April 1998 Issue | Derrick Lonsdal, M.D.

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Welcome to *Functional Medicine Update*™ for April, 1998. There is definite clinical payoff to our focus for this month, which is a continued discussion of Functional Medicine applications to disorders of gene expression.

Patient-centered assessment is a principal tenet or construct of functional medicine. I was pleased to see in the *Journal of the American Dietetic Association* (98;177:1998) an article entitled, "Patient-Focused Care and Its Implications for Nutrition Practice." In this paper, the authors explain that the individual needs of patients should be the focus of nutritional therapeutics and care providers, and patient-centered, or patient-focused care is the direction nutritional medicine is going.

That article validates the concept we have discussed in functional medicine, in which antecedents are overlaid by triggers, which give rise to mediators, which give rise to signs and symptoms. It is a very different model from the differential diagnosis model. It is not antithetical to, nor does it replace the differential diagnosis pathophysiology-based model. Instead, it amplifies, complements, and provides a different means for evaluating patients. It gives a broader array of questions that might be asked during the physical, history, and inventory assessment. It is patient-centered assessment, looking at genetic antecedents, followed by triggering factors that work upon or lay themselves upon the genetic antecedents. Finally, mediators are derived from that process. These are the cell-signaling messengers, such as interleukins, leukotrienes, eicosanoids,and chemokines, a complex array of substances secreted by the body that trigger different types of physiological responses. Finally, from these triggers, signs and symptoms arise.

Practitioners who use patient-centered assessment and patient-centered care look at patients as the center of their own symptoms rather than just trying to define a disease code for which reimbursement is provided by a definition through an ICD9 or CPT code. Pathophysiology remains an important determinant in healthcare delivery, but it is not the entire reason a patient arrives with a sore elbow, a headache, a gastrointestinal complaint, sleep disturbances, mood swings, and inflammation of the esophagus. There is an interconnected, web-like pattern in those multiple-organ symptoms that might be better understood from a patient-centered concept than a pathophysiology-based concept. I applaud the *Journal of the American Dietetic Association* for talking about patient-focused care and its relationships to nutritional practice

When we talk about antecedents, we are really speaking about the genome of the individual and his or her unique genetic characteristics. Understanding the genome of the individual, the genetic pleuripotentiality, the pleomorphic nature of our genes, and how they can be expressed more effectively is a focus of the

advancing frontier in health sciences. "The U.S. Human Genome Project (HGP) is a joint effort of the Department of Energy and National Institutes of Health, formally initiated in 1990. Its stated goal is to characterize all the human genetic material – the genome – by improving existing human genetic maps, constructing physical maps of entire chromosomes, and ultimately determining the complete sequence - all of the more than 50,000 human genes - and render them accessible for further biological study." (*Science. 279;36:1998)*

The HGP, originally a five-year plan, was updated and modified in 1993. Now, in 1998, somewhere in the range of 2½ to 3 percent of the human genome has been sequenced. Even that small amount of sequencing has provided a revolution in understanding how genes control health. As Bishop and Waldholz explained in their 1992 book, *Genome,* knowing the genes themselves does not predict how a person is going to get sick and die. Instead, it tells something about genetic susceptibility. It helps us understand how an individual's genetic characteristics may be expressed as early-stage disease when that person is plunged into a harmful environment.

It may also help us create an environment that could enable that person to optimize his or her pleomorphic genetic potential to express healthy aging throughout life. This theme was discussed in the recent *Science* magazine article, "An Independent Perspective on the Human Genome Project," (279;36:1998). The article describes the diverse scientific fields that are coming together to understand the human genome, its relationship to health and disease, and how that relationship can modify the way practitioners treat patients in the future.

Genetic research was brought to public attention by the Wilmut studies with the sheep, Dolly, and the lamb that was cloned from a single cell of an adult sheep. This research demonstrated the power of cloning technology. A fierce debate is taking place about cloning, ethics, and selecting for different types of characteristics through molecular engineering. (*Science.* 278;2038:1997) The debate over the future of this type of research, from a bioethics perspective, is certainly important. At present, however, the Dolly experiment - coaxing an adult differentiated cell into an embryonic state - shows the need to modify the tenets of Mendelian genetics as we learned them.

Health care is not as deterministic as we once thought it was. We used to believe a person got what she or he got and there was nothing she or he could do about it. Genetics and developmental biology were linear. We could do little to manipulate that genetic structure in terms of its expression as function. Now we know we can modify the function we possess at any chronological age by the way we treat the genome and various characteristics that are expressed. Although we age with time, we might be able to uncover messages associated with slowing biological age and expressing improved function. Although this concept seems implausible in the abstract, we know that if we get into a regular exercise program, our bodies look lean and fit, and we look younger. We know that if we smoke, we look older; we wrinkle faster. We know if we abuse alcohol or drugs, we age faster.

What this new view of genetics is really saying is that we are expressing certain messages in our genes and creating the environment of our bodies. We haven't changed the genes; we have just expressed our function in a different way. The Wilmut study brought the level of the magic of cloning to consumers' attention, but on a deeper level, it questions the determinism of genes in relation to health. Maybe it is not just the "luck of the draw" that contributes to our health and disease patterns after age 40. Maybe those patterns are a consequence of our genes coupled with the decisions we have been making about how to

treat those genes. That is a very different view of how much plasticity or functional capability there is in people's genes, based on the decisions they make and the counsel they receive.

The concept of functional genetic variability is being explored extensively in the literature. One paper, "Exploring the Metabolic and Genetic Control of Gene Expression on a Genomic Scale," appeared in *Science* magazine (278;1998:680). In this article, investigators from the Department of Biochemistry, Stanford University School of Medicine, discussed how metabolism responds to genes and how metabolic control can be modified through different environmental factors. Later in this issue of *FMU*, our Clinician of the Month Dr. Derrick Lonsdale will describe how genotype can be modified in its phenotype, its expression, through the way we manipulate the function of genes and their end products as metabolic process. Over the years, these processes lead to the accumulation of either function or the dysfunction we later call disease.

We are beginning to learn how to analyze uniqueness using DNA, micro-array analysis, and monoclonal antibody analysis. Through tests we have developed in the 1990s, we are beginning to define uniqueness, as Roger Williams would have wished for in the 1950s and 1960s. One example is genotyping the apoE type. Are we an apoE2, E3, or E4 genotype? Do we have a single or double allele of an apoE4 that encodes for greater risk to cardiovascular disease, dementia, and possibly even schizophrenia? If we do carry an apoE4 allele, what do we do to modify its expression so we do not get premature diseases?

These are exciting times in medicine. We have moved beyond a philosophy that advised, "Wait until it is broken and try to fix it," into molecular preventive medicine, which is the basis of functional medicine and the patient-centered approach. Many chronic symptoms patients experience, for which no clear diagnosis exists, are early warning signs of suboptimal metabolism that are a consequence of poorly expressed genetic characteristics. These symptoms accumulate in their damage until eventually a diagnosis can be afforded. If we recognize the symptoms early on and couple them with the antecedents, triggering events, and mediators, we have a therapeutic potential to modify the course of that metabolic dysfunction, improve outcome, and reduce pathology. That is the basic strategy and philosophy underlying functional medicine.

As the human genome gets sequenced, we will learn more and more about the loci on the genome that code for specific factors, many of which may be pleomorphic. Dr. Lin addressed this in an editorial in the *Journal of the American Medical Association* two years ago (1996;276:1511) following the Ambrosone paper on smoking in women and breast cancer. He pointed out that 7 percent of enzymes may have double copies, one of which is being expressed from genes under one set of environmental conditions and the other expressed under a second set of conditions. In other words, if a person eats, lives, thinks, and breathes a certain way, he or she might be expressing a poorly functioning enzyme. Under more optimal conditions, the genes may be expressing a better functioning enzyme from their genes.

What we want to do is optimize the expression of those characteristics that promote proper function. To do so, we discuss gene families and their relation to the control of enzymes, proteins, and messenger molecules. Ultimately, the goal is to establish a molecular milieu associated with resistance, resilience, organ reserve, and lower biological aging.

This leads to the discussion of predictive genetic testing. Some people are concerned that this testing will be used for discrimination, to prevent people from getting certain jobs and certain insurance benefits.

Those concerns are certainly valid, but the other side of predictive testing goes back to what Dr. Emanuel Cheraskin talked about 25 years ago. In his book, *Predictive Medicine*, Dr. Cheraskin argued that medicine of the future would involve improved ability to predict the genetic needs of the individual. The true future of preventive medicine, therefore, would not be just public health mandates of low cholesterol, reduced salt, regular exercise, and modest use of alcohol, but specific recommendations based on predictive genetic evaluation.

We are now seeing articles such as, "Predictive Genetic Testing: From Basic Research to Clinical Practice (*Science.*275;602:1998), that discuss such issues.

This genomic perspective leads us to recognize that disorders that cluster in families are often a consequence of the failure of the family to understand that if they were to modify certain nutritional and environmental characteristics in their lives, they could ultimately prevent or delay expression of certain diseases. Dr. Lonsdale will discuss this theme from his clinical experience, dealing with molecular genetic uniquenesses ranging from frank genetic metabolism disorders of infancy to milder forms of gene penetration into chronic symptoms, as seen in Gilbert's syndrome or other conditions. These milder conditions cause people to be functionally not quite as capable in mid life and to show the wear and tear earlier than people whose genetic needs are being met. The concept of genomic medicine and its relationship to functional medicine and patient-centered assessment frames a new paradigm for the future of medicine.

One interesting application of genomic medicine is to cardiovascular disease. For the past decade medicine has focused on the cholesterol hypothesis as the dominant theme in the production of heart disease. "Hypothesis" here is more than just an idle term. We still don't completely understand how cholesterol is involved as a contributing agent to heart disease. But we do know the two are strongly associated. When LDL atherogenic particles are in high levels in the blood, there is a much higher risk to coronary artery disease.

Statistically, every 1 percent reduction in elevated total LDL cholesterol yields a 2 percent reduction in the probability of heart disease. That fact strongly suggests that cholesterol is an important heart disease risk factor. In and of itself, however, it does not confirm causality; it merely indicates association. Cholesterol may be the "smoke" but not the "fire" so to speak. We have to find the actual fire if we hope to put it out.

INTERVIEW TRANSCRIPT

Clinician of the Month:
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JB: This month's Clinician of the Month, Dr. Derrick Lonsdale, has been a guide and an important figure in my intellectual evolution in the field of nutritional medicine. I first encountered Dr. Lonsdale's work in December, 1980, when he published a paper on red cell transketolase and its relationship to behavior

disorders in children. That paper, which he wrote with Dr. Raymond Shamberger at the Cleveland Clinic, appeared in the *American Journal of Clinical Nutrition*. (Dr. Lonsdale did his pediatric residency at the Cleveland Clinic and stayed on their faculty.)

Because of the "controversial nature" of this paper, the journal's editors felt compelled to include commentators on it, which was not common at the time. One of the commentators was Victor Herbert, M.D., a well renowned hematologist. The dialogue that developed between Dr. Lonsdale and Dr. Shamberger's paper and Dr. Herbert's comments framed the paradigm shift whose emergence we are witnessing today. Since our first meeting in 1980 I have met Dr. Lonsdale at a number of conferences. I have watched him as the pacesetter, showing where this field is going, the questions it is asking, and the kind of science that underpins appropriate answers. Dr. Lonsdale left the Cleveland Clinic in 1982 and is now in private practice.

JB: Derrick, welcome to *Functional Medicine Update*™. How did you get into that red cell transketolase work, which led to the paper I saw in 1980 in AJCN?

DL: I became interested in inborn errors of metabolism in Northeast Ohio, and I helped bring the screening tests for newborn babies into the State of Ohio. So I was looking for the emerging inborn errors of metabolism that were being described in great profusion. One turned up that was actually an intermittent disorder in a six-year-old child who had intermittent cerebellar ataxia. Nobody had been able to find its cause. After two years of thinking and study, we found that this child had a vitamin B1-dependent abnormality in pyruvate dehydrogenase complex. The defect was with the decarboxylating component. He responded to large doses of thiamin and became a pretty normal kid. He grew up and is now in his thirties. He had a brother with a less serious form of the same defect, who subsequently died.

This led me into a thorough research in the library on the metabolism, origins, synthesis, and everything I could find about thiamin, vitamin B1. I discovered that it caused a form of sudden infant death (SIDS). I became very interested in SIDS and starting treating babies considered to be threatened with SIDS, and they responded to thiamin. One thing led to another, and I gradually realized that much of orthodox medicine was really on the wrong track, and we had to change our ways to help the body in its efforts at self repair.

JB: In the 1980 article on children's health and red cell transketolase as a functional measure of vitamin B1 status, you and Ray Shamberger used the term "junk foods" to describe the diets of many of these kids who had these functional B1 insufficiencies. As I recall, Dr. Herbert took exception to the term. In the subsequent 17 years, do you think that term describes some of things that result in functional undernutrition?

DL:

Absolutely. I call it high-calorie malnutrition, and I think it's an extremely dangerous underlying concept in America. I think it's destroying millions of lives. It's creating a functional disease that is so widespread as to be a great threat to our whole society. I think it's the cause of malignant behavior. The limbic system of the brain is really driving the individual's character, and the cognitive brain, which should have a normal dialogue with it, is not powerful enough to say to the limbic system, "Hey, Buddy, you can't do that."

JB: For individuals listening who are not familiar with this functional B1 assay of using transketolase in the red cell, could you tell us what it is and how it relates to things people might see clinically in their patients?

DL:

It's an interesting test. It's an example of a biologic test for vitamin assay. The transketolase is an enzyme that occurs twice in the hexose monophosphate shunt. It is dependent on its cofactor, which is vitamin B1. You simply take a blood sample and do an analysis of the product from the transketolase, which is 7-septohexulose. You measure the amount that is being formed per unit of time: then you add the cofactor, which is the vitamin B1, and measure the acceleration in the activity of the enzyme. You come out with two figures, the baseline figure, which is measured in international units, and the second figure, which is a percentage acceleration of the baseline figure. A typical abnormality would be a relatively low figure for the first one; in other words, the transketolase enzyme is working relatively slowly. When you add the vitamin B1, then you get, say, a 30 or 40 percent increase, or acceleration in that enzyme activity, which demonstrates that it's responding to the cofactor.

JB: Clinically, when a person has a very high activation *in vitro*, showing functional insufficiency, what kind of symptoms might he or she manifest?

DL: They are the kind of symptoms we described in the paper. They're functional symptoms. People become disagreeable; they become irritable. They get so-called psychosomatic symptoms like tachycardia, headaches, gastrointestinal disturbances, abdominal pain, and so forth. They are troublesome people to deal with. When you give them the thiamin and correct the transketolase, their personalities change back to what they are underneath, and they are nice people.

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