March 1999 Issue | Martin Pall, Ph.D.

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Welcome to *Functional Medicine Update*™ for March 1999. As we move into spring, we at HealthComm and the Institute for Functional Medicine are preparing for the Sixth International Symposium on Functional Medicine, which will take place May 23-27 in Tucson, Arizona. Both the symposium itself and the pre-symposium training sessions we will be providing will be exciting. We are offering an introductory course on functional medicine and, for the first time, a clinical nutrition and biochemistry course (Clinical Nutrition and Biochemistry: A Functional Approach) on Sunday, May 23. If you are looking for a primer in nutritional biochemistry from a functional medicine perspective, I encourage you to sign up for this pre-conference course. Also, the workshops we have scheduled this year as part of the symposium are quite remarkable. The workshops are the "how to" section of the symposium.

Candice Pert and Michael Ruff will follow up from their plenary session with their workshop, "Understanding the Mind-Body Architecture for Healing." A workshop titled "Lymphocytes: Mediators and Messengers in Health and Disease," led by a clinician and a diagnostician, will be ground zero in terms of applying some of this information. In a neurotoxicity workshop we will look at the detoxification mechanisms. Titled "Toxicity and Neurodegenerative Disorders," this workshop will be presented by a clinical neurologist. In a workshop on "Applications of Functional Medicine for the Complex Patient," two clinicians will provide clinical case management strategies.

A workshop titled "Gastrointestinal Disorders, a Functional Medicine Perspective," will feature a naturopath and a chiropractor bringing some of these concepts to the clinical application area. Two extraordinary presenters will integrate their experiences on the application of functional medicine in a workshop on "Functional Medicine and the Mediation between Health and Disease."

A workshop on "Stress and Chronic Illness, Case Studies and Clinical Tools" will be led by a naturopath and a medical doctor. "Attention Deficit Disorder in Adults and Children, a Functional Medicine Approach to a Common and Challenging Disorder" will be a workshop given by a medical doctor who has extensive experience in managing these conditions and a nurse who is the clinical nutrition specialist in our Functional Medicine Research Center and who has specialized in children’s and infants’ health disorders.

We will have Rhythmic Aspects of Function, looking at circadian rhythms and medical therapies. Dr. Sidney Baker will introduce this new topic to the functional medicine audience

According to this forecast, there will be dramatic shifts in disease types and prevalence over the next 30 years, focusing more on the chronic metabolic disorders that lock people into processes of homeostatic dysfunction. Some people still maintain the view that the conditions of ill health we experience in midlife are caused by bad genes and "the luck of the draw." We have tried very hard in *FMU* to avoid this genetic determinism model, which says because you inherited bad genes from your parents, your genes inexorably lock you into heart disease at age 54. Instead, we have said that the body's genes are pleomorphic and can be expressed in different ways depending on different environmental exposures—diet, lifestyle, beliefs, attitudes, behaviors, exercise patterns, air, water, and food.

As a consequence, the uncontrolled, non-blinded experiment called life can result in a variety of different outcomes depending upon the choices we make, or the things that befall us throughout our lives. Dr. Steven Rose, Director of the Brain and Behaviour Research Group at Open University in England, described this concept in a recent article titled "Neurogenetic Determinism and the New Euphenics," in the *British Medical Journal*."[2] He explains that we need to take care not to lock ourselves into this deterministic model of disease. He specifically focuses on brain biochemical dysfunction. He states:

> "As we approach the end of what in the United States has been termed the decade of the brain, and with a complete map of the human genome in sight, it may be time to try to re-evaluate what the vast increase in molecular knowledge of brain processes has achieved" in this last decade.
>
> "Certainly there has been no shortage of claims. The abnormal genes and their protein products associated with neurodegenerative diseases such as Huntington's chorea have been identified."

This is brought major breakthroughs in our understanding of the genetic determinants of neurodegeneration. Genetic risk factors have been found for Alzheimer's disease, such as the apo E4 genotype and other genetic markers. The molecular processes that culminate in the devastating neuronal death and malfunction responsible for the disease are now subject to intense investigation. We have come a long way in the last decade in understanding Parkinson's and Alzheimer's diseases. For neither condition has the new genetic knowledge yet brought any effective treatment or demonstrated prevention, however. They may come with the application of these concepts in preventive programs in which the patient can apply specific diet and lifestyle programs that are consistent with their genes to help protect against neuronal injury. Dr. Rose goes on to state the following:

"…when we move beyond the terrain of relative diagnostic certainty represented by traditional neurological disorders, things become much murkier. Gene markers, if not genes, associated with conditions such as schizophrenia or manic depression have been proclaimed, amid great ballyhoo, only later to be quietly withdrawn as non-replicable."

An example would be the dopamine receptor gene that seemed to code for alcoholism. We have believed people are alcoholics because they have the D6 dopamine gene, which makes them susceptible to alcoholism. That theory did not seem to stand up against further scrutiny. It may be that those gene determinants are interrelated, but in and of themselves they do not necessarily predetermine a person to be an alcoholic.

"The trouble is that as each old claim disappears into the mists, newer and even more extravagant ones

appear. Genes, it is said, are responsible for such diverse features of human conduct as sexual orientation; poor behaviour in school; alcoholism; drug addiction; violence; risk taking; criminal, antisocial, and impulsive behaviour; political anti-authoritarianism; religiosity; tendency to midlife divorce; and even compulsive shopping."

> Well-funded programs that are starting to look at this genetic determinism have begun to yield data that says hold it! The genes are pleomorphic. They do not necessarily encode for an outcome. We are not locked into a rigid phenotype from this genotype.
>
> "The universalistic claims made for selective serotonin re-uptake inhibitors such as fluoxetine (Prozac) are by now very familiar; it is as if all too many of us have too little fluoxetine in the brain without regular recourse to the drug. Less well known is the case of methylphenidate hydrochloride (Ritalin), an amphetamine-like drug now apparently prescribed for anything up to 10 {56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of all American children—mainly boys between the ages of 8 and 13—but coming soon to a general practice near you. Some 40,000 prescriptions for methylphenidate hydrochloride were being issued annually in the United Kingdom by the mid-1990s. Methylphenidate hydrochloride is supposed to treat a condition known as attention deficit hyperactivity disorder, characterised by a child being naughty at home and a poor learner and disruptive at school. Furthermore, this disorder in childhood is supposed to predict criminal and antisocial behaviour in adulthood."

This deterministic model requires significant intervention with a drug to manipulate brain chemistry.

> "The condition was almost unknown in the United Kingdom a decade ago, even though it is supposed to be genetically caused."

How did it suddenly appear if it has been in the genes? Did the genes mutate all of a sudden in all these children of the 1990s?

> "This sudden emergence of a genetic disorder is puzzling. The result of mass mutations? Scarcely likely."

Another explanation may be that these disorders arise from something like our philosophy of a person who has individualistic behavior.

"It is all part of the medicalisation of daily life. Naughty and disruptive children have doubtless always existed. In the past their unruly behaviour might have been ascribed to poor parenting, poverty, impoverished schools, or unsympathetic teachers. Of course we might all have conceded that some children were simply wicked. Now we blame the victim instead; there is original sin in them there genes."

The author, Dr. Steven Rose, is not trying to argue that there are not authentic cases of children with dysfunctional genes or adults with faulty neurotransmitter metabolism that are included among the many diagnoses requiring chemical substance application. Dr. Rose is concerned about the label that has become universal. We might conclude from the Human Genome Project that genes determine everything, and their expression is immutable.

Rather than think of ourselves as neurogenetic deterministic individuals, we should be thinking of ourselves as pleomorphic individuals with a wide variety of phenotypes that can come out of our genotypes if, in fact, we are able to practice and be supported by the right things. That is the functional medicine model. It is the model I have advocated for the last 16 years. I believe it represents the increasing understanding of what the Human Genome Project really tells us—not disease determinism, but polymorphism, plasticity, and the matching of genes with the appropriate lifestyle, environment, and diet, to get the most out of the potential.

One genotype we have discussed is the apo E isoform genotype. Three types of apolipoprotein E travel in human plasma, the apo E2, 3, and 4 genotypes. These particular characteristics may encode for different risk to lipid-carrying abnormalities, vascular disease, and even Alzheimer's dementia. Those who carry the apo E4 genotype, either single or double allele, have statistically higher risk for dementia of Alzheimer's and cerebrovascular and cardiovascular disease. We have recently asked whether the apo E4 genotype individuals have higher sensitivity to dietary fat, increased peroxisome proliferation, and increased oxidative stress when they eat cholesterol- and fat-rich diets. Other individuals with different genotypes may have lower risk.

This seems to be confirmed in a recent paper published in the *American Journal of Clinical Nutrition.* The investigators and authors of the accompanying editorial all conclude that the apo E4 genotype does seem to influence the dietary response to saturated fat and cholesterol and how that gets translated into potential atherogenesis.[3,4] Individuals with the double allele apo E4 genotype, whose mother and father both gave them an E4 characteristic, have the greatest response to dietary cholesterol and fat. Even a modest increase in saturated fat in their diet, or modest increase in dietary cholesterol, can result in an elevation in total LDL cholesterol of 10 percent or more. These individuals need to be much more committed to a low-saturated-fat, low-cholesterol, higher-fiber diet and an exercise program. The determining factors are the relative risks the individual carries and the way he or she modifies those risks through behavior and performance.

We need to put some points into perspective to balance our understanding of the prevalence of adverse drug reactions. Several authors recast the data of the Lazarou paper. They explained that articles published from 1965 through 1997 showed the percentage of hospitalized patients suffering from fatal ADRs was as high as 0.8 and 0.9 percent in 1965 through 1970. More recent articles, published in 1987, 1993, 1995, and 1997, have shown very low percentages, less than 0.1 percent. Therefore, critics of the Lazarou paper state, one should not use this older data to reach a conclusion about the prevalence of ADR-induced death in hospitalized patients, because this data was gathered before therapeutic drug monitoring

technologies were used. It was before we had the kinds of sensitivity to pharmacogenetics that we have now, with individual variation. It was before we had the drug interaction evaluation that we have now. Since those procedures have been implemented in hospitals, the prevalence of ADRs, as seen by the data actually provided within the Lazarou paper, has gone down by a factor of maybe more than 8 or 9. That would reduce the number of deaths from 100,000+ down to more like 15,000 deaths, which makes it a less significant problem than was described in the paper.

That point is worthy of our balanced understanding, but I believe it should be taken in context. Recall, for example, the report in the *New England Journal of Medicine* two years ago, which found that acetaminophen toxicity is the most common drug toxicity seen in hospitalized emergency room patients. According to that paper, many of these patients had not taken abusive doses of acetaminophen, in an attempt to commit suicide or by absent-mindedly exceeding the appropriate dose. Often they were individuals who had atypical adverse reactions to acetaminophen at doses listed on the label recommendations of the product. Therefore, the suggestion was that pharmacogenetics, unique differences in the way people respond, could give vastly different outcomes.[7]

Importance of Understanding How Medications Affect Individuals

Previous studies, published in the Journal of the American Medical Association and reviewed in FMU about three years ago, indicate that if a person is fasting, has a poor-quality diet, is nutrient-depleted, or is a high alcohol consumer, he or she has significantly increased risk of adverse response to acetaminophen.8 This response occurs as a consequence of the depletion of critical nutrients necessary for detoxification of alcohol, particularly the phase II detoxifying nutrients involved in glutathione conjugation, such things as glutathione precursors and antioxidants.

I want to keep the problem of adverse drug reactions in hospitalized patients in perspective. Those reactions may not be the fourth to sixth leading cause of death, but I do not want to get off the general theme that, if we can better understand how medications influence function at the individual level, we can design better programs for improving outcome with reduced risk.

Drug Therapy versus Natural Products

How might drugs create greater risk to individuals than natural products? That question has been heavily debated for years. According to proponents of phyto-, botanical, or herbal therapies, the mixture of products found in an herb is much more in sympathy with the body and can improve function without the adverse effects of a single compound found in a pharmaceutical drug. Pharmaceutical scientists respond that it is the activity of the active ingredient that achieves biological action; the higher the potency, the better regulation you have, and the more you can control the dose. Therefore, they state, herbal products, which contain mixtures of ingredients, many of which we know nothing about yet, are not better. They would argue that we have much better control by using a purified amount of the single ingredient shown to have certain biological function. That is an interesting question.

One significant difference is that some single-ingredient medications are produced in a diastereoisomeric mixture. This means they are a mixture of right-handed and left-handed molecules. In nature, organic molecules always have a specific handedness. They may be R or S configuration, recto/sinister. As a consequence, the enzymes and the other asymmetrical molecules that control body function fit hand-in-glove into the molecules that have certain handedness, or a certain shape.

Drugs are frequently manufactured in a way that produces both hands in equal prevalence. In other words,

you get R and S in a 50/50 mixture, one of which may be very biologically active and control function in a certain way. The other, however, is not benign; it actually has a potential adverse effect on the one that does the work. In natural products, you do not have this effect. In a natural substance, the organism nearly always produces only one hand. Examples include D sugars and L-amino acids. It is not so with many pharmaceutical drugs.

An interesting example was described in a recent article in the *New England Journal of Medicine* on a drug called carvedilol.[9] Carvedilol is a beta-adrenoreceptor-antagonist drug with smaller amounts of $alpha_1$-adrenoreceptor-antagonist activity. It was approved in the United States in September of 1995 for the treatment of patients with essential hypertension. In May of 1997, on the basis of the results of several clinical trials, it became the first adrenoreceptor-blocking drug to receive approval for the treatment of symptomatic heart failure. This is a racemic lipophilic aryloxypropanolamine, which means it is a mixture of handedness in molecules. One hand of the molecule produces relatively toxic effects, because it may be a nonspecific blocker, blocking alpha as well as beta receptors.

The other hand of the molecule, the one that might be considered the physiologically most active, is very specific in its mode of action and has lower potential adverse side effects. The difficulty is that the drug is produced with equal prevalence of both the right-handed form and the left-handed form, which means it can result in increased side effects, and the individual needs to be monitored very carefully.

The Importance of Handedness

Granted, this particular medication is more selective than propranolol, for instance, or lebetalol, which have lower degrees of selectivity. It is important, however, to recognize that by putting the handedness molecules together in a single pill you do not get the same effects and specificity in physiology as you would if you used the pure enantiomer that was most selective for the body's action that you are going after. That is the difference between a natural product, which is a mixture of handed compounds that are selective for the biosynthetic machinery of the plant or animal that made them and racemic mixtures that often come from drug manufacturing.

What is the best way of administering medications—orally, parenterally, intravenously, or intramuscularly? The nutritional substance we have discussed most in this regard is vitamin B12. There is a long-standing belief that vitamin B12 requires intrinsic factor for its oral absorption in individuals who have had atrophic gastritis type A or type B, or individuals who have lost the intrinsic factor secreting ability of their stomach lining and may be malabsorbers of B12. In that case, the intramuscular administration of B12 would be considered preferable because you cannot get B12 orally absorbed.

A recent new paper in the *Lancet* discusses the difference in oral versus parenteral therapy for vitamin B12.[10] According to the article's author, compelling evidence from 12 studies now suggests that the belief that individuals with intrinsic factor or hydrochloric acid insufficiencies could not absorb vitamin B12 orally is not true. Giving higher levels orally can increase plasma levels in individuals with malabsorption.

As with any other medicine, compliance may be an issue, especially in elderly patients with dementia. However, a number of studies have shown good compliance with oral vitamin B12. For instance, 64 Swedish patients who took 1000 m g daily for several years had no relapse or a low cobalamin concentration, and their cognitive function remained high. Compliance may also be inadequate with

parenteral therapy. There was an 11 percent relapse in one large study because people did not return in time for their parenteral injections, and they were not getting enough oral vitamin B12.

The author of the article suggests that oral administration leads to higher compliance and that you have to go up to very high oral doses. You cannot use the RDA or two or three times the RDA. You must go into the 50 m g, 100 m g, and maybe even as high as 1000 m g to 2000 m g daily oral doses in individuals who are vitamin B12 malabsorbers to achieve adequate plasma levels and tissue levels.

Oral cobalamin has been advocated for the treatment of mild cobalamin deficiency from other causes. If, as various studies indicate, the prevalence of cobalamin deficiency among older Americans is from 9 to 30 percent, and since insufficient cobalamin relates to cognitive declines and deficits, and maybe even to increased risk of neurodegenerative disease, then the current RDA for cobalamin is probably inadequate for many individuals after age 60. The author believes we should consider revising the RDA for the older-age population, to compensate for these differences in absorption, and that oral administration can improve plasma levels and bring them into normal range.

Another route of absorption is transdermal. A number of medications are now administered transdermally. An example is progesterone, delivered through Progest cream.[11] Many women rely on progesterone replacement through a topical cream. In a recent *Lancet* paper, investigators at the Menopause Clinic at King's College Hospital in the U.K evaluated how much of the Progest cream could be absorbed. The investigators looked at the adequacy of Progest for the replacement of natural progesterone. Twenty patients completed the study.

Progest significantly increased urinary P3G (pregnanediol-3*a*-glucuronide) and plasma progesterone compared with placebos. The median plasma progesterone after 10 days of administration of two to four times the amount of Progest recommended by the manufacturer was only 2.9 nmol/L. This is much below the day one plasma progesterone of at least 30-35 nmol/L observed in fertile women. Therefore, the authors question whether enough progesterone is being absorbed across the skin as Progest cream to balance hormones in menopausal women.

In a previous study, plasma progesterone values surged to 35 nmol/L within three hours of administration of 200 mg of a topical cream of progesterone. The authors suspect the surge is largely responsible for the secretory transformation of the endometrium observed in estrogen-exposed postmenopausal women. They conclude that Progest should not be substituted for the progestogen in conventional estrogen/progestogen hormone replacement therapy. Progest does not lead to adequate plasma levels of the compound and, therefore, might symptomatically reduce some of a woman's concerns, but not adequately balance her hormones to reduce risk of other problems, such as endometrial cancer, or even possibly breast cancer.

Many women now use Progest cream successfully to modulate symptoms, but now a different question arises. Do the levels that have been supplied and absorbed support optimal function? We need to examine this question more fully.

The other point of absorption we have focused on concerns the mucosal transmigration or transport of various substances, and the relationship to nutrient absorption, allergen initiation through large molecule absorption, and even bacterial translocation through compromised GI mucosa. A review paper titled

"Intestinal Mucosal Amino Acid Catabolism,"[12] which appeared in the *Journal of Nutrition*, discusses the gastrointestinal mucosa as an organ system unto itself with huge effects on overall physiological function.

> "The small intestine is not only responsible for terminal digestion and absorption of nutrients, but it also plays an important role in catabolism of arterial glutamine and dietary amino acids."

The GI mucosa may be one of the most important contributors to our overall amino acid metabolism. This is very different from the way I learned about amino acid metabolism, which was to think of it as almost exclusively a hepatic function. In this case, we are looking at the gastrointestinal mucosa as an important contributor to amino acid metabolism. Most of the glutamine and almost all glutamate and aspartate in the diet are catabolized by the small intestinal mucosa, and it accounts for 56 to 64 percent of the metabolized carbons coming from these amino acids from dietary protein.

The small intestinal mucosa plays an important role in degrading arginine, proline, and branched-chain amino acids, and possibly methionine, lysine, phenylalanine, threonine, glycine, and serine. Possibly 30 to 50 percent of these dietary amino acids are not available to extra-intestinal tissues because they have already been catabolized and rearranged at the GI mucosa level. Dietary amino acids are major fuels for the small intestinal mucosa. They are essential precursors for intestinal synthesis of important regulatory substances, including glutathione; nitric oxide (through the arginine pathway); polyamines (which are very important for immune potentiation); purine and pyrimidine nucleotides (related to DNA and RNA synthesis); and amino acids such as alanine, citrulline, and proline. They are all obligatory for maintaining intestinal mucosal mass and integrity.

Therefore, we might consider certain types of amino acids as small intestinal gut fuels. Butyrate, on the other hand, which activates and nourishes the colonocyte, might be considered a large intestine gut fuel. Because intestinal amino acid catabolism plays an important role in modulating amino acid availability to extraintestinal tissues, the health and vitality of the small intestinal mucosa has important implications for the utilization and efficiency of dietary protein in humans, and it may have extraintestinal effects. This is important to remember in dealing with individuals who may have sustained small bowel mucosal injury from immunological upregulation, irritation, or inflammation.

Increased permeability of the small bowel is measured by the lactulose/mannitol challenge test. What we call "leaky gut" may influence or have a relationship to poor amino acid catabolism and physiological function that is derived from these precursors to other molecules. When the small intestinal mucosal barrier breaks down, the potential exists for leakage of larger molecular-weight substances that may systemically activate the immune system. We also have a role through the M cell vesicles for the absorption of some of these molecules, even in the intact human mucosa.

A recent *Lancet* paper titled "Identification of Intact Peanut Lectin in Peripheral Venous Blood" showed that individuals who are sensitive to peanuts actually had intact peanut lectin protein in their peripheral venous blood after they ate peanuts.[13] This large lectin glycoprotein molecule could actually be found

intact within the plasma within about one hour after the ingestion of a peanut-containing meal. For most peanut-sensitive patients maximum concentration of the peanut lectin in their plasma occurred within an hour after eating. Some individuals had a reduced absorption time, however, and their levels reached maximum at four or even five hours.

This study is another demonstration of biological variability, but there is the opportunity for absorption of intact, large-molecular-weight substances across the GI mucosa. Even at small levels, this process can impart information to immune cells such as the mucosal-associated-lymphoid-tissue, the gut-associated-lymphoid-tissue (GALT), or even the Kupffer cells of the liver. Those cells then can activate the body into a proinflammatory response.

This is an interesting concept. We often think that proteins are always broken down to their oligopeptides and then into their amino acids before absorption. We would assume, therefore, that no information from those dietary proteins would remain to impact the immune system.

What happens if you have information that is imparted from a dietary protein to the immune system? For years people have wondered if an upregulation of the immune system could cross-react with the endocrine glands so that an individual who was sensitive to a certain dietary protein might develop symptoms of an adrenal or thyroid problem, such as autoimmune thyroiditis. Could that problem be caused by a cross-reaction with an antibody/antigen process initiated by a dietary food protein that was creating its own misinformation to the immune system?

That theme was described in a recent paper titled "Autoimmune Thyroid Diseases and Coeliac Disease," which appeared in the *European Journal of Gastroenterology and Hepatology*.[14] This paper discusses the potential role of dietary gluten in initiating autoimmune thyroid diseases in individuals with nontropical sprue or gluten sensitivity. The authors describe 152 adults with autoimmune thyroid diseases, many of whose thyroid dysfunction was correlated and exacerbated by gluten sensitivity.

We have learned from other papers that when gluten is removed from the diet of gluten-sensitive individuals endocrine function often improves, normalizes in those individuals who have autoantibodies to their thyroid glands, or autoantibodies to other glands. The question is what role does misinformation from the diet play in activating the immune system of genetically sensitive individuals to produce cross-reactivity with their body’s glands that can result in what we might diagnose as autoimmunity?

In a paper that appeared in the *Lancet* several years ago, investigators measured healthy centenarians and unhealthy 60- and 70-year-olds and assessed the difference in physiological chemistry between the two groups. The most striking difference was that the healthy centenarians had very low titers of autoantibodies to their thyroid, adrenal, pituitary, hypothalamus, and even to their endocrine glands.

Unhealthy younger individuals, in contrast, had much higher titers of autoantibodies to their endocrine glands, which meant they were allergic to themselves. What makes one allergic to oneself? It could be genetic susceptibility encoded through certain HLA-containing antigen antibody reactions and then environmental triggering of their expression as exposure to specific chemical or food-derived material initiates this cross reactivity. This study on autoimmune thyroid diseases and celiac disease merits our clinical interest.

You may recall a report we described a couple of years ago, which indicated a very strong statistical correlation between nontropical sprue, gluten sensitivity, and early-stage dementia. The brain is composed, in part, of glial cells. The microglia are the immune system of the brain that can respond to these proinflammatory mediators and initiate upregulation of function and gene expression that causes oxidative stress and neuronal death. The mechanism was that the gut could be connected to the brain through the immune system and the cytokine-driven inflammatory cascade. Again, genetically susceptible individuals have a higher relative penetration of that condition. This is certainly not the model of genetic determinism that some people derive from the results of the Human Genome Project.

I had the opportunity to give the graduation address at the winter graduating class at the National College of Chiropractic in Chicago. I was reminded while I was there that we use functional medicine in an effort to squeeze the best out of the gene expression and lower the adverse side effects of poor gene expression. In doing so, we employ a complex series of available tools to talk to the genes in the right way and modulate their function. These tools are not just dietary and environmental. They also have to do with how we think, act, and believe, how we exercise, and how we are structurally aligned. As functional medicine practitioners, we have a very large tool kit, which contains a rich array of tools that improve physiological, cognitive, emotional, and physical function in individuals, once we understand something about their antecedents and their unique genes.

A number of disciplines have looked at functionality from different perspectives. In Chicago I was very impressed with the basic philosophical model of chiropractic and how it has evolved in the past 100 years to serve individuals through a better understanding of the musculoskeletal/neurological system and its impact on gene expression and function.

A *New England Journal of Medicine* editorial titled "What Role for Chiropractic in Health Care?" focuses almost exclusively on the role of chiropractic manipulation for improving low-back function.[15] It does not look at some of the broader issues of neurologic/musculoskeletal function. In effect, the author cites the results of a paper titled "A Comparison of Active and Simulated Chiropractic Manipulation as Adjunctive Treatment for Childhood Asthma," which showed no significant difference between the groups.[16]

Another paper, titled "A Comparison of Physical Therapy, Chiropractic Manipulation, and Provision of an Educational Booklet for the Treatment of Patients With Low Back Pain," in the same issue of the *New England Journal of Medicine*, did suggest there was some positive benefit of chiropractic therapy.[17] When I look at these papers and their experimental methodologies and results, however, I note, once again, that we are not looking at cohort analysis.

If you look at the raw data, it strikes me that there are some patients who seemed to have responded very favorably to these therapies and others for whom it did not have as positive an effect. Those who derived positive benefit may have been washed out by what I call the rule of averages, in which by average there is not enough difference from mean, but by individual response, there might be a significant benefit. In functional medicine therapies, we try to individualize or personalize the intervention, realizing that one’s response may be based on a genetic need that is very different from the average.

An interesting article in the *American Journal of Public Health*, titled "Use of Chiropractic Services from 1985 through 1991 in the United States and Canada,"[18] points out an estimated $2.4 billion dollars was spent on chiropractic services in 1988 alone, and use of chiropractic care is growing rapidly. Reasons

extend beyond low back pain to include headaches and other chronic illnesses that might be considered in the purview of primary medicine.

We should consider chiropractic as one of the many tools of functional medicine that can be used to individualize patient outcome. An article titled "Access to Complementary Medicine in General Practice: Survey in One UK Health Authority"[19] appeared in a recent issue of the *Journal of the Royal Society of Medicine.* It explained that individuals in England are seeking comprehensive care and designing their own strategies, using a variety of practitioners with different skills to construct their own individualized programs. Outcomes are improved when patients weave together acupuncture, osteopathy, chiropractic, hypnotherapy, homeopathy, and nutritional medicine, and traditional pharmacology.

Does alternative medicine involve risks of untested and unregulated remedies, as stated in an editorial in the *New England Journal of Medicine*?[20] Certainly, we always want to make sure that anything we administer has passed safety test. We want to look at it in terms of safety. What studies demonstrate its range of safety? We also want to evaluate its efficacy. We want to examine efficacy in a personalized fashion, not just by the law of averages. Much of what is done now in functional medicine is heavily science-based and derived from the same soil, the same nutrient-rich information as pharmacology-based medicine. However, it is interpreted in different ways. An examination of MEDLINE on the Web reveals 112 chiropractic citations over the last year. Those citations often deal with the broad-based effects of muscles, bones, and nerves interacting to give rise to function.

Naturopathic medicine originates from a similar philosophy. According to naturopathy, the body has its own native ability, once the genes are given a chance, to express good health. Naturopathic medicine originated in Europe and came to America at the turn of the century through followers of Dr. Sebastian Kneipp.[21]

Doctors of naturopathic medicine at Bastyr University in Seattle teach science-based natural medicine that employs information to restore the abilities of the individual to maintain high-level homeostatic health and wellness. The way you use information and the objectives you select lead to patient outcomes. Who takes charge? Does the drug or therapy take charge, or do the patient’s genes, given a chance, take charge?

The Homeostasis of Illness

In a recent paper I wrote, which was published in Alternative Therapies, titled "The Use of Complementary Medicine for Healthy Aging,"22 I discussed the reasons why people have chronic illness that goes on for long periods of time and seems to lock them into a new homeostasis of illness. I describe four fundamental factors of aging that increase the risk of age-related diseases at the cell biological or molecular level. These factors include altered mitochondrial function and oxidative stress; increased protein glycation and alteration in insulin sensitivity; chronic inflammation; and defects in methylation, the transfer methyl groups through homocysteine and the tetrahydrofolate cycle.

Those are four common pathways associated with animal and human aging and age-related diseases. I want to discuss the application of these principles to chronic fatigue syndrome or fibromyalgia, a chronic health problem that has become more prevalent in the last 15 years. We are very pleased to have as our Clinician of the Month, Dr. Martin Pall, who will bring insight into the molecular cell biological and clinical implications of chronic fatigue syndrome. If you would like a copy of my July 1998 Alternative

Therapies article, give us a call at 1-800- 843-9660, or e-mail us at healthcomm.com.

INTERVIEW TRANSCRIPT

Clinician of the Month:

Martin Pall, Ph.D.

JB: Our Clinician of the Month, Martin Pall, PhD, is a researcher who is a biochemist at Washington State University in Pullman, Washington. Dr. Pall is a well-known and respected biochemist who, for a number of years, has been making contributions in the fields of biochemistry and biophysics. I met Dr. Pall as a consequence of our mutual interest in chronic fatigue syndrome. Dr. Pall will describe some of the modeling and formulations he has developed with regard to this disabling and debilitating condition that can afflict people for years of their lives. Dr. Pall gave a seminar to our Functional Medicine Research Center staff here at HealthComm not long ago. In discussing chronic fatigue syndrome and chronic fatigue fibromyalgia syndrome, we recognized that what Dr. Pall is developing has broad-based application to other chronic illnesses associated with fatigue. All may have something to do with biochemical function at the mitochondrial level. Biochemists would describe it as depletion of energy reserves in the form of ATP or other energy-carrying cofactors or intermediates.

JB: Dr. Pall, welcome to *FMU*. Your background has taken you through John Hopkins University, through Reed College as a professor. You have spent time at Yale, and you have a longstanding history of contributions to the students at the WSU medical school, where you are doing some teaching. You described the contents of a course related to oxidative stress, which you put together for the basic science years in the medical school program. Would you describe the course and tell us how students are responding to it?

MP: I have had a diverse set of interests over the years. I've done research in molecular biology, biochemistry, and genetics. Two-and-a-half years ago, I started teaching first-year medical students in the medical biochemistry course, and introduced a section on free radicals and reactive oxygen species, which is an area that had not been covered before. The students have responded extraordinarily well to it. I give them the basic chemistry and biochemistry, and then I give them some examples of a variety of medical correlates and how they reflect on current medical thinking. It's been an interesting process, and the students have been at least as interested in that section of the course as in any other

JB: Doctors who attend our Applied Functional Medicine in Clinical Practice training program frequently tell us they need to relearn their biochemistry in the context of the new thought process to see how it applies to chronic illness. They thought they could discard their biochemistry when they finished school. Now they feel they really need to learn it and know it. Do you think that we're starting to see a medicine develop in which the tools of biochemistry will have more applicability to clinical practice?

MP: I think there's no question about that. I also think that one of the frustrations about free radicals and reactive oxygen species is that they are largely ignored in the biochemistry textbooks, including the medical biochemistry textbooks. We now have a large and rapidly growing body of scientific literature in

the area, but the textbooks one uses to try to get information on it just simply ignore it.

JB: Chance and opportunity have intersected. This must be the time for fundamental shifts in both our educational system and our thinking. It's happening all across the health sciences right now. It's a pretty exciting time. It's also a time that probably means a lot of the textbooks we're teaching out of are already out of date.

In the paper you've put together and the modeling you have developed related to chronic fatigue syndrome, you pulled together information about why individuals might have a certain experience in their life, like a viral infection or an exposure to a chemical, and never quite get well. They get locked into this chronic fatigue syndrome. Would you tell us what led you to this model and then what the model is all about?

MP: Many cases of chronic fatigue syndrome (although not all) are characterized by an initial infectious episode, typically a virus infection. People have studied this for 30 years or more, trying to associate it with a particular virus, and have failed to do so. In contrast, it appears that several different kinds of viruses can trigger chronic fatigue syndrome.

The syndrome is characterized by a whole range of symptoms. Characteristic symptoms include not only chronic fatigue, but also problems cognitive dysfunction, memory and concentration problems, sore throat, tender lymph nodes, nonrestful sleep, and exercise intolerance. In addition, symptoms at the physiological and biochemical level include changes in the immune system, mitochondrial or endocrine dysfunction, changes in circulation, and perfusion of the brain. The syndrome includes a complex range of symptoms, and the question is why does it occur. Why is it chronic? Why does it last so long? Why do people have this for many months and, in many cases, many years with no obvious ongoing cause?

The hypothesis I came up with is an interesting one, and it's based on the following general notion. There is no ongoing infection that occurs during this long-term disease. People have looked for such an infection for something like 30 years without establishing one.

The other kind of general model one can think of has to do with regulatory circuitry. If you trigger a response, and if some set of positive feedback loops makes that response a stable one rather than an unstable one, then one could have a chronic disease that can last for many months and many years.

Some parts of my hypothesis are novel and some are not. The initial part is that one has an infection, either a viral or a bacterial infection. This, in turn, triggers the synthesis of elevated levels of inflammatory cytokines. That part had been proposed earlier. What I proposed is that these inflammatory cytokines, then, induce an enzyme known as the inducible nitric oxide synthase (iNOS).

Let me just mention that nitric oxide was the focus for the latest Nobel Prize in physiology and medicine. One has this inducible nitric oxide synthase that, in turn, synthesizes high levels of nitric oxide, which is a free radical, but a relatively unreactive free radical. Nitric oxide, in turn, is known to react very rapidly with another relatively non-reactive free radical—superoxide radical—to form peroxynitrite. I call this the peroxynitrite hypothesis because that is its central focus.

Peroxynitrite is a highly reactive oxidant. It produces a number of changes in cells, such as the

characteristic oxidative stress reactions—lipid peroxidation. It also attacks a number of the elements in mitochondria. This relates to something you mentioned earlier, namely that there is evidence for mitochondrial dysfunction in chronic fatigue syndrome. The reason why they occur has never been explained. The explanation I propose is that peroxynitrite attacks these elements in the mitochondria (that is well documented), and that is what causes the mitochondrial dysfunction one sees in chronic fatigue syndrome.

The other thing that is really central to this hypothesis is related to the changes peroxynitrite produces in the cell. I propose six different positive feedback loops by which peroxynitrite, when it is elevated, can produce changes that come back and increase the levels of either superoxide or nitric oxide. Those, of course, are the two compounds that react with each other to form more peroxynitrite. The idea is that the peroxynitrite, then, through these positive feedback loops can produce quasi-stable dysfunction, which, in chronic fatigue syndrome, leads to the symptoms that one sees.

JB: Could you describe briefly those six different feedback loops? I know it's biochemistry, but I'd like our listeners to know what the various opportunities the body has to lock this into a feed-forward process might look like.

MP:I'll try to describe at least some of them. They're fairly complicated. The simplest one, actually, was one that was proposed by Joe Beckman's lab in Alabama. It is that peroxynitrite reacts with and inactivates the enzyme superoxide dismutase, which is found in mitochondria. The function of that enzyme is to get rid of superoxide. So, obviously, if you inhibit that enzyme activity, the superoxide levels will increase, and that, in turn, will provide more superoxide to react with the nitric oxide to form the peroxynitrite. That's one of the six. There are several others. Let me just mention a couple of them that I think will make some sense.

There is a transcription factor known as NF *Kappa* B, which stimulates the synthesis of a number of different enzymes by increasing the transcription of their genes. We have known for a number of years that NF *Kappa* B is activated by a variety of oxidants. Whenever you have oxidative stress, as would be triggered by peroxynitrite in this example, you get NF *Kappa* B activation. NF *Kappa* B stimulates the transcription of the inflammatory cytokines that we propose to be involved here – IL1, IL6, TNF-alpha, and interferon gamma. It also stimulates the transcription of the iNOS gene that we talked about earlier.

Both by stimulating the synthesis of the inflammatory cytokines, and by stimulating the synthesis of the iNOS gene, one gets more nitric oxide synthesized. This, in turn, can react to form peroxynitrite. Those are two feedback loops going back through those two sets of functions. That gives you some idea.

Let me add that we also propose that, through several different mechanisms, peroxynitrite can both deplete the ATP pools in cells and increase the level of intracellular calcium. The combination of those two can act in several ways to trigger these positive feedback loops. Let me give you one example.

Three isozymes for the nitric oxide synthases have been studied. In addition to the inducible one I mentioned earlier, there are two others, both of which are calcium-dependent enzymes. Any time you increase intercellular calcium, you're going to stimulate those enzymes, and that, in turn, will increase nitric oxide synthesis. I hope that gives you some idea of the kinds of things that we're talking about.

JB: Very much so. In fact, listeners who have been following *FMU* for some time may see the clinical relevance of some information they have heard previously on *FMU.*

You have raised some important issues I want to reinforce. First are the cell-signaling effects you describe, and this whole feed-forward concept. It is common in chronic illness for patients to shift from a state of homeostasis they might have associated with wellness to a new state of homeostasis associated with symptoms of unwellness. Clinicians use the term homeostasis to suggest a state of equilibrium around health. But one could have a state of equilibrium around dysfunction as well. It seems you've described a model for disease beyond chronic fatigue, which might relate to other chronic illnesses, in which the feed-forward web of physiology has locked individuals in a different state, which is not necessarily the healthy state. The genes are expressing a different message.

MP: Yes. I think other examples of that state are better documented than chronic fatigue syndrome. When one looks at the control of blood clotting and what happens in thrombosis, or conditions that predispose toward thrombosis, for example, there is a very complex regulatory system that clearly can shift away from the healthy situation for long time periods. That is one example. There are a number of others.

JB: The clinical takeaway our listeners might derive from this discussion is that if they cannot break the loop or this cycle, they may be treating symptoms for the remainder of the patient's life and never get to the cause of those symptoms, because somehow he or she is in a loop. They're in a stable state, but it's a stable state of unwellness. There has to be some kind of link breaker to restore cell signaling, gene expression, and balance of things like TH1 and TH2 cytokines, to put the patient into a different equilibrium state.

MP: The complication in our case, since I'm proposing six positive feedback loops, is in determining which are the most important. Which ones have to be cut? We don't know the answer, but it is a very interesting question, assuming this hypothesis turns out to be correct.

JB: One exciting part of this hypothesis is that it is based, in part, on the increasing knowledge of altered cellular redox controlled as a consequence of functional changes in the mitochondria and electrolyte membrane transport phenomena. You have talked about this redox shift, in which the cell has shifted more into an oxidative state, with upregulated expression of NF *Kappa* B and AP1, which influences ATP and FADH2. These may have sounded to most medical students like esoteric topics, related to the most extreme of genetic metabolism diseases. Now, however, the language is being applied to chronic illnesses.

Let me take that to the discussion of the initial lesion, or the antecedent or trigger that may have resulted in the symptoms of chronic fatigue. You talked about viral or bacterial infection. Do you feel there may be other triggers, such as chemical substances? Dedra Buchwald at the University of Washington School of Medicine published a paper showing similarities among chronic fatigue, fibromyalgia, and multiple chemical sensitivity. Do you feel that chronic fatigue syndrome could actually be many syndromes with differing etiological factors that trigger the immunological cascade?

MP: Of course, it could be. My hypothesis doesn't really state what parts of the body will be impacted. The distribution of peroxynitrite may be different from one case to another. That may explain part of the

variation from one case to another. That is, a constellation of symptoms show up in one case or another, but not in all cases. Why do they vary from one case to another? That's one question. The question you are raising relates to the apparent overlaps among chronic fatigue syndrome cases, fibromyalgia, and multiple chemical sensitivity syndrome. Why do they seem to overlap? There may be a common etiology, but the distribution in the body may differ from one individual to another. That's sheer speculation, but it's a reasonable way of looking at it.

JB: In about 1990 eosinophilia-myalgia syndrome hit the press. The Centers for Disease Control and the Mayo Clinic were actively involved in looking at its etiology. Contaminated tryptophan appeared to be related to its onset. It had this mysterious peak E along with maybe other nitrogenous compounds that triggered a scleroderma fasciitis and chronic fatigue-like syndrome. The suggestion was that these molecules, with a molecular weight less than 500, could create a polyorgan dysfunction that was life threatening in some cases. Those who survived had some residual chronic fatigue. As you pointed out, many different examples can potentially clinically describe the mechanism you've talked about. It might be a unified mechanism.

One of the enzymes you describe in your paper that may be affected by this feed-forward process is an enzyme abbreviated PARS. We've talked about this in previous editions of *FMU*, the poly-ADP ribosyl synthase. Could you tell us a little bit about how that fits in the scheme, the PARS activation?

MP: Yes. I avoided it earlier on because it's a bit complex, but if you've dealt with it already, that should help quite a bit. The poly-ADP ribosyl synthase is an enzyme that is activated by strand breaks in DNA. It's a nuclear enzyme that produces poly-ADP-ribosylation of nuclear proteins, specifically histones. It does so under conditions where one has lots of nicks in DNA. It turns out that there are a whole series of free radicals that produce these nicks in DNA, hydroxyl radical being the one that's been most studied. Peroxynitrite reacts very much like hydroxyl radical. In fact, there's a debate in the literature—does it actually break down and produce hydroxyl radical or not?

The results of that debate really are not terribly important, except in this context, because we know it produces reactions very similar to hydroxyl radical. What you end up with by some chemistry that is well known, is that peroxynitrite will produce these nicks in the DNA and, in turn, produces a tremendous increase in this poly-ADT-ribosyl synthase activity. The substrate for that enzyme is NAD and NAD and its reduced complement, which is NADH, are essential for oxidative metabolism and energy metabolism in the mitochondria. What happens is you can actually get a massive depletion of the NAD pools in cells. That, in turn, leads to a massive depletion of ATP, and the energetics of the cell deteriorate to an extraordinary extent. This particular control is one that has been described in the literature by other people, so this is not original. It can react to produce a number of responses and, specifically, can lead to increased synthesis of both nitric oxide and superoxide.

JB: Two-and-a-half years ago, Dr. Ferid Murad was a presenter at our Fourth International Symposium on Functional Medicine in Aspen, Colorado. Of all the presenters he had the poorest evaluations by those in attendance, because they did not understand the clinical relevance of nitric oxide. Of course, we were very pleased when, in November, he won the Nobel Prize in medicine and physiology. Now you are discussing some things that might relate to how patients are treated by immunological regulation. When we discuss removing things that upregulate immune-inducible nitric oxide, and getting patients out of these feed-forward loops by blocking links associated with oxidative stress, it sounds as though we are

witnessing the emergence of a molecular medicine that Linus Pauling talked about in 1949.

MP: Literature strongly suggests that peroxynitrite levels are elevated in a number of autoimmune diseases at the sites of inflammation. Basically, because nitric oxide can react with superoxide to form peroxynitrite, both nitric oxide and peroxynitrite may play central roles in a number of these autoimmune diseases. Evidence from animal models supports that notion. I would like to think that these same regulatory changes, these feedback or feed-forward changes that we're suggesting play a role in chronic fatigue syndrome may, in fact, have roles in a variety of other immune disease.

JB: Given this shift in redox as a consequence of the alteration in cell signaling molecules and increased output of TH2 cytokines, and the effect that has on the upregulation of immune-inducible nitric oxide synthase, and then increased peroxynitrite, and the effect that has on mitochondrial oxidative stress, do you feel that research and clinical work should be pushing on into the use of coenzyme Q10, carnitine, N-acetyl-cysteine, lipoate, vitamin E, tocopherols, in modulation of some of these processes?

MP: Yes, I do. Obviously, it's important to do the basic science, but there has been relatively little in the way of clinical intervention trials aimed in these directions. Clinical trials with antioxidants have predominantly been performed using individual antioxidants at high doses. Those can act only on certain aspects of these systems and not on others. Rather than using a combination of things that can down-regulate a number of aspects of these response patterns, people have tended to use individual ones. That may, in general, not be the best way to go.

JB: That message opens a future for more research and keeps us away from the pharmacological model of one symptom/one drug. It looks more at how physiology works as a complex interaction of variables. Dr. Pall, thanks so much. You've stimulated us to greater thought that will lead our clinicians into other avenues of potential success.

Homocysteine Metabolism and Oxidative Modification of Proteins and Lipids

I would like to thank Dr. Pall very much for his most interesting, provocative and insightful comments. I want to close this month's FMU by giving you a few thoughts revolving around Dr. Pall's concepts that might provide some clinical takeaways. First, what about homocysteine metabolism, oxidation, and mitochondrial function? This was described in a review paper by Dr. Olszewski from the Department of Physiology and Biochemistry of Nutrition in Warsaw, Poland, and Dr. Kilmer McCully, father of the homocysteine theory. (Dr. McCully will be a presenter again at the Sixth International Symposium on Functional Medicine in May, so we will have a chance to get an update from him.) This article, which appeared in Free Radical Biology and Medicine, is a review of the implications of altered homocysteine metabolism as a pathogenic factor in a wide range of disorders, including atherosclerosis, neoplasia, and even age-related diseases like arthritis.23

According to the authors, the genetic variants that result in enzymatic deficiency (evidenced by deficiencies in folate, pyridoxine, and cobalamin and elevated blood homocysteine) may be associated not only with an accelerated atherosclerotic process, but also with a variety of other age-related dysfunctions.
Homocysteine and Methyl Groups

We know that homocysteine metabolism is very actively involved with the release of methyl groups that can form 5-methyl-tetrahydrofolate, and this 5-methyl-THF then is the selective methyl donor for constructing proper nucleic acids in the formation of DNA. Therefore, inappropriate metabolism of folate, B6, or B12, as seen through elevated homocysteine, can influence gene construction and result in mutational injury, which is particularly accelerated in the presence of oxidants.

This article goes on to state there is a close correlation between oxidative stress relationships, mitochondrial DNA, nuclear DNA, and the elevation of homocysteine. Therefore, we should not just think about B6 in relation to vascular disease, but we should also be looking at it as a general regulator of function. Therefore, defects in methyl donation or methyl transfer have wide-ranging effects on function. This is important, if you recall that we can modify the expression of these genotypes as phenotype by administering more B6, B12, folate, and betaine, or another methyl donor like dimethylglycine as a methyl donor.

According to an article in the January 1999 issue of the journal *Circulation*, the American Heart Association now recommends homocysteine testing.[24] The simple test, they say, uncovers potential heart problems, and they believe it may become as commonly used in clinical practice as cholesterol testing.

Just a few years ago medicine completely resisted the "homocysteine hypothesis." The prevailing view was that homocysteine testing constituted over-utilization, and supplementing the diet with B6, B12, and folate would just make expensive urine and be of little or no efficacy. Suddenly, we are seeing a significant groundswell of change. The *New England Journal of Medicine* now recommends that we eat a good diet and take a vitamin supplement. That was a profound change in editorial comments with little fanfare or explanation for the change of opinion.

Recent evidence indicates that approximately 50 to 100 percent of people who undergo heart transplants acquire hyperhomocysteinemia.[25] Therefore, it is an adverse side effect, apparently, of heart transplant surgery. Transplant recipients may develop hyperhomocysteinemia as a consequence of the cyclosporine medication they take to prevent organ rejection. Or it may result from other effects that occur as a consequence of altered oxidative chemistry and gene expression. Whatever the reason, it is now recommended that heart transplant patients consider a folate, B12, and B6 supplement.

The author of the paper that correlates homocysteine and cardiac transplant patient recipient levels goes on the say that 1 mg folic acid, 0.5 mg B12, and 10 mg B6, would be considered desirable to normalize hyperhomocysteinemia. That is an order of magnitude or more above the RDI for those nutrients. This is molecular medicine applied across a wide range of disciplines.

One gene that has a mutational variance in our population that can cause, in certain mutational types, an increase in homocysteine, is the methylenetetrahydrofolate reductase polymorphism. This is a gene that obviously responds to folate. Women and men who carry this gene have different variations of sensitivity. Some individuals require much higher levels of folate to get the gene to produce an enzyme that ends up with the right activity, thereby lowering homocysteine levels.

A recent paper in the *Journal of Nutrition* discusses the methylenetetrahydrofolate reductase polymorphism affecting the change in homocysteine and folate concentrations from low-dose folic acid supplementation in women with unexplained recurrent miscarriages.[26] The authors found that even 400 m

g per day (the previous higher RDA levels of folate) was not adequate to prevent miscarriage in some women who had a history of miscarriages. These women needed higher levels of folate, at least 500 m g per day.

In addition to the oxidative stress relationships with various factors, Dr. Pall discussed the impact of mitochondrial function on energy in general. A paper titled "Preliminary Determination of a Molecular Basis to Chronic Fatigue Syndrome" appeared recently in the journal *Biochemical and Molecular Medicine*[27] describing work by Hugh Dunstan and his colleagues in Australia. We had the pleasure of interacting with this group a number of years ago, and I think their work is quite intriguing. They found that chronic fatigue syndrome patients excreted in their urine metabolites the researchers call chronic fatigue syndrome urinary metabolites 1 and 2. These substances appeared to be mitochondrial toxins that uncouple mitochondrial oxidative phosphorylation. They could contribute to increased oxidative injury to the mitochondria and be involved in what Dr. Pall refers to as the "feed-forward" effect.

Some of these metabolites closely resemble secondary metabolites of dysbiotic bacteria in the gut. This fact suggests an interrelationship between gut dysbiosis and the production of mitochondrial toxins that, in genetically sensitive individuals, could contribute to the production of the energy deficits that are called chronic fatigue in these patients. That is an interesting point of molecular endogenous toxicity and how it can relate to small molecules that contribute to energy deficits in chronic fatigue.

Anything that will activate the immunological system may have an impact on energy production and produce the symptoms of fatigue. The rule of reasonableness, I am sure, defines and supports that concept. The last time you had a cold or the flu, did you feel you had high energy? The answer obviously is no. Your energy was wiped out. The reason, presumably, is at the biochemical level. Upregulation of the immunological system utilizes a lot more of your ATP. It is locked in a feed-forward process, protecting your DNA against damage by activation of the enzyme PARS, as Dr. Pall discussed. It further depletes ATP and results in cognitive deficit. You generally can’t do high-order math while you have the flu. You feel very tired; you have sleep disturbances and complex dream patterns. This is all a manifestation of altered mitochondrial energy production as your energy is shunted in different directions during the immunological activation caused by the response to a virus.

The same thing is true in animals. If you immunologically challenge an animal, you will produce fatigue, and it is correlated with increased output of these proinflammatory cytokines. This is the topic of a paper that appeared in *Clinical Immunology and Immunopathology*. It is titled "Susceptibility to Immunologically Mediated Fatigue in C57BL/6 versus Bald/c Mice."[28] The authors found that immunological challenge and increased TH2 proinflammatory cytokines produced decreased energy availability and increased fatigue in the animals. This is obviously a mitochondrial function.

We have talked about effects that can be mitigated at the mitochondria—viral infections, bacterial infections, gut dysbiotic infections with small secondary metabolites that have mitochondrial effects, xenobiotic effects, and possibly even stress, alcohol, and recreational drugs. All load the mitochondria with increasing burden and may contribute to these increased oxidative stress susceptibilities and feed-forward energy depletion processes.

Mitochondrial function is differentially affected by oxidative stress, according to a recent article in *Free Radical Biology and Medicine*.[29] It is a very complex feedback process that increases demand on

antioxidants and depletes glutathione, coenzyme Q10, lipoic acid in its reduced state as dihydrolipoate, vitamin E, and various other kinds of redox active substances found in the mitochondria. This depletion increases the risk of mitochondrial injury or suicide.

This topic is discussed in another paper in *Free Radical Biology and Medicine*. The article describes the differential effect and complex feed-forward damage that occur to mitochondria that can accumulate injury over time. This accumulated injury leads ultimately to mutations of the mitochondrial DNA, preventing adequate energy production, and becoming potentially life compromising.[30] Death is caused by energy deficiency in a specific organ or organ system. One wants to break these links or cycles of energy depletion and oxidative injury to mitochondria, not only to pull the person out of immediate fatigue, but for the later-stage effects it could have if the person is locked for years in a chronic state of increasing mutational injury.

We know the increased levels of various types of oxidative species will correlate with the shift, as Dr. Pall said, to the oxidative chemistry of the cell. The redox balance is shifted and you have an interrelationship between increased levels of secretion of the proinflammatory cytokines from various types of immune cells. So reactive oxygen species trigger proliferation of T-cell secretion. This proliferation then elaborates cytokines and causes more oxidative stress, and the cycle continues, as Dr. Pall indicated. You need to break this cycle by intervening to lower the immunological potential, take away the stimulants of the immune system, lower oxidative stress, rebuild membranes, and detoxify if the person is exposed to endogenous or exogenous toxins. This is a comprehensive clinical strategy that might be employed for looking at chronic fatigue syndrome.

The brain/body reaction also plays a role here. A recent paper titled "Neuropeptides, by Direct Interaction with T Cells, Induce Cytokine Secretion and Break the Commitment to a Distinct T Helper Phenotype," appeared in the *Proceedings of the National Academy of Science USA*.[31]The author of this paper points out that when an organism secretes more of specific neuropeptides, cytokine secretion from white cells is activated. (This is similar to the pioneering work of Drs. Candice Pert and Michael Ruff, which they will discuss at our Sixth International Symposium on Functional Medicine.) The authors of this paper explain that with TH1 and TH2 thymus-dependent lymphocyte imbalances, more proinflammatory cytokines are produced, and this can be triggered by neuropeptides that come from the brain as a consequence of thinking different thoughts, being under stress, or exposure to different stimulants. The result is upregulation of the inflammatory cascade, having more impact on mitochondrial function, and increasing the risk to these processes that we have been describing. So neuropeptides, by direct interaction with T cells, can alter the TH1 and TH2 balance.

TH1 and TH2 balance also plays a role in pain control and inflammation. A recent paper in *Nature Medicine* described how the appropriate balance of these inflammatory and antiinflammatory mediators plays a very important role in pain control after injury.[32] Individuals who have pain and fatigue may experience a complex of symptoms related to altered immunological systems through exposure to toxins, antigens, allergens, stimulating factors, and even stressful environments that increase the output of cortisol and other alarm substances through CRF, corticotropin-releasing factor. This is the mind/body connection to pain and fatigue.

A more comprehensive model is emerging from our discussion with Dr. Pall. Don’t forget multiple chemical sensitivity and the role of small molecules. In discussing the eosinophilia-myalgia syndrome

earlier, we said that a small molecule that contaminates tryptophan could create this autoimmune-like condition characterized by fatigue, fasciitis, and scleroderma. We noted that this process is related to activation of the immune system and cross reactivity of these inflammatory mediators with other tissues. In a new book, titled *Chemical Exposures: Low Levels and High Stakes* (Van Nostrand Reinhold, New York, NY, 1998), Nicholas Ashford and Claudia Miller re-examine multiple chemical sensitivity and its impact on the mediating system of the body.[33]

Uses of Nutrition to Balance Cellular Processes

How does one use nutrition to balance some of these processes? We talked about nutrients like lipoic acid, coenzyme Q10, vitamin E, and N-acetyl-cysteine. A variety of nutritional substances help regulate redox control in the cell. Green tea polyphenols block production of endotoxin-induced tumor necrosis factor. When you drink green tea, you are getting catechins that may actually alter the GALT production of TNF-alpha and other types of endotoxin-induced cytokines associated with dysbiosis. A paper in the Journal of Nutrition last year showed that green tea catechins block the NF Kappa B activation in gut mucosa from an endotoxin stimulation.34

What about the effect of N-acetyl-cysteine on immunological function? Many papers now indicate it can reset TH1 and TH2 cytokine response and help balance inflammatory and antiinflammatory cytokines, one of which has to do with HIV infection. A recent article shows that N-acetyl-cysteine can play a role in reducing the immunological dysfunction in HIV infection.35

What about the polyphenolic substances found in fruits and vegetables? Is there a difference between vitamin C and strawberries, spinach, or red wine? The answer is yes. Again, the symphony of different redox-active substances in whole foods, or food concentrates may have a much more profound effect on regulating redox potential than taking a single vitamin at a time. This topic was discussed in a paper published in the Journal of Nutrition last year.36 Dr. Pall discussed the interrelationship of these redox-active substances.

New Approaches to Chronic Feed-Forward Illness

New thought is emerging about how to approach chronic feed-forward illness. It indicates that new, linked, homeostatic pathways cause chronic illness. These pathways can be broken by reducing exposure to antigens, improving immunological function, and increasing oxidative function within mitochondria.

We will talk more about this in future issues of FMU. Thanks for being with us in the March issue of Functional Medicine Update™.

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