November 2001 Issue | Eugene R. Shippen, MD

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Welcome to *FMU* for November 2001. Throughout this year we have been working to improve our understanding of the etiology and mechanisms that contribute to age-related chronic degenerative diseases. Part of our anti-senescence program has been to understand the possibility of ameliorating the course of events we see as aging. We frequently view disease as a natural part of aging. When one searches the literature, however, few articles appear that indicate disease is an inevitable consequence of aging. In fact, contrary to our usual assumption, the literature suggests that from mid-life on, the major causes of morbidity, which are the chronic degenerative diseases, result from a complex interaction of our genes with our environment to give rise to our phenotype.

The outcomes we call disease are, in fact, modifiable based on the environment. This results in a much more flexible, plastic, or modifiable relationship between age and disease than the deterministic model. That earlier model may be a legacy from the Mendelian period of genetics, which indicates that once you've got it in your genes, your phenotype is fixed and there's little you can do about it. We now recognize that although medicine is built on this deterministic model, it doesn't match contemporary thought about the etiology of chronic age-related degenerative diseases.

In pursuing this theme, we return to examine the concept of hormone balance—the messages that create the outcome at the cellular level, giving rise to tissue and then organ system function. These are the messenger molecules that affect gene expression, including the steroid hormone family. We have talked at length in *FMU* about the role of female sex steroid hormones—progesterone, estrogen, and estrogen metabolites—on cell signaling, cell cycling and genetic expression, and the ultimate risk of dysfunction or chronic degenerative disease that can result from imbalance of these messenger molecules.

This month we will focus on male hormones, the androgenic part of the hormone equation. This does not mean to imply that women don't have androgen molecules. They do, and those molecules are very important. The testosterone family is an important part of the balance in female physiology, but generally are presentin much smaller concentrations than observed in males.

Modifiable Risk Factors for Unhealthy Aging

This month's Clinician of the Month will give us some good clinical insight and news to use in this area, some information that may be quite different from the way you have viewed testosterone in the male. We also are going to relate the concept of endocrine balance and messenger molecules to preventing loss of

function. Loss of function is often a precursor marker to disease. Functional impairment can result in either physiological dysfunction or situations that could be life-threatening, such as falls or automobile accidents. We are going to focus on maintaining one of the important biomarkers of aging, muscle mass and lean body composition, which is a critical area of modifiable risk of disorders of aging.

The March issue of *FMU* featured a COM interview with Bill Evans, MD, an exercise physiologist who had worked with nonagenarian men who were disabled and unable to walk independently. He put them on a strength conditioning program, as reported in *JAMA* in 1990, and found they increased their mean average strength significantly.[i] For most of these individuals it meant the difference between sitting or walking with a walker, and walking independently.

Lean Body Mass and Disease Risk

In the December 2000 issue of *FMU*, we had a discussion with Dr. Don Hayes about biomarkers of aging. We talked about how these particular relationships of aging work together to give rise to the lowered function we often see in individuals. By measuring body composition and phase angle, using impedance measurements, we are able to determine some of the relative risks and a biomarker for aging. A patient could use this as a marker for improvement to track his or her own performance.

In August of 2001, we interviewed Dr. Kursheed Jeejeebhoy, who talked to us about aspects of body composition and lean body mass, and how that interrelates with physiological function ranging from immune function to insulin management, glucose management, and other aspects of aerobic competency. Maintenance of muscle mass and lean body composition, which seems to decline with aging, is a major part of the discussion of biomarkers of aging. Is decline in muscle mass a natural consequence of aging, or does it result from environmental determinants working on genetic patterns to give rise to this loss of function associated with degenerative disease risk?

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Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-intensity strength training in nonagenarians. Effects on skeletal muscle. *JAMA.*1990;263(22):3029-3034.
Let me first talk about some pioneering work that has led to the emergence of functional medicine out of a medicine based on pathophysiology. Many pioneers, both men and women, have been involved with the development of this conceptual thought. At first it seems obvious that we would want to focus on function rather than just on end-organ failure. When we get to the deeper meaning of functional medicine, however, we recognize that many factors have contributed to the intellectual domain that differentiates functional medicine from histopathology-based medical taxonomy. One of the pioneering members of this intellectual community is Dr. Karl Folkers.

Dr. Folkers passed away in 1997 at the age of 91. For six decades or longer he contributed to our fundamental understanding of nutrition and its relationship to function. His history is almost like a mosaic of the 20th century and the advancing understanding of medicine. Early on, he did work describing the roles of vitamin B6 in various biochemical transformations. That research ultimately led him, as an organic chemist, to the synthesis of vitamin B6. While at Merck, he obtained the original patents on the synthesis of vitamin B6. Not only did he determine the structure of pyridoxine, but also its synthesis. From 1940 on, he pursued studies looking at the effect of vitamin B6 in its purified form on a variety of physiological functions that now appear in

every nutritional and medical textbook. He was an early contributor to our understanding of functional nutrition and the role of pyridoxine as a cofactor in enzymatic processes.

B-Vitamin Research

In the 1940s Dr. Folkers carried on research with vitamin B12. He was one of the first to determine how vitamin B12 worked once he had successfully purified and crystallized it. He studied how vitamin B12, vitamin B6, and later folic acid, work together to support physiological function. Anti-pernicious anemia factor, in other words, originated with the work Dr. Folkers did with vitamin B12.

He later extended his work into other areas of the B-vitamin family. He looked at the functional aspects and was able, as a very good chemist, to purify the compounds that would allow detailed and very specific tests to be done. In the mid- to late 1940s and early 1950s, Dr. Folkers started to work with Dr. Roger Williams at the University of Texas. Dr. Williams, as we know, is credited with originating the concept of biochemical individuality and the genetotrophic theory of disease.

Dr. Roger Williams and the Concept of Genetotrophic Disease Concept

Dr. Williams believed that when individuals don't get adequate levels of specific nutrients in their diet they experience diseases of previously unknown origin. These diseases do not present as frank vitamin deficiency diseases like scurvy, beri beri, pellagra, xerophthalmia, and rickets. They are more commonly the chronic diseases, including heart disease, diabetes, schizophrenia, behavioral disorders, and allergies. Dr. Williams referred to these as the genetotrophic diseases. They are associated with the mismatch of the genes and with the existence of a diet inappropriate for the particular individual. It was a remarkable concept to be advanced in 1950. Only now, in 2001, is medicine beginning to appreciate this early pioneering concept of genetotrophic disease.

Dr. Folkers was intrigued by this concept and conducted basic metabolic research looking at the role of nutrients in intermediary metabolism and how that may relate to the concept of biochemical individuality. Through this kind of work, in the 1960s he pioneered research with coenzyme Q10, or ubiquinone, a substance he was the first to synthesize. He began to examine its activity in human physiology. Early on he was so convinced of its importance in physiological function, that he felt it to be a vitamin.

Coenzyme Q_{10} Research

He and a young collaborator, Dr. Robert Olson, now from the Department of Pediatrics at the University of South Florida College of Medicine, undertook studies to investigate CoQ_{10} as a vitamin and did specific studies in animals to examine whether it was or was not, in fact, essential, for the growth and development of the animal. They concluded from their work that CoQ_{10} was not an essential nutrient. They went on to try to determine how it was biosynthesized in animal physiology, reporting the initial findings in 1959, and a full paper in 1960, on the biosynthesis of coenzyme Q_{10}.

This research occurred well before the concept of conditionally essential nutrients evolved. We

have what I call the fabulous 50 essential nutrients—vitamins A through K and the minerals . Basic mammalian function requires an array of micronutrients, along with water, essential amino acids, and essential fatty acids to develop and function. Beyond that, however, in the past 20 years scientists have discovered that a number of other substances (coenzyme Q_{10}, for example) may, in specific cases and for specific individuals, be necessary for function at levels beyond which they can biosynthesize it.

Conditionally Essential Nutrients

These nutrients, while not traditionally considered essential, may become essential for a particular individual because of his or her condition, environment, or genetic state. That important concept is closely related to what Dr. Linus Pauling referred to as orthomolecular medicine, maximizing the orthomolecular milieu of the individual to promote optimal physiological function. Under certain environmental circumstances, stress factors, infection, or genetic uniqueness, one may require higher levels of a specific substance beyond what he or she can biosynthesize for optimal function.

Vitamin C

Dr. Pauling used vitamin C as an example to support this contention. Millennia ago, through evolution, humans lost the enzyme L- gulonolactone oxidase**,** an enzyme involved in the conversion of glucose to vitamin C. We still, however, have times when we require an increased need for vitamin C . The inability to synthesize ascorbic acid means we require an exogenous source.

Dr. Pauling studied animals, like the goat, which have a body mass similar to that of a human but maintain the ability to synthesize vitamin C. He found that when a goat is under stress, it can synthesize 10 times the amount of vitamin C it would produce under normal conditions. Because we humans cannot synthesize vitamin C at all, we are obviously unable to increase that synthesis rate. Despite this evolutionary loss we humans continue to have varying needs for vitamin C under varying environmental circumstances. Although vitamin C is considered an essential nutrient, it may be conditionally essential in varying amounts, depending on circumstances. An individual who is exposed to drugs, alcohol, environmental pollutants, stress factors, or infection, for example, may require increased amounts of vitamin C

Dr. Williams and Dr. Folkers had a very strong intellectual relationship. Dr. Folkers, who was working on the biosynthesis of coenzyme Q_{10}, realized there may be certain aspects of the biosynthesis of coenzyme Q_{10} that are not as efficient in some individuals as others. This realization once again combines biochemical research and the concept of biochemical individuality. At that point he decided to pursue his CoQ_{10} issue much more extensively. In 1963, he resigned his position as vice-president of exploratory research at Merck and accepted a position as president and CEO at the Stanford Research Institute (SRI) to study CoQ_{10} and its functional role in mitochondrial oxidative phosphorylation.

In 1968, he resigned his appointment at SRI to become professor of chemistry and director of a newly created institute for biomedical research at the University of Texas. There he joined Dr.

Williams to form an extraordinary brain trust. At that point, he focused his attention extensively on the clinical and therapeutic value of coenzyme Q_{10}.

Taking an Alternative Path

Up to that point Dr. Folkers had followed a traditional path in academic medicine, through publishing, and presentation to his colleagues. He stayed within the guild, so to speak. When he returned to the University of Texas and focused in on CoQ_{10}, he took a different path. Focusing one's attention on the therapeutic potential of a substance that issynthesized by humans was not generally accepted by his colleagues as something academic professors of biochemistry should be doing. It sounded a bit like nutritional supplementation, which they generally disregarded.

Suddenly, therefore, the focus of his research was cast in a different light. Even though he published some 300 papers on CoQ_{10} over the next 20 years, their reception in the scientific literature and the scientific community was entirely different from his traditional work on vitamin B6 and B12.

Peer Reviews

A recent biography of Dr. Folkers appeared in the *Journal of Nutrition.* Following three pages describing his extraordinary research up until 1968 when he took on the position at Texas and started to focus on CoQ10, the article contained the following comment:

"Unfortunately, many of his ventures in this area (i.e., CoQ10) were with unsophisticated physicians who did not have a critical attitude toward clinical investigations; this work, comprising some 300 papers, has not in general been accepted by the medical profession."[i]

Focus on Function

That quote provides an interesting insight into the guild and its attitude toward the development of new concepts. Dr. Folkers stepped out into a new model, moving away from pathology and pernicious anemia, to embrace function. He was studying the variability in the requirements for a specific substance that individuals normally synthesize, which could be necessary for optimal function and the prevention of age-related chronic disease. Breaking ranks with the old model and beginning to challenge its assumptions can lead to alienation.

> [i] Olson RE. Karl August Folkers (1906-1997). *J Nutrition.* 2001;131:1117-2001.
> We are moving into a new genomics era, defining disease in different ways. This may create an environment in which people like Drs. Folkers, Pauling, Williams, and Hoffer are seen as visionaries, innovators, and people who achieved the breakthroughs necessary for understanding how disease is prevented and function is improved. According to a recent article in *Science* magazine, "The human genome sequence will dramatically alter how we define, prevent, and treat disease. As more and more genetic variations among individuals are discovered, there will be a rush to label many of these variations as disease-associated."

"We need to define the term disease so that it incorporates our expanding genetic knowledge, taking into account the possible risks and adverse consequences associated with certain genetic variations, while acknowledging that a definition of disease cannot be based solely on one genetic abnormality."

Functional Precursors of Disease

We need to focus on the functional aspects of disease that may result from these genetic differences we are describing. We should be very cautious about socially politicizing the genome project into disease entities, rather we should focus on the variation of function and environmental sensitivities.

"Disease is a fluid concept influenced by societal and cultural attitudes that change with time and in response to new scientific and medical discoveries." Even the term “diagnosis” can change as new techniques, tools, and technologies become available for evaluating aspects of human function and dysfunction. If all you have is the sense of taste, touch, sight, and sound to diagnosis, it will lead to a different type of disease nomenclature or declension than if you have CT-scans, MRIs, nuclear magnetic resonance, radioimmune assays, and the like.

A Different View of Disease

The definition of disease changes with our view of it. Our view of pathology has changed as we have gained more of these tools. One of the disciplines in medicine that is most focused on functional medicine, ironically, is radiology. New technologies in radiology are facilitating assessment of the functions of the body, not just the presence of tissue pathology.

"Historically, doctors defined a disease according to a cluster of symptoms. As their clinical descriptions became more sophisticated, they started to classify diseases into separate groups, and from this medical taxonomy came new insights into disease etiology." Only recently has the etiological underpinning of chronic age-related diseases begun to be understood and dissected at the fundamental mechanistic level.

Genetic Abnormalities as Diseases

As an example, let’s consider what happens when we label someone as diseased who has some genetic uniqueness. "Irrespective of disease symptoms, the label itself may lead to significant distress." Individuals with asymptomatic conditions, when told they have a genetic uniqueness implying disease, may feel it is a very negative stigma. Human genome sequencing will reveal many single nucleotide polymorphisms, distributed among some 30- 60,000 genes as well as non-coding regions. Translating such genotypic differences into phenotypic states, i.e. visible characteristics and disease attitude, is prone to pitfalls.

Genetic abnormalities differ in their penetration; not everyone carrying a particular geneticvariation experiences an adverse consequence. It depends on the environment into

which the individual plunges his or her genes—including lifestyle, environmental factors, and nutritional factors. We now know that many diseases have complex etiologies that depend on a number of different genes working in combination. Single-point genes are not as important as the interaction between different families of genes. "Automatic genetic sequencing is becoming increasingly sophisticated, but distinguishing between normal variation in genes (polymorphisms) and alterations that are detrimental (mutations) remains extremely difficult."[i]Understanding the difference between the two is still in the early stages.

We need to be cautious not to label a genetic variant as a disease. We should refer to them, as Dr. Williams taught us, in terms of biochemical individuality, different susceptibilities and strengths, and uniqueness. This different way of categorizing the new medicine does not rely on medical taxonomy, histopathology, and a pathology-based diagnostic marker.

Gilbert's Disease

Some conditions we might consider benign also have polymorphisms that may produce symptoms but have not been associated with an acute pathology. Gilbert's disease is an example. Polymorphisms of the UDP glucuronosyl transferase enzymes are associated with the transference of glucuronic acid to bilirubin to produce a detoxified and ultimately excretable bilirubin byproduct. When an individual with Gilbert's disease is under stress, he or she may turn orange or yellow as a consequence of the inability to properly glucuronidate bile.

Because no pathology occurs as a consequence of this jaundice-like condition, we have referred to it as a benign condition associated with polymorphism of UDP glucuronosyl transferase enzymes. In traditional medical thought, since the condition is benign and has no adverse effects, patients are advised just to live with it, disregarding the fact that under stress they continue to turn orange. If we look at this fundamental premise from a different perspective, however, we may come up with a new way of assessing this particular association.

New Answers from Changing Perspective

The individual with the polymorphism for inadequate glucuronidation of bile may also be a poor glucuronidator of other endogenous or exogenous substances, which if not properly glucuronidated, can lead to increased toxicity. This is a different way of viewing the future of medicine. Although an immediate pathology may not be evident from this particular genomic uniqueness, it may serve as an indicator. Decades of living and being exposed to the same substances that for a person without Gilbert's uniqueness are benign may produce untoward effects in one with Gilbert's. He or she may experience toxicity, immunotoxicity, neurotoxicity, or some other damaging effect from that endogenous or exogenous toxin that he or she was unable to detoxify adequately.

Support for that model appeared in the journal *Gastroenterology* in 1992.[ii] Researchers examined a group of Gilbert's patients with varying degrees of UDP

glucuronoysyltransferase insufficiency. This genetic uniqueness does not result from a single gene. It is a multigene condition with degrees of variability. They looked at individuals with mild to severe Gilbert's, again assuming it to be a benign condition.

Detoxification Irregularities Beyond Gilbert's

The researchers wanted to know not simply how these patients detoxify bile, but how they detoxify other substances that require glucuronidation. In this specific case, they looked at acetaminophen, or paracetamol, which also requires glucuronidation for its elimination. In an acetaminophen challenge, they found that individuals with Gilbert's uniquenesses, these polymorphisms, were defective in their ability to detoxify acetaminophen as well as bile. This was only demonstrable within the first two hours following intravenous injection of acetaminophen when decreased plasma levels of acetaminophen glucuronide were observed. There was no difference when urinary recovery was determined after twenty-four hours. They concluded that Gilbert's may not be altogether benign in terms of future toxic exposures. Gilbert's sufferers might be more susceptible to the adverse effects of both endogenous and exogenous toxins.

This example demonstrates the difference between pathology-based medicine and functional medicine, the medicine of post-genomics. Functional medicine will be the new model as proteomics translates gene expression into physiological function. You may wish to counsel a person with the clinical symptoms or history of Gilbert's about exposure to specific toxins. That individual may not want to work in an environment that would expose him or her to substances that could require more glucuronidation. The Gilbert's individual may want to be given the appropriate support to enhance glucuronidation at the physiological level by proper nutritional intake, or perhaps, in the future, with medications that would support glucuronidation.

UDP Glucuronosyltransferase and Carcinogenicity

This same theme has been demonstrated by using a bacterial expression system to evaluate the genotoxicity of activated amines. A recent issue of the journal *Carcinogenesis* contained a paper titled "The Contribution of UDP-Glucuronosyltransferase 1A9 [one of the isoforms of UDP glucuronsyltransferase] on CYP1A2-Mediated Genotoxicity by Aromatic and Heterocyclic Amines."[iii] The results of this study, conducted under very controlled conditions, indicate that this polymorphism that may be associated with conditions like Gilbert's can control the outcome of a genotoxic response.

The results indicate that while a potential toxicant can serve as substrate for glucuronidation, the capacity of the detoxification pathway may be insufficient to prevent a mutagenic or carcinogenic phenomenon or outcome. Therefore, an individual with a poor glucuronidation phenotype as determined by his or her detox genotype, may be at much higher risk, in this case, of mutagenicity or carcinogenicity. We might want to redefine "benign" when we talk about Gilbert's when we are looking at it from a functional perspective.

This is just one example of many that demonstrate the differences between histopathology-based medicine, which is built around differential diagnosis and medical taxonomy, and a functionally based medicine, which is built around the etiologies of disease that relate genotype to phenotype through environmental relationships.

[i] Temple LK, McLeod RS, Gallinger S, Wright JG. Defining disease in the genomics era. *Science.* 2001;293:807-808.[ii] DeMorais SM, Uetrecht JP, Wells PG. Decreased glucuronidation and increased bioactivation of acetaminophen in Gilbert's syndrome. *Gastroenterol.* 1992;102:577-586.

[iii] Yueh MF, Nguyen N, Famourzadeh M, et al. The contribution of UDP-glucuronosyltransferase 1A9 on CYP1A2-mediated genotoxicity by aromatic and heterocyclic amines. *Carcinogenesis.* 2001;22(6):943-950

INTERVIEW TRANSCRIPT

Eugene R. Shippen, MD

9 East Lancaster Avenue
Reading, PA 19607
(SR--Double-check address

Welcome to the Clinician of the Month interview in this month's issue of Functional Medicine Update. Our guest, Eugene Shippen, MD, is a long-time colleague and friend, as well as a leader in our field. Dr. Shippen is an internist from Reading, Pennsylvania, who has been in the field of nutritional medicine and on the cutting edge of functional medicine for more than 25 years. He is the author of the recent book titled The Testosterone Syndrome, and a well-known specialist in hormone replacement therapy, the focus of today's interview. This area has great implications for rectangularizing survival curves, compressing morbidity, and improving the health span of individuals.

Testosterone is a molecule that has received mixed reviews in the literature. As an important part of male vitality and female libido, it has positive benefit. On the other hand, the suggestion has been made that men's high testosterone levels may increase their risk of heart disease and prostate cancer and may explain why many men live shorter lives than women. Anti-testosterone drugs, such as estrogen, have been used without success in an attempt to help prevent heart disease in men. The testosterone issue has been a growing area of confusion and controversy. Dr. Shippen has sorted facts from fiction and helped us understand this complex molecule.

Testosterone and Heart Disease

JB: Eugene, it's wonderful to have you as a member of the Functional Medicine Update family. I would like to begin by asking you about testosterone and heart disease. That controversial area has led some people to believe testosterone is the cause of heart disease in males and increasing heart disease in women. Your work and your book tell a different story.

ES: When I started writing the book and began my research, I found that in some of the oldest literature

published, going back to 1946 when testosterone was first used, improvements in cardiovascular disease were shown. In 1946, an article was published n the Journal of Endocrinology on 100 patients with angina pectoris. They were administered testosterone by injection, and 91 of the 100 patients with angina had improvement, 51 of them markedly so. There were seven placebo controls, all of whom later responded to testosterone. Ten other studies were reviewed at that time, showing similar results. With that kind of start, you might think this was going to be the new treatment for cardiovascular disease. Here we are in the year 2001, however, and I challenge you to find any cardiologist in the country who is apt to do a testosterone level measurement in one of his cardiac patients.

Research in the interim has produced a steady number of articles supportive of the whole mechanism of coronary artery disease and plaque rupture, from the pathophysiology that has been proposed with lipid abnormalities, to the clotting factors, to the proinflammatory factors, and to things like nitric oxide production. Every facet has positive effects between testosterone, or deficiency in testosterone, and the rising increase in the various risk factors as we know them.

Testosterone and Male Health

JB: What you have just said reflects a view that probably differs from the way practitioners currently feel about testosterone. Where did we go wrong? What is the sequence of events that led us to such thinking about testosterone and male health?

ES: I'm not sure. From the 1940s to the 1950s, testosterone never got its fair shake, perhaps because it was a new hormone, and people were hesitant to deal with it. Once it began to be overutilized by athletes who abused steroids, such as high doses of cortisone, which had adverse side effects, steroids in general became anathema to treatment. With the lipid hypothesis that arose with Anitschkow and the people who studied lipids early on, lipids took over and no one would look at anything else.

We know the dismal history of the narrow focus that's been given inappropriately to cholesterol. That's dominated the scene for many years because of the bad effects perhaps of the synthetic analogs of testosterone and high-dosage depressing HDL, causing increases in blood pressure and hypertrophy of the myocardium, and in fact inducing some heart attacks. That perhaps created reticence to use testosterone in people with cardiovascular disease.

Testosterone and Testosterone Analogs

JB: You just indicated that testosterone analogs are used today under the guise of testosterone, as opposed to natural or nature-equivalent testosterone. This resembles the case of progesterone versus Depo-Provera®. Is there literature that shows a difference in the physiology between the analogs of testosterone and testosterone itself?

ES: You're right on target, Jeff. It's what we've learned from the Prempro™ studies, which had already been demonstrated in the primate model. They do not have a primate model for testosterone, although they're now doing rabbit studies, castrating them and inducing plaque formation just by reducing testosterone. In reference to the analogs, whenever you have a hormone that is an analog, it is metabolized through normal pathways. You then get excessive hormone stimulation through the receptors, or you get some liver effects or fluid retention effects that are not part of the normal metabolic

pathways and processing of hormones that are natural to us.

Testosterone is really a prohormone, so it has its beneficial effects by being converted both into estrogen and into dihydrotestosterone. Dihydrotestosterone is known as the “bad one” because it causes enlargement of the prostate. Now they’ve found that if you give just dihydrotestosterone, the prostate shrinks, so estrogen seems to be the culprit, or at least an imbalance in the hormones. When you give an analog that has side chains, it can’t be switched into estrogen or into dihydrotestosterone. It has a life of its own that doesn’t follow a natural metabolic pathway, and it’s just common sense that these will be hormones that have specific effects that are out of the natural control. So you run into the problems they did with Prempro™.

Effects of Natural Testosterone

JB: Let’s look at the literature as you’ve reviewed it, on the effect of nature-equivalent testosterone on things like lipids, clotting factors, endothelial relaxing factor, and nitric oxide. It sounds to me, from what you found, that the real testosterone has a different effect than the synthetic on each of those factors.

ES: It’s interesting that in some studies, for example, testosterone is given and then a blocker of aromatase, the enzyme that converts testosterone into estrogen. Some of the beneficial effects, particularly on vasodilation and nitric oxide (that is vascular nitric oxide, the endothelial nitric oxide), are inhibited. Testosterone does have some effects on nitric oxide synthetase itself, but the estrogen conversion seems to be one in the coronary arteries that’s significant. It’s important that those testosterone molecules have the ability to be aromatized in the endothelium, but when you have endothelial dysfunction from a sick milieu of the arterial wall, you get less aromatization locally and less vasodilation. Hence, you’ve got to take your own nitric oxide in the form of nitroglycerin to get vasodilation.

The pathways that spin off of testosterone from clotting factors and proinflammatory factors are even more interesting. Everyone talks about nitric oxide inducing the inducible nitric oxide pathway, which is proinflammatory. If we give testosterone, are we going to activate the proinflammatory pathway and then induce C-reactive protein and the cascade of prostaglandins and interleukins? Indeed, testosterone reduces inflammatory pathways, which is why it’s been useful in arthritis. Some of the old literature on arthritis says that testosterone is great for rheumatoid arthritis or inflammatory arthritis, and indeed, it’s good for the inflammatory cascade, which occurs within the plaque that induces plaque instability.

Affecting the Interactions of Molecules

JB: As the old literature gives way to the new literature, we discover we don’t really learn much that’s new. We simply learn old things in new ways. It appears that what is emerging is something about an interrelationship in metabolism of these androgenic and estrogenic molecules in males in different tissues that give rise to balance and function. Perhaps what we’ve done is to intervene synthetically at different parts of this pathway to get a specific endpoint, but we haven’t looked at the interactions of these molecules, one to the other.

ES: One of the areas I talk about in the book is the balance of the transformation of testosterone into estrogen, or testosterone into dihydrotestosterone. One of the things that does happen (men don’t like to

hear this) is that estrogen is actually a far more powerful hormone than testosterone. The transformation from testosterone into estrogen is very critical. If you get powerful increasing of estrogen, the body has ways of downregulating the hormone pathways and the receptors, so that high estrogen states in men are not good.

You intimated they have already done some studies of giving estrogen, with disastrous results. We knew from the estrogen treatment of prostate cancer that there was an increased cardiovascular thrombotic risk. Still, the balance needs to be there. We need some estrogen. What goes wrong? We start to get obese. We get syndrome X. We get central obesity. The central obese cells have a high aromatase level.

Measuring Hormone Levels

Interestingly, we have learned that aromatase is activated by the proinflammatory cytokines, which are generated in the fat cells. You get a self-increasing level of aromatase activity and estrogen in men with syndrome X, whereas men who are lean are at lower risk. Those who have lean body mass without the central obesity are the people who live longer. The waist-to-hip ratio theory fits with the imbalance of estrogen to testosterone. I measure estrogen and testosterone in all my male patients. It's surprising. Sometimes the estrogen is high and the testosterone is low. If they're both low, then they have so much deficiency, they don't even make estrogen. These men are in trouble from lack of nitric oxide production because they don't have enough even to make the basic positive factors.

The men with syndrome X have low testosterone suppressed by too much estrogen. This balance concept is very interesting. It's different in every man.

The Role of DHEA

JB:Many men take dehydroepiandrosterone (DHEA), either by self-supplementing or under recommendations from their physicians. DHEA, as we know, is part of the androgenic precursor molecules. From your experience, what role, if any, does DHEA play in this balance?

ES: If you look at the pathway, DHEA goes basically down into estrone. In males, the major byproduct of DHEA is estrone. If you give DHEA to someone with syndrome X, and he's got a lot of aromatase, he's going to make more estrogen. One of the side effects from DHEA is weight gain. In someone who's lean and mean (they need a little estrogen), DHEA is very effective. It's needed for libido; it's needed for bone density.

In women, however, DHEA is converted into a major source of testosterone. Researchers are now doing interesting studies about DHEA, speculating that it may be one of the better ways of replacing hormones for women because it provides a natural supply of estrone, weaker estrogen, and testosterone. In men, however, it provides mostly estrone, which men need, but if you have excess estrogen, you'll find it's going to get worse with DHEA supplementation unless you can correct the pathophysiology by reducing aromatase activity.

Clinical Testosterone Administration

JB: We know now that when testosterone is administered to individuals, it is not well absorbed. It is first-

pass detoxified in the liver and thus has no clinical benefit. What is the clinical approach for administering testosterone?

ES: The testicles produce testosterone, and the highest concentration of testosterone goes through the spermatic vein into the plexus of veins at the base of the penis. Also, there is a source of testosterone through the tubule that carries the sperm, so your spermatic duct actually has very high levels of testosterone, which are sustaining the sperm. How many men get erectile dysfunction when you interfere with the pathway by cutting that spermatic duct?Many people claim it doesn't happen, but Carruthers in England indicates it does. And my own experience with a lot of men with vasectomies is that they start to get erectile dysfunction, even though their testosterone levels are relatively normal.

This concentration of testosterone in the pelvis is much higher than it is systemically. The reason I'm saying this before I talk about replacement is that when you go to topical replacement on the skin, you may get nice blood levels, but that pelvic area may not be getting the same relatively high concentrations that one would when producing it normally. I like to get the testicles to make their own testosterone as long as they will, so I talk about giving chorionic gonadotrophin to stimulate the testicle to make its own testosterone, which will bathe the pelvic organs in a higher level of testosterone before it goes out systemically.

Testosterone Replacement

I choose testosterone replacement last, and boosting first. Studies have shown you lose effectiveness of chorionic gonadotrophin with each decade. But I find that some men in their 60s and 70s still have plenty of reserve and respond nicely to chorionic gonadotrophin two to three times a week. That's one way of boosting. Obviously, there are many forms now, from topical gels to creams that pharmacies can make up, pellets that can be implanted under the skin, all of which bypass the liver first-pass defense and allow a sustained application of testosterone. But it doesn't concentrate in the pelvis.

I've found a lot of men who take transdermal forms of testosterone, or even the pellets, need a small amount topically to the penis and scrotal area to concentrate, much as the testicles would, when we're doing replacement. That's not really needed with the chorionic.

Testosterone Therapy and Cardiovascular Disease

JB: You present some wonderful case histories in your book. Tell us how this approach works with men who have the symptoms of cardiovascular disease.

ES: I generally get good to excellent results in men who have stable coronary artery disease. Where you have to be careful is with an aging man who has congestive heart failure, borderline heart failure, or perhaps very weak myocardium. You will get some fluid retention from any of the steroids. In healthy people, our kidneys take care of it and it's not really observable. If you jump in with full replacement in someone whose kidneys are aging, whose GFR is down, and whose heart is a little flabby and can't use all the testosterone, you can certainly induce fluid retention and congestive heart failure.

I would warn anyone whose patients include elderly males to tiptoe in with small doses or allow the patient to gain some anabolic strength over a period of months before you get up to full replacement

doses. Younger guys respond very quickly to full replacement doses.

Therapeutic Ranges of Testosterone Replacement

JB: What is the range you generally employ for replacement?

ES: The endocrinologists are saying we shouldn't go more than 700. If your level is still in the normal range, if it's 500, you're fine. The replacement studies done with the patch indicate that if you don't replace levels up to 500, if you keep your level below 500 total, (we're not talking about the free testosterone, which is a slightly different issue), bone density continued to lose ground up to 500. In the 500 to 700 range, bone density was neutral. In other words, there is no bone loss. Above 700, there was a positive bone density response. I use that in my thinking in general. There are some healthy men with lower testosterone at 500 who are fine. In your treatment, when the cup is full, adding more testosterone doesn't help. I tell people that if they take higher levels and don't feel any better within a reasonable length of time, they don't need that much. In general, I shoot for levels of 700 or higher in the aging men, and you'll see that you get better responses in general. But as you get to 700 and higher, you'll get higher estrogen conversion, so you have to be more aware of the balance.

Testosterone and Cardiovascular Disease: A Case History

JB: You described one interesting case history in your book having to do with giving testosterone to a person with a cardiovascular disorder. Some people might find that counter-intuitive. Would you tell us about that?

ES: Henry has now been on testosterone for about five years. He's about 85. We started him when he was 79 or 80. I put pellets in him. He had stable cardiovascular disease and immediately had a positive response, which I write about in the book. He went down and kicked all the seniors on the golf circuit in Florida over the winter. He was 80 and playing the guys who were 60. I know from playing with Henry and being beaten by him when he was 80, that he's a good player.

When his testosterone was down, however, his cardiovascular disease symptoms (shortness of breath, mild angina) resulted in his not being able to finish 18 holes with his usual level of play. When we would replace his hormone, he would immediately improve in all those factors. As he's gotten older, now when his testosterone declines, he starts to get congestive heart failure. So, he's one in whom we maintain the level very carefully. When he's out of gas, he's in trouble and you have to replace it carefully. I've got him on a balanced regimen with a topical preparation with which we can now vary the dose. The pellets are a little too strong for him. Henry has a delicate balance. Too much and he gets into fluid retention; too little and he gets cardiac weakness and gets into cardiac decompensation. He's now 85. I played golf with him last week and darned if he didn't take a dollar out of my wallet. But thank God for Henry because he's my hero.

Testosterone and Prostate Cancer

JB: In using testosterone to improve cardiac function, people might start wondering what the tradeoff is. Is there risk of prostate cancer because testosterone and prostate cancer have been closely linked in the minds of many people? Would you discuss the theory that testosterone causes cancer through some kind

of cell cycling effect, or at least its metabolite DHD?

ES: The data on prostate cancer and testosterone are fascinating, and nobody has a firm handle on the subject. Life Extension magazine did a great review on 34 or 35 studies. Out of those, I think four or five studies showed a positive relationship between incidence of prostate cancer and testosterone. All the rest were neutral or negative. If you read them carefully, you'll see that the dihydrotestosterone, the most powerful testosterone, is associated with a larger number of those cancers that become aggressive and spread.

Testosterone, in the male in the tissue culture model, seems to maintain differentiation. It seems to maintain the androgen receptor activity. The androgen receptor and the genes activate the p53 self-destruct genetic network that we have within ourselves for causing apoptosis in cells that are transforming into abnormal cells. This is a normal mechanism. Maintaining adequate androgen receptor activity maintains the apoptosis mechanism.

The Importance of Diet

What we see, interestingly, is that the incidence of early prostate cancer, the little adenomas, or PIN, is the same in all cultures. If you take Japanese men (who have very little aggressive prostate cancer and in whom the death rate from prostate cancer is very low), and American men, and do blind biopsies, the number of incidental adenomas is the same. What happens in American men is that they get much more prostate cancer and die from it because it becomes more aggressive. This obviously has to do with diet. Green vegetables and phytochemicals certainly have an impact, but the idea that these early cancer transformations may in some way be augmented by testosterone has not been proven.

In a recent study in which they gave Proscar® to downregulate DHT, the “bad testosterone,” they found men with biopsy-proven PIN, or prostatic intraepithelial neoplasia. PIN, they believe, is an early transformation before it becomes cancer. They give half the group (about 80 men) Proscar®; half were controls. Of the Proscar® group, within a year, eight had developed prostate cancer. So, by removing DHT, I believe you remove the controlling factor that was maintaining self-differentiation and self destruction.

Testosterone Effects

In the tissue model also, testosterone may stop some cell cycle growth for a period of time. It may help to downregulate it so that some models show testosterone actually decreases this cyclical activation, and when you take it away, it disinhibits that and allows it to start multiplying without direction, without control. There are many indicators that maintaining testosterone may actually be preventive or, as I have seen, when prostate cancer arises, it arises in a more differentiated, easier-to-treat fashion. Every one of the individuals in whom I have seen prostate cancer arise (and it can arise when you’re treating it) has gone into easy remission (they’ve been highly hormone-sensitive). They don’t develop highly aggressive types of prostate cancer that are hard to treat.

Signs and Symptoms of Testosterone Need

JB: In the clinical use of testosterone, are there markers you look for in considering testosterone levels

and considering replacement? Are there clinical signs and symptoms? Is there an age threshold? What leads the clinician toward this potential exploration?

ES: The fingerprint of hormones is different for each person. This is where we get back to clinical medicine. Just as you have the biochemical individuality for nutrients, we have biochemical individuality for hormones. If I use my clinical judgement more than the laboratory values, I can have a man who has a testosterone of 700, which is clearly well up into the normal range, who has symptoms. He's already having erectile dysfunction, is tired, and so on. If you look at sex hormone binding globulin, sometimes if that's high, he has very little free testosterone. If you look at total testosterone, you get fooled very often. You need to look at free levels that are determined by measuring the calculation through sex hormone binding globulin, which is available at the lab.

Aside from that, as I intimated earlier, some men do very well with a testosterone of perhaps 350 or 400. They may have been that way all their lives. They're not symptomatic. They don't come in complaining of tiredness, erectile dysfunction, depression, and so on. As a clinician, I look for a pattern of symptoms—fatigue, depression, lack of initiative, sexual changes, decrease in libido, loss of muscle, prostate BPH symptoms (that's another subject). If they come in with a panorama of low testosterone symptoms, and their testosterone is X, I take it to Y and look for results. If the cup is full, filling the cup more will do no harm, but it will not result in an improvement. If they have a wide range of symptoms, it's worth giving them a clinical trial of testosterone, boosting or replacement.

Measuring Salivary Testosterone

JB: One area of laboratory assessment that is still controversial is salivary measures of hormones. Do you believe salivary testosterone measurements are of clinical use?

ES: For screening purposes, some studies indicate salivary levels may be a little better at showing the bioavailable levels at the tissue level. Once you start transdermal therapy, it throws the dynamics off enough that I don't trust salivary levels. In fact, if you give pellets, there may be also some changed dynamics. Anything that's away from your normal production may throw that off. I tend not to trust salivary levels, particularly if you're using transdermal replacement. But for screening purposes, I think it's an excellent, inexpensive way to monitor patients who are not being treated and for whom you just want a year-by-year measure of their hormone pattern.

Clinical Approach to Testosterone Management

JB: I know you conduct seminars educating physicians on this type of therapy. Could you provide a summary of the high points for clinicians to begin dealing with this area, recognizing its importance?

ES: When I first started, I did testing, I looked at symptoms, and I treated. And I got good results. That seemed initially to make me feel there was a great effect from testosterone. The longer I do it, the more I find there are a number of reasons for low testosterone—drugs people are taking, high estrogen levels, and a whole range of pituitary problems. First you diagnose, and then you treat. I don't care how old the patient is; you still need to do some diagnostic workup and find out whether the low testosterone is testicular or central.

I do teach about some tests in my conferences. They include trials with chorionic gonadotrophin to stimulate the testicle to see if it will still produce testosterone, which I still think is a better way for many men than replacement. For diagnosis, if somebody comes in with symptoms, do your diagnostic workup and find out with your best diagnostic capability if it's just an age-related decline or some kind of undiagnosable decline that you think is a male menopause thing. If it's clearly just a downregulation, find out your best way of treatment by either stimulating the testicles or replacing testosterone, and move on from there. The lesson I've learned is that more men benefit by boosting than by replacement. I get better results from giving some of the boosting factors.

Functional Endocrinology

JB: This interview has opened a new view of testosterone in male physiology and health. I urge our listeners to read your book, The Testosterone Syndrome, which has made a tremendous contribution to our understanding. It sounds to me that what we call functional endocrinology may be at the cutting edge of the whole area of healthy aging. You certainly opened a wonderful chapter in that discussion for us.

ES: It's all interlinked between the biochemical individuality of our nutritional system, our enzyme system, and our hormone system. They are intimately interrelated. In the year 2000 the Endocrine Society had the first consensus committee meeting on the male andropause. That tells you how far behind the times we are in looking at hormones for men as antiaging, age-modifying, or health-modifying factors. We are, however, at the doorstep of a functional hormonal or functional endocrine situation, much as you have with functional medicine through the nutritional and lifestyle pathways.

Praise for The Testosterone Syndrome

JB: Thank you. We wish you the best and we'll be back in touch soon.

Dr. Shippen's book, The Testosterone Syndrome, may be purchased at the bookstore on our website at www.functionalmedicine.org.

Following from Dr. Shippen's comments, I would like to go back and review the paper I described on side I of this month's *FMU*—"Basal Muscle Amino Acid Kinetics and protein Synthesis in Healthy Young and Older Men." Reduction in lean body mass also contributes to the potential development of a variety of age-related chronic diseases, including diabetes and osteoporosis, which may be related to cardiac function. As a general biomarker, sarcopenia may point to a number of different outcomes.

Numerous hypotheses have been suggested to explain why sarcopenia occurs with aging. Among these hypotheses are DNA damage, reduced protein synthesis, fiber type changes, inactivity, inadequate nutrition, and hormonal changes. It appears, as Dr. Shippen pointed out, that a combination of factors is probably responsible for these age-related changes that interrelate genetic susceptibilities, the circadian rhythms of aging, and our lifestyle and environment, to give rise what might be considered modifiable factors in aging. Certainly, Dr. Evans spoke to that with his concept of anaerobic and aerobic exercise in older men, showing improved strength and body mass index.

In the *JAMA* to which I referred above, the finding that contradicted earlier presumptions was that when they measured basal muscle protein and amino acid kinetics based on stable isotope techniques, they

found net muscle protein turnover does not appear to explain muscle loss that occurs with age. Therefore, there is no genetic program that prevents muscle protein from being synthesized in older individuals. Nor is it necessarily broken down more rapidly in older individuals. In fact, the results tended in the opposite direction—toward a higher protein synthesis rate in older men. This study indicates other variables may lead to sarcopenia.

Importance of Protein Stores

In a companion editorial in the same issue of *JAMA*, Drs. Roubenoff and Castaneda commented on sarcopenia, understanding the dynamics of this aging muscle as a gross biomarker for generalized risk for diseases of other age-related diseases.[i] They point out that protein stores are important for maintenance because, unlike fat, which is truly stored in the sense that it is reserved for times of starvation, body proteins are in use all the time as contractile proteins and muscle, antibodies, and enzymes. Therefore, if you have serum albumin as a reserve for essential amino acids, it can be catabolized and utilized for building up other proteins. This mechanism affects not only the structure but also the function of the body. Protein loss means loss of function.

Second, during illness nitrogen must be mobilized for muscle to provide amino acids to the immune system, liver, and other organs. Nitrogen is involved with gluconeogenesis in the liver to maintain proper blood sugar levels and provide support for the immune system. If adequate nitrogen cannot be provided for muscle, either endogenously or exogenously from the diet, the body's capacity to withstand an acute insult declines. Recovery and healing can be compromised.

Maintaining Muscle Mass

The determinants of sarcopenia are important. The results of this paper suggest they're not just under genetic control, but environmental factors also play a role. Dr. Evans explained the importance of proper exercise, which includes both resistance training or anaerobic exercise, and cardiovascular-building aerobic exercise.

According to this paper, however, we should also consider other factors in designing a program for the person to maintain or build muscle mass in older individuals who may at risk for protein-wasting conditions. These factors include providing the stimuli that aging muscle needs in order to become anabolic.

Promoting Anabolic Function

Dr. Shippen talked about some of these stimuli, which are the messenger molecules that help to promote anabolic function. Diet and exercise are also very important, perhaps because hormonal or immunological changes that occur with age no longer favor anabolism. The person is tipped into catabolic function as he or she would be with chronic inflammation, and upregulation of the stress genes occurs. We have to increase the anabolic messages to the genes in order to maintain equilibrium between rebuilding and breakdown.

One common thing that happens in aging individuals is that even if they don't gain weight, they develop a higher percentage of body fat, so the scale is not the sole determinant of sarcopenia. Covert Bailey

described this phenomenon more than 25 years ago in his “Fit or Fat” concept. You may look thin, but if you measure your body composition, you may find you have moved toward fat and away from muscle. Muscle is regained as a consequence of stimulating anabolic function, resynthesis, while accelerating catabolic breakdown of stored energy from triglycerides in body fat. There's a much more interesting concept of regulation of cellular physiology, functional aspects of the balance between anabolism (building back up) and catabolism, breaking down to form energy.

Diet and the Balance between Anabolism and Catabolism

In a 2000 study published in the *Journal of Clinical Endocrinology and Metabolism*, Volpe et al. found that response of muscle protein anabolism varied depending on the breakdown of the diet, and dietary protein and carbohydrate affected this anabolic function.[ii] Giving an individual a high sugar, as glucose, diet had a more catabolic response than providing a balanced amino acid and carbohydrate meal.

It is important to recognize that insulin may play a role in this process. Insulin resistance, glucose transport and regulation, mitochondrial function to produce fuel and the formation of ATP, all of these factors play a role. It comes back to what Dr. Jeejeebhoy recognized in his study looking at ATP recharge rate and synthesis at the mitochondria in muscle of older, undernourished individuals. It's seen as a decline in energy processing.

Combination of Factors Leading to Inflammation

Taken together, insulin resistance and activation of inflammatory factors from the immune system, such as these catabolic cytokines, acting in the postprandial state, appear to be an important cause of sarcopenia. Insufficient exercise, not enough potential anabolic hormone messenging, and catabolic signals that come from poor insulin and glucose control and poor immunological control can combine to move a person into an inflammatory state.

These observations also suggest that interventions aimed at treating or preventing sarcopenia should maximize the response of muscle to these anabolic stimuli, such as diet and exercise. This course of action is preferable to simply trying to increase basal protein synthesis by giving anabolic replacement agents as "anti-aging therapies" in the absence of diet and lifestyle modification. The latter may be impossible to achieve or require potentially harmful doses of anabolic agents, such as growth hormone, insulin-like growth factor-1 or testosterone. Diet, exercise, and lifestyle considerations may greatly reduce the need for these exogenous materials, enhance functional outcome, and decrease risk of adverse effects from the replacement therapy. The way we speak to the genes through lifestyle, diet, and environment plays a very important role in determining outcome.

Clinical Management of Sarcopenia

In dealing with sarcopenia in clinical practice, the practitioner can benefit by answering a number of questions. Are you measuring body mass? Are you measuring muscle mass?Are you measuring the effects of a specific treatment intervention over time? If you are not measuring it, you will never know. As Covert Bailey explained, a person may look fit enough until you measure his or her body mass index, look at phase angle, determine his or her intra- and extracellular fluid ratio related to muscle mass loss, and asses the patient’s general state of physiological vigilance.

We are doing a whole organism approach, which may seem simplistic. We're not using very sophisticated biochemical markers. We're not looking at mitochondrial oxidative stress. We're not looking at Krebs cycle intermediates. We're not examining specific aspects of biochemical energetics. We're not studying immunological markers such as cytokines. Nor are we measuring insulin and insulin determinants like glucose transport phenomena. This is looking at the whole organism and asking if the individual, for his or her age, has adequate muscle stores or is suffering from sarcopenia. If sarcopenia exists, it can be one biomarker to use in developing a program to build back anabolic function and reduce inflammatory and other catabolic processes that decrease biosynthetic rates of protein.

Integrating BMI Measurement into Practice

I encourage those of you not measuring body mass index as one gross determinant of aspects of physiological function to integrate BMI within your practice. It is truly in the scheme of things, a functional medicine based approach that differs from a histopathology-based differential diagnosis. We are looking at gross determinants of disease and how genes and environment can be modified in their expression to produce a more favorable outcome.

I hope you've received some news to use from this discussion and also recognize that we are at this extraordinary threshold of a change in how medicine will be practiced.

[i] Roubenoff R, Casteneda C. Sarcopenia--understanding the dynamics of aging muscle. *JAMA.* 2001;286(10):1230-1231.

[ii] Volpi E, Mittendorfer B, Rasmussen BB, Wolfe RR. The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. *J Clin Endocrinol Metab.* 2000;85(12):4481-4490.

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