February 2002 Issue | Richard Wurtman, MD

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Welcome to *Functional Medicine Update* for February 2002. In this month's issue we continue our theme of functional medicine related to the management of chronic illness. This month's focus is on neurological disorders and their relationship to nutrition.

This will also be a topic at our Ninth International Symposium on Functional Medicine, which begins May 25, 2002, with pre-courses followed by the plenary sessions on May 27, in Ft. Lauderdale, Florida, at the Westin Diplomat Resort. On May 27, the topic will be the GI tract and Functional Neurology. The May 28 topic is Functional Approaches to Depression. On May 29 we will discuss Psychoneuroendocrinology. This month's Clinician/Researcher of the Month will be one of our keynote plenary speakers at the symposium. You will hear from him on side II of this month's *FMU*.

I recently read a new book published out of the National Institutes of Medicine, National Academy Press. It is titled *Crossing the Quality Chasm: A New Health System for the 21st Century.* This book is a manifesto based on a blue ribbon panel's investigation of the present state of our healthcare system and a discussion of what this system needs to become as we move further into the 21st century. The book's Executive Summary, which sets the tone for the rest of the information provided, is a detailed and scholarly review of the healthcare system, forecasting what changes need to occur to improve it. I quote from that Executive Summary:

"The American healthcare delivery system is in need of fundamental change. Many patients, doctors, nurses and health care leaders are concerned that the care delivered is not, essentially, the care we should receive. The frustration levels of both patients and clinicians have probably never been higher. Yet the problems remain. Health care today harms too frequently, and routinely fails to deliver its potential benefits.

"Americans should be able to count on receiving care that meets their needs and is based upon the best scientific knowledge. Yet there is strong evidence that this frequently is not the case. Crucial reports from discipline review bodies document the scale and gravity of the problems. Quality problems are everywhere, affecting many patients. Between the health care we have and the care we could have lies not just a gap, but a chasm.

A Chasm in Health Care

"At no time in the history of medicine has the growth in knowledge and technologies been so profound. &ldots;As medical science and technology have advanced at a rapid pace, however, the health care

delivery system has floundered in its ability to provide consistently high-quality care to all Americans. Research on the quality of care reveals a health care system that frequently falls short in its ability to translate knowledge into practice, and to apply new technology safely and appropriately.

"The health care system as currently structured does not, as a whole, make the best use of its resources. There is little doubt that the aging population and increased patient demand for new services, technologies, and drugs are contributing to the steady increase in health care expenditures, but so, too, is waste.

A Wasteful System

"For several decades, the needs of the American public have been shifting from predominantly acute, episodic care to care for chronic conditions. Chronic conditions are now the leading cause of illness, disability, and death; they affect almost half of the U.S. population and account for the majority of health care expenditures.

"Yet there remains a dearth of clinical programs with the infrastructure required to provide the full complement of services needed by people with heart disease, diabetes, asthma, and other common chronic conditions. The fact that more than 40 percent of people with chronic conditions have more than one such condition argues strongly for more sophisticated mechanisms to communicate and coordinate care. Yet physician groups, hospitals, and other health care organizations operate as silos, often providing care without the benefit of complete information about the patient's condition, medical history, services provided in other settings, or medications prescribed by other clinicians. &ldots;It is not surprising, then, that studies of patient experience document that the health system for some is a 'nightmare to navigate.' "[1]

This excerpt mirrors a 20-year theme of *FMU*. As we look at where the system is heading, I'm reminded of the scholarly and clinically meaningful discussion that occurs on the *IFM*Forum on our website for our Institute for Functional Medicine members. Dr. Val Treloar, a dermatologist, provides the following example of the quality of communication of our doctors:

"As a dermatologist, I found the treatment of acne presented one of the greatest contradictions between my conventional training and the functional medicine approach. The conventional dermatologist says to the patient: "Your acne is not affected by your diet; do not worry about what you eat." This, of course, horrifies the functional medicine doc.

Diet and Acne

"Trying to reconcile these disparate views, I looked to the literature. My Medline search, 'diet and acne' turned up a fairly short list of references. In the most recent review of diet and acne, written in 1982(!), the author states: 'It is still surprising how few studies have examined the direct relationship between diet and clinical acne.' Since 1982, few, if any, new studies have added to the field. The studies quoted in this review suffered many weaknesses in design, power and interpretation. Suffice it to say the potential for functional medicine treatment of acne is huge.

"I figured I would start by looking at essential fatty acids in the treatment of acne. Their roles in acne could include:

-Linoleic acid and its effects on epidermal barrier function of the follicle;

-Alpha linolenic acid and modulation of inflammation via prostaglandin synthesis.

Linoleic Acid and Acne

"In 1986 Downing and colleagues speculated that linoleic acid could play a pivotal role in acne. As sebum production increases in puberty, the percentage of linoleic acid in the final secretion decreases.

"Lipids in the serum and in adipose tissue reflect dietary lipids. Remember that, unlike protein and carbohydrates, which are broken down into their 'building blocks' when digested and absorbed, fatty acids are absorbed directly into the circulation.

"Lipids in sebum, on the other hand, do not reflect the serum/dietary lipids, but are synthesized by the sebocytes. The differentiated sebocyte does not incorporate significant amounts of serum/dietary lipids into sebum. However, until the cell commits to differentiation, it does continue to take in serum lipids. We may be able to increase the linoleic acid in sebum by increasing dietary linoleic acid. Because it takes two weeks for a sebocyte to reach maturity and rupture and release its contents into the follicular lumen, you would not see the clinical effects of this dietary change for at least two weeks.

Topical Linoleic Acid Treatments

"In the 1970s, Pochi et al tried topical application of linoleic acid to the lower extremities of both normal and acne patients to see if any systemic effect from cutaneous absorption might occur. They found no changes in linoleic acid concentration in the sebum, nor did they see improvement in the acne. However, in a 1998 double-blind, placebo-controlled randomized cross-over study, Letawe et al showed a 25{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction in the size of comedones after one month of topical linoleic acid treatment in acne patients. Pochi did not consider using oral supplementation of linoleic acid, but Burton states: 'D.T. Downing has also found that prolonged administration of EFA improves acne.' The medical literature offers little more than this."

Other Fatty Acids

We also know that gamma linolenic acid and alpha linolenic acid may play a role in acne prevention through the modulation of the inflammatory cascade.

"The other essential fatty acid, alpha-linolenic acid and its metabolites EPA and DHA, are likely to benefit acne in their role as precursors for the less inflammatory series 3 and series 5 prostaglandins

"Strauss et al demonstrated that an arachidonic acid analog which inhibits both cyclooxygenase and 5-lipoxygenase resulted in significant reduction of sebum production and acne activity.

"Much to my surprise, a Medline search crossing 'omega-3 and acne' produces no references exploring this issue.

"So, what are the clinical implications?"[2]

Removing Food Antigens

It appears one might approach acne prevention and treatment by utilizing dietary modulation, fatty acid manipulation, and other types of vitamin and mineral therapy.

I will end this discussion by saying clinically, from an anecdotal observational perspective, it is fascinating to see how many individuals who have had adolescent or even adult acne experience remarkable improvement in their skin problems with appropriate nutrition. Such a program focuses on removing food antigens, increasing vitamin and mineral density of the diet, modulating dietary fatty acids to improve essential fatty acids, and lowering saturated fats and partially hydrogenated trans fats.

A Functional Medicine Application

Therefore, the acne problem may be one of those below-the-waterline issues that is functional in nature. Doctors have been able to treat acne symptomatically with antibiotics, suppressing it and causing it to be out of sight and out of mind. It continues to be symptomatic, however, or reflective of other functional physiological processes within the body that relate to immunological defense mechanisms and inflammatory balance. This is a beautiful example of a functional medicine approach to what is otherwise considered to be a localized bacterial problem.

I thank Dr. Treloar for this discussion on the *IFM* Functional Medicine Forum that defines the quality of thinking and strategic approach that characterize functional medicine.

In 2002 we are defining functional illness, or chronic illness associated with dysfunction, as rooted, in part, in the gene/environment connection. We are into the era of genomic medicine and, as we have said in the past, the human genome sequence is dramatically altering how we define, prevent, and treat disease.

Single Nucleotide Polymorphisms (SNPs) are Not Diseases

As genetic variations are increasingly discovered (scientists estimate the existence of nearly 3 million singular nucleotide polymorphisms or SNPs), there will be a rush to associate many of these variations with diseases. As I have said in the past, however, we need to exercise caution in identifying a genetic uniqueness with a disease. It may be a susceptibility factor or a biochemical strength or weakness and not a disease.

"Disease is a fluid concept influenced by societal and cultural attitudes that change with time and in response to new scientific and medical discoveries." [3]

The Problem with Differential Diagnosis

The ways people experience ill health remain rather constant, but the way they define ill health can change, based on social covenant, technologies, and social history. Historically, doctors define a disease according to a cluster of symptoms. As clinical descriptions became more sophisticated, they started to classify diseases in separate groups. This classification led to a medical taxonomy called the differential diagnosis.

Diagnosis labels someone as diseased through clinical, laboratory, and pathological findings, combined with clinical knowledge and judgment. Disease is generally considered an attribute of a patient, whereas diagnosis is driven by an assumption that the patient has a disease, an assumption that may or may not be true.

Misleading Labels

In using a single diagnosis to describe a set of clinical findings, important information can be effectively communicated to other clinicians and care providers. It's a simple way to apply for reimbursement for services, through an ICD9 diagnostic code. Diagnoses are intended to inform patients and tell clinicians whom and how to treat, but they may ultimately mislead the patient and/or the doctor in understanding the underlying mechanisms or processes related to that dysfunction.

"Labeling someone ‘diseased,’ however, has enormous individual, social, financial, and physical implications."[3]

Therefore, if we look at genetic uniqueness in the age of genomic medicine, we have to be cautious not to define uniqueness as a disease. To do so might lead to stigmata for the patient and also produce a significant focus on a specific genomic predisposition or uniqueness to only one disease pattern.

Changing the Focus

"Scant attention has been paid to defining disease in clinical medicine. Heslow has argued against the need for a definition of disease, stating that patients can be treated without one. However, the importance of the term disease to patients, clinicians, and society cannot be disputed. Boorse defines disease as ‘a type of internal state which is either an impairment of normal functional ability—that is, a reduction of one or more functional abilities below typical efficiency—or a limitation of functional ability caused by environmental agents.’”

This is the environment/gene connection leading to dysfunction that underlies the basic philosophy of functional medicine. “This type of philosophical definition is impractical clinically, and more important, is unlikely to make the interpretation of genetic variations any simpler.”

BRCA Genes and Breast Cancer Risk

If we start looking at conditions we consider tightly connected to genetic risk, such as breast cancer in women who have the BRCA1 or BRCA2 genotypes, we need to step back and ask if these are hard-wired causes of disease—breast cancer in this case.

"For example, it was originally estimated that 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of Ashkenazi women with mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 would develop breast cancer; subsequent studies revealed that the risk was closer to 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. Thus, genetic mutations are not sufficient in themselves to lead to adverse consequences. Furthermore, individuals lacking an identifiable genetic mutation are not necessarily 'disease-free.' For example, among non-Ashkenazi women who develop breast cancer, only 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} have a BRCA1 or BRCA1 mutation."[3]

Genetic Mutation Not a Definition of Disease

Environmental factors, as we have said many times in *FMU*, may predispose women to breast cancer and create for them the same or even an increased risk of adverse consequences when compared with women carrying an identified genetic mutation. Thus, a genetic mutation is not an absolute prerequisite for a disease and cannot be used as the sole defining feature of that disease.

"The human genome sequence is likely to reveal many harmless genetic variations that will turn out not to be associated with disease. Until we resolve questions about polymorphisms, incomplete penetrance of genetic mutations, and the contribution of environmental factors to disease etiology, we will not be able to assess the probability of adverse consequences associated with a particular gene abnormality.

"Until a mutation is shown to demonstrate a defined risk of developing adverse consequences, individuals carrying that mutation should not be considered diseased. Defining adverse consequences and determining the risk of myriad small genetic variations is a mammoth task." [3]

This is probably the fundamental tipping point within the new medical paradigm.

"But it is only with this information that clinicians can accurately define the term disease in the genomics era, and in so doing, be able to advise their patients appropriately."[3]

If we look at the way this information influences neurological-related illnesses, dysfunction, or chronic symptoms, we see a pattern emerge that is different from simply defining a diagnostic code using medical taxonomy.

Genes and Subtypes of Schizophrenia

Schizophrenia is an example. At one time schizophrenia was considered to be a single diagnosis. We now recognize it is a heterogenic disorder that renders identification of a specific etiology extremely difficult. It is a prototypical multigenic condition. A recent article in *Trends in Molecular Medicine* described schizophrenia from a functional genomic perspective. According to this article, schizophrenia is a multigene-related complex interaction of pathways relating to neurochemical function and neurobiology, which ultimately gives rise to the variety of signs and symptoms we cluster together with the DSMs to call schizophrenia.

Genomics and Predisposition

In discussing the relationship of genomics to predisposition and environmental influences on the expression of predisposition, the authors of this article go on to say, “Defects in different combinations of genes, which converge on the same functional pathway, could lead to a common, diagnostically-reliable, clinical phenotype, yet with differences across individuals in specific clinical features.”

We might talk about singular mechanisms that give rise to different diseases, or we might talk about the underlying genetic uniqueness that is influenced by the environment to give rise to the expression of what we label as a disease.

“Because of the currently unknown number of susceptibility factors and potential protective genes, studies of large pedigrees, more homogenous cohorts with narrower subtypes of schizophrenia, as well as subjects with disease-associated traits (e.g., endophenotypes) will be a major focus of ongoing and future studies.”[4]

Modifying Environment to Affect Outcome

This focus will help us to understand the genotypes that correlate with outcomes related to schizophrenia and the modifications to the environment that may yield a different outcome. This much more plastic view of medicine differs from the hard-wired, deterministic, view that describes specific gene abnormalities (i.e., mutations) as specific diseases that require specific drugs. That linear, simplistic model describes a single gene/single disease/single drug to modulate the symptoms of disease.

We are seeing a more complex matrix effect that relates to a web of interaction of genotypes with the environment to give rise to the outcome we call dysfunction. Certainly, neurological disorders and psychiatric disorders fall within this theme.

The Role of Methylation in Mammalian Epigenetics

It is not just gene expression alone; it is gene expression in combination with epigenetic effects, those that occur after the transcription/translation process. These effects include methylation events, the transfer of a methyl group to a cytosine residue to create a different expression pattern.

The strands of DNA in our chromosomes are not all being read all the time in every cell. If so, we would be a total mess, because in its 23 pairs of chromosomes every cell contains the genetic information necessary to make any other cell. Expressing all of that information simultaneously would lead to chaos. What we require through developmental biology, therefore, is the sequential expression of specific portions of the genetic message in specific cells at specific times to give rise to regulated cell function. This occurs in part by silencing portions of the genome with appropriate control so that not all genes are “on” all of the time.

Gene Silencers

What are the gene silencers? One is the presence of methyl groups in DNA under the control of

methylating enzymes. Genes constitute only a small proportion of the total genome present in the nucleus of cells. The precise control of their expression presents a substantial regulatory problem . We used to describe non-coding DNA as “junk DNA.” It is represented by introns, repetitive elements, and potentially active transposable elements and requires effective mechanisms for its long-term silencing.[5]

Along with other mammals, humans appear to have taken advantage of the possibilities afforded by methylation to provide a heritable mechanism for altering DNA protein interactions to assist in gene silencing. Therefore, when we talk about how genes are read at specific times in specific tissues, this gene-silencing methylation pathway, an epigenetic pathway, is important.

Epigenetic Processes

The term epigenetic refers to events that occur after the translation/transcription process. Epigenetic events include the transfer of a methyl group to cytosine residues that are found in a specific context throughout the genome. The methyl groups originate in S-adenosine methionine, or SAM. Folic acid is essential for SAM formation. Ultimately, 5-methyltetrahydrofolate donates its methyl group to homocysteine producing methionine that is readily converted to SAM. SAM serves as a methyl donor in several key pathways including catechol-O-methyltransferase, N-methyltransferase, and DNA cytosine-O-methyl transferase, the enzyme responsible for a bulk of the gene silencing. DNA methylation illustrates the close relationship of the folate cycle and SAM.

SAM has been used as an antidepressant drug in Europe and most recently, and here in the U.S. (Its availability is allowed under the Dietary Supplement & Health Education Act.) This natural product undoubtedly works in brain chemistry through its ability to methylate intermediaries and create downstream metabolites that have neurochemical activity, and/or its effect on gene expression activities.

Dr. Karl August Folkers, who died in 1997, was a principal investigator into the folate cycle.[6]Dr. Folkers was the world’s resident expert on vitamin B6. He studied the influence of B6 on a variety of physiological functions. Much of his biochemically ground-breaking work occurred before the genomic era. Now we could describe the effects and results of much of his research using this genomic model. Some of this work was related directly to the folate cycle activities of vitamin B6, working along with folate and vitamin B12.

Clinically, vitamin B6 can be used to lower estrogen activities and estrogen-stimulated drive on various tissues, such as breast, endometrium, and ovarian effects. The nutrition literature has recognized this fact for some time. By giving supplemental doses of vitamin B6, you can modulate estrogen-type activities. This was felt to be a consequence of the role of vitamin B6, pyridoxine, on modulating estrogen receptor activities.

In a recent paper, Barbara Davis and Brandy Cowing examined vitamin B6 supplementation and its ability to reduce cell proliferation and DNA synthesis in estrogen-dependent and -independent mammary carcinoma cell lines. They found the growth-inhibiting properties of pyridoxal phosphate and vitamin B6 pyridoxal were not affected by the presence, or absence, of the estrogen receptor. Furthermore, pyridoxal did not inhibit the estrogen induced synthesis of pS2 mRNA. Pyridoxal is thus working by an unknown mechanism that is independent of the estrogen receptor.[7] We might wonder if this effect occurs through its effects on methylation reactions and epigenetic silencing.

When we look at cross-symptomatic or cross-disease relationships in the pyridoxine/folate/B12 SAM pathway, we see that homocysteine has effects beyond cardiovascular disease. It affects Alzheimer's dementia, inflammatory diseases, secondary effects of diabetes, and cognition and dementia. These connections of vitamin B6/pyridoxine (i.e., folate/cobalamin/vitamin B12) move through a functional state of dysfunction. They are associated with a variety of organ-specific diseases and may occur at the genomic expression level.

Plasma Homocysteine, Cardiovascular, and Non-Cardiovascular Mortality

I recently read an *American Journal of Clinical Nutrition* article titled "Plasma Total Homocysteine and Cardiovascular and Noncardiovascular Mortality: the Hordaland Homocysteine Study."[8] The authors of this study found that elevated plasma homocysteine above 8mmol/L was a strong predictor of both cardiovascular and non-cardiovascular mortality in a general population of 65- to 72-year-olds. They believe these results should encourage studies of the association of homocysteine beyond cardiovascular disease, because it is associated with dementia, diabetes, and other inflammatory conditions. We can look at singular mechanisms that cut across many diagnostic disease codes, going back to functional medicine in the genomic era and how this interrelates to broad-based function.

Dr. John Lindenbaum, a Clinician of the Month in *FMU* in April, 1995, described his experience using vitamin B12 and folate for the treatment of depression in older-age individuals, and also for reduction in some of the neuropsychiatric symptoms associated with presenile dementia. Even in the absence of clinical signs of vitamin B12 or folate insufficiency, meaning normal hematological indices, these individuals still responded favorably. You could detect this deficiency only by metabolite assays of homocysteine in the urine or plasma, or methylmalonic acid.

We are beginning to see that these general mechanisms cut across a number of diagnostic codes and interrelate with multigene components of expression and epigenetic influences.

Cost Effectiveness of Vitamin Therapy to Lower Plasma Homocysteine Levels

According to a recent study in the *Journal of the American Medical Association*, titled "Cost-effectiveness of Vitamin Therapy to Lower Plasma Homocysteine Levels for the Prevention of Coronary Heart Disease," substrate or cofactor interventions can prove quite cost-effective.[9] The authors of this study showed that supplementation with folic acid and vitamin B12 was cost-effective in many population subgroups and could have major epidemiological benefit for primary and secondary prevention of coronary heart disease.

I would extend this and say that given the previous discussion, the benefits extend beyond coronary heart disease. This cost-effectiveness can be demonstrated in many age-related chronic illnesses.

Nutrient Modulation of Homocysteine

The most recent of an increasing number of articles on homocysteine and nutrient modulation appeared in the *New England Journal of Medicine.* Titled "Decreased Rate of Coronary Restenosis after Lowering of Plasma Homocysteine Levels," the article describes a nutrition program in patients following coronary angioplasty.[10] This prospective, double-blind, placebo-controlled, randomized trial compared 1000 mg

of folate a day, 400 mg of cobalamin vitamin B12, and 10 mg pyridoxine vitamin B6 daily to a placebo in 205 patients following successful coronary angioplasty. Treatment with a combination of folic acid, B12, and B6 significantly reduced homocysteine levels and decreased the rate of restenosis and the need for revascularization of the target lesion after coronary angioplasty. According to the authors, this inexpensive treatment, which has minimal side effects, should be considered as an adjunctive therapy for patients undergoing coronary angioplasty.

We are starting to witness the emergence of this new molecular medicine, which we have been calling functional nutritional medicine, as a significant part of 21st century medicine, bridging the chasm described by the National Institutes of Medicine book.

Nutrient Modulation of Homocysteine

In addition to methylation, another event that we now know is a fundamental process related to dementia is brain inflammation, due to microglial activation. A recent paper in the *Lancet*described *in vivo* determination of microglial activation by monitoring the binding of a specific benzodiazepine receptor ligand by PET scans .[11]

A number of triggers may initiate inflammatory responses and translate into brain biochemical dysfunction and increased apoptosis of neurons and cell death. One such trigger may be antigenic insults. A recent paper in *Neurology* showed that headache and central nervous system white matter abnormalities, as measured by MRI, were associated with gluten sensitivity. These were people with low-grade gluten reactions to their diet.

When gluten was taken away, there was symptomatic response and improvement in their MRIs. This result points to connections among the gut, the immune system, the gut-associated-lymphoid-tissue (GALT), and the blood/brain barrier transference of that information through inflammatory mediators. This connection may ultimately be mediated through nitric oxide release, peroxynitrite production, and neuronal mitochondrial uncoupling that leads to oxidative stress and premature cell death.[12] I am speculating on the latter mechanism, but I am not speculating on the clinical observational studies that connect early-stage dementia with gluten sensitivity. We should be looking at many triggers that might precipitate neurological dysfunction from a functional perspective.

Immunonutrition

Immunonutrition can be important for modulating the immune system. A meta-analysis in the *Journal of the American Medical Association* evaluated the effect of enteral nutrition supplemented with some combination of arginine, glutamine, nucleotides, and omega-3 fatty acids on infectious complication and mortality rates compared with standard enteral nutrition**.**[13] In 2419 patients involved in 22 randomized trials, there seemed to be some positive benefit through this immunological modulation using certain dietary combination to lower inflammatory mediators like essential fatty acids, gamma linolenic acid (GLA) or alpha linolenic acid (ALA) or eicosapentaenoic acid (EPA).

An article in the *Journal of Nutrition* discusses dietary supplementation with these fatty acids and shows a decrease in lymphocyte proliferation (*ex vivo)* in healthy older humans when they were given fish oils or GLA.[14] The amount of fish oils and GLA that demonstrated a decrease in lymphocyte proliferation in

these patients was not extraordinary. It represented about 4 gm per day of total fatty acids. This included about 2 gm/day of the GLA-containing oil, which provides about 680 mg of GLA, and 1 gm of EPA/DHA. It was a balanced mixture of GLA-rich oil and EPA-rich oil. It could be two 1 gm capsules given twice daily of EPA/DHA, along with the GLA-containing oil, which could be primrose oil, borage oil, or blackcurrant seed oil. The results were dramatic, showing improved immunological function in terms of balance of inflammatory process and cytokines.

Nutrient Modulation of Osteoarthritis

The potential for this type of intervention can be seen in conditions like osteoarthritis (OA). For years it was said that osteoarthritis was not an inflammatory disorder, as is rheumatoid arthritis. In a recent issue of *Arthritis & Rheumatism,* the authors of an article titled "Osteoarthritis, an Inflammatory Disease"[15] state the following:

"There is now strong evidence that the structural changes globally observed in OA are due to a combination of factors ranging from the mechanical to the biochemical. The disease process affects not only the cartilage, but also the entire joint structure, including the synovial membrane, subchondral bone, ligaments, and pariarticular muscles. In OA synovium, the inflammatory changes that take place include synovial hypertrophy and hyperplasia with an increased number of lining cells, and also an infiltration of the sublining tissue with a mixed population of inflammatory cells. &ldots;Synovial inflammation is clearly reflected in many of the signs and symptoms of OA. &ldots;The question is whether synovitis in OA is an 'innocent bystander' or truly participates in the structural changes of the disease."

Cause of Joint Space Injury

Strong evidence now indicates that release from the chondrocyte of matrix metalloproteinases and their effect on inflammatory mediator production is a principal event in the production of joint space injury. This is associated with proinflammatory cytokine release. Therefore, antiinflammatory cytokines and cytokine antagonists such as niacinamide may play important roles in preventing apototic cell death and inflammatory messages that come from the upregulation of gene expression.

Excess production of nitric oxide is another precipitating event, particularly when it combines with superoxide to produce peroxynitrite. Proinflammatory eicosanoids and leukotrienes, the prostaglandins and leukotrienes, also participate. This is a classic example of activation of the inflammatory cascade through the arachidonic acid cascade, and its influence on cyclooxygenase and lipooxygenase. Ultimately, that process influences second- and first-signal messengers of inflammation.

Looking for Triggers and Mediators of OA

We would approach OA by looking at its triggers, examining its inflammatory mediators, and looking at the array of substances available through reducing antigenic stimulus, mechanical trauma, and oxidative stress, and increasing proinflammatory balance, the same processes we have been talking about for neuronal injury.

Things such as the release of heavy metals like iron in tissues due to tissue injury can accelerate oxidative

stress and inflammatory relationships. The body uses a number of mechanisms, such as proper profusion of tissues, to protect against oxidative stress. Ischemic events also increase oxidative damage and increased breathing, exercise, mechanical manipulation, massage, and deep tissue work can all improve the delivery of oxygen to tissues that can serve as an antiinflammatory process.

This is the functional medicine model we are describing, looking at ways of modulating gene expression of inflammatory mediators. Let's turn to side II and look specifically at nutrition and its relationship to brain biochemistry.

INTERVIEW TRANSCRIPT

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JB: This month's Clinician/Researcher of the Month on *Functional Medicine Update* is Dr. Richard Wurtman. Dr. Wurtman is the Cecil H. Green Distinguished Professor at MIT, as well as director of the MIT Clinical Research Center. Dr. Wurtman and his wife Judith have made numerous contributions in the area of diet and nutrition and its influence on brain chemistry. They have pioneered the field of nutritional neuroendocrine immunological function and the influence of nutrition on brain chemistry and neurological function. I first learned of Dr. Wurtman's work through a paper he published in 1975 in the *Scientific America.* I have followed his work closely ever since.

Tryptophan Studies

Dr. Wurtman, what led you to a field that didn't exist before you focused your energies on it?

RW: Thank you for the generous way in which you express what happened. I was interested in the pineal gland and melatonin. That got me interested in circadian rhythms. I thought I'd look to see how many things in the blood vary as a function of time of day. We did some studies at MIT on amino acids and found that blood levels of all the amino acids tend to go up and down. I assumed this was due to some biological clock but found that wasn't the case. These changes during the day were the consequence of eating. Depending on what you ate, blood levels of tryptophan did or did not go up. The blood levels of a lot of amino acids were changing, and I wondered why. Are there any consequences of a change in blood tryptophan, blood tyrosine, and so forth?

Basically, I'm a brain scientist, and thus tryptophan was of special interest to me. It's the precursor for serotonin, and I was working on that. I did some experiments to see what happened if you gave rats little tiny doses of tryptophan. Did that result in changes in brain serotonin levels? We found it did. Unfortunately, we didn't patent that, because lack of a patent led to companies later selling impure

tryptophan. You know about the eosinophilia myalgia syndrome.

Effects of Insulin

We found that doses of tryptophan would increase brain serotonin. We decided to do something that lowers blood tryptophan and see whether brain serotonin goes down. Nobody knew how to lower brain tryptophan, but if you give insulin to people or animals, it tends to lower most amino acids in the blood. We gave some animals insulin and found, to our surprise, that brain tryptophan and brain serotonin levels continued to go up, not down. We thought it must be an artifact of hypoglycemia or something.

Instead of giving insulin, we decided to have the animals secrete their own insulin, so we gave them a carbohydrate meal. That was the beginning. We found that carbohydrates worked via insulin and actually increased brain tryptophan and brain serotonin. Later, we found the reason for that was that the amount of tryptophan that gets from the blood into the brain doesn't just depend on blood tryptophan levels. It depends more on blood levels of other amino acids. What the insulin was doing was lowering the blood levels of these large neutral amino acids.

"Carbohydrate Cravers"

By the middle of the 1970s, we had a formula. If you ate carbohydrates specifically, you could produce insulin-mediated changes, food-mediated changes, which led to big changes in brain chemistry. For a number of years, we worked on the "so what" question. When you get an increase in brain serotonin, having eating various things, does that have consequences? At that point I started collaborating with my wife. She's the nutrition person; I'm the brain person. She discovered there were a lot of people overeating carbohydrates who were, as she put it, "carbohydrate cravers." We figured out they were overeating carbohydrates precisely because they increased brain serotonin.

They tended to be people who were anxious or depressive, who might have seasonal depression or PMS. In actuality, they were self-medicating with food. By eating carbohydrates, they were increasing brain serotonin, getting, if you will, a Prozac-like effect. This was making them less sad; it was also making them fat, as it turned out, because the foods they chose usually had a lot of fat in them as well as carbohydrates.

Nutrients and Neurotransmitters

We found that eating carbohydrates, eating proteins, would affect brain chemistry by changing brain levels of an amino acid, in this case tryptophan, which was a precursor for a neurotransmitter. It was a short jump over to asking if brain levels of any other neurotransmitters were affected by nutrients. We found there were a lot of them. Acetylcholine production depends on brain choline levels. Catecholamine and dopamine production can depend on brain tyrosine.

Most recently, we found the ability of brain cells to make membranes is really important because the neuron is mostly membrane. This ability is controlled by the levels of uridine and cytidine in the bloodstream, and also by choline. A lot of reactions in the brain are susceptible to nutritional control. I believe these mechanisms have many potential uses for treating patients.

Melatonin Research

JB: You passed quickly over your work on melatonin, which was another area of pioneering research. I've heard countless people cite your work on melatonin. Since melatonin is derived metabolically, or biosynthetically, from tryptophan, have you found any relationship between melatonin and the carbohydrate/insulin connection in terms of delivering tryptophan to regions such as the pineal that influences its synthesis?

RW: Believe it or not, in that case, the answer is no. There are two reasons for that. One is that the pineal gland, even though it sits in the middle of the head, is outside the blood/brain barrier. The availability to it of things in the bloodstream is not determined by the same rules that apply for the brain.

The other reason is that the enzymes that convert serotonin in the pineal to melatonin (it goes tryptophan/serotonin/melatonin) are tightly regulated. It is the activity of the enzyme that seems to be important, not the concentration of the substrate. Most hormones in the body are quite independent of nutrients. We all eat cholesterol and make testosterone or estrogen from cholesterol, but there is no evidence that eating more cholesterol will give you more testosterone. The brain is quite special. It is very unusual for important reactions that generate really active compounds, like transmitters, to be susceptible to nutritional control, but that's the way it is.

Tryptophan and Hormones

JB: Tryptophan has a number of other metabolic fates. Are any of those modified by insulin and/or other hormones?

RW: No. It's surprising, too, that the other fates seem not to be affected by insulin. What are they? First, incorporation into protein, and that's not limited by tryptophan, except in the liver. In most tissues, it's limited by the amounts of these neutral amino acids—leucine, isoleucine, valine—and the metabolism of tryptophan in the liver is a function of how much protein you are eating, and the portal circulation delivering the tryptophan. It's just the brain that is so susceptible to this nutritional control.

A very wise brain chemist named Seymour Kaufman once pointed out to me that the brain is different because most of the enzymes in the brain have very high Kms. That means they have very low affinities for their substrates. You need a lot of substrate to desaturate them. Most of these substrates, of course, are nutrients. This doesn't apply in liver, muscle, or bacteria or anything else.

Kynurenin

JB: What about the kynurenin metabolic process? Considerable literature exists about neurotoxic reactions and some of the neuroactive components associated with kynurenin, which come ultimately from the serotonin/tryptophan pathway?

RW: At the risk of being controversial, I must say I'm underwhelmed by the evidence that endogenous kynurenin has any real neurotoxic effects. I think it's a question of dosage. You can give a compound in massive concentrations and produce some sign of toxicity, but I've never seen any *in vivo* evidence that

you could produce enough kynurenin metabolites to produce neurotoxicity. In any case, it's not controlled by insulin.

5-Hydroxy-Tryptophan

JB: There seems to be interest right now in nutrition circles in 5-hydroxy-tryptophan (5-HTP). Have you had any experience in your studies on intermediary metabolites?

RW: We're doing it right now. I think this is an understudied compound. For instance, it had been assumed, until we did our work, that if you give it by itself, it doesn't really do anything. You have to give a dopa decarboxylase inhibitor with it. We've shown that's not the case. If you give people oral 5-hydroxy-tryptophan in quite low doses, you get dose-related increases in blood levels of 5-HTP, and in rats in brain levels of 5-HTP and of serotonin.

You don't have to give it with a drug, a decarboxylase inhibitor, to make it active. In fact, its uptake into the brain is by the same transport system as that for tryptophan, so it's also affected by eating carbohydrate or protein. You want to get more into the brain? Give it with a carbohydrate. You want to get less into the brain (you wouldn't want to do that), give it with protein, just like L-dopa. We're doing studies right now on the use of it in particular types of obesity situations, and finding that the dosage range is critically important, obviously. But it can be very useful, so stay tuned.

Dopaminergic Aspects of Tryptophan

JB: I know you've done work not only on tryptophan with essential amino acid effects on neurotransmitters, but also on the phenylalanine/tyrosine side, the dopaminergic side. Would you tell us something about that?

RW: It's interesting. The ground rules there are slightly different from those for tryptophan and serotonin. In the case of tryptophan and serotonin, there's no homeostatic control. Whenever you increase or decrease brain tryptophan levels, you're always going to get a proportionate change in the production and release of serotonin. I think the reason there's no control is that that system is more or less designed to provide the brain with information about what you are now digesting. Brain serotonin has an important impact on satiety. It's a major satiety signal.

In the case of tyrosine and dopamine, it's a little different. The enzyme that starts the process of converting tyrosine to dopamine, mainly tyrosine hydroxylase, can exist in two states. It can be relatively inactive or it can be activated. It's activated when the nerve that contains it fires a lot. The enzyme protein itself becomes phosphorylated. When that happens, the enzyme suddenly becomes limited by the amount of tyrosine that's available. The non-activated state is limited by the amount of cofactor, but in the activated state, when the nerve cell is firing fast and releasing a lot of dopamine, the main limitation in how much dopamine it can make is brain tyrosine levels.

Changing Dopamine or Norepinephrine Release

We found you can really amplify dopamine release or norepinephrine release from nerve cells that are

firing rapidly. You can take an animal that is in shock with very low blood pressure because the animal has had a hemorrhage. In that case, certain nerve cells, sympathetic nerve cells, are firing very rapidly, but brain cells are not. Those sympathetic nerve cells are now going to be sensitive to tyrosine. You give the animal some supplemental tyrosine and blood pressure goes right back up to normal.

Conversely, you can take an animal that is spontaneously hypertensive and in those animals, you have brain norepinephrine neurons that are firing rapidly, but not the sympathetic neurons. You give those animals tyrosine, and you increase norepinephrine production within the brain. This tends to lower blood pressure. You get into these paradoxical situations in which the same dose of tyrosine can either raise or lower blood pressure, depending upon what the starting blood pressure is, and thus depending upon which nerve cells are activated.

Genetic Polymorphism and Metabolic Pathways

JB: That begs a question around the whole theme of genetic polymorphisms and genetic diversity in some of these metabolic pathways. As we uncover the genomic connections, are we seeing a lot of polymorphisms within these pathways.

RW: I think that is an extremely important question, but I don't think there's much data yet on this. We know that with certain vitamins, people will have tremendous differences in the quantities of vitamin they need in order to saturate enzymes that utilize them as cofactors. The same may very well be true for these neurotransmitter precursors, but it's hard to think of any solid data on it. I'll bet that five years from now there will be.

Acetylcholine

JB: The last of the neurotransmitters with nutritional precursors is acetylcholine. Would you tell us about choline as a precursor to acetylcholine?

RW: I am delighted that a former student of whom I'm very proud, Steve Ziesel**,** and others managed to convince the Food and Nutrition Board that choline ought to be listed as an essential nutrient. It's based on studies he did as a graduate student in my laboratory. It is an essential nutrient. We know the body can make some of it, but it can't make all that it needs.

Choline levels are limiting in the production of acetylcholine. Choline levels can also be limiting in the production of membranes. Cholines have two major fates. Every cell uses some choline to make phosphatidylcholine, which is the major constituent of most biologic membranes, that and the other phosphatides.

Enhancing Acetylcholine Production

In addition, certain cells convert choline to acetylcholine. In both cases, both enzymes that start these reactions, choline kinase for phosphatidlycholine and cholineacetyltransferase for acetylcholine, are classic, low-affinity, high Km enzymes that are unsaturated under normal conditions. If you provide more choline, you can enhance the production of acetylcholine; you can enhance the production of membrane.

Membrane production is not limited solely by choline. It is also limited by the levels of citidine triphosphate (CTP). The way that is regulated in people is by blood levels of uridine. The optimal way to promote membrane synthesis is to give something that provides choline and uridine for the blood. For instance, we have done a lot of work on a compound called citicholine. If people eat that, it raises blood levels of choline and uridine. I think this can be useful in situations in which you want to promote membrane formation in the brain. You want to make bigger synapses; you want to take nerve cells that have been partly damaged due to a stroke or an accident, and enhance their regrowth. We're doing a lot of work on this right now.

Choline and Alzheimer's Disease

As far as giving choline to make more acetylcholine, the last word isn't in yet. If you take somebody with Alzheimer's disease and give them drugs, cholinesterase inhibitors, that slow the breakdown of acetylcholine, these drugs can help the patient out for six months or perhaps a year or two. They are FDA-approved. One would imagine that giving choline along with those drugs would potentiate the effect. On the other hand, I'm not aware of any studies that have looked into that directly.

Tardive Dyskinesia

JB: A number of years ago choline was used to manage symptoms of tardive dyskinesia in patients treated with psychoactive drugs. The problem was that the dose used often led to bacterial deamination reactions in the gut and production of trimethylamine and a fishy odor. Then people said that if you used high-purity phosphatidlycholine you could deliver the same effects without getting adverse side effects. What about the phosphatidlycholine connection?

RW: The story had a sad ending. I was working with a company in Holland that had enormous amounts of lecithin, and they were looking for some use for it. I think I convinced them that if they purified it adequately and put it into food in a way that made it palatable, people could use it as a supplement for exactly this purpose.

It took years to get it to adequate purity, and it took years to make it palatable because if you've ever tasted lecithin, it tastes awful. There's an awful mouth feel to it, basically. Finally, they got to the point where they were making a soup and a sausage that were enriched with pretty pure lecithin. We were all set to start doing some experiments on the utility of it when that particular company broke up. They had a Dutch branch and an English branch. I learned one day that the English branch had sold its pilot plant to another company that was going to use it for an entirely different purpose. That was the end of the project. The answer is, I don't know.

Phospholipid Connection

JB: What about the whole phospholipid connection? I see there is quite a bit of interest in phosphatidyl serine and some other phospholipids for improving memory and brain function.

RW: The thing about phosphatidyl choline is that when you break it down, you get a very metabolically expensive compound, choline. The body can't make phosphatidyl choline from glucose directly. It has to

have a choline source. On the other hand, when you break down phosphatidyl serine, all the constituents, such as serine, are readily made from glucose.

Moreover, when you take phosphatidyl serine, it is completely broken down. The original idea was that somehow it would pass through the gut unchanged, get into the bloodstream, and then pass into the brain. As far as I can tell, that has never been demonstrated, even though the question has been raised countless times. The burden of proof is still on somebody who would claim it has a useful effect in brain function.

Ginkgo biloba, St. John's Wort

JB: Getting back to a discussion of serotonin, two botanical species have received considerable attention in the literature recently, both of which purportedly influence the serotinergic pathway. One is *Ginkgo biloba* and the other is St. John's Wort. Do you have any thoughts about how they may influence serotonin metabolism and/or production?

RW: I'm afraid I have to pass on that. I've done no studies on either compound. I'm as dependent as anybody else is on trying to read and interpret the literature.

Serotonin and Diet

JB: Let's go back to the discussion of serotonin and the diet. I think this extraordinary discovery you and Judith have made has obviously opened new avenues for clinical dietetics and clinical nutrition. In your books, you talk about differentiating carbohydrate-sensitive individuals and the relationship to mood, mind, memory, and behavior.

RW: First, for you and me, the ability of carbohydrates to increase brain serotonin is one factor in determining what we choose to eat next, the dessert after the meal. But it is only one of maybe 100 factors that affect nutrient choice. You don't see it operating every day. You can I average 13 percent of our food intake as protein. But we don't do that every day. We do it every week, or every month. In normal people, dietary carbohydrates and proteins can affect food choice.

On the other hand, many people seem to behave as though they have a deficiency in brain serotonin. It's not documented, but a couple of papers have now showed that women, as a group, have only about two thirds as much serotonin in their brains, and they synthesize only about two thirds as much as men. This may be why the incidence of depression and obesity tends to be higher in women.

Mood, Appetite, and Serotonin

The incidence of recidivism in women who have tried to stop smoking is a lot greater than in men. Why is that? It's because nicotine tends to release serotonin. You withdraw the nicotine and you generate a serotonin deficiency. There are several clinical situations in which people present with two types of symptoms—mood symptoms and appetite symptoms. The mood symptoms are usually depression, anger, sadness, and loss of energy. The appetite symptoms are carbohydrate craving and subsequent weight gain.

We first observed this in a large number of ordinary obese people, especially women carbohydrate

cravers. Then my wife observed this in women with PMS. The fact that women with PMS have both sets of symptoms suggested to us that serotonin was involved. This, in fact, has led to two products. One product that is on sale now on the web, is called PMS Escape. It's a mixture of the right carbohydrates to generate the brain serotonin rapidly, but also for a period of time. This helps most women with PMS.

But we also invented a marvelous drug for treating those women who can't respond to carbohydrates. I'm sure you're familiar with Prozac. We showed that you could use Prozac as a treatment for a late luteal phase dysphoric disorder and Lilly now sells it under the name of Saraffin. That's not for all women; it's just for women who have severe PMS. Again, the clue was the presence in women with PMS of these two types of symptoms—mood disturbance and appetite disturbance.

Seasonal Affective Disorder

A similar disease (we didn't discover this; a group at the NIH did) is seasonal depression, SAD, or winter depression. The NIH people discovered that many people, when they are depressed, have profound carbohydrate craving. They gain weight when they're depressed, as opposed to most depressive people who lose weight when they're depressed. The optimal treatment for these people is a drug that increases brain serotonin, like the uptake blockers, for instance.

Another group is smokers, people who have tried to stop smoking. Nicotine enhances serotonin release, but it downregulates the nicotinic receptor. When you withdraw nicotine, not only do you no longer have a stimulus to serotonin release, but now you have receptors that won't respond very well to what they should be responding to, namely brain acetylcholine.

I think the list will go on and on. Sets of people who have learned that eating carbohydrate-rich, protein-free or protein-poor foods, snacks usually, can make them feel better. The trick then is to give them carbohydrates, but carbohydrates that are not associated with fat or protein. We think we may have a preparation that you can use for treating obesity on this basis, because so many obese people have obesity as a consequence of carbohydrate craving. We even gave it a name, Seratrim. Stay tuned.

Protein Sources and Tryptophan Delivery to Brain

JB: One thing you mentioned, at least indirectly, is protein composition in terms of amino acid composition. There are differences between the tryptophan content of a vegetable, protein percentage molar ratio, and that of animal proteins. Many years ago researchers studied suicide rates in countries where there were low tryptophan levels of protein in the diet. These were associative studies. I think there were even some animal studies looking at pain threshhold and tryptophan content of the diet. Have you found a difference in dietary protein type as it relates to delivery of tryptophan to the brain?

RW: You have to differentiate two different time scales here. Your body cannot make tryptophan, so all the tryptophan we get comes ultimately from dietary protein. Obviously, if you are relatively protein-depleted, you are going to be relatively tryptophan-depleted as well. However, if you consider the effects of each meal or snack, it's really counterintuitive. At any particular meal, the more protein you have, the more tryptophan you have in the meal, and the less tryptophan gets into the brain.

The reason is that tryptophan is only about 1 percent of protein. The competing amino acids, leucine and isoleucine, are about 25 percent of the protein. The more protein you put into food, the more competition you have that keeps tryptophan out of the brain. The optimal meal for raising brain tryptophan and serotonin is, counterintuitively, a meal that contains no tryptophan because it contains no protein.

The Thanksgiving Effect

We just got past Thanksgiving. Every year, reporters tell us we are going to be drowsy because we are going to eat Thanksgiving turkey. It's exactly wrong, because the turkey is very rich in protein and, sure, it raises blood tryptophan, but it raises many times more the blood levels of these competitors. If you are drowsy after Thanksgiving dinner, it's not because of the turkey; it's because of the dessert—the carbohydrate and the fat.

The Wurtman Diet

JB: Putting this together, then, one would develop, as Judith has done, a diet and recipe plan that would consist of balanced carbohydrate, low saturated fat, and adequate levels of tryptophan. But it would not be so rich in amino acids as to create an overload of the receptor sites.

RW: Exactly. Judy and I do not believe it's right to put people on the so-called protein-sparing, modified fast diets to lose weight. They were tried here in our clinical center 15 or 20 years ago, and they were tried nationally. What happens is that if you put people on very high protein, low-carbohydrate diets, they do lose weight for a while. You put people on any diet that restricts the choice of foods they can have and they get tired of the foods and lose some weight. Also most of these people get ketosis.

The problem is that very many of them will develop behavioral consequences due to the depletion of brain serotonin. For instance, insomnia is a classic complaint. So are mood disturbances, anger, and so forth. As soon as you stop the diet, they immediately lunge for the carbohydrates and put all their weight back on. I think you're right. I think the way you want to go is to get enough protein at times of day when you want to be alert and awake, and you have the tyrosine in the protein. For instance, breakfast and lunch are very good times to do so. But in the evening, you want to have very little protein if you can (pasta is great), and present carbohydrates, particularly to people who are very sensitive to the effects of these nutrients on the brain, those I mentioned who have both the mood disturbance and the appetite disturbance.

Clinical Benefits

JB: For the last half hour, we have a number of topics, which represent only the tip of the iceberg of areas you've touched in your work over the years. Thank you for the quality of that work and for your eloquent way of communicating these complex concepts. You have given practical information for our clinician listeners who will be dealing with patients with dysphoric disorders and other kinds of brain biochemical disturbances that might trigger thoughts about diet. I really appreciate your time today.

RW: Thank you very much. It's been a pleasure to work with you.

Amino Acid Regulation of Gene Expression

One theme Dr. Wurtman left us with is the protein/carbohydrate balance and its relationship to brain function in the serotonergic pathway. We now recognize that amino acids can help regulate gene expression, which is consistent with the functional genomics model. In a recent article Leonard Jefferson and Scot Kimball discuss the regulation of gene expression by amino acids, which is mediated through a number of mechanisms affecting both the transcription of DNA and the translation of mRNA.[16] Amino acid sufficiency, the type of amino acids, and how they are delivered affect these translation/initiation and signaling pathways. Dietary protein is not used just to build body proteins; it is also, as Dr. Wurtman pointed out, a source of amino acids that modulate specific messenging substances or processes.

Insulin plays an important role in this process. As Dr. Wurtman pointed out, it reinforces what the authors say in their article on amino acid regulation of gene expression. On page 2463 of that article they show the role of insulin on the phosphorylation of various proteins that influence regulatory amino acids. That process dissociates the various factors associated with gene expression and turns on other factors that change messenger RNA production and, ultimately, protein synthesis. Thus certain amino acids have a regulatory effect on gene expression. When we consume protein in relation to carbohydrates and fat, we are contributing to this signaling mechanism.

Obesity and Brain Chemistry

That leads us to a discussion of obesity and diabetes, insulin signaling, depression, and brain chemistry. All of these factors are clinically interrelated. A paper in the *Journal of Nutrition* explains that type 2 diabetes is an increasingly common disorder of carbohydrate and lipid metabolism. Approximately 16 million individuals in the United States have diabetes, and 800,000 new cases are identified each year. Two important characteristics of this disease are insulin resistance, or the failure of peripheral tissues, including liver, muscle, and adipose tissue, to respond to physiologic doses of insulin, and failure of pancreatic b-cells to secrete insulin adequately in response to elevated blood glucose levels.[17] These characteristics work together to produce the metabolic syndrome.

Much of this process can be understood as the inappropriate signaling mechanisms associated with the risk factors we ultimately call obesity, heart disease, hypertension, depression, and inflammation. People often seek out non-prescription weight-loss products to try to ameliorate the symptoms, without knowing that they may be creating changes at a fundamental level that may be much more profound. The physiognomy may be the signs of something much deeper going on in this orchestration of messengers.

A recent *JAMA* paper looked at the use of non-prescription weight-loss products.[18] The authors of this paper found that about 15 percent of people with long-term extra weight are using non-prescription products such as phenylpropanolamine (PPA) or ephedra to try to improve “burning of fat,” with attendant associated risks. They are doing a symptom-based approach rather than looking at the underlying mechanisms.

A recent article in *Nature Medicine* pointed out that we are what we secrete.[19]

Obesity and insulin resistance enjoy a complex relationship that gives rise to a range of metabolic disorders that include brain biochemical disturbances, as Dr. Wurtman explained. The notion that the

adipocyte is merely a cargo space for fat has undergone a dramatic change in the past few years. Previously, we thought of adipocytes as unexciting cells, tissues into which we dumped triglycerides for storage for the rainy day that never came.

Now we are taking a different look at adipocytes. We no longer view them as inert depots for storing fuel as lipid. We see them as metabolically interesting cells within a complex matrix that is part of our endocrine system. Adipose tissue is considered an endocrine organ that releases hormones in response to specific extracellular stimuli, or changes in metabolic status. Dietary variables like protein, carbohydrate, and fat levels, exercise, and environment can influence the working of adipocytes. The secreted proteins from the adipocyte include inflammatory mediators such as TNF-a, leptin, and a new molecule, adiponectin. Adiponectin appears to be an important messenger that helps regulate muscle lipid metabolism, increasing expression of the genes encoding CD36 and acyl CoA oxidase, and uncoupling protein-2 that relates to maintaining our core temperature, body heat, and combusting and releasing as heat, stored fuel, metabolic fuel.

Insulin and Adiponectin

We now see that insulin sensitizing has an influence on adiponectin and its ability to stimulate fat metabolism, presumably due to changes in gene expression. Future studies are likely to focus on the mechanism of action of the adiponectin molecule, its signaling pathways, and the possible interaction with other adipokines that might act in synergy with leptin and TNF-a.

We should understand our fat tissue is an active part of our endocrine system that is communicating with our brain and immune system. Changes in our physiognomy and body shape, or waist-to-hip ratio, may be a reflection of this complex orchestration. Two articles in *Nature Medicine* illustrate this point. One is “The Fat-Derived Hormone Adiponectin Reverses Insulin Resistance Associated with Both Lipoatrophy and Obesity.”[20] The other is “The Adipocyte-Secreted Protein Acrp30 Enhances Hepatic Insulin Action.”[21] Both show the interrelationship of body fat, lipid levels, hepatic function, insulin activities at peripheral sites, and, ultimately, brain central mechanisms through the hypothalamus and pituitary axis.

Insulin and Fat Composition

Insulin stimulates an array of functions that operate in combination with leptin, adiponectin, neuropeptide g, and the serotonergic pathway. It is no surprise that depression, low energy, and fatigue are frequently associated with weight gain, insulin resistance, hypertension, dense LDL particles, and elevated triglyceride-to-HDL ratios.

Changing dietary fat by replacing partially hydrogenated trans fats with essential fatty acids can influence this process. The authors of an article in the *American Journal of Clinical Nutrition* show that trans fats increase insulin resistance and the risk of type 2 diabetes.[22]Trans fats are the partially hydrogenated vegetable oils. Substituting the native oils for the trans fats can reduce insulin resistance and the risk of type 2 diabetes.

Diet, Lifestyle, and Insulin Sensitivity

We also found that phytonutrients derived from various types of spices and herbs influence insulin sensitivity. Cinnamon, for example, seems to have a hydroxychalcone constituent that is a mimetic for insulin and activates adipocytes. This is the topic of a recent paper in the *Journal of the American College of Nutrition*.[23] You might consider using certain phytonutrients other than G*ymnema* to influence insulin sensitivity.

Exercise is a primary therapy for improving insulin sensitivity, insulin signaling, and the inositide pathway that controls glut4 and glut2 translocation to the membrane and proper glucose transport. We cannot overlook exercise as an important therapeutic tool. To be effective, an exercise program can be quite modest. A diabetes and insulin resistance study showed that walking on level ground 20 minutes a day improved glucose transport and insulin sensitivity. Exercise also lowers hemoglobin A1c. A paper in *JAMA*[24] showed that we cannot avoid discussing the importance of exercise with patients.

Diet and lifestyle are probably the two most important variables in lowering the risk of type 2 diabetes and improving insulin sensitivity and insulin signaling and their role in a whole array of different functions. A *New England Journal of Medicine* article titled “Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women”[25] discusses this topic. The article showed that the majority of the cases of type 2 diabetes could be prevented by the adoption of a diet and exercise component.

Diet, Lifestyle, and Prevention of Gene-Associated Illness

Even conditions we thought may be tightly locked into our genes, such as pancreatic cancer, are now being connected to diet and lifestyle variables and concomitant insulin sensitivity. A paper in *JAMA*, titled “Physical Activity, Obesity, Height, and the Risk of Pancreatic Cancer,”[26] and an editorial that follows it, described the role of insulin resistance and hyperinsulinemia in pancreatic cancer. According to the authors of the editorial, which is “Is pancreatic cancer a preventable disease?”[27], promising research results seem to indicate pancreatic cancer could be a form of cancer that might be preventable through the modification of lifestyle habits and exercise programs to improve insulin sensitivity.

You can see that single mechanisms cut across many different diseases. This is the new functional genomic model of medicine, which the National Institutes of Medicine is talking about. This is an exciting time in which this new information is not so esoteric that it cannot be applied clinically. I urge you to start applying these concepts.p>