April 2007 Issue | Paul Cheney, MD, PhD The Cheney Clinic

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Welcome to the April 2007 edition of *Functional Medicine Update*. In this edition we are going to focus on what truly is a functional medicine concern, chronic fatigue syndrome. We have discussed chronic fatigue syndrome throughout the last 15 years of *Functional Medicine Update* with some of the world's leaders in this area, and we have attempted to try to find out more about the emerging understanding of the etiology and treatment options for this very complex energy-deficit-related family of disorders.

Only recently, have we started to see meta-analysis studies done and various clinical randomized trials published that have helped us to understand that chronic fatigue syndrome is not a disease, per se, but rather it is a complex condition-a state of energy deficit-that ranges with differing degrees of severity, duration, and frequency from patient to patient. It should not be thought of as a single entity, but rather as a kind of resting place for a series of multiple etiologies that contribute (in the outcome of that patient) what appear to be immunological deficiencies or dysfunctions, alterations in the hypothalamus-pituitary-adrenal/thyroid axis, changes in musculoskeletal function, changes in cardiac function, and a general alteration in the systemic ways that the web of physiological function is balanced.

It is this complexity that makes chronic fatigue syndrome (or "syndromes" probably would be more be more appropriate) a condition of the 21 st century. To understand the etiology of this condition, one has to look at the interface between genes, environment, lifestyle, and diet, and through that we will better understand both where it has come from and possibly what to do. Each patient will undoubtedly require some form of personalized therapy based upon his or her own unique manifestation of the condition.

This sounds like a systems approach to patient-centered health care, and of course that is one of the fundamental tenets of the functional medicine discipline. Functional medicine is built around the precept of web-like interaction-what we call homeodynamic interaction-among different parts that give rise to what we call our function. Recently in the *Journal of the American Medical Association* there was an editorial titled "A Systems Approach to Patient-Centered Care."[1] In this particular editorial, the authors outlined some of the tenets they felt are required to deliver a systems-related, patient-centered care system.

The criteria described in this article sounded very reminiscent of many topics we have been discussing in *Functional Medicine Update* for 20-plus years. The authors suggest the necessity of redesigning the system to include better access and continuity of patients to the healthcare system in continuity within their own patient management needs; the need to find ways of keeping patients involved, engaged, and committed to long-term therapies that are associated with the remediation of chronic disease; and the need for increasing opportunities for patients to participate in their own care process. When a patient is a

participant in his or her own process, he or she starts owning their condition to a greater extent. He or she invests energy into his or her own care and recovery then gets seen as a positive healing force. This is obviously a very important part of the functional medicine model: with patient-centered care, you try to engage the patient in his or her own natural process of recovery and healing.

Tools for Patients with Chronic Disease

The authors suggest that tools to facilitate setting an agenda for patients with chronic disease help patients become more active, especially those who present without having new complaints. Agenda cards have been used in Europe as an application of how a patient can denote where they started and track their performance over time. This provides a positive feedback process to show patients they are making progress against what might be considered a long-term chronic disability or dysfunction. The cards can contain statements of improvement to help a patient remember where he or she started. Often over a course of therapy that may require months of intervention, patients can forget how bad they felt when they started treatment, and they are just still focusing on the one or two symptoms that are nagging, forgetting that they've taken out multiple tacks and they only have but one tack next. (This is Dr. Sidney Baker's Tack Rule: If you sit on two tacks, taking one tack out does not reduce the pain by 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}.) We have to start looking at ways of managing expectations in these patients and helping them to chart their own process toward recovery and getting them involved in their own healing process.

Self-Management Support for Patients

The third area that is discussed in this article is to provide self-management support so that the patient actually understands their therapy and there are things that they can do, rather than taking a new-to-nature molecule that they don't really understand how it works in their body and expecting to have a miraculous recovery. We are teaching them how to employ things that they can do everyday that they will see the results of-eating, exercising, thinking, breathing, relaxing, and staying away from toxic exposures. All of these things are, I guess, what you would call rules of reasonableness. The patient can actually understand these things and they can become the master of his or her own destiny, or the master of his or her own universe, we might say.

Coordination of Patient Care

The last point they talk about with this patient-centered systems approach is to coordinate care among different practitioners and to recognize that most patients with chronic illness have distributive problems that require distributive systems. No one practitioner is a master of all therapies that are necessary for that patient, so coordinating the best treatment program for each patient may require multiple practitioners with different expertise.

In concluding this article the authors state, "...ensuring open access to and continuity with clinicians, improving opportunities for patients and families to participate in their care process, providing active self-management support, and coordinating care among settings are among the basic system redesign components that can result in an optimal care environment from the patient's point of view, as well as that of the clinician's." Of course, those are all tenets the functional medicine model has been championing for some time.

The question is: How do you bring into this model the most recent discoveries? We are going through an epic period of discovery right now at the basic sciences, the biological sciences, and the clinical sciences

level. Many things are happening everyday that may have tremendous impact on improving patient outcome in the areas of certain chronic diseases. How do we translate these discoveries that are occurring in clinics and laboratories into effective patient-management programs without waiting 2 decades for them to filter through a cumbersome process of screening and being written into textbooks and ultimately become a standard of practice? And how do we, then, make sure that we don't move things too quickly and prematurely into clinical practice, before they have been adequately demonstrated to be safe as well as effective? These are really questions that are at the forefront of what has been called "translational medicine."

Translational medicine is taking the systems biology approach to medicine and translating new discoveries into clinical applications. There are now whole institutes of translational medicine being built. Pennsylvania has the Institute for Translational Medicine and Therapeutics (ITMAT), just recently opened at the University of Pennsylvania School of Medicine. Trying to get things more rapidly into clinical practice is a trend we are now seeing that could facilitate improved patient outcomes. NIH has invested roughly 70 million dollars in the clinical translational medicine approach and trying to find ways to take new concepts and get them more quickly and effectively into integrative practice.[2] ,[3]

A question I was recently asked by one of our FMU listeners is an example of this desire for the integration of new concepts. The question (paraphrased) is, "How long is it going to take for medicine to recognize there is something about vitamin D status and multiple sclerosis that should be put into clinical practice?" Of course, that is part of the whole new discovery frontier related to the role that vitamin D has beyond that of just a bone hormone (or a bone vitamin), where we are now recognizing it has complex and very important influences upon the neuroendocrine immune system function. One might ask, "We've heard about this work that has been done on vitamin D and its relationship to multiple sclerosis. We had a major presentation at one of our recent Symposia for the Institute for Functional Medicine about this. Why is it taking so long to get it into practice?"

Fortunately, we are seeing translational medicine start to accelerate the process to some degree. I was very pleased to see an article in the *Journal of the American Medical Association* titled "Serum 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis."[4]

This article discussed the results of a study suggesting that high-circulating levels of 25-hydroxyvitamin D are associated with a lower risk of multiple sclerosis. This is in a case-controlled study protocol, again looking at serum levels of 25-hydroxyvitamin D as the assessment tool. They broke this down to the higher quintiles of 25-hydroxyvitamin D (which is greater than 99 nmol/L), and they found that these had a very significantly lower incidence (in fact, for whites, a 41{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction in multiple sclerosis incidence for every increase of 50 nmol/L vitamin D).

There does seem to be an emerging translation of this observation that we heard about some 8 to 10 years ago into more prominent clinical understanding. But there is still so much that is happening on the frontier of basic discoveries and clinical discoveries, and it takes so long to get it into the limelight and be up on the platform of understanding by the clinicians. There is a need for this translation trend to occur and to accelerate.

We are starting to see some fundamental new discoveries around chronic fatigue syndrome that may

allow for better patient intervention and more successful outcome. In this issue of*Functional Medicine Update* we are going to be exposed to one of these interesting new observations and developments through the eyes, ears, and brain of one of our great conceptualizers in the field of chronic fatigue syndrome and functional medicine, Dr. Paul Cheney, who you will hear from later. Before we get to Dr. Cheney, however, let's do a quick review of what is known about chronic fatigue syndrome in early 2007.

Recently in the *Journal of the American Medical Association* , there was a summary/quick editorial comment about chronic fatigue syndrome answers being sought.[5] It says what I think most of us recognize: for 20 years, we have been trying to understand better this clinical entity, chronic fatigue syndrome, but it still remains a very puzzling condition. Dr. Julie Gerberding, the Director for the Centers for Disease Control and Prevention (CDC), says, "Sometimes people question if Chronic Fatigue Syndrome is real or not real." In addition to demonstrating that this illness is real, researchers are now uncovering potential triggers and treatments. That is where we are going to be focusing the energy and emphasis in this issue of *Functional Medicine Update*.

Data from the Wichita Chronic Fatigue Syndrome Surveillance Study
Some information has emerged from the Wichita Chronic Fatigue Syndrome Surveillance Study, which was launched by the CDC researchers in 1997. Investigators collected information on 90,000 individuals in Wichita, Kansas and conducted extensive clinical assessments of about 7000. The group found that the age that was most affected include individuals between 40 and 59 years, that an incidence of about 373 per 100,000 women are affected (which is about 4 times the rate found in men, by the way, so there seems to be a higher prevalence in women, reminiscent of what we also see as the difference between genders in the prevalence of autoimmune diseases; maybe it is coincidental, but it is certainly an interesting observation), and that the prevalence was even higher in non-white women (they are affected more than white women at a rate of 495 per 100,000 as compared to 352 per 100,000). This was published by Reyes et al. in the *Archives of Internal Medicine*.[6]

Monitoring patients with chronic fatigue syndrome in Wichita revealed that the disease may be associated with both genetic and environmental determinants, which is the way we have been describing this condition for the last 15 years on *Functional Medicine Update* . Efforts to decipher the causes have found that many cases may be linked to stress and childhood trauma. In a case-controlled study of 43 adults with chronic fatigue syndrome and 60 non-fatigue controls, it was found that exposure to childhood trauma was associated with a 3- to 8-fold increased risk for chronic fatigue syndrome across different trauma types, including emotional, physical, and sexual abuse, and physical neglect. This data was published in the *Archives of General Psychiatry* in 2006.[7]

The authors of this article suggest that studies analyzing the psychological and neurobiological mechanisms that link childhood adversity to chronic fatigue syndrome risk may provide targets for prevention.Once again we are reminded (in a chronic fatigue example) of the functional medicine model. In the functional medicine model, the environment (the psychosocial/emotional environment) in which each individual is bathing his or her genes with experiences is represented by the embedded roots of a tree. Being impoverished, as we have learned, is more than just being deficient of having money. Being impoverished means having no attribution, no love, no support, feeling at risk or not at home-all of these things have direct effects upon gene expression patterns and ultimate physiological function. We are starting to recognize that there is at least some correlation between psychographic patterns, emotional

patterns, experiences in life, and chronic fatigue syndrome.

Recently published results from a prospective case-controlled study found that higher emotional instability and self-reported stress were reported to be a very significant risk factor for chronic fatigue syndrome. This was also in *Archives of General Psychiatry* in 2006.[8]"There are now over 4000 published studies that show that there are underlying biological abnormalities in patients with chronic fatigue syndrome." This is a direct quote from a recent presentation that Dr. Anthony Komaroff of Harvard Medical School made on chronic fatigue syndrome. He was actually interviewed about his understanding of chronic fatigue syndrome in *Functional Medicine Update* (he was in our September 2003 edition). What we are starting to witness the understanding that this is a multiple-etiology condition with multiple biological mechanisms that are ongoing, and we shouldn't look at it as a single disease caused by a single agent. Among the suspected causes are mechanisms that relate to impairments in metabolism and dysfunction of the immune and nervous system. These are things we'll be talking about in greater detail with Dr. Cheney.

A Comprehensive Meta-Analysis of Treatment Approaches to Chronic Fatigue Syndrome
If we were to summarize all interventions for the treatment, management, and rehabilitation of patients with chronic fatigue syndrome and do kind of an updated systematic review, what would it tell us? I have the benefit of being able to borrow from a very nice paper that was recently published in the *Journal of the Royal Society of Medicine*.[9] The authors have done an elegant job in reviewing and grading the quality of the research on all the chronic fatigue randomized controlled trials (RCTs) that have been published to date. This is a very nicely done paper that gives a wealth of very good "news to use," as it relates to what is known in the literature about successful interventions for chronic fatigue syndrome.

The first thing that can be said (in looking at the tables that are provided in this paper) is that most of the pharmacological interventions that have been used have not been successful. In fact, when the researchers grade the validity scores of these various studies, these pharmacological intervention trials mostly have very low-graded scores (meaning they didn't really work much better than placebo). Many different drugst have been attempted, including SSRIs, corticosteroids, anti-virals, and immunologically active agents. The quality of the research outcomes related to these drugs are marginal at best, I think we can say.

There are some modalities, however, that seem to suggestd improvement after therapy (against placebo). The first is cognitive behavioral therapy (CBT). There are multiple studies that seem to all demonstrate improvement. The other is what we would call graded exercise therapy. There are five RCTs that concluded that graded exercise therapy is a promising intervention. Those, along with the three relevant randomized control trials on cognitive behavioral therapy, appear to be the best clinical outcome studies that have been published to date with regard to chronic fatigue syndrome. You'll notice that we are dealing with elements that modify the psychosocial and psychological environment of the patient, as well as try to improve exercise tolerance, which has something to do with energy dynamics in the individual. We'll come back and talk with Dr. Cheney a little bit about these two suggested positive therapies.

The next therapy that rose up in the meta-analysis -- which reviewed about 10,768 publications published on interventions surrounding chronic fatigue syndrome (that was the number of papers reviewed for this meta-analysis) and selected 70 that met the selection criteria --, was the use of inosine pranobex. A couple of clinical trials seem to demonstrate improvement in patients with the use of inosine pranobex, although

there were side effects with this treatment. Inosine is an orthomolecular material that tends to improve cardiac function. We'll also talk a little with Dr. Cheney about this. Other papers (2) describe some positive benefit using hydrocortisone given at fairly low dose (these are physiological doses of hydrocortisone). This is very reminiscent of what Dr. Mck. Jeffries talked about in his book, *Safe Uses of Cortisol* , many years ago.

Two other reports talked about DHEA. Those appear to be of marginal clinical significance. One study was in women who had low libidos, low sense of well-being, and fatigue-related symptoms. DHEA supplementation at 30 mg/d had some improved outcome versus placebo. Another series of trials that looked encouraging were related to homeopathic preparations (there is some suggestion that certain homeopathics might have benefit in this condition, as well ascetyl-L-carnitine and propionyl-L-carnitine, which have shown some positive effect given at the doses of 1000 or so mg/d. Finally (probably rising up to a higher level of clinical significance relative to the meta-analysis of published studies) there are essential fatty acids in the omega-3 family, and also magnesium (probably essential fatty acids having more clinical validity than does magnesium, but both do have some evidence of clinical value based upon this meta-analysis study).

What I have really started to develop here is kind of a multi-focal approach. There is no one magic bullet that is going to lead to complete remediation of chronic fatigue syndrome. At this point, we really don't have any single therapy you can give all patients with this condition. Determining treatment requires a much more complex review of systems and (I would say) a functional medicine approach (looking at the web and what we call the matrix) to understand how an alteration in a patient's web of physiological function might result in these energy-deficit-disorder-like symptoms.

One of the things that we obviously have heard much about over the years related to chronic fatigue syndrome is that it has an infection-related component. It could be a viral infection, or it could be some kind of a stealth organism. There is now some evidence suggesting that there are very small vectors that are associated with Lyme disease that can actually be found inside mitochondria and may "infect" mitochondria. This isthe discovery of an Australian postdoctoral candidate, Nate Lo, who was working at the University of Milan.[10] He was looking at this whole Lyme disease situation and found what he thought were microbes living inside the mitochondria of patients who had Lyme disease. Now his finding has been confirmed by other investigators. Scott O'Neill, a specialist in invertebrate endosymbiotics and head of the School of Integrative Science at the University of Queensland, said this was a very novel observation and that it was surprising to see a bacterial species living inside the mitochondria, which itself was a bacterium (in its progenitor history), but it looks like it is potentially significant.

So, again, we might have some unusual types of organisms that can infect cells at even the subcellular level and can induce, then, mitochondrial disruption, bioenergetic catastrophe, and oxidative stress. We have talked about vectors playing a role, but it is more than just an infectious agent; there are other things going on. These small virus-like subparticles (or bacterial parovirus or infections) don't explain the whole of chronic fatigue syndrome. It seems to be a multifactoral condition with stress, and the preceding life history of the individual going all the way back to their childhood, and exposure to xenobiotics, and gut dysbiosis, and alterations in hepatic detoxification systems, and alterations in oxidative stress and redox potential-these are all parts of the complexity of this condition.

Erythrocyte Metabolism, Oxygen Delivery, and Erythrocyte Shape May be Linked to Chronic Fatigue

Syndrome
In a recent paper from 2007 in *Archives of Medical Research*, Ross Richards and his colleagues discuss evidence of oxidative damage that has been observed in the red blood cells of chronic fatigue syndrome patients.[11] With reticulocyte alterations, the cells undergo membrane deformation. These authors also reported finding more stomatocytes in the blood of patients with chronic fatigue than expected. These are examples of what happens with oxidative stress. The authors looked at malondialdehyde levels and reduced glutathione levels and correlated that with the alteration in red cell confirmation in patients with chronic fatigue syndrome versus healthy control subjects. They concluded there is a strong likelihood that the increase in erythrocyte alterations is associated with the presence of stomatocytes, and that oxidative free radicals may be implicated in the pathogenesis of chronic fatigue syndrome. Therefore, erythrocyte metabolism, oxygen delivery, and erythrocyte shape are all linked. A deformed erythrocyte can't deliver as much oxygen. It is less efficient in transporting an essential nutrient (which oxygen is), and it may actually participate then in free radical initiative reactions as a consequence of promiscuous oxygen in various forms such as hydrogen peroxide, singlet oxygen, superoxide, or even hydroxyl radical.

We have really talked, here, about oxygen as being implicated somehow-about oxygen not being where it should be at the level it should be to be used effectively for oxidative phosphorylation. This idea brings into play the whole question of mitochondrial medicine. Is there some correlation between a mitochondrial dysfunction and chronic fatigue syndrome? We've seen many reports over the years that have implicated (or at least suggested) that. There is a report that appeared in *Cell Metabolism* in 2006 titled, "Mitochondrial Medicine: A Metabolic Perspective on the Pathology of Oxidative Phosphorylation Disorders."[12] We know in examples of severe inborn errors of mitochondrial function that you have extraordinary muscle-related fatigue problems and cognitive dysfunction. That is the outer edge, probably, of the mitochondria dysfunctions. But what where you get injuries to mitochondrial DNA and you get mitochondrial deletions that are produced not as a consequence of genetic alterations, but induced problems through environmental exposures (these induced OXPHOS disorders)? That is what is discussed in this particular review. How these disorders of mitochondrial function may associate themselves with what we see as fatigue in various tissues and functional alterations in tissues, like cognitive decline, or energy problems, or even resulting in things like a blood sugar abnormality through alterations in adenosine monophosphate kinase, which is coupled with ATP formation in the mitochondria, which can induce, then, a type 2 diabetic-like situation. In chronic fatigue patients you often see abnormal blood sugar regulation, and you see what appears to be metabolic syndrome (even type 2 diabetic-like situations).[13]

This is a very complex web of distortion that is often present in the patient with chronic fatigue syndrome. It seems to tie together things that relate to environmental exposures, potential infections, alterations of the immune system, and alterations in oxygen delivery and utilization in the cell, which then subsequently ties together with mitochondrial oxidative stress and cellular injury. Trying to find the answer may be less important than trying to find the environment in which function can be reestablished. We have talked about this as being graded (or a sequence of severities). Chronic fatigue syndrome does not present with one type of severity; it can range from fairly mild to life-threatening (in which cardiomyopathy may ultimately be contributing to risk of death).

We start to see much more connection between this mitochondrial function, oxygen utilization and oxidative phosphorylation, and how that connects to the neuroendocrineimmune system function and how

the environment may contribute to alteration in this functional state. I think it is very important to put into this oversight or review the cognitive behavioral therapy and graded exercise therapy components. In both of these cases, we are dealing with situations that may go way back in the life experience of an individual; back into childhood, or maybe even infancy. Certain situations related to deprivation or impoverishment or poverty (in the broadest sense of the word) has influenced energy transmission systems in such a way as to make them more vulnerable or susceptible to things like environmental exposures, or pathogenic organisms, or gut dysbiosis, or all these other factors that we seem to associate with the spreading effect or the multiple layer effect that we call later chronic fatigue syndrome.

Mitochondrial dysfunction and oxidative stress relate to so many different organ- and tissue-specific dysfunctions. We can talk about the sarcomeres and the myocytes related to muscle dysfunction. We can talk about neuronal mitochondrial oxidative dysfunction that relates to neurodegenerative diseases and cognitive dysfunction. We can talk about energy deficit disorders in the beta cells of the pancreas that leads to apoptosis and decline in number, which ultimately is associated with type 2 diabetes. You notice this is a central theme that cuts across many age-related chronic diseases.[14],[15]

Mitochondrial Resuscitation

Can you do anything to repair these processes once they are in place? This is what we discussed with Dr. Martin Pall on *Functional Medicine Update* on two occasions. At Washington State University, Dr. Pall has been looking at these oxidative injuries that are associated with chronic fatigue syndrome and trying to introduce ways of resuscitating proper mitochondrial function (that's a term that we have actually borrowed from Dr. Paul Cheney, who talked about mitochondrial resuscitation some 15 years ago).

If you look at the papers that have been published in this area since Dr. Pall published his papers on oxidative stress, mitochondrial dysfunction, and chronic fatigue syndrome, we see papers like the one that appeared in *Free Radical Biology & Medicine* in 2005.[16] It talks about the role that mitochondrial function decline has in aged animals and that long-term intervention with N-acetylcysteine, N-acetylcarnitine, and Co-enzyme-Q10 had a positive effect on these aging animals to improve mitochondrial function. This is very reminiscent of what Dr. Bruce Ames (who we interviewed on *Functional Medicine Update* a number of years ago) has been speaking about with his work as well: using N-acetylcarnitine, N-acetylcysteine, and Co-enzyme-Q10 to try to improve oxidative chemistry in the mitochondria, improve redox function, and lower oxidative stress.

I don't think, in and of itself, this intervention is the cure to chronic fatigue syndrome, but it may be part of the puzzle as we try to eliminate those factors that induce oxidative injury and improve intake of those agents that help buttress proper redox control within the mitochondria and oxidative chemistry. As we'll see from the presentation of Dr. Cheney, this concept has a much broader implication (both anatomically and physiologically) than just looking at the subcellular organelle called the mitochondria. We have to look at the whole of how the body accommodates the alteration and the utilization of oxygen and the delivery of oxygen-how that is seen through the range of symptoms from early-stage fatigue all the way (possibly) up through the most pathological states of chronic fatigue syndrome. With that as a context, what we are really speaking to here is a functional medicine web. It is a web of understanding of agents that might either induce alterations in function or improve function within this neuroendocrineimmune system.

We have learned that one thing that could cause dysfunction of energy processing centers (which has

been part of our diet for some time) is trans-containing fats. I take some small degree of pleasure in recognizing that we started talking (on *Functional Medicine Update*) about the potential concerns about trans fats in our food supply over 20 years ago. It wasn't considered very fashionable at that point. In fact, there was some criticism that was levied against us for suggesting that this partially hydrogenated vegetable oil material called trans fats had anything other than a nutritional benefit. But over the years, obviously, this has changed its complexion considerably, and there is now the general consensus that excessive intake of trans fats in the diet has a deleterious effect on health.

It is starting to be recognized that trans fats may affect not only heart function and mitochondrial function, but also possibly the developing fetus or even conception. It has recently been suggested that trans fats in a woman's diet may actually have an adverse effect on conception ability. This whole trans fat/conception (or fertility) relationship is recent work; this was a study done by individuals at the Harvard School of Public Health in Boston (Walt Willett's group). The study looked at 18,555 women trying to conceive and found 438 cases of ovulatory problems. The researchers found that women who took 2{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of their energy intake from trans fats instead of carbohydrates or polyunsaturated fats had a 70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} greater risk of infertility through lack of ovulation. Those women whose energy came from trans fats instead of monounsaturated or polyunsaturated fats were twice as likely to have problems as those individuals were eating what we consider a diet low in trans fats.

Dr. Jorge Chavarro said, "It's really a small amount of fats that we observed having a significant effect on infertility." This finding was the surprise of the study. This paper (published in *the American Journal of ClinicalNutrition)* suggested that women wanting to conceive should watch their trans fat consumption. Trans fat consumption is also related to the appearance of polycystic ovary syndrome (PCOS) because it has an adverse effect on energy production, insulin stability, and androgen/estrogen balance.[17],[18]

We are starting to witness a redefinition of what might be considered toxic effects. Trans fats would not be a direct toxin to the extent that if you fed them to animals they would have LD50 that would suggest they immediately be removed from the diet, but rather they are modulators of function in such a way as to produce an outcome that we call dysfunction. In this case the dysfunction is an energy deficit in certain tissues that then has significant effects on things like pregnancy. We might consider this a disruptor at some level.

We know disruptors are out there in the environment as both symbiotic and xenobiotic materials. We have heard a lot about endocrine disruptors triggering fertility problems in multiple generations and we have often thought of those as being things like fungicides and pesticides, which are known to be toxic to animals. But now there seems to be a darker side, because various chemicals used in agriculture can also cause fertility defects in animals, and these seem to be able to be passed down to subsequent generations by an epigenetic effect. A recent paper appeared in *Science Magazine* titled, "Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility."[19] This article and others specifically look at male fertility and sperm-related defects that seem to be passed down in subsequent generations.[20]

We could have xenobiotic (foreign) molecules and also symbiotic molecules (maybe more natural to our

food supply). I guess we could argue whether you would call trans fats xenobiotic or not. All of these messages that our body is receiving can modulate our function. You then have varying genotypes that respond to these in differing ways of sensitivity (the "yellow canary syndrome," as it is said). And then we get these statistical changes in distribution of certain outcomes. In the case of reproductive biology, as I have talked about, a 70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} greater risk of infertility through lack of ovulation in women who had higher than 2{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} trans fats in their diet.

If we were to start assembling a list of everything known to potentially have an adverse effect upon cellular function that we are exposed to, how long would the list be? That can be a total load effect on the energy processing centers of cells. Now add new organisms, infection, and altered immunological function. From that is born what we call chronic fatigue syndrome.

With all of this in mind, I think it sets a very nice stage for taking the next step in our evolution of understanding and that is with Dr. Cheney as our guide. He is a person who has helped us over the last two decades to better understand the complexity of chronic fatigue syndrome and ways that we might throw a net over it so we can actually improve clinical outcome in patients. With that in mind, let's move to our discussion with Dr. Paul Cheney.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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We are very fortunate (to say the least) to have as our clinician/researcher of the month this month, Dr. Paul Cheney. Some of you undoubtedly know the name. He is an icon in the field of functional medicine and in the area of chronic fatigue syndrome research. We actually had the pleasure of first introducing Paul Cheney to the Functional Medicine Update audience in January 1994. I can't believe that 13 years has gone by. It is stunning to me how fast time travels; it's a little bit scary and disconcerting. For someone like Dr. Cheney, I guess that's not too unexpected because he was a nuclear physicist, so he was familiar with the quantum world well before he went to medical school.

If you are not familiar with Dr. Cheney, let me introduce him through the writings of Hillary Johnson, who wrote a very interesting book on the history of chronic fatigue syndrome titled Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic (it was published in 1996).21 To kind of personalize Dr. Cheney and his background, I want to quote a little bit from a section of Ms. Johnson's book.

The author talks about Incline Village in Nevada, which is a place where Paul and his colleague were

practicing a number of years ago. She says, "Neighbors liked to speculate about her financial lineage. A few confused souls were amused by the notion that the heir to the West's largest raisin dynasty lived among them. To those people she was 'Mrs. California Raisin.' To most of the citizens of Incline Village, however, she was just one more rich person who spent her summers in a town on the rim of Lake Tahoe. In truth, she was not the raisin heiress; she was married to a prosperous oilman, and each winter the couple returned to their home in Houston. Her life was one of ease and affluence. When her health began to fail in late August, she went directly to the Cheney-Peterson Medical Office on Alder Street in Incline Village. A number of such folk residing in the mountain hamlet routinely packed their overnight bags when they wanted to see a doctor and headed for the Reno airport an hour away. However much Incline was loaded with wonders of the natural world, it had-for years-been short on doctors, until it had the benefit of getting Dr. Daniel Peterson and Dr. Paul Cheney as the principal physicians serving the community. It was not entirely surprising, then, when her fatigue struck-this intense and sudden fatigue-that the oilman's wife went directly to the medical offices on Alder Street of Dr. Cheney and Dr. Peterson."

And so it goes on, then, to talk about this remarkable group, and Dr. Cheney, specifically, saying that Dr. Cheney was one of those unusual people who had a penchant to learn and was constantly searching.

Dr. Cheney decided to enter medicine when he was already a Duke University-educated PhD in nuclear physics. His conversion from physics to medicine occurred when he realized his entrance into the provocative would be through the latter. "The golden age of physics was the first after the century, said Dr. Cheney. "Medicine is in the second half."

Upon graduation from Emory University's distinguished medical school, Dr. Cheney formed a general practice. He became, really, one of the first people to make observations of this condition that seemed to follow on from the HIV story in the early 80s, which was to be called chronic fatigue syndrome. Dr. Cheney, today, is in Asheville, North Carolina with the Cheney Clinic, which is specializing in chronic disease care. He has a curriculum vitae that is very long and rich, as you can imagine, with his background and his board certification in internal medicine and his work in immunology at the Centers for Disease Control (CDC). Dr. Cheney has worked extensively in trying to develop methods of understanding of the etiology of chronic fatigue syndrome and has probably seen more chronic fatigue syndrome patients than any other practitioner (I would say) living. He has patients from over 48 states and 20 foreign countries, and has done extensive research in the area going back into the late 80s, early 90s.

It is with a great amount of pride that we welcome you once again, Paul, to Functional Medicine Update . I think it is quite timely now (13 years down the road since our last visit with you) to do a check-in because you have gone through a very interesting evolution and refinement of your own thought about this condition that we know to be very complex for which the CDC says there is no known (yet) unequivocal origin or etiology. I think these most recent discoveries that you have made and observations that you are bringing to the attention of the medical world put this whole condition into a slightly different framework.

So, once again, Paul, thanks for being with us and welcome to FunctionalMedicine Update in 2007.

PC: Thank you, Jeff.

JB: Let me, if I can, start with your story, because as we were talking about it not too long ago, your story (since we last visited) has been very dramatic and (I think) almost paradigmatic in terms of the discoveries you have made. I'd like you to tell your story, as you see it-where you've come in your knowledge since 1994.

A Community Outbreak of CFS in 1985

PC: Well, of course, everything has a beginning. My beginning with this was the witnessing of the epidemic in a small community on the north shore of Lake Tahoe in 1985 (actually it was the late fall of '84, but it peaked in May of '85). That was an epiphany for me. I had never seen an epidemic like that before, of middle-aged adults (average age 38) coming down with a mononucleosis-like illness and then failing to recover from it. It is unusual to see epidemics in adults of mono. It seemed like mono, but yet, it had certain features about it that appeared later that made me wonder whether it was or wasn't.

Having witnessed that epidemic, I was always impressed that this disease had a (usually-in stories that people tell you) defined onset, usually with a viral-like onset. Mono is not the only type of viral onset. There are also other types of flu-like or even encephalitic-like onsets. Then there is a certain population that do not have abrupt onset. That was sort of the beginning of it and from there I (as most people would) began to look at what I would call the microbial onset (or causality) of this disease.

Looking for Causality

It seemed (in the beginning) that that might bear fruit. Responses, for example, to IV acyclovir that we were seeing clinically, and other features of laboratory testing strongly suggested some sort of viral etiology. But, unfortunately, it appeared more and more over time that although viral onset might be important, it was not the center of gravity of this illness. And so then I evolved sort of an epiphany (in the mid-90s) where I began to look further a field from a sort of single-agent cause. Maybe it's some sort of process that is a trigger in some way. And we began looking at the immune system. We began looking at the GI tract, which seemed to be potentially involved in this illness in terms of xenobiotic stress and distress. And we began looking at nutritional approaches and broader methodologies of dealing with chronic complex illness. And that's when I met you and met the functional medicine movement, and I really got attracted by that conceptual framework of complex chronic disease and how it might be addressed.

From there, however, after many years of working in nutritional aspects of this illness and gut management and so forth, I was still puzzled by the refractory nature of this disease and how well some people respond (most people didn't, or if they responded, they may not respond for long). I began to evolve into the idea that maybe there was a deep-seated energy problem somewhere at the cell level, and although it was difficult to find out, exactly, the locust of control of that defect, it seemed to be what I would call "Rome." (All roads led to it, and maybe there were many roads. And many roads led from it.) But somewhere in this disease there had to be a locust of control-some core problem that everybody had. You could get there for different reasons and you could emanate from there with different complications, but there would be a core.

A Personal Illness Leads to Considerations of Low Cardiac Output

It was at that time-at that moment, when I began to think about that-that I became ill myself with an abrupt onset of what would be called an idiopathic cardiomyopathy (following a mercury removal, interestingly, from my teeth, combined with a viral infection in the fall of 2000). By 2001, I was in

congestive heart failure. Through a steady decline of approximately 3 years, I began to sort of slowly exit out, functionally, from medicine, until my transplant occurred in October of '03. On return to practice in July of '04, someone handed me a paper across the table. It was written by Natelson and Peckerman and published. It showed that about 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of chronic fatigue syndrome patients had low cardiac output. I, of course, was intimately familiar with what happens and how you feel and body system issues related to cardiac output. I had just gone through it in spades and knew all about it. I began to reflect on the fact that many of my symptoms of low cardiac output including gastrointestinal disturbances, inability to eat, food intolerances, xenobiotic stress, chemical sensitivities, and drug sensitivities actually could be explained by low cardiac output state.

I began to wonder how this might be related to chronic fatigue syndrome, because until that moment, I had never thought of this disease as a low cardiac output state. I did not understand how that might be, in fact, related to energy, anyway. At that moment, I decided to recapitulate Peckerman's article. I obtained a research-grade impedance cardiograph machine and began to do studies.-Indeed, Peckerman is absolutely correct, except in my patient population, 82{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} had low cardiac output compared to control groups, as opposed to their 48{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. That is merely reflective of the fact that we have a sicker patient population.

Diastolic Dysfunction a Common Thread among Study Patients

I was puzzled, though. If they had a low cardiac output, why didn't they end up like I did? Why did they seem to not go on to death, or even (as far as we know) have any abnormalities on echocardiography (such as I did)? I picked out those with the lowest cardiac output on impedance and had about 5 or them echoed all in a row, in different parts of the country, and received the echo reports all about the same time. They all said, essentially, "Normal ejection fraction, normal chamber size, normal wall thickness, no valvular problems. But it mentioned a phrase at the bottom: "There is type 1 diastolic dysfunction." It was present on all of these people. I was sort of struck by that. Partly, I didn't know what that meant-"diastolic dysfunction." I called up a cardiology friend and said, "What does that mean?" He said it is a problem you can see in aging; you can see it in hypertension; and you can see it in diabetes (where the wall compliance is affected). But (he said) the underlying mechanism involved in diastology is an energy problem. I asked him to repeat that because I wanted to make sure I heard him. He said, "Yes, diastolic dysfunction is what the heart looks like when it does not have energy at the cell level." I said, "Well, I'll be damned."

Expanded Studies on CFS Patients

I began a journey that started, next, with the acquisition of a high-technology echocardiograph machine made by General Electric, and began to look at over 100 consecutive patients. Depending on how you define "diastolic dysfunction" (there are different definitions in different hands), the range of diastolic dysfunction ranges from 70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} (on the low end, if you have a more strict criteria) up to 97{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} (if you use a less strict criteria). So, indeed, these patients do have diastolic dysfunction. It characterizes their disease. And diastolic dysfunction is not necessarily an "old person's" disease. These patients are not hypertensive, nor are they diabetic, therefore the only reasonable explanation for their diastology is that they have an

underlying energy defect.

I began to investigate the different parameters of echocardiography that lends itself to understanding energy. There are several parameters measured in milliseconds, or ratios that are very energy-sensitive. And if you look at these parameters, they are very strikingly abnormal. It is very suggestive (in my opinion) of a deep-seated energy defect expressing itself in the heart. When you have diastolic dysfunction, of course, you fail to fill properly. And a pump is a pump is a pump. A pump has two functions: to receive blood, from which it then pumps. There may be pump failure, or there could be a filling failure (you can't pump out what you don't fill with). And the heart is no different; if there is a failure to fill, there will be consequences, in terms of output.

What has been intriguing to me, in this long journey, is that the human physiological response to a lack of filling is to squeeze harder and to squeeze faster. Therefore, there are a lot of interesting things on the echo that suggest to me that a lot of these patients are compensating for this filling problem by hyperadrenergic tone, both by chronotropy and inotropy, driven (probably) by the adrenergic system, including the contents of the vasomotor center in the brain, primarily norepinephrine, but also supplemented by the adrenal glands, including epinephrine and norepinephrine, and perhaps cortisol. And so a model began to arise of a deep-seated energy problem, reflecting itself (partially, but not exclusively) in the heart, and that that defect is compensated for, in human physiology, by hyperadrenergenic tone, and as long as that is satisfactory, you may not even experience low cardiac output symptomatology. But when you see hyperadrenergic failure or exhaustion, which will obviously come to most in time, at least, then you will express the problems related to low cardiac output. That can begin to generate many of the symptoms we see in this illness.

The next problem that I faced was (after identifying the energy problem) determining where the locust of control was, exactly. And I cannot, Jeff, exactly tell you-I guess it is my non-linear thinking; I don't know how this came to me; it probably came to me by just holding several ideas that were not linearly connected all at the same time and deducing that maybe something could explain all of this. I noticed there was a defect on echo when these patients are tilted into the upright position, they cavitate their left atrium. I also noted that they had elevated pulmonary pressures by measurement of the tricuspid regurgitant pulmonary gradient, which is an indirect measure of pulmonary pressure (they had elevated pulmonary pressure in about
15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}), and about
50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} had left atrial cavitation.
Physiological Evidence of a Lack of Oxygen
I was fumbling through Google search engines, and found that left atrial cavitation is a feature of high altitude climbing. It is found in people in hypobaric oxygen chamber in which they are echoed. They show that the higher the altitude, the greater the degree of left atrial cavitation, and the greater the degree of pulmonary pressure elevation, suggesting that high altitudes produced effects on echo reminiscent of what I was seeing in chronic fatigue syndrome. That gave me the first clue that maybe this may have something to do with oxygen (or the lack of it).

At the same time, I also was intrigued by an article I read about the contraindication to neurosurgery if you have a patent foramen ovale (PFO). Neurosurgery is often done with the head-up/body-down position, so the surgeons can gain access to the brain, and in that upright position (which is similar to

what I do on tilt) there is an increased incidence of PFO-driven air emboli to the brain in neurosurgery, which is why you don't take someone to surgery who has an active PFO. So all of this was being held in my brain at the same time, and I suddenly decided to look for whether or not there was a patent foramen ovale (PFO) in these patients because they had several interesting features that might suggest that they might have a PFO. One is their cavitating left atrium, which means they could be getting a very low pressure-sudden low pressure-drop on the left side of the atrium, combined with pulmonary pressures elevated on the right side, sufficient to give a pressure gradient from right to left, blowing past the septum foramen, allowing a hole to open up (which is normally open in utero, but typically closes at birth). And so I decided to look for this and lo and behold, 90{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of these patients have a PFO in their hearts. They have evidence by saline bubble contrast echocardiography of a hole that exists, and they typically shunt from right to left, very similar to what you see in fetuses, which is, of course, a continuous hole. Whereas about two-thirds of patients, the hole is only evoked by Valsalva, which quickly and transiently increases the pressure differential, right to left, blowing past the septum primum. A whopping one-third of the patients were shunting constantly across-in effect, they have a functional ASD-suggesting that there is a significant pressure differential problem in a continuous fashion from right to left.

At that moment, I began to view this disease as some sort of problem in oxygen because what mountain climbers and fetuses have in common is that they lack oxygen at the cell level. In the case the climber, the lack of oxygen is due to the fact that there is not enough oxygen at the altitude they are at. In the infant's case, the lack of oxygen is due to the fact that they are in the uterus, where the partial pressure of oxygen is about equal to Mount Everest, and then that combined with the fetal hemoglobin, which causes a left shift. (Or in the first 8 weeks, neonatal hemoglobin which causes a really big left shift.) They may be at almost a facultative anaerobe. The reason they are that way is, in part, because they have not yet coded for the enzymes that handle oxygen; they have not been coded and they are not coded for until about 35 weeks (5 weeks before they are born).

And so I began to view this disease as sort of somewhere between a fetus, on the one hand, in which maybe oxygen can't get in because it is being kept out because of a defect in the handling systems for oxygen, or like a mountain climber, in which some other external problem is blocking oxygen from entering. That began to evolve into my current idea from this work, which is that this disease is a disorder of energy, and the locust of control of that defect in energy lies at the level of oxygen handling. The putative defect in the mitochondria may not really lie within the mitochondria itself, but rather perhaps in some enzymes within its inner mitochondrial membranes or even outside the mitochondria that handle the oxidative byproducts of oxidation phosphorylation, particularly superoxide. I'm drawn to that idea because of the physiology of infants (of neonates/fetuses), that is, they evolve their oxygen-handling systems late in pregnancy, and until those systems are well-developed, giving them oxygen can actually kill them. That is why you don't give high doses of oxygen to newborns, especially preemies born before the age of 35 weeks, gestational time.

To sort of link this together-this string of ideas-I decided to administer oxygen to these patients and monitor several things. First, I would monitor their PFO status, because if they were acting like babies (or fetuses), then we should be able to modulate the PFO grade (it can be graded from 1 to 5, depending on the number of bubbles that you see). I also monitored the energetic characteristics of the echo in response to oxygen therapy. Lo and behold, nearly all of these patients have near-total closure or partial closure of

their PFOs with 15 minutes of 4-liters-per-minute oxygen. They act just exactly like fetuses act in response to oxygen. Secondly, in terms of their energetic response to oxygen, about half of them seem to get better with oxygen, making them look more like mountain climbers, and about half of them get worse with oxygen, making them look more like fetuses. So the patients seem to be split into those who look like they can't get oxygen in for some external reason, and about half of them look like fetuses-trying to keep oxygen out lest they get killed by oxidative stress.

That led me, finally, to ask what possibly could cause a defect in this central handling system for oxygen. The only thing I have been able to come up with that seems to reflect my own experiences going back to Lake Tahoe days is viruses (and the best model for this, of course, is the HIV virus). HIV codes for a peptide called the TAT protein. Is has been recently published (in the last few years) that TAT protein specifically inhibits superoxide dismutase (SOD) and the glutathione peroxidase systems, which are exactly the systems that babies do not code for until 35 weeks of gestational time. Therefore, these viruses that are involved or associated with this disease may be acting to downregulate these oxygen-handling systems, rendering these patients (functionally) into fetuses (in terms of their ability to handle oxygen). This process is actually keeping oxygen out of the system. I'm not sure of the exact mechanism of that, but it may actually be at the sense mechanism, just as it is in fetuses. They keep oxygen out to keep from getting killed by it, but in so doing, they equilibrate at a lower energy state, thereby (meaning) that chronic fatigue syndrome is not the problem; it is a sense response to a deeper problem in oxygen handling.

So that is sort of a very short order, I guess, of the sequence of my thinking and how it has evolved over the years since Lake Tahoe.

JB: Well, I want to compliment you. That was the most eloquent and beautifully understandable explanation of a very complex process. Even those of us who are not cardiologists would, I think, be able to follow that explanation very well. There are a number of obvious questions. We could probably go on for hours and hours with question and answer response, here, because there are so many things that are raised by your observations and extraordinary thinking. Let's ask the most obvious questions based upon the observations that you have made and the way you have assembled this information (which, I think, based on the presentations that you have made recently and I believe the data you have assembled looks very compelling).

When we suggest-from a functional medicine model-that removal of agents that might precipitate this transition resulting in a PFO in these patients is one part of the potential therapy, the other part would be trying to find a way to enhance both oxygen delivery and detoxification of oxygen's secondary metabolites. Knowing that if this is kind of a functional ischemic event, you get this whole xanthine oxidase conversion and you get a bunch of secondary oxidants that result, so you basically have an oxygen burden paradox that too little oxygen is the time of greatest oxygen stress, which seems very paradoxical to many people, but that is actually what happens during ischemic events. So it seems like your observations may call for two things, one of which is identifying the agent that initiates this PFO transition, and the second is trying to prevent (to the extent possible) the toxic effects of ischemic outcome.

PC: Yes. I understand your thinking and I agree. The first order of business is to understand (as best as one can) how the locust of control of this, which I believe is centered (I think) at the level of superoxide

handling (that sequential step-SOD) and then either down two pathways: glutathione peroxidase to water or catalase pathway to water. I believe that is the best locust of control that I can come to. There may be other loci in this, but I like this pathway because that is the pathway inhibited by viruses. Therefore, I'm inclined to go there because that is the clinical scenario that I have been branded with since Lake Tahoe.

How do I bring viruses into this mix? They don't have to be specific viruses, mind you-just any microbe that has learned how to downregulate the redox state for its own survival, and therefore, this is one mechanism they do. Now if that's the case, then we have to figure out how we can resuscitate that locust of control. Does resuscitation mean that we can induce the coding of those enzymes at the gene level someway somehow, and secondly, could the agent that is doing this be inhibited in some way so that perhaps you get resurrection at that locust of control because the virus that is inhibiting it is inhibited?

Readapting to a New Reality

And then you have to turn your attention to the consequences of all this, which are two-fold. One consequence, of course, is that you have significant oxidative stress involved, and so there are all kinds of things to do for that. On a deeper level, though, there is something that I think is worth mentioning because it was a definite epiphany to me and may be very involved here. When I had my heart transplant and they congratulated me for having a 25-year-old heart pumping 10 liters a minute, as opposed to my old dying heart pumping 2 liters per minute, they said, "You are now the owner of a brand new heart that is completely normal and, since that's your only problem, we fixed you." And I said, "Well if I'm so fixed, how come I feel so bad?" And they said, "Well, that's because it takes years and years to adapt to a 2-liter-per-minute flow, and it make take... " get this... "years for you to readapt to a 10-liter-per-minute flow." The body has to adapt to defend itself, and then it cannot readapt quickly when you change the primary problem. Therefore, the other hurdle for getting people better, I think, is-even if you fix their locust of control-to get them rapidly to readapt to that new reality. Because if you don't do that, they may take years, and maybe never readapt to the reality that you have generated for them, and that may be because they phenotypically adapted. For so many years they lose their way back, or they even have genotypic problems that may have supervened, so they may have new genes in play (mutated or otherwise) through the allo insertion regions so they have to be genotypically transformed. That may, therefore, bring into play such things as stem cell approaches.

There is more to this than simply fixing the locust of control. You then have to figure out how to get these people who have been sick for 10, 20, and even 30 years back to some level of normality, even after you have fixed their central problem. And that is a problem I am extremely interested in because I think that is the problem of all chronic medical illnesses: How do you get people to readapt to the new reality that you have created for them?

JB: I think that's really a fantastic way of moving to my last question. As you look at the number of studies that have been published (of which there are many) on chronic fatigue syndrome with different interventions, we can come to conclusion that there is no magic bullet (obviously), and that it looks like a multifactoral condition (as you've described it). But there are 2 therapies (of those that have been tried) that seem to have the greatest number of potential positive hits from RCTs and those are cognitive behavioral therapy and graded exercise therapy. There are something like 6 or 7 trials on each of those that show some positive nature. So, if we map those against your discoveries, would you be able to make a connection as to how cognitive-behavioral therapy and graded exercise therapy could connect to this?

Opinions on Cognitive Behavioral Therapy, Graded Exercise, and Rebreathing
PC: I think it is easier to make a connection with cognitive behavioral therapy, and maybe one to graded exercise. I'm reminded of an experiment I recently read about where 10 people were asked to hold in their hands a vial of suspended white cells in a physiologic buffer. Five of them were asked to think bad/negative thoughts and five of them were asked to think good/positive thoughts. And then they took the vials that they were holding and they analyzed the DNA and found that the DNA transcription sites were very open and there was much more mRNA transcription being done in the ones with happy thoughts, and that the genes were being shut down in those who were thinking bad thoughts. So I think, perhaps, one's mental attitude affects the phenotypic expression of your entire genome. So I think cognitive behavioral therapy might act there.

In terms of exercise therapy, one of the greatest stimulants to the handling systems for oxygen is, in fact, oxygen itself. Indeed, it seems reasonable that oxygen-the mere production of superoxide itself-would actually stimulate the very enzyme systems designed to handle it, and therefore, as long as the system is graded, one might see a benefit (I suspect). But what bothers me about this is that it would be so easy to cross over the line. If there is an absolute inhibition in defect in oxygen handling, and you force oxygen into these people by exercising them, then you can do significant damage. I am always reminded when I rounded medical school as a young intern with J. Willis Hearst (a cardiologist), we came upon a bed with someone who had idiopathic cardiomyopathy. He warned us to never ever exercise someone with cardiomyopathy because you would kill them. I always remembered that. And so, I think in a system in which there could be a deep-seated energetic, shall we say, "metabolic cardiomyopathy," they may not be able to handle significant oxygen loads any better than a baby born 6 weeks premature (34 weeks gestational time) would be damaged irreparably by excess oxygen. I think that is why I am a little concerned about graded exercise therapy, per se. For every person that you might help with it, you could irreparably hurt 2 others.

JB: Yes. And I think you have pointed out in previous discussions and in your writings that chronic fatigue syndrome is kind of a generic catch-all for a whole variety of different degrees of severity. So we have people that have kind of a garden-variety fatigue that have called themselves chronic fatigue patients all the way up through the patients that you often see, which are very severely impaired and often the cause of their death will be something related to these energy-deficit disorders. Sometimes it is defining what we are talking about, I guess, as it relates to the patient and where they are in that sequence.

PC: Yes, exactly. I wonder, in my own mind, how I would differentiate those who should be submitted, for example, to graded exercise versus those who should be not presented for such therapy. I would do it simply by looking at how they respond to oxygen. There are several ways to analyze how someone responds to oxygen. The one that we use here is we simply look at how the heart responds using the most energetically sensitive parameter, called the "Isovolumetric Relaxation Time" (measured in milliseconds). And if, on oxygen, that IVRT goes up, they should not be submitted to exercise, because that is saying that oxygen is making their heart worse. If, on the other hand, that IVRT goes down, that would be an oxygen-tolerant person; they are actually benefiting and it is almost like giving oxygen to a high-altitude climber (he suddenly feels like it is manna from heaven). And that person I think might do very well on a graded exercise. In my practice, it is bisected about 50-50. Fifty percent look like mountain climbers and would probably benefit from oxygen loading (by exercise or any other way), and 50 percent looks like they are getting creamed by it. That could change over time, I suspect. If you have other interventions in mind they may not be fixed in time, but that is an example of why I think the blanket statement that

exercise for this disease is good in all cases is simply untenable.

JB: Paul, as you are speaking I am reminded of a conversation we had years ago with Glenn Doman, who is the co-founder of the Institutes for the Achievement of Human Potential in Philadelphia. He talks about how with his kids that often have certain types of brain injuries, using this rebreathing technique, where they mask these children and they then get an increased carbon dioxide level, which then improves oxygen delivery and they train them to do this (the parents, actually, are trained to train the child). He feels that is a very effective way of increasing the oxygen environment in the central nervous system. Have you ever thought about this rebreathing concept?

PC: Yes, I have. Here, again, I get a little concerned. When you undergo rebreathing approaches, you basically shift the oxygen hemoglobin dissociation curve to the right because as you are rebreathing the CO2 you are shifting the PH and you are actually offloading oxygen at a greater rate. That would be a very bad idea if someone is oxygen toxic. One of the interesting things, Jeff-one of the things we have observed-is that if you administer oxygen to these patients and monitor their breathing rates, we get three different varieties of breathing responses to the administration of low-dose oxygen. In one group, they start to pant, and in one case, the panting was 130 breaths per minute on the administration of oxygen. In another patient, the administration of oxygen resulted in the cessation of breathing and they became obtunded. In the administration of oxygen of a third set they seemed to just not be bothered by it; their breathing rate remained identical. So I think there is a very odd distribution of responses to oxygen. One group actually almost seems to act like someone that is in such a chronic hypoxic state that they no longer are CO2-driven; they are oxygen-driven. Just like the chronic COPD person; you put them on oxygen and they actually stop breathing. And another group, when you give them oxygen, they hyperventilate to the point that they actually countermand the excess oxygen by vasoconstricting to keep the oxygen you are giving them out of the cell. And a third group that seems to handle it rather more normally. So I think, again, that in disease that we are talking about here-chronic fatigue syndrome and other diseases that affect energy systems-if the locust of control lies at the level of the handling of oxygen, then the use of oxygen is very problematic.

JB: I think you have done just an absolutely superb job of defining (at a fundamental level) what we would call in our parlance a functional illness. To define a pathophysiology is probably going to be not as important an understanding as you helping us to understand the mechanisms that relate to this dysfunction. Paul, I want to thank you. This has been quite a journey you have been on and to share this with us has been extraordinarily important. I know this is just a weigh station along your continued discovery process and we hope we can check back in. We're so pleased that you are feeling better and that you are part of our community. You are a major contributor and we wish you well. I just thank you so much for doing all that you are doing with your patients.

PC:Thanks very much, Jeff.

JB: Thank you.

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