March 2001 | William Evans, PhD Nutrition, Exercise and Metabolism Laboratory

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Welcome to the March 2001 issue of *Functional Medicine Update.* We are moving into spring and preparing for our Eighth International Symposium on Functional Medicine, to be held in Vancouver, British Columbia, at the Westin Bayshore Marina Resort May 22-26. The topic this year will be advanced in functional endocrinology. In this month's *FMU* we will focus on modifiable factors of aging, looking at aspects of the human aging process and how we might modify some factors associated with senescence. Our Clinician/Researcher of the Month, Dr. William Evans, will also discuss these modifiable factors of aging. He will bring us news-to-use in relation to slowing the biological clock, reducing senescence.

The difference between senescence and aging is related to factors that can be modified. We may have little ability to modify some fundamental processes that underlie aging, but many other factors relating to senescence or unhealthy aging may be modifiable. We will discuss those factors, not only this month but in subsequent months this year in *FMU*, in relation specifically to the endocrine system and the balance and dance of hormones. We will also discuss that modifiable area at this year's Symposium.

The Classical versus the Modern Paradigm in Health Care

I begin this month by asking a question that is on the minds of many of us. Why do we describe some therapies as "alternative medicine," a label that seems to imply they are not in the mainstream of modern medicine? Don G. Bates, MD, a professor at the Department of Social Medicine at McGill University, McIntyre Medical Sciences Building in Montreal, Quebec, Canada, discussed that topic in a recent article. This article appeared in *Perspectives in Biology and Medicine* in the summer of 2000. The title of the paper is "Why Not Call Modern Medicine 'Alternative?'"

This is a good lead-in to our discussion this month about the modifiable factors of aging. Some things we will be discussing do not fall within the standard practice of what we call modern medicine. Are they necessarily alternative, or do they represent a historic theme of medicine? Would it be better to describe what we call modern medicine as alternative medicine?

Orthodox or Alternative?

Dr. Bates begins his article by stating, "We call it 'modern' medicine, 'scientific' medicine, and 'biomedicine,' but if the term weren't already in use, we could just as reasonably call it 'alternative'

medicine. That only becomes obvious, though, if we look at the orthodox medicine of the 20th century in a broader historical and cultural context."

What we now call modern medicine might be called alternative medicine.

That theme permeates this thoughtful article. Dr. Bates refers to the ancient Hippo-Galenic tradition, represented in the early 19th century by what is called heroic medicine or allopathy, in which agents to treat conditions emerged. This is the beginning of the classical paradigm that was to underlie the development of 20th century medicine.

Two Features of Modern Medicine

"&ldots;By 20th-century, I also mean that model of medicine I was taught in the 1950s and which had two particularly striking features: the remarkable domination of the germ theory as the chief model of a disease and its treatment; and the equally remarkable hegemony of scientific medicine, and corresponding lack of medical diversity, especially in North America."

We started to focus our medical perspective into one channel of thinking, the reductionistic, analytical, disease-focused entity. It was a fairly new construct in medicine, and during the development of medicine over 2000 to 3000 years it has undergone a narrowing of perspective. Dr. Bates go on to ask how we can contrast the classical paradigm of medicine to this more 20th century medicine paradigm, which he calls "alternative."

A Definition of Health

Let us look first at the definition of health, contrasting the classical paradigm to the 20thcentury "alternative" modern medicine paradigm. Dr. Bates notes that in the classical paradigm, the individual person was the focus of health. In the 20th century paradigm, the focus is on the universal body, public health, the average person, the statistical 70-kg human. The classical paradigm focused on body and soul interrelationships. In 20th century scientific medicine, the focus is on the materialistic body, reducible (at least in principle) to physics and chemistry. In the classical paradigm, the body was viewed as a container of humors and energies, all flowing together and mixing to give rise to function. In the 20th century paradigm, the body is seen as a highly complex machinery of minute, interacting parts and chemicals. In the classical paradigm, ecological physiology is contrasted to 20th century physiology focused on the interior of a universal body and, I might add, compartmentalization into organs and organ systems.

The classical paradigm focused on dynamic equilibrium that is "natural," harmonious, and based on the homeodynamic principle. In the 20th century paradigm, the focus is on "normal" structures, functions, and chemistry. This is a Gaussian view of human function and, therefore, a Gaussian consideration of physiological chemistry—the normal reference range, so to speak

Definitions of Sickness

Similarly, the definition of sickness in the classical paradigm is in contrast to the 20th century modern medical paradigm. In the classical paradigm, illness was a particular event, but in the 20th century paradigm, disease is a generic entity. This is medical taxonomy. If you know the name of the disease, you

know the disease. By classifying, using a specific linguistic definitional pattern, one supposedly knows more about the individual.

The classical paradigm talked in holistic terms, whereas the 20th century paradigm talked in terms of location, focusing on illness at a given point. The classical paradigm considered multiple, interacting causes, conditions, and correspondences. The 20th century paradigm talked about "the" cause of the illness, which derived its origin from the vector disease model, the bacterial origin of various specific diseases. This model has proven to be less applicable to chronic illness that plagues individuals as they age. Finally, the classical paradigm focused on imbalances, while the focus using the 20th century paradigm is on pathology or deviation from the norm.

Comparing Cost, Diagnosis, Prognosis

These characterizations are important as we look at an aging population and consider how we can keep these individuals healthy and demanding fewer medical services. Waiting until pathology occurs and then treating it is very expensive. Looking at imbalances and perceived pathology, and modifying these processes through the multiple interacting causes may be much less expensive. Therefore, traditional medicine, the classical paradigm, may be more appropriate for improving health and function of the aging population than the 20th century modern "alternative" paradigm.

In terms of diagnosis, the classical paradigm advocates knowing the person. The 20th century paradigm advocates knowing the disease, which again relies on medical taxonomy. The classical paradigm looks at the person and his bodily discharges. In the 20th century paradigm, the approach is hands-on, even invasive, examination. In other words, what kind of information is woven together in the understanding of the disease? The classical paradigm looks at symptoms, and the 20th century paradigm looks at signs. The classical paradigm looks at describing the event; the 20th century paradigm looks at identifying the cause. And finally, prognosis in the classical paradigm is more important than it is in the 20th century paradigm.

A Medical Philosophy for Treating Dysfunction in an Aging Population

If we are looking at the medical philosophy that might best help us develop an effective way of managing dysfunction in an aging population, the classical rather than the "alternative" modern medical paradigm may be more effective, according to this article.

Last, let's look at therapy.

Classical Paradigm	**20th-Century Paradigm**
personal hygiene/prevention	treat the disease
manage, care for	eliminate the cause, cure
assist healing power of nature	often actively oppose nature
gentle, often herbal, dietary,	often aggressive, chemical,
"natural" (do no harm)	"artificial"
efficacy of *treatment* perceived	efficacy of *outcome*

by patient and doctor alike	measured and decreed by doctor

Have the RDAs Outlived Their Usefulness?

How does nutrition interface with this changing paradigm of modern medicine? The Recommended Dietary Allowances, and more recently the Reference Dietary Intakes, have been standards of identity in nutrition. The RDAs and RDIs are government standards for providing adequate nutrition to meet the needs of practically all healthy people. Dr. Walter Mertz, a principal trace mineral researcher at the Beltsville, Maryland, USDA Research Laboratories, has helped us understand the role of nutrients like chromium in human health and function. Dr. Mertz, who has decades of experience in the field and was on the Food Nutrition Board establishing the RDAs, wrote an article titled "Three Decades of Dietary Recommendations," which appeared in *Nutrition Reviews.* In this article he explains that with our evolving understanding of nutrition and its role in human function, the RDAs may have come to the end of their usefulness as tools for specific dietary evaluation and intervention in patient management.

The RDAs still have value as public health guidelines, but Mertz discusses their limitations based on the increasing understanding of genomic diversity and the functional aspects of nutrition in establishing specific needs for the individual. He talks about his own experience as a member of the Food Nutrition Board for many decades. That board carried on an active and evolving debate over recommendations above the minimum daily requirements to prevent vitamin-related or nutrient-related deficiency diseases.

Nutrients and Function: The Vitamin C Example

Mertz discusses the increasing complexity, from 1941 to 1989, of the understanding of the influence of nutrients on function. He describes the Dietary Reference Intakes, DRIs, and their influence on thinking in the late 1990s. They represented an attempt to focus more on assessment of functional aspects of nutrition than simply on such indicators of nutrient deficiency as scurvy, beriberi, pellagra, xerophthalmia, rickets, kwashiorkor, or marasmus. Our understanding is increasing, according to Mertz, regarding the role of nutrients in physiological biochemistry.

He cites Dr. Mark Levine's *in situ* kinetic work in human metabolism of vitamin C in apparently healthy men. That research indicates that focusing on the functional aspects of a nutrient like vitamin C with a specific enzyme, in apparently healthy individuals, reveals a much different effect and sensitivity of that nutrient on individual function than we would get by examining gross morphological changes associated with scurvy. The Levine work, therefore, helped us recognize that the need for vitamin C can be at least twice as great as the RDA level when we start looking at function.

Subtle Effects of Nutrient Deficiencies

According to Mertz, functional evaluation of nutrient need at the biochemical, physiological level changes our perspective in significant ways. We begin to consider folate, vitamin B12, and B6 related to homocysteine metabolism and examine the rate of depletion of folate at specific sites related to the activation of the folate cycle. We begin to consider that interaction may have tissue-specific effects well before one can observe such gross abnormalities associated with B12 and folate deficiencies as megaloblastic or pernicious anemia. Neurological deficits, psychological disturbances, or cardiovascular

risks occur, but they are not as obvious as a vitamin deficiency disease. These disturbances represent functional disorders that may have unique impact in genetically susceptible individuals. The theme becomes much broader than the Food Nutrition Board understood back in the 1940s, 50s, and 60s.

The one-nutrient approach is also under question because we might ask, what is the relative bioavailability of that nutrient in different foods, in different forms, in the presence of other nutrients or other agents in the diet, or interactions of one substance with another, to give either synergy or antagonism. We begin to consider the form of the food, the availability and density of nutrients, and the presence of other macronutrients. The subject becomes more complex when we start examining individual expressions.

The Evolving View of Nutrition's Role in Health and Disease

Weaving this information together, according to Mertz, we are beginning to develop a different view of the role of nutrition in health and disease. It is a functional role. Thus the RDAs, which, being public health minded, try to prevent nutritional deficiency symptoms and diseases, may be only partially adequate. We need to adopt what might be considered a more classical, or traditional medicine view of nutrition, in which we consider how nutrients impact health. The construct of nutrient deficiencies related to disease is a more "modern construct" that is really alternative. It is not a construct with a long record in the history of the way we have viewed nutrition's effect on health and disease.

We seem to be coming full circle. We have gone through the age of deficiency to the age of function. We are looking at the interaction, the dance, the dynamics, the kinetics, the equilibrium of how nutrients interact with physiological processes and genes to give rise to the outcome of either high-level function or dysfunction that we often associate with age-related dysfunction and disease.

Biomarkers—The Ten Keys to Prolonging Vitality

That subject is described in a by Drs. William Evans and Irwin Rosenberg, which we will be discussing on side II of this month's *FMU.* In that book, titled *Biomarkers—The Ten Keys to Prolonging Vitality*, the authors describe how, based on these biomarkers of aging, an individual can help control the biological senescence process. The individual can use modifiable risk factors, intervention by diet, exercise, lifestyle, and environment, looking at the right biomarkers and tracking them back against specific variables that individuals control every day, including what they eat and drink, how they think and act, and how they exercise. This is not a new topic for *FMU* or for individual preventive medicine, but the book states it in an eloquent and simple way. The authors discuss how to measure and manage these factors in the clinic.

With Dr. Evans on side II we will discuss body composition, muscle mass, the relationship to intermediary metabolism, and controlling overall defense against degenerative disease. We are talking about gene/environment, gene/diet, gene/exercise relationships. It is the genotype/phenotype connection we have frequently discussed in *FMU*.

Human Natures—Genes, Cultures, and the Human Prospect

Dr. Paul Erlich recently wrote a book that makes a wonderful literary contribution to this topic. In the

1960s, as a biology professor at Stanford, Dr. Ehrlich wrote a bestseller called *The Population Bomb*. His more recent book, *Human Natures—Genes, Cultures, and the Human Prospect,* will complement your understanding of where we are going in personalizing and humanizing the Human Genome Project. It does not tell us how people will die, but it does tell us how people may live more effective long lives with good health. This process can come about by interweaving the cultural means that support proper behaviors that give rise to the full expression of healthy phenotypes from their genotypes.

This book, published in August 2000 by Island Press, takes us through the whole evolutionary construct of aging and age-related function. It humanizes the Human Genome Project in a useful way.
The *Biomarkers* book by Evans and Rosenberg is currently available in paperback. Published by Simon and Schuster in 1991, it is still well worth reading and should be on everyone's bookshelf.

Gene-Diet Interactions in Obesity

Let us consider the role of genes in conditions like obesity or any dysfunction or disease. We continually hear of the discovery of the gene for this or that characteristic. Most often, this means that the gene for susceptibility for this or that characteristic has been found. Only by plunging the person's genetic type into a harmful environment specific to his or her unique genotype is the phenotype of disease, or a phenotype of dysfunction manifest. This interaction is the subject of a recent paper in the *American Journal of Clinical Nutrition.* In this article, titled "Gene-Diet Interactions in Obesity," the authors indicate that a number of genes have been found that relate to the ways calories are processed. These genes, which may be called "fat genes," affect how food is converted into energy or stored energy as triglyceride fat in adipocyte tissues.

In reality, they are metabolic uniqueness genes. The way they express themselves in the phenotype depends on the way they are treated. It is true that identical twins may have increased risk of obesity if their parents are obese. It is also true that identical twins don't necessarily share similarities in body composition. They may have elected to treat their genes in a different way, by pursuing a different lifestyle, a different environment, or different exercise and nutrition programs. It is once again the interaction between genes and environment. We talk more about susceptibilities than distinct causes and effects that are locked rigidly and deterministically into the genes. The model I am describing is obviously much more classical than modern in its view of medicine. The modern view is the discrete model, the disease model, the imperfection model, the deterministic model, which, as Bates has pointed out, is more of an alternative to the model we have historically held.

Genetic Response to Dietary Fat and Cholesterol

The responses of the body to dietary fat and cholesterol are highly variable, as a couple of recent papers have demonstrated. You cannot give a certain dose of dietary cholesterol to two individuals and expect to get the same response in terms of blood cholesterol levels. This is the topic of an article titled "Influence of Genetic Polymorphisms on Responsiveness to Dietary Fat and Cholesterol," which appeared in the *American Journal of Clinical Nutrition.*Different apolipoproteins transport fat and cholesterol, and they have different genetic susceptibilities. For instance, the polymorphic forms of apo E—apo E2, apo E3, and apo E4—have different influences on the risk of heart disease and cerebral vascular disease from high saturated fat diets. The apo E4 represents much higher risk and is, therefore, more responsive in an adverse way to high saturated fat than the apo E2 or 3.

We need to develop a medical philosophy and delivery system, a means of communicating to patients, and a system of practice in which we begin to individualize treatment based on this genotype/phenotype interaction. We have to get away from the deterministic model, which states that if characteristics are rooted in your genes it is inevitable that you will develop a certain condition. Perhaps we need to work harder with a patient who has the apo E4 genotype to manipulate his or her phenotype in such a way as to be associated more with healthy aging.

The same theme is mirrored in a paper titled "Individual Cholesterol Variation in Response to a Margarine- or Butter-Based Diet," which appeared in the *Journal of the American Medical Association.* This article plays up the fact that individual variation and response to a cholesterol-lowering diet is a familial trait. We carry genetic propensities toward some of these tendencies, but we do not necessarily carry the rooted outcome in the absence of specific environmental modulators.

Statins and the Risk of Dementia

Let us move from body composition to look at secondary effects associated with that, or other age-related effects. How about the central nervous system and dementia? Neurology publications increasingly indicate that brain aging and dementia are strongly tied to chronic inflammatory mediators, particularly those produced by the microglia, the brain's immune system. Conditions that enhance microglial activation of proinflammatory mediators may result in progression of neuronal injury and apoptotic cell death. The result is ultimate depletion of reserves of specific regions of function in the brain, causing adverse functional outcome, i.e., dementia.

A recent paper in the *Lancet* causes us to think through what might appear to be unconnected variables that relate to this model, and how from a different context, the classical model of weblike dynamic physiology, they start to make sense. I refer to an article titled "Statins and the Risk of Dementia." Statins are hydroxy-methylglutaryl-coenzyme A reductase inhibitors, the so-called HMGCoA inhibitors that lower cholesterol. As such they have traditionally been used to manage heart disease risk associated with elevated LDL by blocking the rate-limiting step in *de novo* cholesterol biosynthesis in the liver.

Abandoning the One Drug/One Condition View

We thus develop a very discrete view of one drug for one condition--hypercholesterolemia, heart disease, and HMGCoA reductase inhibitors. Evidence we have seen over the last several years, however, suggests that the statins, these fungal metabolites, not only influence the potential for heart disease risk, but also for conditions as seemingly far-afield as dementia. That is the conclusion one draws from the results of this recent *Lancet* study, in which individuals age 50 years and older who were prescribed statins had a statistically significant lowered risk of developing dementia, independent of the presence or absence of untreated hyperlipidemia. This means they did not necessarily have elevated LDL or exposure to non-statin drugs. The available data do not distinguish in this paper between Alzheimer's and other forms of dementia. They just looked at total reduction in the incidence of dementia. How could a statin drug have this impact?

It has been increasingly reported in the last few years that statins have an influence on the inflammatory cascade. Cholesterol is a signaling molecule, and adipose tissue is a signaling tissue that elaborates proinflammatory cytokines. Cholesterol is part of a process through its oxidized derivatives that may

influence this inflammatory potential. Something may be going on in regard to LDL metabolism that is more than just cholesterol reduction. It may have to do with other influences of this inflammatory cascade—lowered C-reactive protein, lowered tumor necrosis factor a , or lowered inflammatory IL-2. These particular processes, if arrested or diminished, seem to be associated with lowered risk of brain injury and dementia that accumulate with aging.

Modifying the Risk of Dementia of Aging

The emerging view is that there is a modifiable risk factor for the dementia of aging. In a previous issue of *FMU* we pointed out that Alzheimer's incidence was 50 percent lower in individuals who took nonsteroidal inflammatory drugs (NSAIDs) for the management of osteoarthritis over many years. This is another indication of a lowered anti-inflammatory connection to lowered risk of dementia.

This does not mean we should all be on statins and selective COX-2 inhibitors. Everyday factors in our diet and lifestyle alter inflammatory mediators but do not necessarily require drugs for their manipulation. Stress, allergens, toxins, and heavy metals upregulate inflammatory mediators. A genotypically sensitive individual who consumes a poor-quality diet that is high in saturated and oxidized fats has increased risk of inflammatory response. Over the length of a person's life, those factors become as important as a crisis or acute infection. Chronic, gut-associated infection or localized or systemic infection can increase inflammatory mediators. All these mediators of inflammatory activity have an impact on neuronal aging, the senescence process.

Cancer and Advanced Chronological Age

Cancer is another area example of the dynamic genotype/phenotype relationship. Cancer incidence increases significantly with advancing chronological age. Advancing age is the most potent of all carcinogens, according to the data. In humans, the incidence of cancer rises exponentially in the final decades of life, culminating in a lifetime risk of one in two for men, and one in three for women. This dramatic age-dependent escalation in cancer risk is fueled largely by a marked increase in epithelial carcinomas from ages 40 to 80 years, as opposed to cancers of mesenchymal or haematopoietic origin.

The epithelium is the barrier that separates us from the outside world. Epithelial cells are our insulating cells and tissues that are constantly exposed to irritants and carcinogens. They include the gut mucosa, the lungs, the oral mucosa, and the skin. These areas, which are continually exposed to outside irritants, are those in which we see the greatest prevalence of cancer from age 40 to 80. If we can modify exposure or response to exposure to these agents, we may be able to reduce cancer in older individuals. It is not genetically determined and locked in stone that we will get cancer as a part of aging.

Genome maintenance is an important part of the study. We know that in animal studies the more disturbed the genome becomes by mutagenic agents, the more cancer develops. Ultraviolet radiation to the skin or carcinogen consumption in the diet enhances the relative incidence of cancer. It is not solely genetic. Just because one carries a mutated oncogene, he or she will not necessarily experience cancer as the outcome. An article titled "The Age of Cancer," which appeared in *Nature,* looks at this modifiable link between advancing age and increasing incidence of cancer.

Cancer Chemoprevention - A Clinical Reality

This observation opens the door for the field of cancer chemoprevention. Can we find ways of preventing the genome from expressing unregulated cell growth with increasing age? In the past several decades, chemoprevention of cancer has been a central focus of research in NCI and NIH studies. It is becoming a clinical reality, according to the *Journal of the Royal Society of Medicine*.

In 1867, the Viennese surgeon Theodor Billroth claimed that cancer could be cured with surgery. A later review of his results, however, showed this was seldom true. Despite advances in surgery, radiotherapy, and chemotherapy over the past century, cancer is an increasing cause of morbidity and mortality in most countries. Now the construct of chemoprevention, the genotype/phenotype interrelationship, is where some exciting progress is being made. In the example of gastrointestinal or colonic cancer, we can look at the histological stage of cancer. One goes from having normal epithelium to dysplastic crypts, to tubular adenoma, to villous/dysplastic adenoma, eventual carcinoma, and later metastatic disease. All along that series of steps, mutation or alteration in the expression of different genes must occur.

Stages of the Cancer Process

The first steps may have to do with the genes controlling b -catenin elaboration. The next steps may be involved with K-ras mutations followed by dysfunction in p53. It is not just a single hit; multiple hits along the pathway are involved. Together they work to our detriment and ultimately result in a metastatic carcinoma.

The good news is that chemoprevention can occur at each of these steps before the development of a metastatic carcinoma. We can look at detoxification mechanisms, oxidative damage to the DNA, or antiinflammatory responses as targets for intervention. Such thinking has led to the new work being done with selective COX-2 inhibitors in prevention of colorectal cancer. We can look at anti-angiogenic substances that limit metastatic spread. We are finding in each of these areas that there are modifiable factors in our lifestyle or nutrients that are under our control, which influence each of those steps. There is a biomarker that relates to the appearance of each of those steps, and there is a modifiable factor that tracks back against certain mutated genes or modified genetic expression, which can then produce normal function, rather than the function of malignancy.

Avoiding Toxicity

Avoidance of toxicity is important in cancer chemoprevention. Perhaps that begins to explain the chemopreventive effects of aspirin in colorectal cancer. Individuals who take salicylic acid equal to a baby aspirin a day have a 50 percent reduced incidence of colorectal cancer.

How does that relate to inflammation, tumor expression markers, cell replication, and the various stages of quiescence or replicated growth, the mitogenic factors? Dietary factors, such as increased intake of various fibers, in the presence of friendly bacteria in the colon, produce more butyrate, which silences certain genes involved in cell replication. What role does this play in chemoprevention? We are beginning to understand the mechanisms and science of that web, that dynamic. That increased understanding

supports the classical view of medicine, not the modern view. As Bates pointed out, we might consider the modern view of medicine the alternative view. The modern view is of a single event, a single hit, a single outcome, a single disease, and therefore a single therapy. We can tie that discussion to that of Dr. Mertz regarding the RDAs. We are changing our whole philosophy in understanding the role of nutrients how they can be optimized to for the benefit of the individual.

Parkinson's Disease

Parkinson's disease is another example. You may have heard about a recent article in *Nature Neuroscience* on the link between pesticides and Parkinson's disease. Once again, this article illustrates the possible link between polymorphisms in certain detoxification enzymes. Individuals with specific polymorphisms exposed to certain pesticides, may have significantly increased risk of neuronal degeneration of the nigra striatum and potential loss of dopaminergic effects or function. Everyone does not have this same risk. These same environmental factors play upon genetic propensities to give rise to increased feed-forward cycles of apoptotic cell death in the nigra striatum.

This paper confirms much of what we have been saying. Chronic systemic pesticide exposure reproduces features of Parkinson's disease in models by uncoupling complex I in the mitochondrion, producing oxidative products that shift the cell toward premature death or apoptosis. This confirms this modifiable factor of age-related dysfunction and carcinogen or neuronal loss.

Pharmacogenetics and Individual Reactions to Drugs

Individuals differ widely in their responses to drugs. The emerging field of pharmacogenetics driven by the pharmaceutical industry and their concerns with adverse drug effects. We are learning that two individuals may have very different reactions to the same drugs, based on their genetic propensity toward detoxification through their cytochrome P450 super-family of detoxification enzymes or their phase II conjugation enzymes, such as glutathione transferase, or glucuronidation or sulfation effects.

A paper in the *Lancet* considers pharmacogenetics and adverse drug reactions. Polymorphisms in the genes that code for drug-metabolizing enzymes, drug transporters, drug receptors, and ion channels affect the individual's risk of having an adverse drug reaction. We cannot properly describe such a reaction as atypical. It is typical and reproducible in that person. If we know about his or her genetic polymorphisms of various cytochromes, it is predictable. We look at cytochrome P450 2D6 polymorphisms and see people who have problems metabolizing various SSRI drugs. Or we look at cytochrome P450 1A2 or P450 2E1 polymorphisms and find people with problems in metabolizing certain anti-arrhythmic drugs or certain agents related to the management of schizophrenia. If we do not take these polymorphisms into account, a typical dose of a drug can cause an adverse or perhaps even fatal response in a genetically susceptible individual.

Exercise and Detoxification

Nutrition plays a role in modifying detoxification. Would you be surprised to learn that other environmental factors, such as exercise, also influence detoxification? A paper published in*Medicine &*

Science in Sports & Exercise describes the clinical results of a study on anesthesia-induced hepatotoxicity in individuals who did and did not exercise. Researchers found enhanced cytochrome P450 detoxification of halothane in patients who exercise regularly.

Regular exercise improved the detoxification ability of the liver to resist the halothane-induced toxicity. This may have to do with the induction by exercise of many of the detoxification enzymes and the phase II conjugation factors, as well as the antioxidant factors associated with the protection of the liver, such as superoxide dismutase, catalase, superoxide, and glutathione peroxidase and reductase. I emphasize the reducibility of some of these constructs of determinism to modify the factors of aging.

Why Do We Age?

Why do we age? That question was discussed in a recent commentary in *Nature*. The evolutionary theory of aging explains that aging occurs to insure genomic diversity, allowing new organisms to come into the gene pool and producing new opportunities for modification and resistance to a changing environment. We recognize that there is a set template, or biological mechanism of aging, called chronological aging. We superimpose on that template, however, the senescence model of accelerated biological aging, what Dr. James Fries described as losing organ reserve, and increasing the risk of age-related diseases. That superimposition of environmental factors often gives rise to the skewed use of medicine, heroic intervention, and the increased prevalence of specific diseases.

I would like to take this theme to the next level on side II of this month's *FMU.* Dr. Bill Evans, our Clinician of the Month, will tell us about reducible or modifiable factors of aging in things that people can do every day of their lives.

Interview Transcript

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Exercise and Functional Medicine

JB: Each month in *Functional Medicine Update*, we have a Clinician or Researcher of the Month who talks about where our field is heading and adds new tools to the practitioner’s toolkit. This month I am proud to introduce clinician/researcher William Evans, Ph.D. I have quoted Dr. Evans frequently in *FMU* in reviewing the literature and important work in functional medicine. Dr. Evans is director of the Nutrition Metabolism and Exercise Unit at the University of Arkansas Medical Sciences Center. Before he took that post, he was actively involved at the Human Nutrition Center on Aging at Tufts University in Boston, working with Dr. Irwin Rosenberg’s group there. He is co-author of *Biomarkers—The 10 Keys to Prolonging Vitality*—and has written a number of scientific papers, some

of which we will discuss with Dr. Evans today.

As our current Clinician of the Month, Dr. Evans brings expertise about an area in which we need to do more, the exercise interface with nutrition and functional medicine. Dr. Evans, what led you to focus your energies in this area?

WE: Thank you for your kind introduction. It is a pleasure to be on this program. I was trained as an exercise physiologist at Ball State University, under Dr. David Costill. While I was a graduate student, we examined how nutrition and training can enhance athletic performance in elite athletes. I was involved in a study in which we looked at athletes like Steve Prefontaine and some of the very best runners to see what made them so special. I was fortunate to be invited to participate in the new activities at the Nutrition Center at Tufts University in Boston. The initial director decided to invite people with expertise in various areas, not necessarily aging, to apply their knowledge to understanding aging. That's how I joined the group. I had some expertise in exercise science and functional status, which is really what exercise physiologists do.

We approached the idea of how to improve function in older people. Clearly, the basic tenet of exercise training is to exercise at a sufficient intensity to produce an appropriate effect. We brought to this area the idea that we could be a bit more aggressive and a bit more intent on improving overall function in elderly people who have lost a tremendous amount of muscle mass and muscle function. We have seen that the capacity to respond appropriately and robustly is preserved into very late life, and that is good news for everybody.

Sarcopenia and Maintaining Muscle Mass

JB: I believe you coined the term sarcopenia, which defines the area of lowered body muscle content. You have identified sarcopenia as a biomarker of aging. How does your research relate to what some people say is the inevitable consequence of aging, that we are all going to lose muscle as a matter of biological predestination?

WE: Like every biological phenomenon, sarcopenia, which means age-related loss in muscle, has many different causes, and we are trying to examine all of them. One obvious cause is the "use it or lose it" phenomenon. As we become less physically active, we are much more likely to lose muscle. There may be an age-related phenomenon. Aging of the brain and central nervous system may affect how muscles age. We also know that as hormones change, as women lose estrogen and men have decreased testosterone, that also decreases the rate of muscle protein synthesis and ultimately may result in loss of muscle. Sarcopenia may have many different causes.

We have been addressing the secondary consequences of loss of muscle. We think loss of muscle may be the most important biomarker, because it leads, for example, to decreased basal metabolic rate and a decreased need for calories. As our need for calories decreases, most of us don't decrease our calorie intake to match this declining need. One consequence of advancing age is increasing body fatness. Unfortunately, as we grow older, we accumulate a lot of that fat around our waist, which is an independent risk factor for diabetes and heart disease. We think loss of muscle may be the root cause of many of the changes we see with advancing age, from loss of bone mass and osteoporosis to a decreased ability to thermoregulate, or control one’s body temperature.

Exercise and Aging

JB: Tell us about the results of the study you published in *JAMA* a number of years ago about exercising octogenarians and nonagenarians.

WE: We actually published two papers, the one in *JAMA* and a larger follow-up study in the *New England Journal of Medicine*.[7] We were looking for the population that most needs our intervention. Those are people who are very frail, very old, and who can hardly walk because they're so weak. Those are the institutionalized elderly, people in nursing homes.

We took our basic concepts, which are high-intensity weight training, weight-lifting sorts of exercise, and applied them to a group of people over age 80, with an average age of about 87. The oldest person in our study was a 98-year-old with multiple chronic diseases. In 10 short weeks we found we could triple and quadruple their muscle strength. We increased the size of their muscle mass and their gait speed. We improved their balance, their ability to climb stairs, and their activity levels. All of the factors that may lead to a fall and a broken hip are improved with this type of exercise. Our subjects were far less depressed after participating in this project. It showed everyone that if a 98-year-old nursing home patient can participate safely and effectively and make really substantial changes, then anybody can do it.

Encouraging Compliance

JB: Many clinicians might say these improvements are possible, but you are talking about the Tufts University Human Nutrition of Aging Study. It was conducted under appropriate conditions and compliance was probably high, but I don't think my patients would do this.

WE: I think that is a copout. We have implemented statewide, community-based programs in Massachusetts and Pennsylvania. Our program is training peer leaders in the community, people who really have no background in exercise science and nutrition. We train them to lead an exercise program for older people, and we have had spectacular results with a minimum of equipment. Using weights you can buy in any store, weights you make yourself, or rubberized tubing, you can increase strength and functional status in anybody. It's a matter of wanting to do it. The thing that often happens is that an older person will go to his clinician and say he has heard about this strength training and wants to participate. He may be told it is not appropriate for them, because strength training will increase his blood pressure, for example. The fact is that it doesn't do that.

Strength training has now been used in stage I cardiac rehab programs. We see very little change in blood pressure, even in heart rate, with strength training. We think that resistance training for elderly people is at the forefront of what they should be doing.

Strength Training versus Aerobic Training

I've come full circle on this because as exercise physiologists we've been trained that aerobic exercise is the very best. I don't want to diminish the positive effects of aerobic exercise, but the most fundamental deficit many older people have is weakness. Weakness affects virtually every aspect of their functional capacity. It affects their ability to climb stairs, get out of a car, and perform the activities of daily living. By improving overall strength, we get older people to be much more physically active. It is both

extraordinarily effective and can benefit everything else—like the rising water raises all boats.

Cardiovascular Endurance Program versus Resistance Exercise

JB: You have described the resistance exercise program. Could you explain how you would differentiate between what many people think of as a cardiovascular endurance program and this program?

WE: We lose a tremendous amount of strength and muscle mass as we grow older. Even regular aerobic exercise like walking, running, or swimming does not seem to prevent that. We use what we call resistance exercise training. That essentially is lifting a weight that tires you out after about 10 lifts. If you can lift a weight 20 times, it's too light. It is not going to improve your strength to any great degree. You must lift a weight that tires you out after about 10 lifts. That’s the most important concept behind what we do. The intensity of the exercise is critically important to produce the positive effect.

This information is available from a wide variety of sources. You mentioned our book, *Biomarkers*. The National Institute on Aging in Bethesda, Maryland, also has a wonderful exercise book that I helped put together that is either free or very inexpensive. You can contact the National Institute on Aging and get this book. It explains in great detail how to initiate and continue with a strength training program.

Sarcopenia and Lack of Exercise

JB: You mentioned earlier that sarcopenia may have many contributors. Lack of resistance exercise may be one, and perhaps hormonal changes with aging, as well as things like chronic inflammation that increases cytokines. In your experience, when you look at these in the average individual who has sarcopenia with aging, does lack of exercise rank up there at the head of the list in most individuals?

WE: Lack of exercise is probably fundamentally the most important factor. If you look at epidemiological studies, it certainly appears as though we begin to lose muscle mass when we're young, 30 years old, when we have adequate levels of hormones circulating in our blood and we're healthy and relatively disease-free. That would indicate that around that age, as we get involved in our careers and our lives and become less physically active, we begin this process of losing muscle and that continues throughout life.

I think the overriding factor here is a reduced level of physical activity. Then there are a whole host of modulators added to that. Perhaps the two most important ones are menopause for women, and perhaps andropause and the reduction in circulating testosterone levels in men. A host of other factors, such as poor diet, may also be contributors.

Resistance Exercise and Nutrition

JB: Your book, *Biomarkers--The 10 Keys to Prolonging Vitality*, which you wrote with Dr. Rosenberg, should be on the bookshelf of everyone in our field. It takes a variety of complex topics and distills them down into how-to information. In that book, you talk about the relationship between resistance exercise and nutrition. So much has been written about different dietary approaches—low carbohydrate, high protein versus the high complex carbohydrate, lower fat diet. What has been your experience regarding the interface between these two approaches?

WE: Much of our research now focuses on resistance exercise training and its impact on nutrition status. One thing our research is showing is that as we grow older, we have an increased need for dietary protein. It may be because of this changing hormonal status; that is, at a time when our energy and protein intake begins to go down, we need more protein. One thing resistance exercise does is help the body metabolize protein much more efficiently. So for many older people who may be losing muscle, participating in an exercise program will enhance their use of protein and make it more efficient.

The other interesting thing we've seen is that resistance training significantly and substantially increases basal metabolic rate, the number of calories you're using at rest. Many older people are overweight, and because they're overweight they have a high risk of diabetes and high blood pressure. They need to lose weight, but losing weight is very difficult when you're over age 60. Sixty is the most difficult age to begin and to sustain a weight-loss program. What resistance training can do is boost your metabolic rate, and as you begin to lose weight, you hold onto that valuable muscle as you lose fat. I think that for many older people, and for many people in general, initiating a resistance training program may be the key to sustaining fat loss—rather than worrying about weight loss—to decrease the risk of chronic disease.

Body Composition Measurement

JB: In the *Biomarkers* book, you talk about the importance of doing body composition measurements to look at the various compartments of fat. Do you find that as an individual gets into the programs you're describing a clinician can measure fairly rapid changes in body composition, or does it change over weeks or months?

WE: Changes in body composition take time to manifest themselves. There is inherent error in measuring body composition, but I think it is a good place to start. Measuring body composition gives you a good handle on where you stand right now. I would say, however, that measuring body composition once every two or three months is the best way to see changes. I would not try to do it weekly or monthly just because of the inherent error in the measurement.

If you are participating in an exercise program, particularly a strengthening exercise program, as you lose weight virtually all of that weight you lose is going to be fat. For example, if you go on a low-calorie diet just to lose weight, without any exercise component at all, at least a third of the weight loss will be lean body mass, or muscle mass. That's very discouraging because it further lowers your metabolic rate so you need to eat even fewer calories to lose more weight. Then you exacerbate those losses. The best strategy is one that allows you to hold onto the muscle and boost your metabolic rate.

Bioelectrical Impedance Technology

JB: Can a clinician use bioimpedance technology with a degree of confidence?

WE: Absolutely. I think it's a perfectly appropriate one to use. In fact, I think that over the next couple of years large bodies of epidemiological data will be generated using bioelectrical impedance measurements rather than body mass index, which is only weight for height. Bioelectrical impedance is relatively inexpensive and very portable. I think you'll be seeing some very large survey studies with thousands and thousands of body compositions looking at risk of chronic disease. I absolutely think that bioelectrical impedance, making certain that a patient is fully hydrated when the measurement is taken, is a very

reproducible and good measurement of body composition.

Anthropometric Measurements

JB: What about anthropometric measurements, such as waist-to-hip ratio, which is in the news lately in relation to central adiposity and visceral adipose tissue?

WE: Clearly, increased waist-to-hip ratio is an independent risk factor for diabetes and heart disease. There is evidence that increased waist-to-hip ratio is a product of the male andropause and female menopause. As we reduce our sex hormones for whatever reason, there is a direct link to increased waist-to-hip ratio. Waist-to-hip ratio is the easiest anthropometric measurement to make. You take the circumference of the waist at the level of the belly button, the circumference of the hip at the largest circumference around the buttocks, and you look at that waist-to-hip ratio. That gives you a very good index of risk. It is an independent risk factor.

Other anthropometrics like skin folds, are much more difficult to measure, I believe. In the hands of someone who has not done that technique very often, those measurements can yield some real errors.

Waist-to-Hip Ratio

JB: Do you think the 0.9:1 or greater waist-to-hip ratio is a good screening tool?

WE: I think it's a good screening tool for any clinician. In fact, if you have a patient who is in that very high risk category according to his or her waist-to-hip ratio, it is appropriate to be very aggressive in the way you treat the patient to prevent diabetes or the symptoms of diabetes or heart disease. For example, in a patient with a low waist-to-hip ratio, I think just participation in an exercise program without being so worried about weight loss is appropriate. For someone with a high waist-to-hip ratio who is overweight, however, a much more aggressive stance on producing weight loss may be the thing that will get that patient into the lower-risk category.

Modifying Basal Metabolic Rate

JB: Let me go back to resting energy expenditure, or basal metabolic rate, for a minute. A lot of debate in the literature has centered on the origin of these differences from person to person and how they can be modified. Is it related to thermogenic brown fat that is found in hibernating animals but never identified in humans? Is it a mitochondrial effect? Is it driven by noradrenaline? Are we beginning to gain a better understanding of the physiological mechanism of the effects of exercise on resting energy expenditure?

WE: A great deal of fuss is made over inherent differences in resting energy expenditure based on metabolic rate. I don’t believe that basal metabolic rate is a big component of risk of obesity, because we rarely see really important differences from individual to individual. Much more compelling evidence seems to indicate that overall levels of physical activity may dictate risk of obesity. For example, you may be familiar with the studies that showed that fidgeting or just involuntary movement boosts daily energy expenditure. We’ve seen that in a study we've done and some others have seen that. That may be a very strong genetic component.

We know that if your parents are relatively lean, your risk of obesity is pretty low. Maybe the gene for that is in higher levels of overall physical activity, rather than inherent differences in metabolic rate. It is possible to affect basal metabolic rate. If you go on a low-calorie diet, for example, your body will produce less thyroid hormone and you'll downregulate your metabolic rate. For most of us who are weight stable, however, there is very little difference, and the inherent differences in metabolic rate are mostly controlled by how much lean body mass we have.

Resistance Exercise and Mitochondrial Activity

JB: Does the resistance exercise training program you've developed affect the number or activity of mitochondria in muscle? Does it influence energy metabolism in that way?

WE: We have seen in some of our early studies, when we took muscle biopsies from our subjects, that the mitochondria increased their oxidative status, or their oxidative capacity. That was an unexpected effect and I'm not exactly sure why that is.

We saw that the ability to oxidize fats was increased, and the ability to use oxygen was increased as a result of strength training, which is thought to be mostly an anaerobic type of activity. I'm not exactly sure why that is. It's the same type of change we see as a result of aerobic exercise training. It may well be a direct effect of the strength training or the fact that as our older subjects got stronger, they tended to exercise more often, or climb stairs more often, or just be more physically active on their own. There does seem to be a pretty strong effect.

Upregulating Enzyme Expression

JB: In the physiology/biochemistry literature I have been following reports that placing tissues under oxygen debt, such as low-level ischemic effects, upregulates gene expression of some of the enzymes involved not only in anaerobic metabolism, but also in aerobic metabolism. This may be a compensatory reaction. You are raising the number of enzymes that are available, so when you reintroduce oxygen, you've got more units available for metabolism.

WE: I think that may be the central mechanism by which we all respond to aerobic exercise. One thing that happens to our muscles as we become more physically active is that we get the same sort of upregulation of mitochondria. We get increased numbers of mitochondria, increased numbers of enzymes in the mitochondria, and increased capacity of muscle to use oxygen. Muscle essentially becomes much more like heart tissue in its total enzyme profile. I think the central factor that causes that is this relative ischemia. As the muscle demands more oxygen and we don't have the capability to deliver it, we get a huge upregulation in oxidative capacity. Interestingly, in an elite athlete, the ability to use oxygen during maximal exercise by muscles far exceeds the capacity of the body to deliver it. That's the concept upon which blood doping is based; increasing the hematocrit artificially enhances performance in aerobic athletes.

Introducing Exercise Programs in Clinical Practice

JB: If clinicians want to do more to get their patients onto an exercise program, how would you recommend they begin?

WE: There are two things. First, do a little reading. The NIH exercise book is a great resource. (Text from the NIH exercise book can be accessed at www.nih.gov/nia/health/pubs/nasa-exercise/intro. Our book, *Biomarkers,* is a good resource. Look in your community to find places where you can recommend that patients go. YMCAs and health clubs often have programs specific for older people, particularly if there is someone who is certified by the American College of Sports Medicine. That means it's a high-quality program.

If there's nothing in your community, it represents a fantastic opportunity for you or someone you know to start a basic strength training or exercise program in your community. You can get information to hand out to your patients to help them begin their own personal program, or you can search out a program in your community that they can participate in.

Future Research

JB: Let me close with one last question. What are you doing now in your research? Where are your questions taking you?

WE: Our questions are taking us more into patient-oriented research. For example, we have a big project looking at patients with chronic renal failure. One thing that postpones onset of renal dialysis is a very low protein diet. The consequence of that may be an exaggerated loss of lean body mass. So we have a large group of older patients with renal failure that are exercising.

We are about to initiate a project in men with prostate cancer. One of the key treatments for prostate cancer is what's called testosterone ablation, or greatly reducing testosterone levels so the tumor won't grow. The consequence of that, again, however, is exaggerated loss of muscle. We want to look at strategies for helping those men preserve their function and muscle mass. Our research is focusing on those older individuals who are very likely to have chronic impairments that may affect the quality of their lives. I do think, as you say, it's a message of hope. Many people we might never expect to participate in an exercise program respond so remarkably well that it should be the standard of care.

Contacting Dr. Evans

JB: I want to thank you, both for the quality of your work over the years and for the way you articulate it. It's highly motivational. No one can listen to this interview without wanting to place more emphasis on exercise in his or her practice. If listeners want to look at the website he described that has the electronic text version of the monograph on aging and exercise, it is on the website of the National Institutes of Aging, which is www.nih.gov/nia/. In the menu, look for the selection titled "Exercise—A Guide." It is supported by full text and has animated pictures of the various exercises that are suggested. It is a useful tool for both you and your patients.

You can e-mail Dr. Evans directly at evanswilliamj@uams.edu. Those websites will be on this month's summary cards.

The Nutrition Component in Modifying Gene Expression

Let me follow up from the eloquent and insightful comments of Dr. Evans with a few comments about

biomarkers and what we might do. Dr. Evans has given us a prescription for exercise intervention for improving muscle mass and reducing the risk of sarcopenia. Let me talk about the nutrition component.

We know from Dr. Richard Weindruch's work that nutrition is involved in the modification of gene expression. Dr. Weindruch, one of two Clinicians of the Month in December 2000, talked about nutrient modulation of gene expression. He is an author of a paper that appeared in *Science* magazine, titled "Gene Expression Profile of Aging and Its Retardation by Caloric Restriction." This article caused us to think about how nutrients relate to the expression of genes and modify the phenotype.

Calorie Restriction in Animals

If you want to follow up on this calorie restriction/nutrient modulation connection, Dr. Weindruch has published a more recent paper in *Free Radical Biology & Medicine.* It is titled "Restriction of Energy Intake, Energy Expenditure, and Aging." This paper explains, across a range of animal species, that an animal's life expectancy or life span is influenced by calorie restriction without nutrient restriction. An interesting linkage can be seen between this fact and modulation of the expression of various genes, particularly the oxidant stress genes, the stress genes in general, and the repair genes seen in his earlier work. The repair genes are turned off, or slowed down in their expression, and the expressed genes are turned up, or increased in their expression.

Even in the absence of large-scale human intervention trials on calorie restriction, we recognize that nutrient modulation of the right type is likely to produce changes in genotypic expression translated into the phenotype. Therefore, reduction of factors that increase inflammation, increase oxidant stress, or increase dysglycemia or dysinsulinism is an important objective in developing an anti-senescence program, trying to prevent the premature aging associated with senescence and related diseases.

Oxidative Stress in the Biology of Aging

We are gaining increasing knowledge about the role of oxidative stress in the biology of aging. A paper in *Nature*, titled "Oxidants, Oxidative Stress and the Biology of Ageing," describes the paradox of living in an oxygen environment. We need oxygen to support beneficial aerobic metabolism, but we pay a price as a consequence of the release of these high-energy oxidants or promiscuous molecules. Defending against this damage is part of the process.

Chronic inflammatory mediators enhance oxidative stress. Again, this shows the web of interaction of variables. They don't stand as discrete isolated principles of disease; they interact.

Exercise and Oxidative Stress

The same is true of hormonal imbalances, estrogen and testosterone imbalances, cortisol imbalances, insulin imbalances, thyroid imbalances. All of these imbalances show an interrelationship with increased oxidative stress. As Dr. Evans pointed out, ironically, exercise of the right type—aerobic and anaerobic—does not necessarily increase oxidative stress. It can actually decrease oxidative stress. An article that appeared in the journal *Medicine & Science in Sports & Exercise* describes the effect of exercise on heart transplant recipients. Exercise did not induce oxidative stress in these heart transplant recipients.

Through exercise training, with a combination of aerobic and anaerobic training, you may induce the appropriate mitochondrial oxygen-managing and antioxidant enzymes. In doing so you put oxygen where it needs to be, oxidizing substrates to end products to produce energy in the mitochondria. You defend against untoward oxidants, such as superoxide, hydrogen peroxide, and hydroxyl radical, by the levels of antioxidants that are induced through exercise training, superoxide dismutase and the like.

You have the greatest oxidative stress when you have the least oxygen present. That is the paradox. Excessive oxidative stress generally occurs in an untrained, exercise unfit individual who may smoke, drink, be under stress, and eat a high-fat diet. Now you have loaded the dice toward increased senescence through this oxidative pathway. Dysregulation and chronic inflammation go together. Body fat accumulation and increased TNFa production are covariables that interrelate to increase senescent risk factors.

Measuring Oxidative Stress

Clinically, it is desirable to measure oxidative damage in an individual. Oxidative stress is a biochemical biomarker of age-related phenomena that can come from a variety of different mechanisms and imbalances of the gene/ environment link. In a recent article, Dr. Barry Halliwell, a leader in oxidative stress research, discusses DNA damage mechanism from oxidative stress. By measuring DNA damage, we get some sense of the degree of oxidative stress that is not being protected against in an individual. Lymphocyte DNA damage, white blood cell DNA damage, appears to be the clinically most readily measurable. The most commonly analyzed compound is 8-hydroxy-2'-deoxyguanosine (8OHdG).

Many laboratories are beginning to offer lymphocyte 8OHdG analysis as a biomarker for oxidative damage to DNA. That damage is associated with the process of chronic inflammation, exposure to prooxidants, antioxidant insufficiencies, hormonal imbalances, stress, and those things that are, to a great extent, modifiable risk factors.

80HdG Measurement

There are different ways to measure 8OhdG. One should not assume that because a laboratory has this on its panel of analytes, it is measuring it correctly and getting reproducibly sensitive and precise data. Over the last 10 years, as Dr. Bruce Ames explained in his interview with us on *FMU*, the sensitivity for 8OHdG analysis has come down to between a factor of 10 and 100. We can now measure much lower levels of this substance, which is much more sensitive than measuring for or defining clinical risk of oxidative stress.

In his review article, Dr. Halliwell discusses the difficulty of measuring 8OHdG accurately because of the potential for producing artifacts during isolation hydrolysis or the derivitization of white cell DNA that results in the analysis of this compound 8OHdG. It takes good lab technique and methods, and good internal quality control, to produce good numbers. However, it does appear, when it is done correctly, that 8OHdG analysis is a sensitive tool for evaluating the relative damage to DNA from oxidative sources.

Reducing 80HdG Damage with Polyphenols

Between one third and half of oxidative DNA damage can come from the nervous system. Therefore,

indirectly, it has some impact in our assessment of neuronal aging through oxidative mechanisms. We also know, from Dr. Ames's comments, about the importance of dietary constituents, including polyphenols in fruits and vegetables.

Vitamin E or vitamin C may not be as active as polyphenols in reducing oxidative damage in 8OHdG. Therefore, giving vitamin C, vitamin E, and carotene may not be the primary approach one would want to use to reduce damage to DNA as a consequence of oxidative stress. Polyphenols, the flavonoid families found in fruits and vegetables, appear to be more active in preventing damage. N-acetylcysteine, lipoic acid, and coenzyme Q10 also play important roles. Beyond vitamin E, vitamin C, and carotenoids, specific nutrients found in abundance in various fruits and vegetables appear to help prevent 8OhdG formation, which is a biomarker of one aspect of senescence.

Serum Lipid Peroxide Test

Biomarkers of oxidative stress can also be revealed by looking at oxidized lipids, using the serum lipid peroxide test or the TBA analysis (thiobarbituric acid analysis). This is probably a later-stage marker, looking at oxidized lipids. Another analysis, which may be a bit more sensitive, if you want to look at oxidative effects on lipids, is the hydroxynonenal analysis, which is used to evaluate aspects of degraded lipids, particularly the omega 3 and omega 6 fatty acids, by oxidation. These are probably later-stage markers of biological rancidity than the 8OHdG, but they also measure a different part of the process. They measure membrane-bound lipid oxidation. We should look at a variety of ways of influencing oxidative stress by measuring the potential biomarkers of radical induced damage.

Lipid peroxides are more modifiable than 80HdG using vitamin E, vitamin C, and carotenoids. We may be looking at different processes that have different nutrient protection. That is why we argue about a complement of various redox-active nutrients in patients who have different risk factors of oxidative stress and inflammation. No single nutrient at high dose can cover all these bases because of the various ongoing mechanisms. An analytical approach toward measuring biomarkers of oxidative stress is discussed in an article in *Current Opinion in Clinical Nutrition and Metabolic Care*.

Total Antioxidant Capacity as a Tool to Assess Redox Status

Another way to evaluate antioxidant status that buttresses against oxidative stress is to measure total antioxidant capacity, the oxygen reducing absorbent capacity (ORAC). This is a way to examine the reserves of antioxidants in biological fluid. This plasma analysis can be used to evaluate the relative defense that resides in the plasma. It could be tissue proteins like tissue total protein albumen, glutathione, or an array of antioxidants that are bound to lipoproteins in the plasma. These substances together give rise to resistance to oxidation.

I emphasize that in this case we are measuring extracellular antioxidant potential, which we believe, has some clinical relationship to intracellular antioxidants, although it is not the same. Using ORAC or total antioxidant capacity measurement as a tool to assess redox status has some value, but it is a secondary, not a primary, assessment of what goes on in the cell. What one really would like to know is what the intracellular redox potential is. A good review article on the use of total antioxidant capacity as a tool to assess redox status appeared in *Free Radical Biology & Medicine* titled. This article, titled "Total Antioxidant Capacity as a Tool to Assess Redox Status: Critical View and Experimental Data," describes

the strengths and weaknesses of this measurement.

The theme of this discussion is that no single test measures all aspects of oxidative stress and its relationship to senescence. By pulling together various tools, including clinical observations, signs and symptoms, and some of these biomarkers, we start to develop a much better ability to evaluate the gene/phenotype relationship.

The Salicylate Challenge Test

A test frequently used to measure physiological stress or oxidative propensity is the salicylate challenge test. In this test, standard dose salicylate is given to a patient. The urine can then be examined for the salicylate metabolites. Specific metabolites of salicylate are trapping agents for oxidants, particularly hydroxyl radical, the most promiscuous of the oxidants. High concentration of 2,3-dihydroxybenzoic acid (2,3-DHB) in the urine or plasma indicates increased hydroxyl radical trapping. In this case, it is as though salicylic acid is being used as an antioxidant trap for hydroxyl to produce higher levels of 2,3-DHB. A number of laboratories now use this method. This is another test for evaluating the production rate of oxidants in the body.

We have total antioxidant capacity to look at its reserve of antioxidant potential trapping. We have the salicylate challenge to look at the rate of production of radicals. We have the 8OHdG analysis for looking at the rate of damage downstream by radicals of DNA. And we have the lipid peroxide analysis and the hydroxynonenal to look at oxidized lipids and membrane degradation. Pulling these tools together gives us molecular biomarkers of oxidative relationships to the process of senescence.

I hope we have given you a sense of the reducible risk factors of aging. We will continue with this theme in the interest of promoting healthy aging and moving back to a classic model of medicine. We look forward to talking with you in April.

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