October 2001 Issue | Richard Shames, MD

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Welcome to *Functional Medicine Update* for October 2001. This month's focus is on our continuing theme of promoting healthy aging and preventing premature diseases of aging, both of which are associated with appropriate application of functional medicine. Five years ago in *FMU* I predicted we would see the end of the phenomenon of managed care in the near future. A recent article in the *Journal of the American Medical Association* contained what I consider to be the obituary for managed care. That article, by James Robinson, PhD, from the School of Public Health, University of California, Berkeley, is titled "The End of Managed Care."[i]

According to Dr. Robinson, "The protagonists of managed care are now in full retreat. As we know, they are broadening physician panels, removing restrictions, and reverting to fee-for-service payments. Governmental entities are avoiding politically volatile initiatives to balance limited resources and unlimited expectations. By default, if not by design, the consumer is emerging as the locus of priority setting in health care. The shift to consumerism is driven by a widespread skepticism of governmental, corporate, and professional dominance; unprecedented economic prosperity that reduces social tolerance for interference with individual autonomy; and the Internet technology revolution, which broadens access to information and facilitates the mass customization of insurance and delivery."

Expensive, Unsafe Medications

We have seen an inflationary spiral in the cost of the healthcare system, especially in the cost of medications, in the past 10 years, despite the fact that the cost-effectiveness of many medications is being questioned. An article titled "Poisoned Pills? FDA Pulls Popular Prescription Drugs"[ii] discusses these questionable new drugs. It presents case histories of patients who had adverse, even lethal responses to approved medications.

"It is the nature of today's system," says Dr. Raymond Woolsey, a leading expert on drug safety. "With the advent of direct-to consumer advertising, doctors are now under rising pressure to satisfy their patients' demands besides just treat their legitimate conditions." Dr. Woolsey, a professor and chair of pharmacology at Georgetown University Medical School, continued, "It is inescapable, since they would otherwise lose their patients." If they don't prescribe these new drugs, and often they don't look adequately at the benefit-to-risk ratio. While all medications have side effects, both known and unknown, experts say a specific case can be made against these new medications. They are the ones that are supposed to have higher value and to prevent consumers from taking unnecessary risks. However, we are starting to see risks develop in the system as a consequence of the push by direct-to-consumer advertising, consumers demanding a specific medication, and physicians wanting to support patients by

providing those medications without a clear understanding of their risks.

Compliance is crumbling; prices are increasing. We have seen a more than doubling of the price of prescription medication as a percent of the total dollars spent on health care now going for medications. And as we look to the future, since 1997 the FDA has withdrawn about 11 popular prescription drugs, five of which were on the market for only a year or so when they were removed. Critics of the federal agency say it is because the FDA is approving new drugs too quickly, and in part the federal agency agrees.

Rezulin Removed from Market

Rezulin, a peroxisome-proliferated-activated receptor agonist drug, was touted as a wonder drug. It was used as an adjunctive medication for the management of type 2 diabetes until it was recently pulled from the market. The drug's manufacturer, Parke-Davis/Warner-Lambert, agreed to FDA's request to remove this drug because of potential liver toxicity.

Recent articles describe the risk that was known about this drug and suggest it was economic pressure that resulted in marketing of this drug in the first place. There may, in fact, have been no need for Rezulin, because existing medications were effective in managing type 2 diabetic patients. Rezulin provided no significant benefit over existing medications and contributed additional potential health risk.[iii]

[i] Robinson JC. The end of managed Care. *JAMA*. 2001;285:2622-2628.

[ii] Twersky O. Poisoned Pills? FDA Pulls Popular Prescription Drugs. July 18, 2001. http://webmd.lycos.com/content/article/1728.68157.

[iii] Willman D. Risk was known as FDA OK'd fatal drug. *Life Extension.* June 2001;48-51.

An article titled "Lessons from the Glitazones" appeared in *Lancet* recently.[i] The author, Dr. Edwin Gale, discusses the way drugs get to market. "The rise of modern medicine has largely been based upon new drugs, and most of us can expect to hobble to our graves on the crutch of polypharmacy," according to Gale. "Valuable and necessary though it is, drug development is expensive and wasteful. The process has developed into an evolutionary struggle between manufacturers, who wish to maximize sales and profits, and regulators, who wish to ensure that new agents are safe and effective."

Dr. Gale talks specifically about the glitazones and the Rezulin issue. He asks how troglitazones actually ended up on the market. What clinical data were compelling enough to approve drugs with known potential hepatotoxicity? The article contains data comparing troglitazone to drugs that were already on the market. Troglitazones provided little or no clinical efficacy in improving hemoglobin $A_{1C\ or}$ fasting plasma glucose levels in type 2 diabetics. Some patients actually experienced decreased ability to manage blood sugar effectively on the troglitazone medication over previous drugs with lower potential for toxicity.

> [i]Gale EA. Lessons from the glitazones: a story of drug development. *Lancet*. 2001;357:1870-75.
> When I was in Australia recently, I saw an article in the major newspaper, *The Australian*, titled

"The Pill That Could Break Medicare."[i] It was talking about Celebrex, which had at first seemed like a godsend to those with arthritis. Now it seems to have the potential to break the bank. Insurance reimbursement by the Australian government for this one medication was so great that it was actually threatening to cause the financial system to come down.

In April of this year, Pharmacia, the company that markets Celebrex in the United States, at the request of the U.S. Food and Drug Administration, sent a cautionary letter to healthcare providers.[ii] In part, that letter stated, "This letter is being sent to you at the request of the U.S. Food and Drug Administration (FDA). The FDA's Division of Drug Marketing, Advertising, and Communications has notified Pharmacia Corporation that it considered audio conferences concerning Celebrex (celecoxib) given on behalf of G.D. Searle & Co. (now a subsidiary of Pharmacia), as well as other promotional statements and actions by or on behalf of Pharmacia to be false or misleading and therefore in violation of the Federal Food, Drug, and Cosmetic Act. Therefore, the FDA has requested that we correct these promotional messages accordingly."

Letter From Pharmacia Cautioning Healthcare Providers About Celebrex

The letter noted, "In post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving Celebrex concurrently with warfarin. Therefore, anticoagulant activity should be monitored, particularly in the first few days after initiating or changing Celebrex therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications.

"Serious gastrointestinal toxicity such as bleeding, ulceration, or perforation of the stomach, small intestine, or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, including Celebrex.

Celebrex Contraindications Differ From Consumer Impressions

"Celebrex is contraindicated in patients who have demonstrated allergic-type reactions to sulfonamides.

"Celebrex is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs."

This letter contains information that is probably very different from the way the average consumer feels about this drug when he or she reads or views consumer ads for Celebrex or other selective COX2 inhibitors about the safety and effectiveness of the medications.

[i] Shine K. The pill that could break Medicare. *Sun-Herald (*Australia*)*. June 10, 2001:21.[ii] Pharmacia Corporation. Important correction of drug information. Correspondence, April 2001.

How does that Celebrex information contrast to what was considered to be the anecdotal nonscientifically supportable claim that a natural substance, glucosamine sulfate, could be used

not only to reduce the pain of mild to moderate osteoarthritis but also to promote joint healing? Two papers on this topic have been published in the past six months. One, titled “Long-Term Effects of Glucosamine Sulfate on Osteoarthritis Progression: a Randomized, Placebo-Controlled Clinical Trial,” appeared in the *Lancet*.[i]

Participants in the clinical trial were patients taking 1500 mg of glucosamine sulfate, an approved prescription drug in Europe, orally a day versus placebo for three years. It showed not only a reduction of pain and tenderness with glucosamine sulfate, but also inhibited progression, which is not reported with selective COX2 inhibitors of the osteoarthritis-stricken joint.

Glucosamine As A Conditionally Essential Nutrient

The second article, titled “Preferential Incorporation of Glucosamine into the Galactosamine Moieties of Chondroitin Sulfates in Articular Cartilage Explants,” appeared in *Arthritis and Rheumatism*.[ii] It discusses the mechanism by which glucosamine sulfate might have its impact. It shows there is preferential incorporation of glucosamine into the galactosamine moieties of chondroitin sulfates in articular cartilage explants from steers when glucosamine is given as a conditionally essential substance or nutrient in these *in vitro* experiments. The results indicate glucosamine may be necessary for repletion of chondroitin composition and synthesis or joint space lubricant.

A number of letters to the editor appeared in *The Lancet* in response to the original clinical trial report.[iii] Various opinions are given in these letters in support of the benefit of glucosamine sulfate on collagenous growth, even on keratin, protein-rich tissues like fingernails and toenails. The letters support this substance both in remediation of discomfort and in promoting healing.

[i] Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet.* 2001;357:251-256.

[ii] Noyszewski EA, Wroblewski K, Dodge GR, et al. Preferential incorporation of glucosamine into the galactosamine moieties of chondroitin sulfates in articular cartilage explants. *Arthritis Rheumatism.* 2001;44(5):1089-1095.

[iii] Halbekath J, Lehnert R, Wille H. Glucosamine sulfate and osteoarthritis. *Lancet.*2001;357:1617-1619.

We are starting to see a swing of the pendulum even with regard to conditions like irritable bowel syndrome (IBS). *The New England Journal of Medicine* recently contained a review on IBS.[i] The authors explain that IBS accounts for an estimated $8 billion annually in direct medical costs and $25 billion in indirect costs due to absenteeism and other problems that cause work loss.

The authors describe three components of the etiology of IBS: visceral hypersensitivity, altered motility, and psychological factors that influence neurotransmitter balances. Infection has an effect; inflammation has an effect. They discuss compelling evidence that inflammation of the

enteric mucosa or neuroplexis initiates or contributes to symptoms associated with IBS. The mucosal inflammatory cytokines may activate peripheral sensitization or hypermotility with inflammation messenger molecules like TNF alpha and interleukin-1.

Lotronex Versus Diet in IBS Treatment

We know there are three basic types of IBS: the pain-predominant form, the diarrhea-predominant form, and the constipation-predominant form. The drug Lotronex was recently marketed to manage the diarrheal form of IBS, which is considered the most prominent form. It was released with great fanfare. *Wall Street Journal* articles touted how this drug was going to fill the necessary gap in the pharmacopoeia that would generate a billion dollars. This drug promotion information contrasts to that presented in the *NEJM* article, which indicates the number one recommendation in all three forms of IBS is change in diet.

How do you relate a diet to an inflammatory process in the GI mucosa? It has to do, of course, with understanding the complex environment we describe functionally, of the gut flora, the gut contents, the transit time, the gut antigen load. All of these things play a role in the functional determinants of IBS in genetically sensitive individuals. Makers of Lotronex, however, approached this problem by trying to affect the selective serotonin pathways in the gut mucosa and alter motility by changing the vasomotor tone through the alteration of these transmitter molecules.

Lotronex Removed From Market

The history, of course, is clear. Lotronex did not stay on the market very long as a consequence of some fairly severe problems with regard to constipation and some apparently very severe outcomes in patients. Glaxo Wellcome, at the request of the U.S. Food and Drug Administration, announced it would voluntarily withdraw this prescription medication, Lotronex (alosetron HCl), for the treatment of women with a diarrheal-predominate form of irritable bowel syndrome.

The company disagreed with the FDA’s assessment of the drug’s safety, but announced it would cease distribution. This is a consequence of a number of very severe problems that occurred by modifying with a medication the chemical communication systems of the gut rather than exploring the way other variables in the environment, diet, commensal enteric bacteria influence the messaging system.

Significant questions are being raised as we move into the transition of 2001 about the future of medicine. Will it be more functionally based or will it be more pharmacologically based? That is, I think, presaging the dawn of a new era of personalized medicine. It is what Dr. Linus Pauling called molecular medicine and what some now call genomic medicine.

[i]
A recent article by Dr. David Baltimore in *Nature* magazine, titled “Our Genome Unveiled,” signals the start of this new era.[i] Dr. Baltimore is the president of the California Institute of Technology and a Nobel Prize winner himself for his work on reverse transcriptases in molecular biology. He wrote, “I’ve seen a lot of exciting biology

emerge over the past 40 years. But chills still ran down my spine when I first read the paper that describes the outline of our genome," which was published in *Nature*. "Not that many questions are definitively answered—for conceptual impact it does not hold a candle to Watson and Crick's 1953 paper describing the structure of DNA. Nonetheless, it is a seminal paper launching the era of post-genomic science."

Baltimore asks, "What have we learned from all of these AGCTs? It is important to remember that no statements can be made with high precision because the draft sequences have holes and imperfections, and the tools for analysis remain limited." He explains, however, "The sequences are about 90{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} complete for the euchromatic (weakly staining gene-rich) regions of the human chromosome. The estimated total size of the genome is about 3.2 Gb (that is gigabases, the latest escalation of units needed to contain the fruits of modern technology). Of that, about 2.95 Gb is euchromatic. Only 1.1{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} to 1.4{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} is sequence that actually encodes protein; that is just 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the 28{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the sequence that is transcribed into RNA. Over half of the DNA consists of repeated sequences of various types; 45{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in four classes of parasitic DNA elements, 3{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in repeats of just a few bases, and about 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in recent duplications of large segments of DNA."

Reverse Transcription DNA

Dr. Baltimore goes on to say, "I find it striking that most of the parasitic DNA came about by reverse transcription from RNA. In places the genome looks like a sea of reverse-transcribed DNA with a small admixture of genes." Much of our genome, therefore, appears to be non-coding for proteins. What does that mean? Is it only a relic of historical archival library of what we have been exposed to in our past evolutionary history, or does it have other functional capabilities yet to be learned?

"In humans, virtually all of the parasitic DNA repeats seem old and enfeebled, with little evidence of continuing reinsertions. However, there has been very little evolutionary scouring of these repeats from the human genome, making it a rich record of evolutionary history." These artifacts stuck within our genes are made up of largely meaningless (at least in terms of our present knowledge) sequences that are interspersed between widely spaced genes. They represent a larger fraction of human DNA than in the genomes of the few species that have been sequenced to date. They may, therefore, be one of the things that differentiates us from other organisms.

Human Superiority Not Based on Gene Numbers

What interested Dr. Baltimore most about the genome? The number of genes is high on the list as he looks at things that were surprising. Rather than hundreds of thousands of genes, which were initially expected to be found, the project estimates there are about 31,000 protein-encoding genes in the human genome. That is the estimated number of coding genes and can be compared to about 6,000 for a yeast cell, 13,000 for the fruit fly, 18,000 for a worm, and 26,000 for a plant. A plant actually has almost the same number of protein-encoding genes as a human.

But unless the human genome contains a lot of genes that are opaque to the assessment of today, it is clear that we do not gain our undoubted complexity over worms and plants solely by our numbers of genes. Understanding what does give rise to our complexity, our enormous behavioral repertoire, our creative ability, conscious actions, physical coordination, precisely tuned alterations in response to variations in the external environment, learning and memory, remains a challenge beyond the number of genes themselves.

Importance of Junk DNA

Where do our genes come from? In fact, only 94 of the 1278 protein families in our genome appear to be specific to vertebrates. The most elementary facets of our cellular function, basic metabolism, transcription of DNA and RNA, translation of RNA into protein, DNA replication, evolved just once and have stayed pretty well fixed, according to Dr. Baltimore, since the evolution of the single-cell organisms, yeast and bacteria. The biggest difference between humans and worms or flies is in the regulatory complexity that governs the synthesis of our proteins.

We wait with bated breath to see the chimpanzee genome. But, according to Dr. Baltimore, knowing how few genes humans have, it is doubtful if we will learn much about the origins of speech, the elaboration of the frontal lobes, and the opposable thumb, the advent of the upright posture, or the sources of abstract reasoning ability from a simple genomic comparison of humans and chimps. It seems likely that these features and abilities have mainly come from subtle changes, for example, in gene regulation.

New Answers for Old Questions

Biology today obviously is entering a new era with a new methodology for answering old questions. Those questions are some of the deepest and simplest: “Daddy, where did I come from?” “Mommy, why am I different from Sally?” As these and other questions get robust answers, biology will become an engine of transformation of our society.

Instead of guessing how we differ one from another, we will understand and be able to tailor our life experiences and our medicines to our experiences. Much of this may be found to be modifiable on the basis of environmental factors—diet, environment, exercise. We are creating a world in which it will be imperative for each individual person to have

sufficient scientific literacy to understand the new riches of this genomic knowledge so we can apply them in a wise fashion.

[i]
Baltimore D. Our genome unveiled. *Nature*. 2001;409:814-816.

Horwitz BJ, Fisher RS. The irritable bowel syndrome. *NEJM*. 2001;344(24):1846-1850
This theme is taken up when we look at the future of this personalized genomic medicine. In an article titled “Single Nucleotide Polymorphisms…to a Future of Genetic Medicine,” Dr. Aravinda Chakravarti states, “It has become clear that the two genomes that each of us carry inherited from our parents most often differ from each other and from the genomes of other humans in terms of what are termed ‘single base changes’, single nucleotide polymorphisms.”[i] The 20th century saw the identification of only a few thousand of these so-called single nucleotide polymorphisms or SNPs, until the Human Genome Project. Now more than 1.4 million of these single nucleotide polymorphisms or SNPs have been found, about one SNP/2kBp. This means that more than 90 percent of any stretches of a sequence of 20 kilobases long within our DNA will contain one or more of these polymorphisms.

Using SNPs to Manage Patients of the Future

These data provide interesting first glimpses into the pattern of biological variation across the genome and illustrate what Dr. Roger Williams called biochemical individuality 50 years ago. Strikingly, humans vary least in their sex chromosomes, because they probably have the least opportunity for genetic recombination during meiosis. Perhaps not surprisingly, some genomic regions have significantly higher diversity than others. One of the most diverse regions of our genome, which has the highest numbers of polymorphisms, appears to be in the histocompatibility locus antigen region, the region that controls our immune function.

These encoding proteins that present antigens to the immune system show the greatest diversity in our genetic background, and the most polymorphisms. The main use of human SNP maps will be in dissecting the contributions of individual genes to diseases that have a complex multi-gene basis. Variations in genome sequences underlie differences in our susceptibility or protection from all kinds of diseases, in the age of onset and severity of illness and the way our bodies respond to treatment. By comparing patterns and frequencies of single nucleotide polymorphisms or SNPs in patients and controls, researchers in the future can identify which SNPs are associated with which diseases.

Such research will bring about this personalized medicine in which the knowledge of our uniqueness will alter all aspects of medicine perceptibly and forever, and make the textbooks we have been studying out of all archaic. Although 82 percent of SNP variants are found at a frequency of more than 10 percent in the global human population, the micro-distribution of SNPs in individual populations is still not known. By identifying

variations across the whole genome, the SNP map may be our best route to better understanding the roles of nature and nurture in controlling our function.

Understanding SNPs is not where the action is. It is in understanding how these nucleotide polymorphisms affect expression in the individual in cells, tissues, or organs. It is the expression patterns. The translation of mRNA into active protein, so-called proteomics.

SNPs in themselves may only help us understand the relative risk of disease. It is the genomic expression of those polymorphisms and ultimately their translation to various functional proteins that will determine how they translate to the phenotype of health or disease. This new functional genomic and functional proteomic medicine that is emerging supports Dr. Linus Pauling's molecular medicine and Dr. Roger Williams's biochemical individuality and genetotrophic disease.

This also holds true with regard to the way we view the immune system and why some people are susceptible and some people are resistant to certain exposures. A review of this topic, titled "Immunogenetics and Genomics," appeared in the *Lancet* recently.[i] The author discussed the relationship between HLA genotype and susceptibility to various immunologically determined conditions and ultimate manifestation as disease.

Pathways for self-tolerance in the treatment of autoimmune disease are therefore likely to involve the understanding of these polymorphisms in the HLA region and modification of the environment in order to reduce the antigenic exposure or to minimize the effects of the antigen/antibody reaction.

INTERVIEW TRANSCRIPT

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This month we are pleased to have Dr. Richard Shames as our Clinician of the Month. Dr. Shames is a graduate of Harvard College and the University of Pennsylvania Medical School. He is a founding member of the American Holistic Medical Association. He has served as an adjunct faculty member at the University of California San Francisco Medical Center and for several years had a private practice in Mill Valley, California. With his wife, who is a PhD RN, he recently relocated to Boca Raton, Florida, where he is now in a general practice with a functional medicine emphasis. Dr. Shames and his wife are the authors of a new book, Thyroid Power: 10 Steps to Total Health.

Functional Thyroid Disorders

JB: Richard, from a functional thyroid perspective, according to your book and your clinical experience, thyroid dysfunction seems to be very common. Could you tell us about your experience dealing with thyroid disorders?

RS: It is a pleasure to talk about this particular topic. I believe an epidemic is going on. If you ask a pharmacist to name the most common category of medicines for which he fills prescriptions, he would immediately identify thyroid medications. Synthroid is the second or third largest selling medicine in the country. Just that one brand alone, and there are several other brands that are popular. It appears that we have a hidden epidemic that has only gotten worse since Broda Barnes first described it in the 1970s, with Hypothyroid, the Unsuspected Illness.

Doctors at the Columbia Presbyterian Medical Center in New York suggest 20 million Americans may currently be receiving treatment for thyroid problems. Chester Ridgeway at the University of Colorado Health Sciences Center gave TSH tests to 25,000 people at health fairs in Colorado and found the incidence and prevalence of the condition was much greater than one would suspect. He feels mild hypothyroidism might affect one out of 10 people in the United States. And it goes up to 20 percent for older women.

Testing Thyroid Function

JB: One of the ways Dr. Barnes assessed functional thyroid abnormalities was by measuring the axillary body temperature test on awakening. Do you feel this test, or using the achilleometer, is a way to get better information than relying strictly on the blood tests?

RS: Absolutely. As a clinician for 30 years I have been very troubled by the number of people who come in to see me after consulting other doctors, even endocrinology specialists, who have been told their thyroid is fine. What that means is that the doctor has done a TSH, maybe done a T4 panel, with a T3 uptake and an FTI and they are told they are in the normal range.

Even the newer tests, which measure the free fraction, the free T4 and free T3, sometimes do not pick up what functional tests can pick up. You could make a possible diagnosis of hypothyroidism by having a person take her axillary temperature, or you could check a reflex and find it is difficult to elicit or has a very slow recovery rate.

The Achilleometer

JB: Have you had any experience with the achilleometer? That instrument was found useful in the early stages of assessing thyroid function, but it seems to have fallen out of favor.

RS: I remember it from the early days of my medical training. It certainly is something I wish I had now. The achilleometer was a machine that did the ankle reflex and printed the result on what was most akin to cardiograph paper. You had a curve, which could be very sharp and steep, very long and drawn out, low or high. All of that was useful information. Clinicians at the time would scrutinize it and compare it to the blood tests, which were sometimes confirmatory and sometimes not. They were able to effect an

improvement in the patient's function utilizing the reflex tests over the blood tests.

Thyroid Dysfunction: Cause or Effect?

JB: What is your feeling about whether thyroid dysfunction is the cause or the effect of other problems?

RS: That is a fine question. I would be delighted if I had a better answer. My general feeling is that for many people it seems to be primary cause. I believe this epidemic we are seeing is in large part due to pollution of the air, food, and water, affecting one of the more sensitive of the endocrine glands by way of immune disruption. That is this autoimmune low-thyroid situation. The idea that the other endocrine glands are involved is a possible coincident factor for many people. The primary problem seems to be with the thyroid, and it seems to be correctable with attention to the thyroid.

Signs and Symptoms of Hypothyroid Condition

JB: What are some of the more common presenting signs and symptoms of low thyroid function?

RS: Frequently, low thyroid situations coexist and commingle with other endocrinopathies. So when a person has low adrenal or sex hormone abnormalities, he or she can present with very similar symptoms. But you try to figure out what you can do. Doing anything anywhere, in the functional approach, will help everything everywhere. It is not a linear cause and effect relationship among all these glands. There is a warp and a weave.

I have found for many of my patients, and from my reading of the literature, there seems to be this primary endocrinopathy that is slowing everything else down. Symptoms of the slowdown include fatigue, depression, overweight, feeling chilly all the time, excess hair loss, dry skin, cracking nails, headaches, low sex drive, high cholesterol, constipation, allergies, and unexplained aches and pains. It also includes a long list of female problems, with everything from infertility to endometriosis, miscarriages, PMS, or severe menopause. A strong correlation exists between a hypothyroid condition and a polycystic ovary condition, which is related to other conditions, including syndrome X in particular.

Thyroid Function and the Biomarkers of Aging

JB: That was a fantastic list. It is important for our clinician listeners to be aware of those symptoms.

RS: A list of the biomarkers of aging, a favorite topic of yours, in general reads just like the hypothyroidism list in a textbook. A person might not have the exact symptoms I mentioned. He or she may have general loss of strength or flexibility, decreased cardiovascular endurance, increased body fat, a slower metabolic rate as far as decreased resting energy expenditures, decreased kidney clearance, decreased vibratory sense, altered smell and taste. Increased autoantibodies, in this case to the thyroid gland, are indicative of someone who is having generalized unhealthy aging, a mixture of the accelerated aging biomarkers. Or it could simply be a person who has this autoimmune thyroid condition. The thyroid is a favorite target organ for all of the pollution that is coming back to haunt us.

Assessing Thyroid Function

JB: A study from Italy, published in the Lancet a number of years ago, looked at the difference between healthy centenarians and unhealthy younger (60- and 70-year-old) individuals. The researchers were looking for biomarkers that could differentiate these healthy 100-year-olds from the unhealthy younger folks. The one that stood out was autoantibodies to the endocrine glands, principally the thyroid gland. If the person had, in a sense, become “allergic” to his or her own endocrine glands as he or she grew older, the individual had increased health difficulties compared to the individual who stays with high vitality up to 100 years of age.

In your book you state an assessment panel should include an autoantibody or thyroid autoantibody assessment component to look at the various functions of the thyroid. Could you describe a panel that might adequately represent thyroid function for the clinician?

RS: The standard panel you would do is a TSH test alone, or TSH with a free T4. This is the new standard that replaces the TSH with the T4 panel, the old T4 total, T3 uptake FTI. The TSH and free T4 is supposed to be diagnostic, but it misses a great many people. In addition, you might get a total T3. I found it very useful. It correlates very well with a number of people who seem to have this low thyroid condition. It may correlate even better than the free T3. This might be a useful part of the testing profile.

But absolutely, whatever you do about those, get the thyroid peroxidase antibody and the thyroglobulin antibody. Sometimes it is one, sometimes the other, and sometimes both of those are affected.

Peroxidase Antibody

JB: The peroxidase antibody, for those who may not remember their basic endocrinology, has to do with the iodinization reaction, the oxidation/reduction that produces an available iodine that ultimately deiodinates tyrosine to become thyroxin. So you are talking about antibodies against both the iodinating component and the component that is related to the function of the gland.

RS: You are correct.

Xenobiotic Exposure and Thyroid Problems

JB: In a paper published in the Journal of Endocrinology a number of years ago, the author described a group of individuals in Colombia, South America. There was a very high prevalence of autoimmune thyroiditis in their little village. The condition, he found, could be traced back to the contamination of their ground water and drinking water with phenols from a chemical processing plant. When they cleaned up the water this idiopathic thyroiditis went away. Do you feel, from your experience, there is a close correlation between idiopathic thyroid antibody problems and a body’s generalized reaction to xenobiotics?

RS: Absolutely. It has been demonstrated a number of times that these autoimmune conditions seem to exist in extraordinary clusters around toxic waste sites and other places where there have been toxic spills. If you generalize from that to the population at large and the number of things people are exposed to, you are dealing with what could be an enormous onslaught. In addition to industrial pollution, we expose ourselves daily to a number of chemicals at home in house cleaning, and self-care.

I was particularly moved some years ago by the Colborn-Dumanoski project called Our Stolen Future. It detailed how we are threatening our intelligence, fertility, survival, and health by all of these chemicals. We may be trying to have be less and less of these chemicals in our lives, but they are hard to avoid.

Hormonal Chaos

This impression was sharpened here lately. Sheldon Krimsky produced a wonderful volume called Hormonal Chaos. This is the environmental/endocrine hypothesis, the fact that these chemicals seem to have a direct toxic effect on thyroid tissue but also have a direct effect on the delicate balance of the immune system. That affects people who are genetically prone to making autoantibodies, and it appears that number is 20 to 25 percent of the population.

According to the great thyroidologist Lawrence Wood in his book Your Thyroid, 25 percent of individuals may have the unfortunate capacity to make these autoantibodies, the fragments of their own body cells. We are doing more and more of this. Krimsky is eloquent about the scope and nature of the problem, which is enormous. It is an absolutely enormous problem. The EPA has been charged with assessing 15,000 of the most common chemicals that are used in products and services in this country to find out which ones are hormonally disruptive. It is mind boggling.

Reverse T3

JB: There is a lot of discussion in the field about the value of reverse T3 (RT3) in assessment of thyroid function and if RT3 levels are at all reflective of alterations in enzyme patterns that are impacted by xenobiotic exposure. Do you have any opinions or experience about the value of reverse T3?

RS: I would say it is in the same category of quality of information as the other tests for thyroid assessment. If the test shows a positive finding, you can trust it. You can utilize it. It might be handy information. But if the test is normal, it doesn't mean the problem does not exist. This test, the reverse T3, as well as every other test we mentioned in the list of what might comprise the ideal work-up, is useful but not definitive. Doing all of these tests could be fairly expensive and therefore not ideal.

The tests have many more false negatives than they do false positives. There are very few false positives, in fact. So if you have a reverse T3 that shows an abnormality, you could figure that perhaps there is some difficulty in T4 and T3 conversion. But if you don't see that, you could still have what appears to be that difficulty.

I say it appears to be, because it is often correctable. Sometimes with the person who is taking synthroid alone, you could add T3 with their synthroid or their levoxyl and get quite a bit of improvement. It is startling. It is shocking how many people get tremendous improvement with that little bit of a change. Even those people who do not show up with the reverse T3 abnormality.

The Need for Pattern Recognition

JB: You are describing the functional web of physiology. Rather than homeostasis, it is homeodynamic and constantly changing, based upon Circadian rhythms, environmental exposures, and so forth. It is necessary for the clinician to develop pattern recognition. You have to look at signs and symptoms, blood

tests, axillary body temperature, Achilles reflex, and put everything together. The pattern that develops then leads you to clinical judgment. You don't put all of your eggs into one diagnostic basket.

RS: Absolutely. In fact, in the book Thyroid Power, we have a section called "Ten Steps to Total Health." Step 4 is to realize you may still have low thyroid despite normal tests. That goes back to what we were talking about before. The standard thyroid tests have a disturbingly high rate of false negatives.

A clinician may have a patient who comes into the office and says, "I was checked for my thyroid, and it's been fine, but my sister has low thyroid; my mother has low thyroid; my grandmother has low thyroid. I have this whole laundry list of low thyroid symptoms, but the test doesn't show I have it." Well, you can still have it, even with the normal tests.

Similarly, a person who has been on levoxyl for some time may have a fairly normalized TSH but not have regained full function. (This is what I love about functional medicine, by the way. We don't rely just on lab tests. The person has to be feeling better, has to have some improvement in a variety of symptoms in addition to his or her overall total vitality. If they don't have that, then regardless of what the tests are showing, you can have a problem.) That is just one of the 10 steps.

Medical and Legal Considerations of Functional Thyroid Treatment

JB: Clinicians may be concerned about the medical and legal risks of assessing thyroid function by this complex means and conclude that thyroid support was called for. One of my colleagues who doesn't understand this assessment method would point out there was no evidence of hypothyroidism and you are over-treating. I know medical/legal concerns have been raised with doctors who have treated functional thyroid problems. Do you have an opinion about that concern?

RS: We had for many years a TSH range that was considered normal. The normal range was .5 to 5.5. That range had actually come down. I remember a time when normal TSH range was considered to be 7.5. So like cholesterol ranges, that range has come down. The American College of Clinical Endocrinologists and National Endocrine Society recently came out with a statement saying they realize that although they had been insisting for almost 20 years that this was the normal range, now they have decided that the range would be .5 to 3.0. So it is a much more narrow range.

The medical/legal concerns regarding using just these tests that most people realize are not adequate for the job, I believe, are relatively small. Arem Ridha, MD, a professor of endocrinology at Baylor, wrote a wonderful book called The Thyroid Solution. As he said, even if the TSH is in the lower end of the normal range, the "desirable range," you could still be borderline hypothyroid. More and more endocrinology people are insisting that we need to broaden our view on this.

The legal risk is quite small if you are able to document a variety of other factors. You could document the symptoms we just mentioned, the signs you could get from a physical exam, the reflex that we talked about, low skin temperature, lack of body hair, changes in terms of lowered blood pressure. You might have high cholesterol with fairly good dietary intake. The family history can be very compelling, as are associated illnesses, and if you have a low basal temperature. If you base your diagnosis not just on one laboratory value but on signs, symptoms, family history, associated illness, metabolic rate in terms of the axillary temperature, you have pretty good footing for considering a functional intervention.

Functional Intervention: The 10 Steps

JB: That takes us to what the functional intervention might be. The 10 steps in your book, Thyroid Power, do a nice a job of providing a checklist. Could you guide us through that list?

RS: Step 1 is to consider thyroid a hidden factor in the patient's overall health. Just be aware of it. The rationale is that more and more studies are suggesting a surprisingly high incidence of borderline hypothyroidism, which can cause symptoms in itself or can exacerbate other symptoms.

Step 2 is to learn how low thyroid can make any other illness worse. The rationale is that coexistent subclinical hypothyroidism often exacerbates other disease symptomatology. A person with arthritis, sometimes rheumatoid and sometimes osteoarthritis, can have much less of a problem and need much less medicine if a coexistent hypothyroidism is treated well.

Signs, Symptoms, Family History

We already talked about Step 3 a little bit. Use signs, symptoms, and family history to support a diagnosis. Accurate diagnosis of mild hypothyroidism requires a detailed history, a high index of clinical suspicion, and a good physical exam, looking for these possibilities.

Step 4, which we already talked about, is really at the heart of the matter. Realize you may still be low thyroid despite normal tests. Whether it is diagnosing someone de novo for the first time or whether it is to see if a person who has been on thyroid intervention for some years is at the proper, optimal intervention. The standard thyroid tests have a disturbingly high rate of false negatives.

Assess Patient's Unique Needs

Step 5: Discover the best dose, brand, or mix of medicines, because no single method of thyroid treatment is optimal for all patients. Jeff, this is what you have talked about over and over again, genotype uniqueness. A person may have a family trait for autoimmune glandular disease or especially autoimmune thyroid. People who have diabetes in the family, or rheumatoid arthritis, have certainly enough of a family history to call this one.

The idea of being on just one medicine or finding just the right medicine is now giving way to the idea of what is the proper mix of medicines. Sometimes the mix is not just the T3/T4 combination. But the T3/T4 combo along with natural desiccated thyroid might be the better solution.

Step 6: Know you can get further improvement by rebalancing the reproductive system. This last year, Jeff, I know you were involved in a number of seminars regarding female hormone balance and the intricacies of that. Rebalancing the reproductive system, for women, might mean some progesterone added, for men it might mean a small amount of testosterone, not necessarily for symptoms of lack of those substances. But instead, it is that doing so will improve the thyroid condition that you are trying to treat.

Assessing Adrenal Function

Step 7 is a little harder. Determine if low adrenal should also be treated. Adverse hormonal effects of autoimmune situations can include low function of the adrenal as well as thyroid tissue. Hypofunction of adrenal tissue due to autoimmunity is perhaps as unrecognized or given as little credit as low functioning thyroid in autoimmunity. It is a very important factor and much more common than we realize. It is much more difficult to test for.

We know the difficulties of the thyroid test. The difficulties encountered with adrenal testing are much greater because of the time of day that is involved and the quality of the test. Measuring four separate samples of urine or four separate samples of saliva to give an adrenal stress index might be more useful than the standard blood tests. Long before you would have abnormalities on any of those tests you would have low adrenal reserve. So the possibility of testing for that would be ACTH stimulation test, although it needs to be interpreted a little more generously than the standard interpretations. The same thing is true if you have total negative normal results on the thyroid test, the panel we just mentioned. You can do a TRH test, very similar to the ACTH stimulation test for the adrenal, you could do the TRH test for the thyroid. That is supposed to be the gold standard, but still is just one test. It is the same with adrenal testing. I don't know how much faith you can put in any one test. You need a whole picture.

The Clinical Program to Improve Thyroid Function

Step 8: You can boost whatever medication protocol a person is on or you put a person on with natural therapies, vitamins, minerals, amino acids. All of that is very crucial for thyroid function. Perhaps the most crucial aspect for thyroid would be the antioxidants. Jeff, you are fond of the antioxidant approach for other endocrinopathies. It is similar for the thyroid. High doses of A, C, E, CoQ10, lipoic acid, N-acetylcysteine, carnitine, quercetin are very helpful. Why? We are dealing with thyroid inflammation. Autoimmune thyroiditis is an inflammatory condition and not just of the thyroid tissue.

All of the normalization that we are very fond of with functional medicine is important, all of the diet and nutritional tailoring that we can apply, the nutrient enhancement. All of that is very helpful for thyroid sufferers. Exercise training, stress management, promotion of structural integrity, all of that is crucial. Counseling for purposeful living, environmental adjustment. All of those go along with trying to normalize the intracellular and intercellular communication, by enhancing what could be low thyroid hormone.

Improving Autoimmunity

Step 9: Improve the underlying autoimmune condition. We in functional medicine do a lot of that. Generally, conventional medicine practitioners will give thyroid hormone if a lowered TSH results in less stimulation of the thyroid gland as a factory producing thyroid hormone. Then we have less of the likelihood of the autoantibody situation getting worse and worse. So a low TSH, less autoimmunity, sometimes you can even measure the antibodies as a barometer. But sometimes the antibodies will not come down even though the person improves.

So any one of these tests to be used as a barometer is fraught with difficulties. If it works, use it. It is very handy to show other clinicians and the patient that the thyroid peroxidase antibody is less now that they have embarked on treatment, that they are feeling better, that their basal temperature is improved, their exercise tolerance is better, they have more stamina, more vitality. That's great. Keep doing it. But there

are other ways of improving the underlying autoimmune condition that is part and parcel of the functional medicine that you have been talking about for a number of years.

The Goal: An Empowered Lifestyle

Step 10: Reach optimal recovery with an empowered lifestyle. The chances of optimal recovery are greatly improved with optimal lifestyle behaviors. It may be helpful to eliminate caffeine, alcohol, tobacco, sugar, salt, the risky behaviors that people get involved in. They are very risky for thyroid recovery. So there is much you can do in terms of counseling in stress reduction, activities you can encourage. All of that would be helpful for an optimal thyroid recovery program.

So there it is. Ten steps. Sometimes you don't have to take them in that order. Sometimes the thyroid is not the main event. I don't mean to say I think it is the main event all the time or most of the time. It is just that in a significant percentage of people it is apparently much more the main event than we thought. It is the throttle for all the other organs and all the other chemical reactions we are trying to encourage. Sometimes it is the sine qua non. So try to isolate and figure out which people those are, and then work with these steps.

Remarkable Recoveries Documented

JB: You have done a great job of summarizing a lot of information. You book contains that information in more detail. You have a tremendous reference list at the back of the book. You've got a lot of facts. You have the summaries of your 10-step program, and a good rhetoric that underlies the logic of this approach. You have taken a vast amount of clinical experience and woven the conventional together with the body/mind functional approach in a way that makes sense. You describe a number of case histories in the book that have experienced remarkable recoveries in people who have had mysterious lingering chronic conditions.

RS: It is worth considering that there are some people who seem to have this particular endocrinopathy. They may have polyendocrinopathies, but this particular condition might be eclipsing a variety of other things because it is more fundamental and more basic. If you don't have thyroid hormone you can't do a lot of other things you are trying to accomplish in the functional approach. Millions of people are suffering needlessly from it.

Oddly enough, this is one of those conditions over which there is a current debate about what would constitute a true diagnosis of hypothyroidism. That is missing the point. We are dealing with a situation that needs the functional perspective so you can get some earlier intervention. You can do a diet and lifestyle modification. You can use vitamins, minerals, and herbal preparations to intervene on this condition long before there is this pathology. Why wait until, as conventional medicine would say, you have definite pathology and definite organ shutdown before treating what could be a condition that is going to cause enormous problems everywhere? I think millions of people are suffering needlessly. If we could just look at this in a slightly different way, they could have help.

Understanding the Web of Function

JB: You have helped us see it in that different light. This topic and the way you have described it fits so

nicely into the healthy aging focus we have on functional medicine. It gets us to think in broader constructs of the web of interaction of the sex steroid hormones with the adrenal function with the hypothalamus, with pituitary function, and with the thyroid and how that controls basal metabolic rate and other functions within tissues and cell physiology that gives rise to these complex symptoms. We often look for the magic bullet when the bullet is really the understanding of the approach more than just the single medicine or single lab test.

RS: For clinicians who are listening, for the difficult and complex patients just keep this in mind as a possibility because it can be very helpful.

Thyroid Power: Ten Steps to Total Health

JB: Thank you. Thyroid Power: Ten Steps to Total Health by Dr. Richard Shames and his wife Karilee Halo Shames is a very good book. I think it will help open up this topic toward remediation. The book can be purchased through our website at www.functionalmedicine.org

One of the principles Dr. Shames describes in his discussion of thyroid function and its relationship to other factors in regulatory control is the interrelationship between adrenal hormones and sex steroid hormones. This is a clinical pearl that, I think, deserves comment, particularly in light of a recent paper that appeared in the New England Journal of Medicine.[i] The author, Dr. Baha Arafah, discusses the increased need for thyroxin in women with hypothyroidism during estrogen therapy.

This study considered 11 postmenopausal women with normal thyroid function and 25 postmenopausal women with hypothyroidism who were being treated with thyroxin. Thyroid function was assessed before they started estrogen therapy and every six weeks for 48 weeks thereafter. The women with hypothyroidism included 18 women receiving thyroxin therapy and 7 women receiving thyrotropin-suppressive thyroxin therapy. On each occasion, serum thyroxin, free thyroxin, thyrotropin, and thyroxin-binding globulin were measured.

Thyroxin Need Increases in Hormone-Supplemented Women

The study found that in women with hypothyroidism treated with thyroxin, estrogen therapy may increase the need for thyroxin. As we know, many women who may have symptoms of functional hypothyroidism and receiving some degree of thyroid replacement and may also be getting oral sex steroid hormone replacement of estrogen. These data indicate that some of these women with hypothyroidism need more thyroxin, due to estrogen-induced increase in the serum concentration of thyroxin-binding globulin. This increases the need for thyroxin in women with hypothyroidism who are receiving moderate doses of thyroxin intended to replace normal thyroxin secretion.

Thyroxin-binding globulin is a glycoprotein produced by the liver, which binds thyroxin with high affinity. About 75 percent of the thyroxin in the blood serum is bound to it; nearly all the rest is bound to albumin, with less than .1 percent remaining free or unbound. The physiological function of thyroxin-binding globulin is not known, but it may serve to distribute thyroxin evenly among the tissues, particularly the liver.

Effects of ERT on Hypothyroid Women

Serum concentrations of thyroxin-binding globulin are similar in men and women, indicating that in post-menopausal women the production is not due solely to the different rates of estrogen production that occur with the onset of menopause. However, oral treatment with 0.625 mg of conjugated estrogens daily raises serum-binding globulin concentrations in a woman by approximately 50 percent. This is true in both women with normal thyroid function and those with hypothyroidism. This is when we start being concerned about an adverse impact of estrogen replacement therapy on thyroid hormones in the hypothyroid women. The estrogen-induced effects increased the serum thyroxin-binding globulin concentrations in a dose-dependent fashion, and it occurred with any orally administered estrogen, whether given alone or in combination with the progestin, and even in the form of an oral contraceptive, or in combination with medroxyprogesterone in postmenopausal women.

Oral Effects

Serum thyroxin-binding globulin concentrations also increase in women treated with tamoxifen or raloxifene, which are the new selective estrogen receptor-modifying drugs, the SERMs, but they are less potent than the estrogens themselves. Transdermal estradiol therapy, however, does not raise serum thyroxin-binding globulin concentration.[i] This suggests that oral administration, which has a different effect on first-pass liver function, may contribute to the higher levels of estrogen in the portal vein. Therefore, what we start seeing are oral effects, not transdermal effects in this estrogen-thyroxin connection.

It may be suspected that women treated with thyroxin in whom estrogen therapy is begun might need more thyroxin. In pregnant women, serum thyroxin-binding globulin increases to the same extent as in women treated with 0.625 mg of conjugated estrogens per day. And they also lose some thyroxin to their fetuses. As a result of the placental deiodinization of thyroxin to reverse T3, this becomes a biologically inactive form of thyroid hormone.

Increased Thyroxin Need in Thyroxin-Supplemented Hypothyroid Women

As a result of these changes, women with hypothyroidism who are being treated with thyroxin need approximately 50 percent more thyroxin when they are pregnant, according to this study. Conversely, women with hypothyroidism treated with thyroxin may need lower doses of thyroxin when they are treated with androgens, which lower serum thyroxin-binding concentration. That is the other side, the yin and yang of this substance. Androgen-supplemented women have lower need for thyroid hormones; and oral estrogen-treated women have elevated need for thyroid hormone.

Many women, obviously, are taking estrogen either for contraception or to ameliorate menopausal symptoms or other manifestations of estrogen deficiency. And many women are also on thyroid replacement therapy. Therefore, I think it is very important to see that the levels of thyroid hormones are in balance against the sex steroid hormones, particularly the androgens and estrogens, as this article indicates.

[i] Utiger RD. Estrogen, thyroxine binding in serum, and thyroxine therapy. *NEJM*.2001;344(23):1784-1785.

Finding the Balance

This study provides another example of the importance of the balance, the dance, the rhythm of the functional physiology, this homeodynamic orchestration we are describing. Although this may look like a more complex medicine to get one's mind around, it is a medicine that has a lot more exciting variations and a lot more topography for creating for a patient an environment of high treatment successful outcome. That is really the nature of what the new medicine of the 21st century, post-genomic era is all about.

I hope you got some "news-to-use" this month from the discussion of hypothyroidism with Dr. Shames and how it fits into the whole construct of the web of our genome, our single nucleotide polymorphisms, our multi-gene expression patterns, and later our phenotype as we age.

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