two concepts converge beautifully. Dr. Williams coined the term "genetotropic disease," a disorder resulting from an individual's need for specific nutrients for optimal function not being met, which produces suboptimal physiology.² He postulated that many common societal diseases, including alcoholism, various neuropsychiatric disorders, as well as heart disease and diabetes, might be considered genetotropic diseases, and could be prevented by matching the genetic needs of an individual with specific diets. These were the remarkable paradigm shifts being made by Drs. Pauling and Williams.

That leads to the late 1960s when Dr. Pauling published what I consider to be a watershed paper in *Science* magazine, some 19 years after the initial article on sickle cell anemia appeared. The later paper was titled "Orthomolecular Psychiatry."³ If you reread this classic article in the 1968 issue of *Science* magazine, you will find that the concepts are as modern today as they were in 1968. Dr. Pauling spoke about the origin of neuropsychiatric disorders as a consequence of the imbalance between the need for specific nutrients to promote proper brain chemistry and the genetic uniqueness of the individual. Therefore, what might be adequate nutrients to power up the brain in one person may be suboptimal in another, leading to inappropriate brain physiology. Dr. Pauling stated that individual differences related to nutrient need may be vastly greater than previously thought when the Minimum Daily Requirements (MDRs) or Recommended Dietary Allowances (RDAs) were designed. They had a fairly narrow range of what we consider to be requirements for human function. He pointed out that some people fall into categories of deviation far from the mean of the bell-shaped curve, where needs may be much higher, possibly 1000 times the RDA. He gave some examples, such as people with methylmalonic aciduria and Hartnup disease that require extraordinarily high doses of specific nutrients to prevent the

buildup of metabolites that can be injurious to individuals with certain genetic characteristics.

Dr. Pauling showed that, to promote proper brain chemistry, we need to consider a confluence of ideas between genetic metabolism disorders and nutrient needs. He used some very compelling arguments which, for most medical doctors, were not well understood, such as the Michaelis constant and the binding of an apoenzyme to an coenzyme to create an active enzyme. Nutrient need might be defined on the basis of a genetic binding quotient between the enzyme and its coenzyme (a vitamin-derived material), and that could vary tremendously. In his 1968 article, Dr. Pauling discussed binding disassociation and Michaelis constant values, themes that were probably over the heads of most people, unless they were students of physical chemistry and enzymology.

It is ironic that nearly 25 years later, Dr. Bruce Ames published a landmark paper in the *American Journal of Clinical Nutrition* in 2002, in which he talks about the Michaelis constant. He presents tables of data from literally hundreds of papers that have been published since 1968, demonstrating that Dr. Pauling's concept about mass action effects to promote enzyme function with various vitamins is, in fact, correct for many genetic metabolism disorders.⁴ It is not just the frank genetic metabolism orders, but a whole range of variegated polymorphisms that result in differing needs in different people for optimal function. It is a new view of the role that nutrients play in function that came through our traditional concepts of vitamin deficiency and establishment of the RDAs. In fact, the constructs I am describing, those of Williams, Pauling, and Ames, were not incorporated into the development of the RDAs.

The Work of Hoffer and Osmond in Schizophrenia

We are now in the late 1960s and the birthing of the concept of orthomolecular psychiatry the use of nutrients at the level of physiological need. Pioneers Dr. Abram Hoffer and his colleague Humphrey Osmond got involved in this work as well, looking at high doses of niacin, pyridoxine and ascorbate in the management of schizophrenia. They originally worked independently, but later collaborated with Dr. Pauling together, and birthed the concept of orthomolecular psychiatry with David Hawkins. It is a fascinating chapter in the history of the application of molecular medicine to psychiatric and neurological function.

That leads to the early 1980s, a period in which I had the pleasure of working at the Linus Pauling Institute of Science and Medicine in Palo Alto, California and observing the contributions being made by Dr. Pauling and his colleagues in the evolution of the concept of orthomolecular psychiatry. In early 1983, a meeting was held in San Francisco to honor Dr. Pauling and the years of his contributions. I had the fortune of being one of the presenters at that meeting. Dr. Pauling gave the plenary lecture. The title of his talk was, "The Future of Orthomolecular Medicine." I want to thank Dr. Alex Vasquez for sharing a PDF file with me that he found on the web. It is the hand-annotated original draft of the manuscript for Dr. Pauling's speech, which I had the privilege of seeing in 1983 before it was presented, but I had long ago lost my copy. Dr. Vasquez was adept enough at finding this and sent me a copy. It reminded me of the intellectual activity and excitement that was occurring in the 1970s and 1980s around the development of orthomolecular medicine.

I would like to quote some of Dr. Pauling's thoughts to demonstrate how we go back to the future, and how we are relearning old ideas and new ways to make them even more valuable. The following are quotes from Dr. Pauling's 1983 speech.⁵

"The reason that I spend time thinking about medical problems, about vitamin C, for example, is that I believe that we are going to solve this problem of finding out how to keep the world from being destroyed in a nuclear war, and that it's worthwhile to be thinking of making the world a better place for the coming generations of human beings.

"One way in which this can be done is by improving the health of people, by cutting down on the amount of suffering caused by hypovitaminosis C, as Irwin Stone says, from which essentially everybody in the world is suffering. Only a few enlightened persons, who take 10 or 12 grams a day of vitamin C, are in the fortunate position of not suffering from this genetic disease that we have learned to control, but only just barely, by getting a diet that contains enough ascorbate to keep us from dying, but not enough, it's turned out, to put us in the best of health.

"The other talk that I gave to this symposium that I was attending, was on the role of the physical sciences in modern biology. I talked about one aspect of this, and in fact it's quite pertinent to what we have all been talking about: about vectors of disease and about the agents that we use to control these vectors of disease, and about the human body and how it functions.

"I doubt that I thought much about the nature of life until 1929. I was then carrying on research on the structure of minerals and other inorganic substances. Then in 1929 Thomas Hunt Morgan came from Columbia University, bringing with him Sturtevant and Bridges and Emerson and Tyler. Sturtevant and Bridges were two of the three students who had cooperated with Morgan in developing the theory of the gene, in discovering the gene. It wasn't known, of course, that it consists of polynucleotides, but they knew a lot about it even though they didn't know its chemical composition. They kept talking about the specificity characteristic of life. One example of this specificity is that parents have children who resemble them. This resemblance we now know even goes so far as resembling them in terms of amino-acid sequences of the polypeptides that constitute the specific proteins in their bodies, and their specificity in the action of enzymes as catalysts.

"Morgan was working on self sterility of *Ceiora*, the sea squirt. In 1935 and '36 I was working on diamagnetic oxygen as well as triplet oxygen, the normal state, with the idea that we could tell something about how oxygen molecules are held by hemoglobin molecules in the red cells of the blood. The idea was that we could distinguish between two kinds of combination; one involving a mainly physical force that would leave the oxygen in the triplet state, leave it paramagnetic, and the other chemical combination, the forming of chemical bonds that would make the oxygen molecule diamagnetic. So we measured the magnetic susceptibility of venous blood and arterial blood, and found that the oxygen molecules were held in the hemoglobin molecule by forming chemical bonds. We also found a remarkable change in magnetic properties of the iron atoms when the hemoglobin in the red cells is oxygenated.

"I was giving a talk in New York in 1936 at the Rockefeller Institute for Medical Research, a seminar on this subject, and where Landsteiner asked me to talk with him. Karl Landsteiner had discovered the A, B, and O blood groups in 1900, and the others, L and M and Rhesus factor, later on. He had been carrying out experiments in the field of immunology, immunochemistry, and he asked if I could explain his observations. I couldn't explain them, but he told me a great deal in several days of discussion; he told me a great deal about immunology. I kept thinking about what he had said, and finally I reached a decision as to what I thought was going on that permitted antibodies to show such remarkable specificity in their

interaction with antigens. Landsteiner was making azoproteins, using simple chemical substances such as paraaminobenzoic acid, metachloral, orthochloro-benzoic acid or toluic acid, and hundreds of other substituted benzoic acids as well as other substances you could use instead of the benzoic acid.

"By 1940, I had reached the conclusion that I knew the answer to the question, the basic answer to the question of the molecular basis of biological specificity, the molecular basis of life. There were two ideas that had been discussed. A German physicist named Pasqual Jordan published a paper in 1940, about the time that I published my paper about the structure of antibodies and the nature of serological reactions. He advocated one of these ideas which is that identical molecules attract one another more strongly than nonidentical molecules because of the phenomenon of quantum mechanical resonance. Max Delbrucks brought this paper to my attention, and I said, 'I don't believe that the extra energy of attraction that you get from quantum mechanical resonance between identical molecules can possibly be the explanation, because this extra energy is less than the energy of thermal agitation. It just wouldn't work. But if, and this was in my paper on antibodies, if the antibody has a combining region that is complementary in its atomic structure, the arrangement of the atoms, to the haptenic group of the antigen, you get strong and highly selective interaction.' Well, so we wrote a paper in 1940 saying that biological specificity in general results from the detailed molecular complementarity of the interacting groups, and that Jordan was wrong about his idea of quantum mechanical resonance. We also said the gene consists of two mutually complementary molecules, each of which, when they are separated, can act as a template for the synthesis of a replica of the other one, so that gene duplication occurs that way, using one half of the gene for the template for the other half because of its complementarity. Well, of course, some years later examples of complementarity began to show up. The alpha helix and the pleated sheet are arrangements of polypeptide chains in which there are two complementary groups which interact, the NH group of peptide interacting with the oxygen atom of the carbonyl group of another peptide, and that is a highly directed interaction. You can achieve these hydrogen bonds by coiling the polypeptide chain in the helix or by arranging it in a somewhat staggered linear arrangement coming back on itself to make the pleated sheet where the hydrogen bonds are formed laterally. And then, of course, Watson and Crick discovered the double helix 13 years later, in 1953, in which they were able to show that two nucleotides-purine and pyrimidine-form two hydrogen bonds with another and two other nucleotides, purine and pyrimidine, form three hydrogen bonds with one another, and that the gene consists of two polynucleotides which are mutually complementary, adenine combining with thymine and guanine combining with cytosine.

"So now by 1948, my students and my associates, Dan Campbell and David Pressman, who worked for several years on this project, had carried out studies of the interaction of antibodies with haptenic groups, hundreds of experiments, a thousand perhaps, determining equilibrium constants. By 1958 we had tied down these ideas, so far as they are concerned with antibodies and antigens, so tidily that there was no possibility of saying that we were wrong.

"So molecular complementarity, this tight fit of the complex of atoms of one molecule onto the complex of atoms of another molecule, is the basis of life. Biology now is developing, molecular biology is going along strongly, genetic engineering. We are going to get more control of ourselves, with a better understanding of the nature of our own bodies and the way in which these bodies function. I'm not going to make an effort to predict in detail what the future of orthomolecular medicine will be. I think that it's been done already, by the participants in this seminar; but I might make a quantitative statement. Someone sent to me a clipping saying that Dr. Pauling says that we can live to be 100 years old, and I in

fact had said that, that by proper use of supplementary nutrients and other health practices, people in general could live 25 years longer than they do now, live to be a hundred years old, and lead good lives too, not have a long period of debility as the body begins to fail.

"Well, Irwin Stone said that he believed that I could live 50 years; that was 15 years ago when he made that statement, so he would say that he thinks that we can live 35 years more than presently accepted. It may well be that in a generation or two we shall have enough knowledge, especially in the orthomolecular field, to permit people to live to be 110 years old. I think that this is worthwhile: if you can extend the period of well-being, then we shall have extended the ratio of well-being to suffering, and I think that that would be worthwhile."

"I've enjoyed myself for many years, after I got through the initial period of not understanding the world very well. I've enjoyed myself, and it's been a special pleasure for me to have been here today and yesterday. Thank you."

This speech was given in 1983. I think it's back to the future. How far have we come during the past 22 years in the amplification of this concept? The Institute for Functional Medicine is trying to honor and champion the concepts that Dr. Pauling set forth 25 years ago. The emphasis and focus through our Applying Functional Medicine in Clinical Practice training programs, our annual symposium, and our Neuro Module workshops, is an attempt to incorporate these concepts more and more effectively into clinical practice.

If we look at what has happened with the sickle cell anemia story since the 1949 discoveries, going forward to the 1960s and later into the 1980s with Dr. Pauling, it is fascinating. We now recognize that you might be able to actually modulate, with specific signal molecules, the production of fetal hemoglobin at the gene level to dilute the sickled hemoglobin and prevent sickle cell crisis. There are a couple of substances now being used clinically to modulate gene expression of fetal hemoglobin. One is hydroxyurea; the other is butyrate. Infusion of butyrate and hydroxyurea has been demonstrated to upregulate gene expression of fetal hemoglobin, which is not sickled, so that it dilutes the sickled hemoglobin and prevents things that Dr. Pauling talked about the protein/protein interactions that lead to the sickle crisis.

Dr. Pauling's prediction in 1949 was very prescient. He asked whether the environment could be changed to modify the outcome of function if you knew something about the interaction of environment with genes of susceptible individuals.

This is a presaging of what we are going to be talking about in much greater detail at the 12th International Symposium on Functional Medicine coming up on May 24-28 in Palm Springs, California, at the Westin Mission Hills Resort. You may have received information about it, but just to remind you, the title of the symposium is, The Immune System Under Siege: New Clinical Approaches to Immunological Imbalances in the 21st Century. If Dr. Pauling could attend, I think he would be proud to witness how his concepts have evolved over the past 40 years in the kinds of presentations and workshops that will be held at the symposium. We have taken his concepts to a new level as they pertain to the understanding of balancing components of the immunological system, such as thymus-dependent-1 (Th-1) and thymus-dependent-2 (Th-2) lymphocyte function, and how that relates to disorders associated with immunological imbalance.

We are on the horizon of an exciting time. We are going to learn from our Clinician of the Month about some of the constructs laid down through the pioneering work in genetic metabolism disorders and the early understanding of the role that vitamins play in the prevention of deficiency diseases. Those two ideas converged into a new theme of medicine called molecular medicine, later to be called orthomolecular medicine. Then came the concepts of biochemical individuality and genotrophic disease by Dr. Roger Williams, and these have been woven into nutrigenomics and eventually into functional neurology.

For most of the last 60 or 70 years in medicine, we held the belief that there is a step function between health and disease. On one side was health and on the other side, disease. We viewed it almost like an on/off switch. One moment there was health and in the next moment there might be a disease. That concept has been pretty much laid to rest over the last 10 to 15 years. Certainly, Dr. Pauling's insight in 1949 helped us to achieve the tools to address these issues. Now, we are starting to recognize that almost all specific age-related chronic diseases have a gradient effect, a lineage, a precursor marker period, and a subclinical period, and they ultimately arise at a diagnosed disease after significant dysfunction, or when loss of function occurs. The real future of medicine is not in understanding how to diagnose better, but to better understand how to prognose, how to look earlier, how to intervene before the patient completely loses function and requires heroic intervention. There is probably no better part of the body's physiological system where we can focus this concept than the neurological system. As they grow older, most people are concerned about loss of cognitive function, independence, and self-awareness. Understanding how to move away from diagnosis and to focus on prognosis will give us much better tools to treat many conditions, including attention disorders, learning disabilities, schizophrenia, Alzheimer's disease, presenile dementia, Parkinson's disease, multiple sclerosis and others, all of which rob us of productive years of neurological function.

It is time for our Clinician of the Month, Dr. Daniel Amen

INTERVIEW TRANSCRIPT

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JB: In this month's edition of FMU, we are focusing on functional neurology. On Side 1, we talked about Linus Pauling's 1968 pioneering article in Science magazine, titled "Orthomolecular Psychiatry." In that article, he developed a different theme about how we treat neuropsychiatric disorders, setting the stage for how we look at the brain from a functional perspective and how biochemistry plays a role in performance, cognition, mental acuity, and neurodegenerative and neuropsychiatric disorders. This theme takes us into the 21st century and the work of our Clinician of the Month.

Dr. Daniel Amen is a remarkable investigator, clinician, and innovator in the area of functional neurology. I don't know if he shares that term with me, but we'll get a chance to hear from him in a moment. Dr. Amen is a Board Certified psychiatrist and the founder of the Amen Clinics, Inc. in Newport Beach, California; Tacoma, Washington; and Reston, Virginia. He has done amazing work in helping us to understand how various types of scanning, particularly SPECT scanning, can be useful in assessing

altered brain function. This type of assessment often leads to the modification of function without the need for hard-hitting psychotropic or neurologically-modifying drugs.

Dr. Amen has a remarkable background that includes many contributions and experiences. He has written some interesting book chapters, including "Brain SPECT Imaging and ADD in Understanding, Diagnosing, and Treating AD/HD in Children and Adolescents: An Integrative Approach," published in 1999;⁷ and "New Directions in the Theory, Diagnosis, and Treatment of Mental Disorders: The Use of SPECT Imaging in Everyday Clinical Practice," published in 1994.⁸ He has published numerous articles, has made hundreds of presentations, and has written some books that are absolutely required reading. His most recent book is titled *Making a Good Brain Great* and will be published this year by Harmony Books.⁹ Books in print that I had the chance to review over the last couple of months include, *Preventing Alzheimer's*, with neurologist, William Shankle;¹⁰ *Healing Anxiety and Depression*, with psychiatrist, Lisa Routh, MD;¹¹ *Images of Human Behavior: A Brain SPECT Atlas*;¹² *Healing ADD: The Breakthrough Program That Allows You to See and Heal the Six Types of Attention Deficit Disorder*¹³ ; and *Change Your Brain, Change Your Life*,¹⁴ which was a New York Times Bestseller in 1999. That book contains some revolutionary thinking that people talk about all the time.

With that introduction, I would like to welcome you, Dr. Amen, to FMU. My first question is, how does a psychiatrist make a transition into radiology and then into functional neurology? It doesn't seem like the traditional path that most psychiatrists have taken.

From Biofeedback to Imaging

DA: Thanks for talking with me, Jeff. I feel so blessed about the work I've been doing. I got into imaging from biofeedback. Biofeedback is where we measure a person's body with instruments and then teach them how to change their own physiology. We teach people to warm their hands, breathe in a different way, and even change their own brain waves. When I learned how to do that in the mid 1980s, I was so excited. I started looking at things like depression and ADD from a brain-wave perspective. When I went to my first lecture on brain SPECT imaging in 1991, it made perfect sense to me. Of course we should look at the brain because these are brain disorders. I started to feel very uncomfortable being a psychiatrist because, why were we handicapped? Psychiatry is the only medical specialty that never looks at the organ it treats. I thought that was silly. I loved being a psychiatrist, but I thought we needed more information. When I had the opportunity to learn about these scans, order them on my own patients, and see the dramatic positive response on the part many of them, I was hooked. I thought that I couldn't do a good job for my patients if I didn't know what was going on in their brains.

JB: It's fascinating to hear you say that, because I recall that about 20 years ago, I got a notice about a conference on biological psychiatry that I thought sounded very interesting. It followed nicely from my experience with Dr. Pauling at the Pauling Institute in the early 1980s. I felt I should go and see what biological psychiatry was all about. I found out it was all about how to use various types of mind-altering drugs. It had nothing to do with the biological function of the brain. It sounds like you're truly practicing biological psychiatry. You're looking at structure/function relationships in terms of psychiatric and psychological dysfunction.

Psychiatric Medications and the Brain

DA: Absolutely. That's just what we do. We never make a diagnosis from a scan. The scan has to be put in the context of the patient's life. But without having imaging information, you're spending a lot of time

guessing. One of the most important things imaging has taught me is that the use of psychiatric medications can be ever so helpful to the brain, or they can really hurt the brain. How would you know unless you looked? What really got me interested in alternatives to psychiatric medications was seeing that often, the medicines I was taught to use for people with anxiety disorders (at the Walter Reed Army Medical Center where I did my training), like benzodiazepines or antidepressants, certainly helped to calm down the brain, but they gave the brain a toxic look. At that point, I wondered if there were other alternatives we should be offering to patients. It was through very high technology imaging that I became much more interested in using alternatives to help balance brain function.

JB: I notice that you're an Assistant Clinical Professor in the Department of Psychiatry and Human Behavior at the University of California, Irvine. I wonder how your concepts have been accepted by your colleagues and students. I suspect the students probably have a different level of acceptance than your colleagues. Would you tell us about what you have observed in terms of acceptance of these concepts by colleagues in your field?

DA: When we first started doing this in 1991, people would call me a "quack" and they reported me to the Medical Board. It was quite a wild, negative ride, but I believed in what we did, so we kept doing it. Over the years, there has been a softening of that. I wrote a book once, titled *Healing the Hardware of the Soul*.¹⁵ A colleague of mine, a psychiatrist in Berkeley, sent me a very nice letter. On the outside of the envelope, he wrote: "All truth goes through three stages. First, it is ridiculed (well, I've certainly been there). Second, it is vehemently denied. Third, it is accepted as self-evident." We're now between stage two and stage three. I teach six seminar courses to the residents at UCI. The powers that be, our Chairman and Residency Director, think what we do is great and they are fully supportive of it, but a lot of the staff who have little training in imaging think it's a little bit of voodoo. The students, on the other hand, are very excited, interested, and their eyes get big when they observe a suicidal patient and see a scan of his brain that demonstrates a left, temporal lobe deficit. They say, wow! You mean, if I fix that, he's not going to feel as aggressive or dark and negative toward himself? And I tell them yes, that's how it goes. It's like hardware and software; you must balance the brain, and then you have to teach them how to use it better. Doing psychotherapy on people with brain problems is not only a waste of time, but it makes people worse because it demoralizes them.

JB: That's very insightful. Before we get into the specifics, which I want to give you the opportunity to do, I'd like to deal with what is probably the most common question you get from nay-sayers, so we can get it out in the open. I've heard people (traditional neurologists, radiologists, and imaging specialists) to whom I've talked with excitement about your work, and they have responded that there's a variation in the reproducibility of SPECT scans that would prevent its use in determining functional changes in the brain at a level at which you could make a specific assessment. Would you speak to that? You probably have more experience than any one of them, and I'd like to get to the truth here with regard to your experience.

Reproducibility of SPECT Scans

DA: We've done 25,000 scans. Each patient gets two scans. They get a rest scan and a concentration scan. When you concentrate, your brain changes in certain areas, mostly the prefrontal cortex and the cerebellum. Other than that, the scans are actually very reliable and predictable. We've done scans 12 years apart on people and it's basically the same scan. At UCLA, Ismael Mena, who was the Chief of Nuclear Medicine at Harbor-UCLA, did a study where he showed that three weeks apart, there's less than 3 percent variability in the scans. Jonsson et al. have also done a study on the reproducibility and

repeatability of the scans.¹⁶ The notion that your brain changes with every thought that you have is just not true. But there are some interesting caveats to that. If someone has PMS, her brain changes. I got interested in that because I have five sisters, and I thought that there had to be some brain changes in the middle of the month versus right before they start their period. And indeed, there are. If you have multiple personality disorder (we studied that a number of years ago), the brain changes in each personality. By and large, given those couple of caveats, the brain is very consistent over time.

JB: From that, how did you make the observation that SPECT imaging could be useful for the evaluation of conditions like ADD or ADHD?

Evaluating ADD and ADHD

DA: What a lot of people don't understand about my work is that it is not based on my thoughts. It's based on a ton of research done by other people. In fact, one of the things that got me excited about ADD was the research with quantitative EEGs, showing that the ADD brain is different at rest versus when they concentrate. When I started doing imaging, there was an article in *The New England Journal of Medicine* about using PET studies with ADD. PET is a cousin of SPECT. When adults with ADD try to concentrate, they get decreased activity in the prefrontal cortex. On our web site, brainplace.com, you can actually read 1500 scientific abstracts on brain SPECT and PET imaging in psychiatry.

Indications for Brain SPECT Imaging

I had a really busy practice when I started doing imaging. I was working on a lot of my own patients. At the same time, we were going to the medical literature and finding out what people said about it. In fact, according to the Society of Nuclear Medicine today, there are four standard indications for brain SPECT imaging—dementia, seizures, head injury, and vascular disease. These are things psychiatrists see all the time. Even though we have this reputable organization saying that we should be doing it under these conditions, we don't. The reason we don't is that people aren't trained in it. I think that's really the bottom line. The students that I train will use it and make it part of their practice. But if you're not exposed to it, you really don't even think it exists.

JB: There's a classic we've all seen in our lives, that being, if you don't ask the questions, you're not likely to get the answers. Certainly, you've asked the right questions. Would you tell us about what types of patterns you've seen that are interesting from a clinical perspective, and how you categorize them into pattern recognition families.

Blood Flow and Activity Patterns in the Brain

DA: SPECT looks at blood flow and activity patterns in the brain. We really need to understand that, because we see areas of the brain that work well, areas of the brain that are underactive, and areas of the brain that are overactive. Initially, I was much more naive than I am now. I thought there would be a signature pattern for ADD and a signature pattern for depression. When I didn't find one, I was disappointed, until I realized that in seeing real people, not all ADD people respond to stimulants. In fact, stimulants make a great many of them worse. It's the dirty little secret that many psychiatrists don't talk about, but, in fact, it's true. Probably one of the most important things I've learned is that ADD is not one thing. It's at least six different things. There's a pattern in people who get diagnosed with ADD where they have what we call classic ADD. It is pretty healthy brains at rest and they deactivate their prefrontal cortex and their cerebellum when they try to concentrate. It's very clear. That group actually responds fairly nicely to stimulants.

There's another group. They get diagnosed with ADD very early in life, but stimulants make them significantly worse. In fact, according to our research, 70 percent of the time, stimulants will make them worse. This is a pattern we call the "ring of fire," which is diffuse, overall increased activity in the brain. Our feeling is that it may be some inflammatory process going on. They may have early bipolar disorder. They may have some sort of allergy, but they meet all 18 criteria from the DSM4 for ADD. But don't put them on a stimulant because they are going to end up significantly worse.

We also see a head injury pattern associated with ADD when there's damage to the left side of the brain, especially the left frontal and temporal lobe. These are people who clearly have the outward manifestations of ADD, but they tend to have temper problems, irritability, and mood instability. One of my favorite patterns, because I did research on it when I was a child psychiatry Fellow, is what we call over-focused ADD. It's where ADD and OCD sort of cross each other. You get ADD kids or adults who also tend to be argumentative. If oppositional things don't go their way, they get upset. Their problem is not so much that they can't pay attention, but that they cannot shift their attention, so they end up inattentive because they're always thinking about something five minutes ago.

JB: In many school systems in the U.S., there is a very high prevalence of prescription for stimulant drugs to manage behavior in children who are presumably ADD or ADHD. It would suggest, obviously, that some of the children were probably mistreated, based on the fact they weren't evaluated before they were given a one-size-fits-all remedy. What happens if, after a child goes through your studies and is found not to be a candidate for this kind of medication, they have already been prescribed that medication? Does that result in a resolvable conflict, or are there some warnings you would want to pass on from your experience?

DA: Parents, in my experience, tend to be caring and pretty smart. If the medicine is not working, they tend to take the children off it, because they don't like the side effects. When people come to see us, they've often tried six or seven things and come to us with three or four different diagnoses. What I find that works is, the first thing we have to do is clean up their life. We have to clean up their diet, get them to exercise, and get them away from TV and video games, those things in our society that are increasing the expression of ADD. Then, we need a more thoughtful approach to their brain. Our whole goal is based on how we can balance their brain so they "do their lives" better. Most people can do their lives if they have a brain that works right. That becomes the goal. I think there are a lot of people who are misdiagnosed with ADD because we assume it's one thing. As you said, we have this one sort of treatment fits everybody-one-size-fits-all. it's a silly approach and we need to be more thoughtful.

Recently, the FDA has been all over child psychiatrists about using antidepressants. it's not that antidepressants are bad or wrong or ineffective. it's just that one type of antidepressant, like an SSRI, does not fit everybody who is depressed. It's the knee-jerk reaction that doctors do, because there are all the drug representatives that come to our offices, giving us cookies, buying us lunch, leaving us Paxil pens, and so on. We agree, especially the family doctors and pediatricians, that we'll think about this SSRI. So, heretry this. But when there is a ring-of-fire pattern, you're likely to make that person dramatically worse. We simply have to be more thoughtful about what we do. And there are alternatives the notion of using supplements and vitamins. If it's not part of your training, you don't think about it. I have several kids with ADD and I want to use whatever is the safest, most effective treatment for them. Often, I can get supplements to work, so why wouldn't I start there if they have fewer side effects?

JB: That's an exciting message. I was pleased to see that with your diverse background, through biofeedback and hypnosis and looking at a variety of complementary and integrative therapies, that you've developed what I would call a truly integrative functional neurology approach to these syndromes and these conditions. When you look at the integration of these therapies in a child or an adult, how long does it generally take to start seeing clinical effects, and can you then document changes in the SPECT scan over time?

DA: Absolutely. It was one of the things that got me excited about things like St. John's Wort. St. John's Wort works just like Prozac, except you don't get sexual side effects from it. It's cheaper, and you don't ever have to tell an insurance company you took it, so it doesn't affect your insurability. But we would see before and after changes. My experience is that it takes a little bit longer, so when I use a natural approach, I feel that we need to do this for about four months. I tell patients that if they do the things I ask them to do for four months, that even if they need medicine, they're going to need less medicine. People get excited about that. They know we're going to do a followup scan to see how we're doing and if we're doing the right thing. And they get excited. Now, Ritalin works within a half an hour. If you have an ADD family (ADD children come from ADD parents), often they are looking for a quick fix because that's their attention span. But when you work with them and give them simple ways to follow through, it can be ever so helpful. Having said that, for people who are listening to this tape, if they deal with people with ADD, they should know it's a family disorder. If you are seeing a child with ADD, you need to screen Mom and Dad because they got it from one of them.

JB: That's very good insight. I'd like shift the focus slightly. Back in the early 1990s, Dr. Clough wrote an article that appeared in the Lancet on the etiology and pathogenesis of Parkinson's. He introduced a concept in that article called neuroprotective therapy that was picked up in a more recent article in the Journal of the American Medical Association, one on the etiology and pathogenesis of Parkinson's, discussing that if you knew early enough that the person was losing niagra striatal neurofunction, that you could intervene with neuroprotective therapy. Of course, the questions are, how do you know, and what do you do? Your procedure seems to lend itself nicely to addressing both of those questions. Would you tell us about your experience with Parkinson's, Alzheimer's, and other kinds of neurodegenerative conditions?

SPECT Scanning and Alzheimer's Disease

DA: I have a lot more experience with Alzheimer's disease. In my book, Preventing Alzheimer's, which I wrote with a colleague of mine, I was so taken with the scans, and there's research evidence to back this up. We can tell five to seven years before there are symptoms whether or not a person is likely to develop a form of dementia. That's stunning! You have to lose 30 percent of your hippocampus, the structure on the inside of your temporal lobes that's responsible for memory. You have to lose 30 percent of it before you have your first symptom. If I've lost 10 percent, I want to know because I want to do something about it. As we worked on the book, it's just stunning to me, the risk factors associated with Parkinson's disease, Alzheimer's disease, and vascular dementia that we can actually do something about. Diabetes is a risk factor. Depression is a risk factor. Sleep apnea is a risk factor. Heart disease is a risk factor. If only we knew that taking care of our bodies is guarding against risk factors for Alzheimer's disease, we'd do a much better job of it when we're in our 20s, 30s, and 40s. I'm convinced that the information that you put out and that I put out should be part of curriculums in schools. I like the lyrics in one of Paul Simon's songs "When I think back on all the crap I learned in high school, it's a wonder I can think at all." His song, "Kodachrome," starts with that. What are we doing if we're not teaching these kids? I am so excited. I just started a 12-week course for 9th graders called "Making a Good Brain Great." It's all about the

practical brain science one needs to know about. There are things we do in the beginning of life that set us up for trouble at the end of life, and the people who need the information don't have it.

JB: That's a great admonition and a rallying cry for our listeners. I appreciate that insight. I recently saw a few papers in the literature that suggested conditions like post traumatic stress syndrome (PTSD), chronic fatigue, and multiple chemical sensitivity, were early-stage markers for later-age dementia, suggesting that there may be some shared common mechanism with regard to brain chemistry or brain chemical dysfunction. Do you have any experience with those conditions, like PTSD, CFS, or chemical sensitivity?

Post Traumatic Stress Syndrome

DA: I do with the first two. We have had a lot of experience with PTSD. When you get traumatized, it flames your emotional brain. The chronic stuff that goes along with having an emotional brain on fire, starts to kill cells in your hippocampus, so that's a nightmare. When I first heard about CFS, my colleagues were saying that these were really psychiatric patients, people who are depressed or people who are hypochondriacs, until I started looking at their brains. It's easy to call somebody bad if you don't look. But as soon as I started looking at CFS, I went "ouch." These people have severe deficits in their brains. No wonder it predisposes them to a dementia-like process, because it's tearing up significant amounts of brain function. The overall decreased perfusion in their brains is dramatic. When you look at it, it's clear they've had some form of toxic exposure from some toxin or from a brain infection. That's the cool thing that scans do. They teach you to be more empathic and they teach you to ask better questions. I work with Harold Burstein, who is the Director of the Psychiatry and Law Program at Harvard. We wrote a paper together on imaging and quark. Harold says that imaging doesn't give you the answers. It teaches you to ask better questions. If you have a patient with CFS that comes to your office and you can't really decide whether they have a difficult personality or do they really have a serious disorder, when you look and you see the damage in their brain, you don't treat them like they're a crock. You treat them with great respect, as if, in fact, they are suffering.

JB: That leads to a question that probably has no discrete answer, but I'd like to get your wisdom of your intuition to the question. Clearly, what you have just described is a kind of medicine that encompasses a lot of thoughtfulness on the part of the clinician, a lot of pattern recognition, and both deductive and inductive reasoning. It's an integration of not only scanning technology and imaging, but it's also the integration of therapies like biofeedback, nutrition, hypnosis, allergy, or orthomolecular medicine. These cut across many medical subspecialty disciplines. How long does it take for a doctor to get adept at this, or is it something that by becoming skilled in the art, one can start making contributions fairly early?

Time Frame for Developing the Necessary Skill

DA: I think if you're well trained, and if you have a good basic knowledge of psychiatry and an open mind, you can learn what we do fairly quickly; I'd say six months to a year of being immersed in it. I think what you and your organization bring to the table is another critical piece that doctors should be exposed to. For me, after looking at it over 10 or 12 years, I wish it was integrated into my training so that I could use it. This is the most exciting time to be part of psychiatry, because we are going to change so radically in the next 10 or 15 years. It's going to look completely different, and to be part of that change is exciting. What we find is that when you learn something new, your brain makes a new connection. One of the ways to keep your brain healthy over time is 1) be excited about what you do and, 2) keep learning new things. It's the perfect time to be involved in this kind of medicine.

JB: For those of our listeners who want to get started down this road, I would urge you to read some of Dr. Amen's books. They are stunning. You should start with *Change Your Brain, Change Your Life*, which was published in 1999 and continues to be reprinted. It's a classic, and it will open your mind to the tremendous opportunity Dr. Amen is talking about. Is there anything you might guide our listeners to doing? You have four clinics, one in Virginia, two in California, and one in Tacoma, Washington. Are there things you might suggest they could do to step into this area?

DA: I have a fourth clinic in Fairfield, outside of Napa in northern California. That is actually our "mother ship," and was our first clinic. I think reading *Change Your Brain, Change Your Life* is a good place to start. I'd poke around on the web site. There are 300 color images on brainplace.com that people can look at to see the different conditions and what kinds of scans go with it. And then, I'd just poke around in the scientific abstracts until you get comfortable in your own skin. This isn't smoke and mirrors. This is something that's based on hard science, and it's very exciting. One of my favorite books is *Healing the Hardware of the Soul*. It gives you a different thought pattern about your patients. It'll put you on a better path.

JB: I can't tell you how much we appreciate your spending the time with us today. We will all be your students as this technology and integrative procedure makes its way forward. Thank you so much for your contributions.

DA: Thank you, Jeff. It's been a real pleasure.

The Functional Medicine Assessment

It struck me, in thinking about Dr. Kornberg's extraordinary comments, that when we start looking at the functional medicine model from 30,000 feet in a kind of broad-brush evaluation, the approach is very different from that of the traditional differential diagnosis, which is to try to know more and more about less and less, so that you can ultimately get a specific diagnosis. The functional medicine assessment, so eloquently described by Dr. Kornberg, is to keep moving up to higher levels of organizational perspectives to look at where the interconnections occur, and then to drill down into the individual mechanisms of action related to each of the nodes on the matrix. There is a sense that we are moving back and forth between a telescope and a microscope with the functional medicine model. There is a broader-based perspective and then a very small perspective, and a personalized approach for the patient is developed, based upon the interrelationship between the connection of the whole and focusing therapeutic energies into implementation to the individual components.

Oxygen as a Therapeutic Agent

What is one of the most important elements that all air-breathing organisms need to be concerned with, as it relates to dysfunction? That, of course, is oxygen, which is about 20 percent of the air we breathe. Often, we forget about air and water as being very important parts of therapy. Every traditional form of healing, from the dawn of medicine, had something to do with delivering air or oxygen to tissues. It could be deep breathing, yoga, exercise, various types of physical medicine, or dance-any number of things up through aerobic exercise and later, into mechanical intubation.

I am talking about making sure that oxygen delivery and respiratory gases are properly controlled. Low levels of oxygen in tissues produce oxidative stress, which is associated with inflammation and tissue

injury. We want to make sure that tissues are properly oxygenated, and that a person is delivering oxygen to things like the monooxygenase enzymes, which are the cytochrome P450s, the various detoxification enzymes we have talked about that require oxygen for their activity and for proper function to detoxify endogenous and exogenous toxins.

Water as a Therapeutic Agent

Water is also a very important therapeutic agent, because hydration is critically important for establishing appropriate environmental conditions within cells, tissues, and organs for their function. Dehydration increases the solute concentration and changes enzyme function, cellular activity, and membrane transport. Proper hydration becomes an extraordinarily important part of any therapy in making sure that there is proper balance of intra- and extracellular fluids. The nature of the medications many patients take may alter their intra- and extracellular fluid balance and can lead to intracellular dehydration. Anyone who has overdone alcohol sometime in his or her history recalls the effect that it has on intracellular hydration. It produces a dehydration effect and makes one very thirsty because the cells become dehydrated and, as a consequence, there are toxic symptoms. I want to make sure we recognize that sometimes the simplest things become the most important for proper breathing, delivery of oxygen, and proper fluid intake for intracellular hydration.

Again, that obviously ties into the topics that Dr. Kornberg was speaking about as part of the matrix-concepts of GI function, immunological function, hepatic detoxification function, oxidant balance, redox balance, neuroendocrine balance, and body/mind balance. These all interrelate as components of the web in the matrix to things as simple as proper delivery of oxygen and proper fluid intake.

What we have outlined in the course of this issue of FMU is a model that has sprung out of nearly 20 years of the emergence and evolution of functional medicine. It paves the way for increased application of this model to a variety of different complex, chronic disorders that do not necessarily fit into a tidy diagnostic profile. I am holding the *Textbook of Functional Medicine*, which relates to the themes and concepts described in this issue of FMU. This is an 800-page embodiment of the spirit of what we have been talking about for nearly 20 years. I hope you will have a chance to read the textbook and spend some time getting the kind of mastery of these techniques that will allow you to help your patients more effectively.

Thanks for being with us. We will see you in April.

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