April 1999 Issue | Carolyn McMakin, MA, DC

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Welcome to *Functional Medicine Update*™ for April 1999, the last month before our Sixth International Symposium on Functional Medicine in Tucson, Arizona, May 23-26. Speakers at past Symposia have included Ferid Murad, who won the Nobel Prize in Medicine in 1998, and Dr. Kilmer McCully, world-renowned for his pioneering work in homocysteine, heart disease, and stroke. Again this year we have a roster of stellar international presenters scheduled for this year's symposium as well.

Unique characteristics that distinguish functional medicine from other forms of complementary or alternative medicine include patient-centered approaches, biochemical individuality, and health as a positive vitality. A fourth characteristic is the principle of homeodynamics rather than homeostasis. How does the concept of homeodynamics relate to the way you manage patients every day?

This month, we will discuss energy-related functional problems in health care—chronic fatigue syndrome, fibromyalgia, myofascial pain, and fatigue-related problems like those associated with chronic inflammatory disorders. An individual in a state of dysfunctional equilibrium may experience ongoing pain and fatigue that last for years. It becomes necessary, in working with this individual, to undertake homeodynamic restructuring to find a state of functional equilibrium and a new dynamic relationship with the environment. To apply the concept of homeodynamics to clinical practice, we must understand what is meant by homeodynamics.

A hummingbird provides a visual metaphor. Although the hummingbird looks static when it hovers at a flower to gather nectar, its wings are actually beating dynamically to maintain homeostasis in a stationary state. This extraordinary work against the forces of nature is called homeodynamics. The hummingbird is a metaphor for our physiology and the way our brains, hearts, and immune systems respond to a changing environment. Although we maintain rather constant blood sugar, insulin, electrolyte levels, electromotor potential of membranes, and oxidative potential at the mitochondria, our bodies are having to work hard to maintain those levels of threshold function. The dynamics that underlie that process are like the beating of the hummingbird's wings—it is homeodynamics.

Patients in the diabetic wing of a hospital could have an average blood sugar level that would be its own homeostasis, called hyperglycemia. The individual patient would be less able than the average person to bring his or her blood sugar level into what we consider an ideal range associated with good health. Homeodynamics is the process by which homeostasis is obtained. It involves complex self-organizing structures and, in the mathematical and biological theory model, chaos theory.

We generally do not go from one state to another by a linear progression, from having no cold, for

example, to having a cold, or from having no flu to having the flu. We change our state very quickly. We hold on to one state as long as our bodies allow, and then we shift very rapidly, perhaps in seconds, to another physiological state. The abrupt changes that characterize these nonlinear systems, called "emergent properties," can have major and unexpected consequences. A person can go very quickly from a state of reasonable health to a state of ill health.[1] This kind of transition is connected with the individual's homeodynamic resiliency. To use Dr. James Fries' term, how much "organ reserve" does the person have? The more organ reserve one has, the more resilient he or she is. The more capacity the individual has for change. Therefore, one objective of functional medicine is to build reserve against the change.

One hallmark of the chaotic system is extreme sensitivity to its initial conditions. For example, human brain recordings exhibit nonlinear dynamics. Billions of neurons interact by cell-to-cell communication to form collective systems that emerge as more than the sum of the individual neurons. Thus we get synergy. The whole is greater than the sum of its parts. These self-organized neuronal interactions within the brain respond to their external environment and form dynamic neural networks that collectively store, process, and rapidly retrieve vast amounts of information, which is displayed as consciousness and can ultimately be seen as creativity.

This nonlinear homeodynamic system gives rise to holographic function, not just linear digital function. It is not analyzed as A goes to B goes to C. Instead, these vast networks of dynamically interacting, time-dependent, changing systems give rise to the real differentiation of a physiologically healthy system from a very linear, monocultural, unhealthy system in which just breaking one metabolic pathway produces health catastrophe. According to this argument, the more redundancy we have, the more complexity, and the more stable the system.

Nonlinear dynamics include chaos theory. This theory is emerging as a new form of analysis for studying complex biological systems, including the brain, the heart, epidemics, and cancer. Complex adaptive systems like the brain (composed of neurons), and the heart (composed of cardiomyocytes) are good examples of this concept of nonlinear homeodynamics. Living systems usually evolve toward a boundary between order and randomness. They are thought to be poised on the edge of chaos all the time. Gradually increasing the strength of the interaction between the individual units making up the system forces the collective system into a phase transition, going from order to randomness. These complex systems adapt toward the boundary between order and chaos by natural selection. In fact, in a recent paper, Kauffman proposed that the maximum fitness of an organism or collection of organisms occurs at the interface between order and chaos.[2] Maintaining yourself at the leading edge without being at the bleeding edge is really the most important part of maintaining health and vitality.

The emerging collective features of self-organization involving neurons in the brain, for example, or cardiomyocytes in the heart are often distributed in interesting ways. They can also be disturbed in a variety of ways that result in disease. Altering the chaotic nature of a biologic system could alter its fitness. It has been proposed that this is what happens in chronic heart failure and during epileptic seizures. Early analyses have revealed a conflicting role for chaos in cardiology. Heart math is a new field emerging from work at the Santa Fe Institute. Researchers are looking at cardiac rhythms that occur throughout the day, which are related to different chaotic events and how the system restores itself to

function. How much noise is there in the system? How resilient is it to homeodynamic perturbations?

Chaos appears to be advantageous to the heart and brain. When it is lost, pathological states appear. As you lose resiliency, weblike function, and complexity, you become more susceptible to disease, just as we have been saying in our definition of functional medicine. Our responsibility as practitioners is to assist people in increasing their physiological, cognitive, emotional, and physical complexity so they can maintain higher resiliency and more homeodynamic plasticity against the changing environment.

This esoteric goal has some big payoffs in the way we approach the patient. "Complex systems with unexpected new properties can arise abruptly and emerge from the cooperative interaction between simple and individual units. Each unit interacts in a cooperative manner with its neighbors to form an adaptive, interactive network. The collective properties that emerge from the network are capable of forming and changing strategies to maximize fitness of the overall system to the changing environment. The roles of chaos and self-organization in these complex adaptive systems are becoming an important focus of many studies in medicine."[1]

This may form the way we look at health, vitality, and function as we move into the new millennium. Homeodynamics will be a major part of one of the strategies, improving homeodynamic resiliency, and looking at functional ways of assessing it.

We often look for simple clinical ways to assess aspects of function. The authors of a recent paper, titled "Midlife Hand Grip Strength as a Predictor of Old Age Disability," in the *Journal of the American Medical Association*,[3] discuss a simple tool most of us may not use in predicting how patients will function as they age. Using a dynamometer and measuring grip strength in the right and left hands is a useful prognostic determinant for overall later-stage disability and problems related to health as one ages.

Among healthy 45- to 68-year old men, hand-grip strength was highly predictive of functional limitations and disability 25 years later. It had prognostic ability. In a deterministic model, you could say that if you have poor hand-grip strength at 45, you are on the road to real problems and there is nothing you can do about it. You've lost your functional plasticity. Your chaos is thrown into a state of limited diversity, and the outcome is determined.

In a different model, you could look at this test and say that if you have low hand-grip strength at age 45, and it is a predictor of disability over the next 25 years, you should make some changes. You should work on your overall metabolic fitness, including physical fitness, psychological fitness, cognitive/emotional fitness, biochemical fitness, nutritional fitness, and all factors encompassed by a fully functioning individual to maximize genetic potential. It becomes part of this model. That model is basic to functional medicine. If we look at the concept of plasticity, weblike behavior, and homeodynamics, we are saying that low hand-grip strength indicates loss of homeodynamic plasticity, which is a predictor of greater disease risk. We need to practice the right things. You might consider adding hand-grip measurements into your assessment protocol. It is a simple thing to do. A standard dynamometer, available at fitness or medical supply companies, is another tool for understanding the function of the individual. You can tie that together with intervention programs to improve function, strength, mobility, fluidity, and metabolic plasticity.

Fatigue is the central theme of this month's *FMU*. The March Clinician of the Month was a researcher, Dr. Martin Pall from the Biochemistry Department at Washington State University medical school training program. He described a model of fatigue-related dysfunction concerned with mitochondrial dysfunction and energy deficits. To some extent fatigue is in the eye of the beholder. A recently published book, *Chronic Fatigue and Its Syndromes*, by Wessly, Hotopf, and Sharpe, looks into the definition of fatigue. The book, published by Oxford University Press in 1998, is a good review of the concept of fatigue.

Asked about their feelings in the previous month, about 19 percent of men and 30 percent of women in the United States say they were "always feeling tired."[4] What does that mean in terms of a medical diagnosis, or is there no diagnosis? The book's authors point out that the term fatigue encompasses many cognate meanings. We all feel exhaustion after exertion. Climbing a mountain would probably lead to your feeling fatigued, even if you were in good physical condition. However, there are other definitions of fatigue. It might encompass the subjective feeling of increased effort required to accomplish a task, or psychological lethargy at the prospect of physical or mental work. Just to consider doing something may lead to fatigue. There are different levels of the definition of fatigue.

The word fatigue originated from a 17th century French word that indicated profound weariness. By the 19th century it could also refer to "a condition of weakness in metals caused by repeated blows or strains." Obviously, fatigue is a word like "love," with many definitions in different contexts in different individuals. Like pain, it is a complex and almost universal human experience, but fatigue inhabits a territory that is less explored by medicine. We can monitor and measure pain fairly easily on a subjective rating scale, but it is much more difficult to measure fatigue. Fatigue may relate to lethargy, exhaustion, lack of interest, boredom, mood changes, anxiety, depression, or disturbances in sleep, libido, and even declines in behavioral performance. It is a complex concept from a medical diagnostic perspective.

Clinical factors associated with fatigue frequently hint at underlying physical disorders. Fatigue is associated with a number of physical illnesses in the general population. It cuts across a lot of diagnostic categories. You can open a medical textbook almost anywhere and find a condition characterized by fatigue, along with other symptoms or signs.

Chronic fatigue syndrome (CFS) differs from fatigue that characterizes other conditions. In chronic fatigue syndrome one experiences profound lethargy that is made worse by minimal physical or mental exertion. After engaging in exercise they formerly tolerated very well, CFS sufferers can be completely exhausted for up to 24 hours. This exhaustion associated with accustomed exercise is at the core in diagnosing patients for whom no clear-cut physical or psychiatric diagnosis can be established. Easy fatigability can be traced to conditions like neurasthenia in the 19th century, nervous exhaustion characterized by undue fatigue on the slightest exertion, both physical and mental. The chief symptoms are headaches, gastrointestinal disturbances, lymphadenopathies, and other subjective sensations.

Chronic fatigue has been a waste basket diagnosis for a number of problems that don't lend themselves to clear medical diagnoses. We are beginning to understand chronic fatigue as a problem of multiple etiology that interrelates with other clinical conditions or symptoms, such as myofascial pain, fibromyalgia syndrome, multiple chemical sensitivity, and perhaps even problems like Gulf War Syndrome. We can identify a number of triggering factors for chronic fatigue syndrome of this type, including viral infections, fever, or flu-like infection. These factors seem to be part of the complex,

although they are not the only etiological agents. A number of agents combine to affect the hypothalamus/pituitary/adrenal axis to influence immunochemical function and general immunological vigilance to change the web-like pattern of homeodynamic physiology into a new state function characterized by metabolic inefficiency and fatigue.

History and Traditional Treatment

In England in the 1950s, a fatigue-associated disorder was called myalgic encephalomyelitis. Later, through the research of Dr. Paul Cheney and his colleagues in Lake Tahoe in Incline Village in the 1970s, it became known as chronic fatigue syndrome. It seemed to be associated with a particularly bad flu season in the Lake Tahoe area. We now know that factors including chemical agents, low- grade infections, inflammatory conditions, xenobiotic exposure, drug and alcohol excess, emotional stress, and trauma can combine to affect physiology and psychology in a manifestation we call chronic fatigue syndrome.

Traditional medical treatment for this condition was with antidepressants. According to the authors of the book Chronic Fatigue and Its Syndromes, antidepressants are worth offering to sufferers of chronic fatigue who report depressed mood. They acknowledge the major side-effects of these drugs but explain their potential benefit in holistic terms. "We commonly (and truthfully) justify their use by describing them as ‘broad spectrum’ agents that can improve pain, sleep, and energy, as well as mood, and thereby diminish the stigmatized psychiatric connotations of such medication."

Manifestations of chronic fatigue syndrome that include depression, mood swings, and sleep disturbances may not be altered at the etiological level by antidepressants. We might want to look at potential mechanisms other than symptom modification.

The authors of a recent *Lancet* paper titled "Low-Dose Hydrocortisone in Chronic Fatigue Syndrome: A Randomised Crossover Trial,"[5] looked at chronic fatigue syndrome patients who fulfilled the CDC criteria for the diagnosis. Of 218 patients in this trial, 32 met the strict criteria for CFS without co-morbid psychiatric disorders. In a crossover trial, these patients were given low-dose hydrocortisone.

If you have been following *Functional Medicine Update*™ for some time, you have heard discussions of Dr. McK Jefferies’s book, *Safe Uses of Cortisone.* Dr. McK Jefferies discussed his book when he was our Clinician of the Month nearly 14 years ago. In his book, originally published in 1981 by Chas C. Thomas (2nd edition titled, *Safe Uses of Cortisol,* 1996), he describes the use of physiological doses of cortisol, hydrocortisone. This would be 5 to 10 mg doses that would not suppress the adrenal gland but would reduce adrenal stress and allow repletion of function. He talked about hypoadrenalcorticism and treating it with low doses of cortisol. Jonathan Wright, MD, has been a strong advocate of this approach and has spoken about it over many years. In interviews on *FMU*, Dr. Wright has talked about the *Safe Uses of Cortisol* for hypoadrenic symptoms and signs.

The authors of the *Lancet* paper are employing the McK Jefferies *Safe Uses of Cortisol*approach without defining it as such. This paper came out of the Departments of Psychological Medicine and Medicine at Guy’s, King’s, and St. Thomas’ School of Medicine and the Institute of Psychiatry in London, and Addenbrooke’s NHS Trust at Cambridge. They report that compared to a placebo, a 5 to 10 mg daily doses of oral hydrocortisone for one month gave significant remission of chronic fatigue symptoms in patients with well-defined CFS.

Altered function of the hypothalamic/pituitary/adrenal axis is a well recognized feature of unrelated, apparently non-endocrine disorders, including depression, obesity, starvation, and fatigue. Evidence is accumulating that HPA function may be altered in people with CFS, who have lower urinary cortisol output than individuals who have no fatigue and normal adrenal function. Therefore, adrenal cortisol testing may be a useful tool. Often, as Dr. McK Jefferies suggests, administering a clinical trial of low-dose cortisol may be the best way of seeing if a person is suffering from this hypoadrenal cortical function.
Hypoadrenia

Investigators in this carefully conducted study found fatigue scores fell to normal in 9 of 32 patients selected from the initial 218 patients, compared with just 3 whose symptoms improved on the placebo. They say that although suppression must be of concern whenever one uses cortisol replacement, it is very unlikely to occur at 5 or 10 mg daily doses. Whenever you use repetitive doses of cortisol replacement, even low doses, you need to be cautious that you are not overly suppressing HPA function.

The concept of functional hypoadrenia was enthusiastically endorsed quite a long time ago. Its first promoter was Dr. Charles Eucharist de Medici Sajous, who in 1917 was appointed as the first president of the American Association for the Study of Internal Secretions, which later became the Endocrine Society.6 Robert Tattersall summarized it recently in a marvelous essay titled "Hypoadrenia, or a Bit of Addison’s Disease." In functional and nutritional medicine, the concept of functional hypoadrenic function has been around for many years, and the treatment has been to use adrenocortical extract or purified hydrocortisol, as Dr. McK Jeffries has described.

This interesting paper suggests that a low HPA functioning in chronic fatigue may relate to some of the symptoms as a consequence of hypoadrenia. One might ask about the source of the hypoadrenia, again getting out of the pharmacological model and into the weblike model. Where did it come from? What was the metabolic, physiological, or psychological stress, the effector of this condition of hypoadrenia? We might not want to just focus on the adrenal replacement alone. Perhaps we should look at other aspects of the pressure on adrenal function that led to its depletion.

Last month Dr. Martin Pall described an inflammatory characteristic associated with chronic fatigue syndrome. That inflammatory characteristic increased levels of inflammatory cytokines, the IL1, IL6, and TNF alpha. It is also associated with increased nitric oxide production from macrocytes. The oxidative stress that occurs during this process has the combination of superoxide combining chemically with nitric oxide to form peroxynitrite. Peroxynitrite increases the generation of nuclear factor Kappa B within cells that shifts cellular physiology. It shifts the weblike physiological state into a new homeodynamic state associated with oxidative stress.

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Recent papers support this model. Investigators have looked at mitochondrial abnormalities associated with age-related skeletal muscle fiber atrophy in Rhesus monkeys, showing a very close correlation. An interesting paper of this type was published in *Free Radical Biology & Medicine* in December 1998.[7] Investigators showed a decrease in normal fibers and an increase in abnormal fibers that was very closely correlated with damaged mitochondrial DNA deletions. A correlation exists between loss of mitochondrial function, altered muscle activity, and increased fatigability. A paper titled "Unusual Pattern of Mitochondrial DNA Deletions in Skeletal Muscle of an Adult Human with Chronic Fatigue Syndrome," published in *Human Molecular Genetics* in 1995, described similar deletions on the DNA from mitochondria in a 54-year-old male suffering with CFS.[8]

We need to consider how we can lower some of the metabolic load. How do we re-establish proper immunochemical function? How do we move a person from an oxidative stress feed-forward cycle into a more balanced reduction/oxidation potential and prevent mitochondrial injury? This is part of the possible treatment program for some patients with this fatigue-like constellation. Chronic fatigue syndrome is a complex condition with multiple etiologies. A reasonable percentage of those who experience this syndrome may suffer from this total load of alteration on their immune system, which has locked them into this new feed-forward of physiological principles of oxidative stress.

A paper that supports this hypothesis in one open clinical trial is titled "Evaluation of the Effect of a Modified Entero-Hepatic Resuscitation Program in Chronic Fatigue Syndrome Patients." The principal investigators are Dr. Scott Rigden in Tempe, Arizona, and Eleanor Barrager in our Functional Medicine Research Center, a long-standing participant in chronic fatigue research.[9] This paper, which appeared in the *Journal of Advancement in Medicine* in 1998, describes patients who were unsuccessful in managing their chronic fatigue by a variety of clinical interventions. Average protraction of illness was 3.5 years. This paper describes the results of an entero-hepatic resuscitation program, which focuses principally on increasing antioxidant levels and decreasing the reactivity of various intermediary toxic substances. It uses supplementation with phase II detoxification support nutrients like glycine, taurine, and pantothenic acid, and upregulators of phase II detoxification enzymes, including nutrients from cruciferous vegetables, indole-3 carbinols and the glucosinolate compounds, which help activate phase II detoxification.

The program focused on lowering inflammation, increasing immune function, and improving adrenal/hypothalamic/pituitary function by intervening with a metabolic support program. The program emphasized improvement of phase II detoxification and reduction of oxidative stress. The majority of the patients had significant clinical improvement, correlated with improvement in their detoxification profiles, particularly normalization of the ratio of phase I cytochrome P450 to phase II detoxification. These people, called imbalanced detoxifiers, started off with a very depressed phase II detoxification pathway. They may have had an unregulated phase I with depressed or suppressed phase II. By normalizing their detoxification profiles by using metabolic intervention, using higher levels of

antioxidants, and lowering immune stress by putting them on a hypoallergenic diet in a clean environment, their function improved significantly over a period of several months. Dr. Martin Pall's concept of a feed-forward mechanism of chronic fatigue symptoms that interface with mitochondrial function has clinical application.

Thyroid function is another interesting part of this discussion. Many patients with fatigue may present with what appears to be functional hypothyroidism. In the 1960s, Dr. Broda Barnes showed that functional hypothyroidism could be assessed by the low axillary body temperature on waking, taking the temperature throughout the month, and finding the average. A low axillary body temperature, even with normal thyroxine plasma levels, suggested functional hypothyroidism. Thyroid replacement therapy could improve thyroid function, mood, cardiac function, cognitive abilities, skin, hair, and GI function.

As the thyroid replacement agent, Dr. Barnes advocated Armor thyroid. It was discontinued as he principal way of replacing thyroid function in medicine because of the concern about nonstandard dosages of thyroid hormones. Medicine moved to synthetic thyroxine and triiodothyronine hormones, so one could administer specific graded doses. Animal-derived thyroid concentrates became little used.

Extracts of animal thyroid tissue, first used in 1892, obviously contained a variety of thyroid hormone-like metabolites including both thyroxine and triiodothyronine (T3). In the 1960s, the recommended daily dose of thyroxine as we moved to the purified thyroid hormones, in most major clinical textbooks, was between 200 and 400 μ g for the treatment of individuals suffering from primary hypothyroidism. These are not functional hypothyroid people, but those with frank diagnosis of primary hypothyroidism.

These doses, associated with high serum thyroxine concentrations, were believed necessary, until it was recognized that thyroxine is converted to the metabolically active triiodothyronine by peripheral monodeiodinization. In other words, it's not the thyroid gland itself that produces most of the physiologically active thyroid hormone, which is T3. Extra-thyroidal tissues pull off an iodine atom. It has been only in the last few years that we have recognized that deiodinase enzyme, which takes an iodine atom off the T4 thyroxine molecule, is a selenocysteine enzyme. This is another example in which selenium insufficiency can produce functional disabilities in the form of hypothyroidism. Under-conversion hypothyroidism describes the inability to properly convert T4 to T3 in extra-thyroidal tissues, or even in the thyroid gland itself. From 10 to 20 percent of T3 is produced in the thyroid gland; 80 to 90 percent is produced in extra-thyroidal tissues, again by the selenium-containing deiodinase enzyme.

Since the 1960s, opinions have changed. Assays have been developed that can distinguish normal from low serum thyrotropin concentrations. Therefore, no longer are the very high doses of 200 to 400 μ g of thyroxine being recommended. Doses of thyroxine sufficient to suppress serum thyrotropin concentrations without necessarily increasing serum concentrations of thyroxine and triiodothryonine in the thyrotoxic range were associated with changes in the function of the target organs. Functional use of thyroid then became more important for improving function of the liver, heart, kidney, and bone. One could use lower doses without risking overt thyroidtoxicosis. Suggested doses were in the range of 100 to 150 μ g per day, which was adequate to restore thyrotropin secretion to normal and to improve thyroid function.

A substantial minority of hypothyroid patients say they do not feel as well as they would like when they take thyroxine in doses only sufficient to restore their serum thyrotropin concentrations to normal. Their

desired sense of well being occurs with doses 50 µ g per day greater than that needed to restore normal thyrotropin secretion. So there appears to be functional differentiation in response to thyroid hormone from one person to another. It may relate to differing T4 to T3 conversion from individual to individual.

A paper appeared in the *New England Journal of Medicine* the re-explores the use of armor thyroid, or mixtures of thyroid hormone that occur in natural tissues, mixtures of T4 and T3. The title of this paper is "Effects of Thyroxine as Compared with Thyroxine Plus Triiodothyronine in Patients with Hypothyroidism."[10] The authors point out that the daily production of thyroxine by the thyroid gland is about 100 µ g, and the daily production of triiodothyronine is about 30 µ g, of which about 80 percent is produced in the extra-thyroidal tissues by deiodinazation of T4 to T3. Authors of this study administered a graded mixture of T4 and T3 to patients to see if they could get improved function over giving T4 alone. They found, in patients with hypothyroidism, that partial substitution of triiodothyronine to thyroxine improved mood and neuropsychiatric and neuropsychological function. This finding suggests a specific effect of triiodothyronine normally secreted by the thyroid gland.

You might believe this validates what Dr. Barnes told us 30+ years ago. These improvements occur without the suppression of thyroidtropin secretion. They preclude the possibility of thyroid toxic effects. Although at first it seems that everyone should be put back on the armor thyroid or on natural mixtures of thyroid, the author of a *New England Journal of Medicine*editorial cautions against jumping too quickly onto that bandwagon.[11] First, he says that in experiments in animals, one tissue behaved differently from the other, and in the cerebral cortex one might have normal T3 despite a wide range of serum thyroxine concentration. We need to understand the individual characteristics of response to T4 and T3 in the patient.

More important, however, currently available combined preparations of thyroid hormones contain an excess of T3, as compared with T4. The ideal medication would contain, they say, about 100 µ g thyroxine and 10 to 20 µ g triiodothyronine, the latter in slow-release form to avoid adverse cardiac effects. They speak from a conservative pharmacological perspective, without a lot of experience in the use of natural mixtures of thyroid hormones, as derived from the animal gland and standardized to T3 and T4 levels. I do, however, advise caution in the use of animal concentrates. In this age of prions (protein infectious particles from animal parts), we at least should recognize that prion-free organ concentrates would be in the best interest of patients if one uses natural mixtures of thyroid hormones.

…agent pharmacological doses of substances versus mixtures of physiological compounds that create balance. One might ask if replacement of T4 and T3 is the only solution to this problem. What about normalizing the body’s conversion of T4 to T3 if it’s not primary but secondary under-conversion hypothyroidism? What about selenium supplementation, proper balancing of zinc and copper levels and their ratios to improve thyroid hormone metabolism? What about essential fatty acids, particularly omega-3 ALA and EPA and their effect on improving thyroid hormone receptivity at the membrane binding site?

These other factors may have an effect, as well as lowering body burden of xenobiotics and toxins that cause antibody to be produced against them that cross-react with the thyroid gland and may increase thyroid reactivity. All of these factors frame an integrated functional approach toward thyroid-related dysfunction. First is improving T4 conversion by selenium and zinc/copper ratio balancing, and iron. Second, provide essential fatty acid supplementation and reduce the saturated fat content of the diet.

Third, lower body burden of agents that enhance antibody production that can cross-react with the thyroid gland, particularly xenobiotic compounds, phenols, and other polynuclear aromatic compounds.

This discussion examines a functional medicine approach to restore proper homeodynamics and resiliency in the system on the border between the environment and the internal function of the individual. That border of chaos is where the thyroid gland often operates. It's at that interface level, as is the adrenal gland. They are two sentinel antennae, interacting with the external environment, sampling how our physiology should respond. They are like hummingbirds' wings, trying to make sure they are at the right frequency of vibration so that they are responding properly and are able to maintain static function.

Side II of this month's *FMU* provides a useful application of these concepts of weblike, homeodynamic function and the concept of energy in medicine. Our Clinician this month will help us understand the interface between the electromagnetic spectrum, energy in medicine principles, and biochemical metabolic energy. They are not separate topics, but a continuum of interacting components that give rise to stability of function in the individual. We will discuss how these principles interface with regulatory hormones that control our response to the environment and help prevent fatigue-related symptoms. These hormones include not only cortisol, but our sex steroid hormones—estrogen, testosterone, the androgen family—and their relationship with pregnenolone and DHEA. Finally, I will close with a discussion of where fatigue might have its center, which is in the central nervous system in functional neurology, an advancing application for the area of functional medicine.

INTERVIEW TRANSCRIPT

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Many listeners have asked if we could integrate the energy in medicine concept into functional medicine and our Clinician of the Month interviews. Energy—electrochemical interactions—is a major component of the function of the musculoskeletal/neurological system and every system in the body. The bioenergetics of the body is an important determinant of overall function. It has often been said that just as electric and magnetic fields are interrelated, the biochemical and electromagnetic energies of the body are also interrelated,.

Our Clinician of the Month is a chiropractic physician from Portland, Oregon, who has focused her attention on this area since 1986. We are fortunate to have Dr. Carolyn McMakin with us. She is the lead physician at the Chiropractic Family Care Fibromyalgia and Myofacial Pain Clinic in Portland. Carolyn began her career by earning a master's degree in counseling, which she has found useful in working with patients who suffer from chronic pain symptoms that create their own psychosocial milieu and complex challenge to the practitioner. She then went to Western State Chiropractic College, which is heavily focused on mechanisms, anatomy, and physiology, and took an array of premedical science courses.

She has been in private practice since 1984. Since 1986, she has focused on frequency specific intervention related to energy in medicine and its application to an array of chronic pain problems, including fibromyalgia and myofascial pain. One of her recent publications discusses the work she's doing—the treatment of resistant myofascial pain with microcurrent, using specific frequencies applied with graphite/vinyl gloves. This work was presented to the American Back Society in December of 1997.

JB: It is a great privilege to welcome Dr. McMakin, to *Functional Medicine Update*™. How did you enter the field at the interface of energy in medicine with pain management and chiropractic?

CM: We started in 1993 and 1994, when I was working with another chiropractor who had access to and information about work done in the early 1900s using specific frequencies to treat specific conditions. There were medical physicians at that time who used electromagnetic therapies to treat various conditions. They had no prescription drugs to speak of. They were using specific frequencies with electromagnetic therapies, and we had access to those frequencies.

In 1996, we bought a microcurrent instrument that came with graphite/vinyl gloves. It was obvious that the gloves would be appropriate for use with a microcurrent instrument capable of doing specific frequencies, and they would be good for muscle work. I took some of the frequencies we had that were for mineral deposits, for example, and applied them to chronic myofascial tissue that feels sort of stiff. There was a remarkable, immediate softening of the tissue. I had done manual trigger point therapy before and never experienced anything like this.

Through 1996, we treated about 215 new patients and found the response was consistent and predictable. We refined the application of the method—which frequencies to use for which type of tissues and that sort of thing. The frequencies from the manual that came with one of these machines from the early 1930s seemed to convert directly to microcurrent. There are frequencies for mineral deposits, fibrosis, scar tissue, and something called allergy reaction that appears to be related to an inflammatory or histaminic response in the tissue. There are frequencies for specific tissues—veins, nerves, arteries, and different organs in the body. There was a group of medical physicians in the early 1900's for whom this was their method of treatment. Some of the work has been preserved. Most of it has been lost. We happened upon a manual that had the frequencies in it. We took the frequencies from the manual, probably in early 1997, and expanded what we had been able to do.

The results have been not only gratifying, but truly remarkable. Patients with chronic pain conditions, who have been through physical therapy, medical intervention, chiropractic treatment, acupuncture, and naturopathic treatment would end up at our clinic. The microcurrent would produce fairly rapid, permanent results, sometimes within 8 to 10 visits. Sometimes it took as many as 20 or 30 treatments over a 3- to 12-week period. Microcurrent wasn't all that we did, but it made the most immediate, dramatic, and palpable change in the tissue. It has been consistent and reproducible, and the frequencies are definitely a feature of the results.

Teaching the Method to Others

In 1997 I started teaching it, because the results we had in 1996 made it clear that we were doing something. The next step in science is to find out if results are reproducible. To do that I had to teach it. We started holding four seminars a year for continuing education for chiropractors, naturopaths, and physical therapists. Through 1997 those students took the method out into practice. By the end of 1997, it

became apparent that the results were reproducible. My students are getting results similar to ours, and many patients are benefiting. It's really quite rewarding.

JB: We had an *FMU* Clinician interview a number of years ago with Dr. Reuven Sandyk, a neurologist on the East Coast who was using microcurrent in the management of MS. He used a device that was placed on the head and used very small amounts of electromagnetic energy to change neurological function. Many of our listeners wanted to know how they could do this. Dr. Sandyk was working on an experimental protocol that was kind of an IND. He was not prepared to release this concept to clinicians. I presume from what you have said that you're comfortable enough with what you are doing that you can teach other people, and you know enough about its safety and effectiveness to transfer this information.

CM: In the work we did in 1996 and 1997, we came up with consistently effective sequences of frequencies that are effective probably in 80 to 85 percent of resistant myofascial pain. We teach these methods in two one-day seminars back-to-back on Saturday and Sunday.

In terms of safety, I'm quite confident. We have had no negative effects with microcurrent, as long as it's sensibly applied. For example, you shouldn't use it through the brain or through a pregnant uterus. Those are standard contraindications for microcurrent. Treatment with microcurrent took two patients who had spinal cord injuries from being numb in specific dermatomes to hyperesthesia. These spinal cord injuries had happened a year and a half before. We know of no contraindication to using this method, and there are no side effects aside from a detoxification reaction that occurs right after the treatment.

We teach students how to manage this with nutritional supplementation and hydration. The treatment protocols have been fairly standardized at this point. We've treated over 800 patients, and roughly 9000 patient visits over the last three years, and there are certain consistent, predictable post-treatment reactions. Other than that, it's completely safe.

Microcurrent is in millionths of an amp; it's very physiologic. It increases APT production and protein synthesis. It restores normal bioelectric conductance to the tissues and doesn't seem to have any negative effects. There's almost no way to hurt somebody unless you don't follow the directions. The frequencies for fibrosis can't be used in the first four weeks after a new injury because fibrotic repair tissue is what the body uses to heal. We found that out the hard way by treating somebody two weeks after a new injury with frequencies for fibrosis. We found that we made them worse for three or four days until the body could re-repair that tissue. In early 1997 that became a standard contraindication warning that's passed on to my students during the class. They go home with a summary sheet that allows them to use the protocols in their first day back in practice, and I'm available for phone calls and consults.

The frequencies are like a language. There are frequencies for conditions such as fibrosis, scar tissue, allergy reaction, old bruising, and mineral deposits. There are probably 15 or 18 frequencies for conditions. Then there are frequencies for specific tissues. If you're treating a tissue, there's a certain logic to apply. It's as if you now have a tool, so you get to think of different nails. You get to think of different conditions that make up the patient's complaint, almost on a cellular level.

Neuropathic pain treatment is our most recent success story. If someone has a disk bulge or just nerve irritation for various reasons, you can address the irritability in the nerve. You can address the need to repolarize the nerve to restore the normal membrane integrity and raise the firing threshold so the nerve

pain quiets down. There's a certain logic that has to be applied to that tissue. My students will hear me in the treatment room say to myself, what is it? What's going on in this particular tissue in this patient on this day that we can address with the frequencies we have available?

This treatment method has totally changed my ideas about what the human body can and can't do in terms of healing. When you use the right frequency and address the right tissue with the right conceptual framework, the results are virtually immediate. We have a frequency that seems to be very effective for shingles, for example. It's the only frequency I use diagnostically. Without biopsy work, without further study, without dissection, we can't say with certainty whether these frequencies are doing what we think they're doing. We have lots of clinical, palpatory, and measurable results that say we're doing something. But on a cellular level, we can't say for sure what we're doing. So we are very careful about that.

There is one frequency that is so effective in shingles and viral infections, however, that I use it diagnostically. This frequency takes the pain away. The pain is in the characteristic dermatomal distribution where it's burning hyperesthesia right along the dermatome. If you use this frequency, the pain is gone in 10 to 15 minutes, and two or three treatments over a week will prevent the blisters from breaking out. We've probably done this 15 times. It's reproducible and consistent, and there's no risk. It either works or it doesn't. In patients who are at severe risk, we also recommend that they take appropriate anti-viral therapy, either medical or nutritional and herbal. When you do the correct thing to the correct tissue, the response is immediate. It reinforces what you and others have said in the last two or three years: there seems to be an increasing awareness of the bioelectric, energetic quantum theory of the human system.

JB: This is a step toward improving functionality and demonstrating how functional medicine works to restore homeodynamic webs and maintain high-level expression of genes and their function. I'm going to turn devil's advocate for a minute. How can we separate this from placebo effect? How do we know these patients don't just feel they're going to get this treatment response and respond appropriately?

CM: Of course that was one of the things I wanted to know. You want to be sure you're treating something that's real with something that's real. I'm teaching microcurrent for the National College of Naturopathic Medicine, where I have interns who helped me in 1996 and 1997. We did trials in which the interns would leave the machine off or unplug it, and the patient and I were unaware of it. We would reach a point where the tissue was not changing, and I'd look at the student and ask if anything was wrong with the machine. The student would say yes, the machine was off during this treatment. He or she would turn it back on; and the results were immediate and reproducible.

Placebo effect may play a part in it. It's a reasonable question.

We had a patient at a facility in Chicago in whom we measured range of motion with very accurate laser measurements. The patient had been in a severe auto accident the previous year. She'd been under chiropractic care and in physical therapy for a year. Her cervical extension, the measured extension on the cervical spine was 17 degrees. After I treated her for 45 minutes, her extension was 43 degrees. Her flexion went from 24 to 45. Left tilt went from 18 to 51. Right tilt went from 22 to 51. If she had been going to have a placebo effect, she would have had it to some other treatment in the preceding year. I have never heard of a placebo effect in producing those kinds of increases of range of motion with one

45-minute treatment. When they measured her again about a week later, most of those improvements had held.

We have designed a control trial in which we'll have a placebo control group, both for the nutritional supplements and for the microcurrent treatment. I'll be very interested to see the outcome of that.

JB: How does this treatment differ from things like TENS, transelectrical neurostimulation?

CM: In general, microcurrent uses more amperage than TENS. TENS produces sufficient amperage to cause muscle contraction. Microcurrent operates at around 100 microamps. A TENS unit is well above that. I'm not sure what the amperage is, but it's enough to cause muscle contraction. Microcurrent is subsensory. It doesn't even stimulate the sensory receptors in the skin, but at 100 microamps, you actually increase ATP levels, according to Dr. Cheng's study in rat skin. He increased ATP levels by 300 to 500 percent. With currents above 1000 microamps, the ATP concentration levels off, and above 5000 microamps they actually are reduced. So, TENS is good at blocking pain impulses by interfering with transmission of the spinal cord. Microcurrent, in my experience, deals with pain by reducing the inflammation at the local tissue. It operates completely differently.

JB: Does the wave form used in microcurrent have a certain shape? Is it a square wave, a sine wave, maybe DC?

CM: I'm not the physicist in the family. My husband has more experience with that. My understanding is that there's a steep, ramped wave that acts as a carrier wave, gets through the skin resistance, and the frequency wave is carried on top of that.

JB: So it involves some reasonably sophisticated electronics that are involved with delivering the right frequency at the right amperage in the right shape.

CM: Apparently. We've had the machine bench tested, and apparently it is quite accurate to about 10 percent, even after two or three years of use. The frequency specificity is two digits. So, let's say you have the frequency; you have the ability to put in two numbers—7 and 6. Then there's a multiplier, so those two numerals—7 and 6—can become 7.6, 76, or 760. The multiplier is .11 and 10. It makes a difference. So the frequency-specific nature of the response is quite marked. If you spend time on a frequency that doesn't produce any change in the tissue, you can stay on it for minutes and nothing changes. It's either a correct frequency or it's not. When you switch to a different frequency, the tissue will soften virtually instantly. It's a sensation that's hard to describe until you experience it.

In the seminars, the afternoon session is spent in practical application. You get your hands on somebody and can feel this tissue—it's firm, fibrotic, hard, stiff—and it softens within seconds. When that frequency is finished, it's done. You can stay on it for another two or three minutes and nothing seems to change. When you switch to a subsequent frequency that may then be involved, it will either soften the tissue or sometimes, at specialty frequencies for allergy reaction it takes away the pain, and the patient comments afterward that it feels warm. The patient feels warming, and he'll feel the pain go down. He or she will ask if we're pressing as hard. Yes, I always press at least the same and sometimes harder, but the tenderness and the pain in the tissue are reduced palpatorily. The patient will find that the tissue feels softer. It's quite remarkable, and it's definitely frequency-specific.

JB: You mentioned earlier that often just a few treatments result in long-term remission of the problem. How many treatments, and how long have you seen patients stay in good management?

CM: In the paper that was presented at the American Back Society in 1997, the average chronicity was about 4.7 years in head, neck, and face pain. In low back pain, the chronicity was actually worse. It was an average of eight years with chronic myofascial pain. Chronic low-back pain averages six visits over six weeks and produces pain reductions from an average incoming pain of 7 to an outgoing pain of 1. Most people can have a nice life if the pain level is 0 to 2. That's our goal. It's very individual. If the injury is just mechanical trauma to the tissues, a single fall or episode of overuse injury without joint damage involved, we get results in three to four visits, and the chronicity doesn't seem to matter.

We had a 48-year-old runner who had injured himself when he was 18. We treated him three times and he's been pain-free for two years. We did two subsequent visits just to follow up and to improve the biomechanics of the area in question. Other patients will need an occasional tune-up, especially for a problem of overuse.

We find that oxidative stress, toxicity exposure, and mineral deficiencies play a part. If their physiology, their unique metabolic character is such that they need higher levels of antioxidants than the general population, or if they are under stress and therefore dump magnesium, we have to supplement with magnesium and make sure they're on a good antioxidant program. We do liver detoxification supplementation, and in those patients the results are quite long-lasting. I don't have what would be called a maintenance practice. Once people are finished, generally they'll be seen maybe once or twice a year, or only if the condition is exacerbated by overuse or injury. That's what's been so remarkable.

Many of these people have been told they have tendencies toward somatization or converting emotional issues into physical complaints. If that were the case, then when they got better, they would create some other sort of physical ailment that would require treatment. We have found that is not the case in the majority of patients. They get better; they stay better. It has dramatically reduced the cost of care and the resources utilization with this particularly difficult patient population.

The Interface of the Biochemical and Biomechanical World

JB: This is functional medicine in its purest application. My feeling, as I listen to you, is that if a tissue is ischemic due to being in tension or torsion, and you relax that torsion so you can get both lymphatic drainage and better oxygenation, the ischemic reperfusion that occurs with that tissue, you're going to get better oxidative phosphorylation. You will get more ATP, as you've indicated. A series of positive downstream biochemical changes will occur. Acid metabolites will go down. Electrolyte levels will be restored. This form and function interrelationship ontology/phylogeny is a classic example of application of that model. You have opened a door to the application of functional medicine—the interface between the biochemical and the biomechanical world. How can listeners get in touch with you to follow up?

CM: We'll be happy to talk to anybody, anytime. This is very exciting work, and I'm very interested in having other people using it in the field and collecting their own data and helping more patients. We're here in Portland at 503/762-0805. The fax number is 503/760-1015.

JB: Those numbers will be on the summary cards and in the digital version of FMU. On behalf of all of us, thanks very much, and continue the great work. We look forward to integrating more of this concept

into functional medicine.

Moving Dr. McMakin's comments to the next level in restoring the weblike, stable, resilient, physiological, and physical functions, consider the endocrine system. It is common practice today to prescribe hormone replacement therapy for individuals in whom saliva, urine, or plasma tests have indicated low levels of these hormones. People are using patches and taking various hormone replacement formulations, one of which is dehydroepiandrosterone or its sulfated derivative.

The authors of a recent paper in *Clinical Chemistry* found that as little as 25 mg of DHEA supplementation in apparently healthy individuals greatly altered their hormone profile pattern. In both men and women it increased the testosterone-to-epitestosterone ratio.[12] In fact, in some individuals taking 50 mg of DHEA a day, the testosterone/epitestosterone ratio, which is an indicator of alterations in steroid metabolism, was greater than 6:1. In drug testing, this level would indicate testosterone abuse. It indicates, therefore, that in some individuals, fairly low doses of DHEA can have an androgenic effect sufficient to drive the androgen system and increase testosterone/epitestosterone to drug abuse levels in drug testing. These are the ratio cutoffs established by the U.S. military.

I think we should view these endocrine replacement agents not as benign, but as having potentially profound influence on physiology. For this reason they should not appear in health food stores. They should be under the control of licensed healthcare practitioners who understand them and have a sense of balance and the weblike relationship of physiology and endocrinology. Along with neurology, endocrinology is probably one of the greatest examples of weblike interactions. I don't want to throw out the baby with the bath water, however, and say that DHEA supplementation or replacement therapy is bad. It is important to use it at the right place at the right time.

According to a recent paper in the *Annals of Internal Medicine,* women who subsequently develop breast cancer were those who in their earlier lives had high levels of serum estradiol and testosterone. As a prognostic marker, women with high total or free sex steroid hormone levels, are about three times as likely as others to develop breast cancer.[13] This work was done at the University of Pittsburgh Graduate School of Public Health. The authors state there may be reason for developing a prognostic screen based on hormones and hormone detoxification mechanisms in women, to determine their relative risk of female-related cancers, and then introduce an intervention program to normalize these hormones. That program would incorporate diet and stress and lifestyle management. One would need to be careful, therefore, about recommending DHEA replacement therapy for a woman with a very high level of estradiol and testosterone. That therapy might drive her levels higher and create increasing risk. The watchword in hormone replacement therapy, therefore, is to monitor what you are doing, understand where the person is in his/her own web, and understand the complex interaction.

Elevated testosterone/epitestosterone levels can increase prostate cancer risk in men, particularly when it is associated with increased levels of insulin-like growth factor 1.[14] A man with elevated testosterone/epitestosterone ratios and high IGF1 levels is clearly at risk of a male sex-related cancer and needs to get into a functional medicine management program.

In older individuals, very low levels of DHEA or DHEA sulfate can be associated with an altered immune response. In a recent study on Alzheimer patients at the University of Pavia in Italy, published in *Dementia and Geriatric Cognitive Disorders* in February, 1999,[15] low DHEA sulfate was associated

with increased response to the inflammatory cytokine IL-2 measured by the increased activity of natural killer cell activity. This type of response could be associated, in genetically susceptible individuals, with increased risk of Alzheimer's disease as an inflammatory component. The authors state that in these cases low-dose DHEA had an immune-modulating effect by normalizing immune function and balancing NK cell activity. Low DHEA in older individuals was associated with hyperresponsiveness of natural killer cells to IL-2. In healthy individuals we might, therefore, think of DHEA as being immune-modulating. This effect shows, once again, the interaction of the endocrine system, the nervous system, and the immune system. They work as an integrated web of interacting systems.

The *Archives of Neurology* recently contained an entire section on neurology, beginning with an editorial titled "Alternative Neurology."[16] The journal explores the area of alternative neurology and states there is an increasing interest in the field of neurology and in the patients who consult neurologists in alternative approaches to improve neurological function. Dr. David Perlmutter, a neurologist in Naples, Florida, has spoken eloquently about integrative functional neurology approaches that use the best of all factors available for patients who have various types of neurological dysfunction.

This issue of the *Archives of Neurology* discusses the Ketogenic Diet.[17] It contains a report on managing epilepsy with the Ketogenic Diet. The same issue describes a multicentered study of the efficacy of the Ketogenic Diet. This diet was effective in substantially reducing difficult-to-control seizures, and it seemed to be successful in a variety of clinical settings.[18] This was a prospective study of the change and frequency of seizures in 51 children with intractable seizures who were given the Ketogenic Diet.

This issue of the journal aptly described the low-carbohydrate, high-protein, high-fat Ketogenic Diet that forces the brain to metabolize ketone bodies as its principal fuel rather than glucose. This very different metabolic approach may to be associated with different kinds of brain intracellular neuronal pH and electrolyte gradients. Practitioners do some pretty remarkable metabolic tailoring in these cases, but the results appear to be very positive. About 40 percent of the children with difficult-to-control seizures had marked improvement with the Ketogenic Diet.

The editorial that follows did not describe the exact mechanism of action. I think it remains an empirical observation in search of a mechanistic explanation. A variety of hypotheses are offered. One that I found interesting is that it improves or alters the neuronal energy field by changing metabolic function at the mitochondrial level. That's a hypothesis. It comes back to what Dr. McMakin said about energy fields, what we described in terms of the biochemical interface of energy fields, and how that may translate into chaotic behavior of the brain. Remember, I talked earlier about seizures as a manifestation of the jump from one state to another through the homeodynamic, almost quantum shift that occurs when the system does not have enough resiliency to accommodate a stress factor like a seizure.

The same issue of the *Archives of Neurology*, in a section titled "Alternative Neurology," contains a discussion of hyperhomocystinemia and its relationship to Alzheimer's disease. I'm not sure we would call this an alternative approach under our definition. The article is titled "Hyperhomocystinemia. A new Risk factor for Alzheimer Disease?"[19] The authors are discussing a paper titled "Folate, Vitamin B12, and Serum Total Homocysteine Levels in Confirmed Alzheimer Disease."[20] They state that low blood levels of folate and vitamin B12 and elevated homocysteine levels are associated with Alzheimer's disease.

This topic is related to an interview we had about six years ago with Dr. John Lindenbaum, a neurologist

at Columbia University Medical School. Dr. Lindenbaum said he believed 10 to 20 percent of Alzheimer's patients were misdiagnosed and were really suffering from functional insufficiency of B12, folate, and B6. As we know, Dr. Kilmer McCully has discussed the relationship to homocysteine and how it is now being seen as a neurotoxic agent. Homocysteine buildup contributes to neuronal oxidative stress.

From our perspective, the best way to measure functional vitamin B12 status is through methylmalonic acid and homocysteine blood or urinary levels. A number of papers have discussed the benefit of measuring homocysteine. One paper, in *Clinical Chemistry*,[21] talks about the prevalence of cobalamin, or vitamin B12 insufficiency in general practice. It explains how measuring the secondary metabolic effects of vitamin B12 status through increased homocysteine and methylmalonic acid levels reveals many more signs of insufficiency.

The authors of another article in *Archives of Neurology* discuss the efficacy of *Ginkgo biloba*on cognitive function in Alzheimer's disease.[22] This meta-analysis is consistent with the *JAMA*paper we reviewed last year. Investigators concluded that 120 to 240 mg of *Ginkgo biloba*extract given daily had a significant effect on objective measures and cognitive function in Alzheimer's patients. They state that additional research is needed to define the ingredients in the ginkgo extract that are producing its effect. This sounds like the pharmacological model—a single agent producing single effects. The overall conclusion we can derive is that *Ginkgo biloba* seemed to improve the cognitive function of patients with Alzheimer's disease. This is work from the Department of Neurology and Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University and Portland Veteran Affairs Medical Center in Portland, Oregon

Another interesting article in the *Archives of General Psychiatry* follows the same theme. Glycine supplementation is used for the treatment of the negative symptoms of schizophrenia.[23]

Over the last several years, you have heard us talk about the neuronal effects of some neurotransmitting substances and explain that they may be quite profound in cases of an imbalance in neurochemical function. In schizophrenia the affinity of the MNDA receptor for its natural ligand glutamate, is decreased. Glycine, acting as an allosteric effector, increases the affinity of the receptor for glutamate, thereby increasing glutaminergic neurotransmission. By giving glycine in very high doses, therefore, they were able to improve function of these schizophrenic patients who did not respond to traditional anti-schizophrenic medications.

When I learned about glycine in my graduate school days, I was told glycine was such a simple amino acid we didn't ever have to worry about running out of it. It just had a hydrogen as its functional group. Thus it was free currency in human biochemistry. Now we see that glycine can be given in supplement form to improve detoxification through glycination reactions. It also may have an effect on improving NMDA receptor site function in individuals with particular problems, such as certain forms of schizophrenia. We call these conditionally essential nutrients, or nutritional pharmacological agents.

One of the greatest problems in neurology is drug interactions with the neurological system. We have discussed the effect of metaclopramide in producing early stages of Parkinson-like symptoms that are often diagnosed as Parkinsonism. An individual may therefore be put on L-dopa therapy inappropriately because he or she is having an adverse neurological effect from metaclopramide (Reglan). Recently, it has been asked if Parkinson's really derives its origin from genes and is it a genetic disorder. A study on

Parkinson's disease in twins was published in the *Journal of the American Medical Association*.[24] In this study, investigators showed there was a very low concordance between identical twins in the penetration of Parkinson's disease. They concluded that genetic factors do not play a major role in causing the typical form of Parkinson's disease, called idiopathic Parkinsonism.

Where does Parkinson's disease originate? We go back to the environmental toxin theory of Parkinsonism. We go back to the brain as a reservoir of neurotoxins that activate apoptotic cell death in the nigra striatal regions, thereby losing the dopamine-secreting ability of the brain. We discussed lowering the activity of these toxic reactions by detoxification, looking for the source of petrochemical toxins, and improving antioxidant protection in the brain. It takes us into a new era of functional neurology, instead of pathology-based neurology, utilizing tools we have described in *Functional Medicine Update*™ over many years

The more drugs we have, the more potential we have for significant drug interactions that can produce adverse side effects. *Postgraduate Medicine* recently contained an article titled "Clinically Significant Drug Interactions: What You Need to Know before Writing Prescriptions."[25] I take pride in this discussion, because we talked about detoxification mechanisms and drug/drug and drug/nutrient interactions years ago in *FMU*. We explained how one individual may be a "yellow canary" in a certain exposure to a substance, while another person can detoxify it and have no symptoms. We need to be sensitive to the relative effects of a drug or substance in one person compared to another. We can look to pharmacogenetics in order to determine the detoxification potential of an individual.

I predicted that medical doctors of the future would have to know about the relative detoxification ability of their patients before they administered medication. If the patient got an adverse reaction because he or she had poor detoxification, the doctor would be medically and legally responsible. At the time, that may have seemed like an inflammatory comment, but it is happening today. Legal suits are being filed over adverse reactions that occur because doctors didn't ask the right questions about cytochrome P450 detoxification systems. He or she didn't seek to understand how that drug would interact with the patient's detoxification mechanisms, whether it was a cytochrome P4501A2, 3A4, 2D6, or whatever the problem might be.
Caution Advised

They talk about problems of drug/drug interaction due to altered effects on the detoxification systems. They discuss cimetidine and ketoconazole, erythromycin and digoxin, iron and tetracycline, problems related to the distribution of drugs, such as taking aspirin and anticoagulants like warfarin together, or problems with regard to metabolism of drugs, such as taking erythromycin with prednisone, or phenytoin with theophylline. One needs to know many things before giving multiple medications. If you don't, there can be adverse reactions, some of which are related to neurological changes. You need to know about cytochrome P4501A1, 1A2, 2D6, and 2E1, whether they are inducible or constitutive, and how they can influence the way people detoxify not only medications, but endogenous sterols and other endogenous substances produced in their own bodies. It's an interaction of total load on the same detoxification system.

The field of medicine is undergoing rapid change. The concept of functional medicine is emerging as a theme, although it may be given other names. If you ask a person what he or she knows about functional medicine, the person may not be able to define it or even understand it. We are beginning to recognize,

however, that the term "functionality," measured by grip strength, physiological resiliency, or physiological, cognitive, emotional, and physical fitness, is not just esoteric. It plays a significant role in how medicine will gain in efficiency and improved health outcomes in patients.

We look forward to seeing you in May at our symposium. Have a great month!

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