November 2005 Issue | Richard Lord, PhD Director, Science and Education

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Welcome to *Functional Medicine Update* for November 2005. It is a pleasure to be with you as we prepare for what is going to be one of our most exciting symposia—Managing Biotransformation: The Metabolic, Genomic and Detoxification Balance Points—which will be held April 19-22, 2006 at the Tampa Marriott Waterside Hotel & Marina in Tampa, Florida. For those of you who have been attending our symposia on a regular basis, I want to emphasize that the date is earlier than usual. As a consequence of conflicts with the Mother's Day and Memorial Day holidays, we are holding the symposium in April. The weather should be beautiful in Tampa at that time of the year, and we look forward to being with you.

In preparation for the symposium, I thought it would be useful to talk about some of the major areas of learning that relate to biotransformation and detoxification. One of those is metabolism. When I say the word "metabolism," many of you may be experiencing a reaction. Think of wall charts, the Krebs cycle, intermediary metabolites, memorization, and trial-by-fire exams to reproduce a grade for your instructor at a level of proficiency that will enable you to move on to the next course. That kind of negative experience with metabolism science can prohibit the effective inclusion of some of these concepts into clinical practice. Clearly, in the course of this issue, we are not going to be able to do a complete tour de force on metabolism, but I thought we could start by introducing some of the principles that underlie the role that evaluation of metabolism can provide in managing some of the complex problems that patients present with that relate to altered detoxification and biotransformation. With that in mind as an objective for this month's FMU, I would like to move into how things have evolved over the past decade, as we begin to examine metabolic relationships to chronic illness.

Most of us studied some of the extraordinary discoveries that were made about the metabolic pathways during the first part of the 20th century. The pioneering work done in this area by early investigators was absolutely extraordinary. It is interesting to study the history of how different intermediary metabolites were discovered and analyzed, and the number of dedicated and exacting investigators who put together the metabolic pathways that ultimately became the charts that we all either have on our walls or have seen copies of. These are multiple-page charts that reflect the intermediary steps that take large molecules to small molecules, or small molecules to large molecules. Breaking large molecules into small ones is called catabolism; building up large molecules from small ones is called anabolism. The anabolic/catabolic pathways are included in the field of intermediary metabolism.

Intermediary Metabolism

We often think of intermediary metabolism as the source of energy of the body, and this is done through aerobic oxidative phosphorylation in the human species. These are the energy-producing pathways. There is much more to the metabolic pathways than just the energy-producing pathways. What has been learned over the last 50 years is that many intermediary metabolites are, in and of themselves, bioactively involved in other pathways. When we begin to look at these intermediaries in a much more realistic physiological manner, we see that they make up a complex web of interwoven wheels. Why did all these pathways evolve? Each is like a single puzzle piece, and they all fit together to form a mosaic called physiological control. An intermediate (e.g., pyruvate, lactate, phosphoenolpyruvate), in and of itself, is a stepping stone toward another metabolite, but each one of those intermediates also has its own biological activity, and they feed back into other pathways. That leads to a very interesting interconnectivity concept of metabolism, not just individual pathways running in isolation, as you might see them on a wall chart.

These pathways occur in time; they change. They are like the tide; they can rise and fall, based upon what flux of need is traveling throughout the body. Different tissues have varying levels of activity in different pathways, the liver being a very active organ involved with intermediary metabolism. We thought the fat cell, or adipocyte, was less active in the energy-producing pathways, but now we recognize that it has more activity relating to the production of adipokines or adipocytokines, which are neuroendocrine modulators that come from fat cells. The differing tissues show differing activities in these metabolic pathways, and they can change in time based upon need, or as it pertains to changing environment, age, stress, and the like. Obviously, we are talking about complexity. To take just a snapshot of metabolism and try to understand the whole of the body from it is simplistically nave, because we need to develop a running record of how metabolism works under different circumstances to understand each individual.

With that limitation, we are still able to make some first-pass better understanding of the individual characteristics of a person by looking at certain metabolic patterns and profiles. When we do that, we are led to asking what to analyze. What specific markers would be useful for understanding aspects of metabolism? Do we look at the outcome of metabolism, the so-called Plato's myth of the cave, where we are looking at the shadows and the surrogate markers, or do we look at the actual intermediary metabolites themselves and try to piece together the patterns from the inside out? These are all important questions that I hope we will be able to address, at least partially, over the course of this month's FMU. Certainly, this month's Clinician/Researcher of the Month, Dr. Richard Lord, an expert in this field, will give us some guidance on this issue. I think you will find his comments to be very helpful, especially if you are new to this field.

With all of that as background, let us now move to what has often been called the nutritional phenotype. What I want to address is how we are contextualizing the most recent understanding of nutrient effects on metabolism from a biomedical and health perspective. In the past, most of us thought our metabolism was hard-wired, based upon our genes. Based on what we received from our mothers and fathers, these genes determined our metabolic profiles, and in cases of inborn errors of metabolism inherited from our parents, we could get the "bad luck of the draw." In those cases, conditions such as Tay-Sachs, Wilson's, Gaucher's disease, or megaloblastic anemia might be present. Therefore, the concept of metabolism was to look at either the genetic alteration of metabolism (in the extreme case, inborn errors of metabolism), or to examine it in pathological cases (such as diabetes or other metabolic disorders), and assume that the absence of either a genetic metabolism disorder or a frank metabolic disease seen during infancy meant having adequate and normal metabolism. But as we began to study these pathways more fully, we recognized that there are variations on a theme that we all possess, based on our genetic uniqueness, and

that these variations give rise to different responses to the environment—stressors, infection, and different states of arousal to different stimuli. This, in part, is a reflection of our uniqueness as an individual.

The markers we might start examining in order to look at some of these metabolic outcomes include panels such as urine or plasma organic acids, urine or plasma amino acids, or fatty acids, which would be either red-cell fatty acids or plasma fatty acids. Various aspects that relate to vitamin and mineral nutriture might also be included in a metabolic profile. I am building up a fairly broad array of potential tests with literally thousands of different data points, which could confuse someone who is used to making a chemical assessment of the body based upon a comprehensive multi-analyte profile, such as a SMAC 24, where only 24 variables are examined, one at a time.

In the case of metabolic assessment, we may be looking at hundreds of variables. That obviously becomes very complex, and we have to start examining patterns. Rather than individual analytes, one at a time, we have to look at how they interact in patterns. This defines what has been called the phenotype of the individual, the metabolic phenotype. We now know that nutrients and nutritional status play a role in determining our phenotype. The phenotype is the expression of our function that arises out of the pleuripotentiality of our genes. What does that mean? It means that our genetic inheritance does not, in and of itself, dictate exactly how we are going to function at any one moment. Rather, it is a potential for how we might respond to a specific set of environmental stimuli. The actual phenotype, or our expression of function, is a mix between our genetic potential and the environmental response factors that give rise to our phenotype. We talk about genomics being translated into proteomics, which are translated into metabolomics, which ultimately are translated into phenomics, or the phenotype.

How a person is functioning and what his or her physiological status is, with respect to each specific nutritional and lifestyle input to gene potential, defines what has been called the nutritional phenotype. As we look at the nutritional phenotype in the age of metabolomics, we begin to see that there is an interesting interface between gene potential, and nutrition and lifestyle inputs, and how those influence protein expression through mRNA into proteins such as enzymes and ultimately, into metabolic control points. When examining organic, amino, or fatty acids, we are not only looking directly at what a person has eaten, but also indirectly at how the control points in the nutritional phenotype are influenced through aspects of metabolic, proteomic, and genomic control.

Our understanding of the relationships among nutrition, integrative metabolism, and health is being revolutionized by advances being made in genomics. Obviously, this interrelates with complex physiological function such as detoxification and biotransformation. The detoxification enzymes are part of the complex array of enzymes that defend us against an imperfect environment. The environment has never been perfect for humans, so we have had to defend ourselves through natural selection over time against these imperfections, and that is part of our detoxification and biotransformation system.

Our detoxification enzyme system, be it either the phase 1 cytochrome P450 or the phase 2 conjugase enzymes, is controlled by a series of genes. In fact, when we begin to look at these families, we find they go way back in history, which means that this has been part of the evolution of mammals since their early beginning. Animals could not have survived without a detoxification system; therefore, we see them as very highly diversified—polymorphic enzymes that control the metabolic principles associated with detoxification. The cytochrome P450 enzymes are the oxidative mono-oxygenase enzymes, so they are involved with oxidative chemistry, and therefore influence oxidative stress and interface with

mitochondrial oxidative phosphorylation. There are indirect associations with metabolic function, oxidative chemistry, mitochondrial chemistry, and ultimately, with oxidative stress.

With that in mind, this ties a different strategy into how lifestyle, diet, and environment influence disease and/or wellness, and regulate the gene expression that becomes our metabolic outcome—the metabolome—which defines our phenome, or phenotype. The practitioner of the 21st century must understand genetic uniqueness, as well as the antecedents that precede the onset of chronic symptoms, and what triggers influence production in an individual of various messenger molecules and various metabolic outcomes. The patterns derived from a patient's history, family history, evaluation of the environment and diet, and certain biochemical markers, are then used to piece together a mosaic as to the etiology of chronic symptoms. That leads to a tactical approach toward the amelioration of the symptoms and, hopefully, directing attention toward the triggering causes that reinitiate these particular processes leading to long-term, chronic illness.

A very interesting article was published in the *Journal of Nutrition,* titled "The nutritional phenotype in the age of metabolomics."[1] It was written by a Blue Ribbon panel of investigators whose names are quite well known in the nutrition research community, from the American Society for Nutritional Sciences. It was a long-range planning committee. When they started looking at the concept of the nutritional phenotype, they describe the fact that most of us were trained in assessing nutritional status using things like anemia, body mass, protein levels in the blood, albumin levels in the blood, and various markers for insufficiency that might pick up occult scurvy, beriberi, pellagra, xerophthalmia, rickets, or marasmus.

They are now saying that if we really want to modernize the concept of the nutritional phenotype, we need to be looking at biomarkers beyond that of just physical attributes that define the metabolic effects of nutrition. These are things like insulin resistance and metabolic syndrome, where we are looking at the triglyceride-to-HDL ratio, which is a surrogate marker for insulin sensitivity. As the triglyceride-to-HDL ratio goes up, we start to see that the person with a higher degree of insulin resistance has more relative risk toward dysinsulinism and problems associated with diabetes, heart disease, or vascular disorders. As we look at these surrogate markers that indicate altered metabolism, it opens the door to go to the next level and ask what caused the elevated triglyceride-to-HDL ratio. What is the metabolic cause? We start digging deeper by looking at things such as organic, amino, or fatty acids, vitamin and mineral levels, or doing other types of functional physiological testing in order to define the nutritional phenotype and how that arose from various aspects of genomic, proteomic, and metabolomic function.

You will notice I am talking about functional measures. I am excited about how often the terms "functionality" and "function" are slipping into the medical and nutritional literature. More and more, it is being recognized that in order to understand metabolic effects, we need to understand function, especially at the cell, physiological, and organ-specific levels.

The nutritional phenotype and its connection to functional measures of metabolic sufficiency takes us into a series of differing multidisciplinary assessments, looking at nutrition, family history, exercise, and the psychology of patients, as well as the environment in which they live and the kinds of environmental exposures they face, which leads to a different type of evaluation tool and panel of investigation.

What are the opportunities and challenges of being involved with metabolomics in assessing the origin of chronic illness? That leads us to another wonderful paper in the American Journal of Clinical Nutrition,

coauthored by a variety of very well-known investigators in the field of metabolomics, including Dr. Helen Roche, who is actively involved in the genomics of metabolic syndrome and its relationship to diet.[2]

Metabolomics has been widely adopted in pharmacology and toxicology, but has not been used much in human nutrition. Only recently has this term started to weave itself into this arena. For those of us who have been in the field of molecular medicine for decades, this is an old concept; but for contemporary nutrition training, it is a new concept. The ultimate goal is to understand the effects of exogenous compounds on human metabolic regulation, and these compounds could be food and nutrients, or they could be things like toxins. All of these things influence metabolic outcome through the signaling pathways. The application of metabolomics to nutritional research is full of unique challenges. Little is known of the extent to which changes in the nutrient content of the human diet elicit changes in metabolic profiles. There are only a few experts in the field who have spent their lives studying that, one of whom we will have the fortune of listening to later on this tape-Dr. Richard Lord.

Moreover, the metabolic signal from nutrients absorbed from the diet must compete with myriad, non-nutrient signals that are absorbed, metabolized, and secreted in both the urine and saliva as a consequence of toxins in the environment, or substances produced by endogenous organisms with their own metabolic personalities. These are symbiotic, parasitic, or commensal bacteria in the gut that are also producing substances that the body has to manage, detoxify, and excrete. It is the total load of these messages or signals-some coming from the diet, some coming from endogenous metabolites, and some from exogenous environmental sources-that triggers alteration in metabolic function. That is why this field is both exciting and complex, because it is not as easy as just taking a number from a lab test, coming back with a diagnosis, and administering a single agent for remediation of the symptom. In this case, it is necessary to look at patterns, and the complex interaction of the environment with the genes and the lifestyle of the patient.

The outcome of this type of strategy is to better define how that person expresses chronic complaints, rather than just uncoupling the complaints by giving a symptom-suppressing medication. We are seeking the origin of the complaint based upon the interface of that patient with his or her environment. This is obviously the strategy that leads to personalized medicine, which many people feel is the medicine of the future. It still has not been put into a mechanized form where it is an algorithm that can be easily plugged into the computer to produce a solution. It forces the clinician who chooses to engage in metabolomic thought and intervention to become familiar with pattern recognition through his or her own thought process. This is exciting and challenging. Interaction of genes with the environment is a complex process. The outcome of all of this is that if you start asking these questions, even at a simplistic level, it leads to possibly discovering how a patient evolved to the illness they are expressing, with symptom severity, frequency, and periodicity. The results may be very different than simply reading the signs and symptoms and trying to come up with a diagnosis.

Let us take this general discussion to one that is more specific. Let us look specifically at protein and reflect on its metabolomic effects. Protein is a very interesting family of macronutrients. We think of it as the building blocks of our endogenous protein; that is, we eat dietary protein to help build our own proteins *in situ*. Proteins are complex. They are composed of amino acids, like little beads on a chain, which are broken down into polypeptide chains and then into individual amino acids by digestive processes. The amino acids are transported across the lumen of the gut through active transport and

passive diffusion, and ultimately reach the liver, where they can be resynthesized or modified through transamination into other molecules. Eventually, a series of endogenous proteins are produced—rebuilt from the individual amino acids—based on the genetic template of the individual.

Albumin

One of the major plasma proteins is albumin, which is synthesized in the liver, and is a major transport protein in the blood. Albumin is uniquely high in its percentage of what are called branched-chain essential amino acids. People have asked why albumin, a major plasma protein, has such a high level of essential amino acids. One of the teleological explanations is that because the body needs to maintain adequacy of the essential amino acids, which are not able to be made from other amino acids and must be consumed directly in the diet, albumin is a control or message protein. Albumin is very high in the essential amino acids and, when a person is on an amino acid-deprived diet, or on an imbalanced diet that does not have adequacy of the eight essential amino acids, particularly the branched-chain amino acids like leucine, isoleucine, and valine, the level of plasma protein albumin is decreased, resulting in hypoalbuminemia. There is at least a partial relationship between dietary protein adequacy and dietary protein quality, and the levels of the major plasma protein serum albumin.

What do we know about these amino acids, other than that they are very important in building the structural substances, like collagen and elastin, that make up our connective tissue, and catalytic proteins that make up the enzymes that regulate function of metabolism in all cells? Beyond that, some amino acids can have direct metabolic activity and serve as putative precursors to neurochemical messaging substances. For instance, the amino acid tryptophan is the precursor to the serotinergic family of neurotransmitters. Phenylalanine, another essential amino acid, is the precursor to the dopaminergic amino acid family through adrenaline and noradrenaline. These amino acids play roles both as parts of protein and as single amino acid-active biological response modifiers. The amino acid glutamate has neurochemical reactivity in the brain. Arginine plays a role in nitric oxide production. Glutamine plays an important role in muscle and gut physiology, and the list goes on. We have all heard about lysine and its role in herpes management. Clearly, it is not just proteins as a combination of amino acids, but also amino acids by themselves that may have effects on metabolic function.[3]

When we eat protein, we are eating information. You have probably heard me say in the past that I believe food is information. It is more than just raw calories; it contains information molecules that modulate function through serving as mediating substances for various functions. Depending upon what information we eat, our genes and our books of life, as encoded by our genes, are read in different ways. If we eat information that is dysfunctional, we get a dysfunctional read, or an alarm, which produces a different outcome than if we eat information that speaks to our books of life in a way that produces harmony. This is a general descriptive illusion as to how diet plays a role in modulating gene expression patterns and ultimately, proteomics and metabolomics. We are really eating information as it pertains to the processing of gene expression patterns through mediators, these nutrient signaling pathways.

Let's go back to protein. Recently, a number of papers have appeared suggesting that protein-rich diets induce satiety, as contrasted to highly refined carbohydrate diets.We might ask why a high-protein diet would induce sustained reductions in appetite ad libitum calorie intake and thereby lower body weight, despite compensatory changes in diurnal plasma leptin or ghrelin concentrations. One of the explanations is that it seems to have an effect based upon the influence some of the amino acids have on the neurochemical signaling mechanisms that regulate appetite. This may be either from the gut-brain

connection, the hypothalamus connection, or from other tissues that, like the liver, help regulate signals to the brain that ultimately control appetite at the lateral nucleus of the hypothalamus.

In a paper in the *American Journal of Clinical Nutrition* looking at satiety, energy balance, and adipose tissue physiology, and its relationship to dietary protein or carbohydrate intake, the investigators found that an increase in dietary protein from 15 to 30 percent of calories at a constant carbohydrate intake produced a sustained decrease in ad libitum caloric intake that was mediated, it seemed, by increased central nervous system leptin sensitivity, and resulted in weight loss.[4]

If we ask if there are bioactive ingredients in food beyond that of just calories, I believe the emerging answer is yes, and that these help to regulate metabolic function. Unfortunately, we got "washed" with the George Atwater concept of the calorie. Certainly, the calorie is a valuable concept. I do not want to throw the baby out with the bath water. But the calorie would imply that all calories are processed in the same way, regardless of the food that they are delivered in. Whether it is a calorie coming from fat or one from protein or carbohydrate would really not matter, because they are all energy units, which is the ability to do work, or to produce heat. Now we recognize that different nutrients may have differing influences on how those calories of potential energy are actually converted into various forms of metabolic energy. That is a remarkable change in our understanding of the role that diet and nutrients play in the regulation of metabolism.

Dietary Protein and Satiety

Could there be a satiating induction by dietary protein? The answer appears to be yes, in part. There is a nice editorial that appeared in the *American Journal of Clinical Nutrition*, titled "The satiating power of protein—a key to obesity prevention?"[5] In this paper, the author states that if we really look at the inclusion of higher amounts of protein than previously recommended, that now appear in the guidelines from the Institute of Medicine, that there is no clear evidence that a high protein intake increases the risk of renal stones, osteoporosis, cancer, and cardiovascular disease. High protein intake does appear to be associated with lowered hunger and improved satiety, and thereby may help lower excess calorie intake and body fat accumulation. This ties back to the relationship to glycemic response to a meal and neurochemical messages received by the hypothalamus that regulate appetite. Dietary protein affects metabolism in more ways than just as a source of calories or building blocks for endogenous protein.

The Effect of Different Proteins on Insulin Levels

Insulin action can be modulated by dietary proteins and their constituent amino acids. Different proteins may have different effects on postprandial insulin levels. This is another important part of the story. We often generalize these nutritional influences on metabolism, thinking that if we use the words "carbohydrate," "fat," or "protein," that they are inclusive to all carbohydrate, fat, or protein. But specific to protein, we now know that is not true. Differing proteins—animal or vegetable proteins—have differing amino acid ratios and different amino acid percentages, which influence their effects on genomics, proteomics, and metabolomics and the outcome into the nutritional phenotype. If we ask what type of dietary protein most influences postprandial insulin levels by helping to smooth them, it turns out to be various vegetable proteins, as contrasted to animal proteins.

It is a much more complex metabolic web than we previously thought. We thought just eating so many calories would lead to feeling full, and we would lose weight. Now, we are beginning to see that different signals picked up by different nutrient-sensing receptors influence metabolic outcome in ways we did not

previously understand.

As a clinician, perhaps it is enough to say that certain dietary proteins produce differing effects on postprandial insulin and that we shouldn't lump everything together and tell patients to eat a high-protein, low-carbohydrate diet and everything will turn out fine. What kind of carbohydrate, what kind of protein, and at what particular level?

Let us move on to how the branched-chain amino acids (BCAA) are involved in specific functions beyond that of building up structural or enzymatic proteins. BCAAs play roles in brain function. Certainly, the work of John Fernstrom in the Department of Psychiatry and Pharmacology at the University of Pittsburgh School of Medicine is foremost in that area.[6] He was previously with Vernon Young at MIT. Dr. Young recently passed away in an untimely manner, and what a tragic loss to our field. He was one of the most important, principal investigators in the area of protein and amino acid physiology. Dr. Fernstrom has continued to study the role that amino acids have on central nervous system function. BCAAs influence brain function by modifying amino acid transport at the blood-brain barrier (BBB). Transport is shared by several of the large amino acids, notably the BCAAs and the aromatic amino acids, which include phenylalanine and tyrosine. Therefore, there is competitive activity for transport of the BCAAs versus the aromatic amino acids.

BCAAs versus the aromatic amino acids

High exposure to BCAAs can drive particular amino acids into the brain via these transporters, modifying the ratio and/or amount of amino acids, like the aromatic amino acids, which serve as precursors to the dopaminergic neurons. We might say that neurotransmitters such as dopamine and ultimately, adrenaline and noradrenaline (derived from phenylalanine and tyrosine), may be modified by high exposure to BCAAs. In some cases, that may be desirable if a person has an overactive dopaminergic pathway. In other cases, it may not be so desirable, because it may imbalance the appropriate production of dopaminergic neurotransmitters. These are bioactive substances and, to use amino acid therapies, we have to be somewhat cautious about the premise that a little is good so a whole lot more ought to be better. We ought to be thinking about balance.

Brain Amino Acid Requirements, Toxicity, and Leucine

That leads us to ask if we could get into a toxicity relationship with excessive intake of these brain-active amino acids. The answer is certainly yes. For example, let's look at the relationship of leucine and glutamic acid with respect to toxicity. Glutamic acid is an important excitatory neurotransmitter in the brain and the intra-synaptic glutamate level must be kept low to maximize the activity and not overly activate the cells through the glutamate pathway.

"The brain must also provide neurons with a constant supply of glutamate, which both neurons and glia robustly oxidize. The branched-chain amino acids (BCAAs), particularly leucine, play an important role in this regard. Leucine enters the brain from the blood more rapidly than any other amino acid. Astrocytes, which are in close approximation to brain capillaries, probably are the initial site of metabolism of leucine. A mitochondrial branched-chain aminotransferase is very active in these cells. Indeed, from 30 to 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of all α-amino groups of brain glutamate and glutamine are derived from leucine alone. Astrocytes release the cognate ketoacid [α-ketoisocaproate (KIC)] to neurons, which have a cytosolic branched-chain aminotransferase that reaminates the KIC to leucine, in the process consuming glutamate and providing a

mechanism for the "buffering" of glutamate if concentrations become excessive."[7]

The process I am describing, which sounds very complicated, ultimately helps to control the brain concentration of these branched-chain ketoacids, and interrelates with glutamate and neuroexcitation. Imbalances can lead to a depletion of glutamate and a consequent reduction in the concentration of brain glutamine, aspartate, alanine, and other amino acids. This results in a compromise of energy metabolism of the neuron, which ultimately interrupts the malate-aspartate shuttle in the brain, lowers protein synthesis, and increases oxidative injury in the neurons in the central nervous system. Here is a case where if you gave too much of the BCAA leucine, you could interrupt proper brain biochemistry, brain regulation of neuroexcitation, and mitochondrial neuronal function. To date, studies suggest abnormal levels may only occur when a metabolic defect blocks metabolism of BCAA, such as Maple Sugar Disease, and suggests these amino acids aren't toxic at reasonable levels in healthy individuals. But, high dosages over extended times has not been adequately studied to form secure conclusions.

We start to see that there may be places for safe and effective use of BCAA therapy, but we shouldn't assume that any dosage is going to be safe and effective. In fact, we ought to be looking at the individual responses in people by evaluating their amino acid balances and their clinical outcome criteria. That, of course, results in our starting to understand more about intermediary metabolism beyond that of just inborn errors of metabolism, and understanding what panels and what tests might be employed to at least take a look at the metabolomic uniqueness of that patient and to titrate therapies against their metabolic web.

There is probably no one better that I can think of to help us understand this interconnection and how to approach assessment than our Researcher/Clinician of the Month, Dr. Richard Lord who, for 30 years, has been making this his principal point of study.

INTERVIEW TRANSCRIPT

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JB: It's time for our Researcher/Clinician of the month. We're very fortunate to have someone who will guide us in the area of metabolism, which, for most of us, was a rite of passage in school. You probably recall that your basic metabolism or biochemistry course was something you had to do, but which you weren't looking forward to. We are going to revisit metabolism in terms of functionality. I know no one better to help us through the daunting process of understanding metabolic pathways than Dr. Richard Lord. Dr. Lord received his PhD in biochemistry from the University of Texas in 1970 and went on to post-doctoral fellowships at the Clayton Foundation Biochemical Institute, the University of Arizona, and the National Institutes of Health. He served as professor of chemistry for 10 years at Life College, where he was instrumental in the initiation and design of a Bachelor of Science degree program in Nutrition Science. He has been actively involved in educating people in our field for the better part of 20 years. He maintains a very high technical content of information. Along with Dr. Alexander Bralley, he is co-author of Laboratory Evaluations in Molecular Medicine (Institute for Advances in Molecular Medicine; 2001),

which I consider a landmark book in our field. He currently serves as the director of science and education for the Metametrix Laboratory in Norcross, Georgia.

It is with great pleasure, Richard, that I welcome you to Functional Medicine Update. When most of us learned about metabolic disorders, we learned about them in the context of genetic metabolism and disorders of infancy, the inborn errors of metabolism, such as Tay Sachs, Wilson's, Gaucher's, Hartnup disease, or phenylketonuria. We were somewhat biased that these things were very uncommon in the population at large, because these genetic metabolism disorders are very rare on a frequency basis, so we could forget them, unless we were going to refer to a specialty in medicine that was focused on these conditions. Now, we have a better understanding of biochemical diversity, which Roger Williams first brought to our attention. It is recognized that perhaps some of these conditions are more frequent than we thought. And, there are less severe conditions that are not controlled by one point gene mutation, but may have polygenes involved. That opens the door to being more attentive to metabolism.

You were telling me off-line that the example of phenylketonuria is probably a good place to start our discussion—to understand the difference between a frank inborn error of metabolism and milder forms of it that may exist more frequently in populations. What are your thoughts?

Frank and Mild Incidences of Phenylketonuria
RL: It's a pleasure to join you today, Jeff, and to be able to discuss some of these concepts with you. Your introduction certainly takes me back a way. When I was getting my degree in Texas, the lab that I occupied shared a wall with Roger Williams, who was a Professor Emeritus there at that time. Little did I know how much the ramifications of his work would have on my life. When I was there, I became aware of what was going on. There was a great team of researchers focusing on nutritional science, including Karl Falkers, Lester Reed, and William Shive. I read Dr. Williams' book on biochemical individuality and nutrition against disease, and became pretty impressed with the knowledge base. I decided it was the kind of thing I wanted to pursue. Finally, I got the opportunity to move into this field and, during the 10 years I was teaching, I tried to impress upon the students the importance of the underlying biochemistry.

Genetic Mutations in Phenylkotonuria
Just recently, I have tried to write another version of a chapter on amino acids, and find myself right in the middle of the whole issue of the genetic diversity that you just mentioned. For example, as I write on phenylalanine and tyrosine, most clinicians will have enough recall to know that has to do with phenylketonuria (PKU), a disorder that's tested on neonates in virtually every state. A small percentage of the population has a manifestation that has to be dealt with immediately after birth to prevent developmental disorders. I came across an updated table on the number of genetic mutations involving that disorder that manifests to one degree or another. It turns out there are over 400 of them. Many of them are in the phenylalanine hydroxylase enzyme, preventing proper conversion of phenylalanine to tyrosine, resulting in an accumulation of phenylethylamineand phenylacetic acid.

There is a whole separate group that involves a different enzyme that creates the cofactor. We have the enzyme itself and we have to be aware that it can create a metabolic block. If it has its cofactor, then it may be able to limp along, but you may have a perfectly good enzyme that doesn't have a cofactor because another enzyme has a problem. The enzyme GTP cyclohydrolase is involved in the conversion of tetrahydrobiopterin (BH4), and now known to produce a whole different set of underlying metabolic conditions which manifest as the same type of thing you see in PKU. In fact, it's still a type of PKU. It

frequently happens.

It's funny how events juxtapose in our lives. Right after doing this research and delving into it for a few days, I got a consultation call about a plasma amino acid profile on an adult woman who had manifestation of various chronic conditions. She had a high/normal phenylalanine (almost high), and a completely low tyrosine. I proceeded to inform the physician that he needed to consider BH4. Of course, he hadn't heard about that. I hadn't been saying much about it in consultations until I renewed my focus on it. It just reminded me of how the procedures work in this field. Those of us who have the luxury of some time to delve into the scientific literature, become aware that there is a whole new spectrum of information that we can apply to day-by-day clinical conditions, and then we actually see a clinical condition that solidifies our understanding of how relevant these otherwise esoteric-appearing scientific reports can be.

JB: Richard, you have touched upon some really exciting thoughts. As you were speaking, I was reminded of the paper that appeared in The New England Journal of Medicine in 2002 on mild-to-moderate forms of PKU that they were able to ameliorate, not by putting the infant or child on a low-phenylalanine diet, but by giving them supplemental doses of BH4, which is exactly consistent with what you just described.8 Sometimes, we think these genetic conditions are hard-wired and there's nothing we can do about them. But then, we see that there are plasticities around how some of these enzymes may function, based upon coenzyme binding or, as Bruce Ames or Linus Pauling have talked about, mass action effects, and that might help to override some of these genetic small points in the pathways.

Tetrahydrobiopterin
RL: Exactly, and now, it turns out that using BH4 in some areas is fairly routine in PKU, just to assure that you have adequate cofactor. We see that in one of the very earliest genetic conditions, we are still evolving in our general medical understanding of giving the patients a little BH4. Now, we are gleaning the reasons that these things fit together this way. Of course, as I'm sure you can appreciate, Jeff, once you latch on to a concept like that, and your understanding and knowledge base fits in nicely with what you've known before, it immediately leads to other connections to this web that we talk about. For example, BH4 is extremely susceptible to oxidative damage, and it's one of the reasons it should be considered a conditionally essential nutrient, even though human tissues can produce it. Even if you have an adequate GTP cyclohydrolase without any mutations that make it a warped enzyme, you still may have oxidative stress that impinges on your ability to sustain BH4 levels. Now, we're into considering antioxidants and how to avoid oxidative stress, the inflammatory cascade, and so forth. Isn't it fascinating how it goes on and on?

JB: You've done a marvelous job in the book that you and Dr. Bralley authored, and also in your teachings over the years, to focus on and emphasize the web-like attachment. When the web is distorted at any point, the whole of the web is distorted. It's not just one cell, because they're all interconnected. As I recall, there's a BH4 salvage pathway in cells that allows it to be resynthesized as it's broken down. That requires 5-methyl-tetrahydrofolate through the methylene-tetrahydrofolate reductase enzyme. What if a person has a double (homozygous) MTHFR polymorphism, which is not that uncommon (10 to 15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} penetrance in the population)? Perhaps they would be more likely to have a low BH4 level. If the individual has a covariable low GTP cyclohydrolase, there is a double-barreled problem. I recall some papers in which they've given high doses of folic acid and have seemingly overcome some low levels of BH4. Have you

seen any studies that show that folic acid could help to stimulate high-dose BH4 activity?

RL: Yes, certainly. That's one of the factors. In some studies on vitamin C helping, it wasn't just mechanistically tied to the regeneration pathway, but probably into the whole oxidative damage and removal of the BH4. That's just one other aspect of the web of interactions that plays in. We see it playing out in the data that we look at in fascinating ways, also. I look at it this way. For every well-known, well-established genetic inherited disorder of metabolism, there are many others, literally hundreds of other finer mutations, or finer alterations of the enzymes involved that result in manifestations that you may or may not even detect, depending on how closely you look. That is true for one enzyme, such as phenylalanine hydroxylase, and now we have the GTP cyclohydrolase, but there are other enzymes involved, as you mentioned, in tetrahydrofolate regeneration. Then, you understand that when a given patient is sitting in front of a given practitioner, at any point in time, with some manifestation of their condition due to their genetic disorders, the chance that you can modify it becomes very great.

JB: That is the reason for a clinician spending some time with this material. Often, I've heard clinicians say that they didn't go to medical school or to health sciences school to become a biochemist. I don't believe your objective, and it certainly is not mine, is to make everybody into biochemists, but there's some level of understanding of these connections that results in the ability to construct a different house. If all you have is a hammer, then you're going to produce a certain kind of house, but if you have a big tool kit, you're going to have more diversity in how you can build a complex structure.

Focusing on Specific Markers

RL: Exactly. You reminded me of how much more relevant it is for a practitioner who's out there struggling with having to go back and learn biochemistry. They'll ask me (and I'm sure they ask you), where they can get a book to refresh them on biochemistry. Of course, I taught from the literature for 10 years. You don't want to send them back to that level because it's complicated. They want to know what part is the most important, as any student does. Of great assistance is for them to put their hands on some real information. We produce laboratory results. If a doctor orders a test profile, we're able to tell him or her that we'll look at some things and ask some questions. When I was in practice doing clinical things, I sort of hung my hat on whether the patient who comes in with a skin condition had a problem with fatty acids, vitamin A, or zinc. It could be any of those things and you would like to be able to settle the issue. You can order a mineral profile and check the zinc, and it looks normal. OK, let's move on. Taking that approach, you learn how to direct your attention at specific points of markers that can guide you to the problem.

JB: That's very well said, and for most of us, we learn by doing or by teaching. You can study it, but it's never fully codified in the neurons until you do it and actually see how it works. I think you're right; learning by doing is the way to learn these particular pathways. One of the questions that often comes up when we start the doing is, what level of some of these substances can be used safely, and what levels are required? There is still the resident feeling that as you go to higher doses of even nutrients, that you're just producing expensive urine and you're not actually producing any benefits. Here's another example of why the testing can be useful, because you can track clinical response to changes in objective criteria based on the metabolic profile. You're not shooting in the dark. You have a much more objective set of criteria upon which you're judging the success of therapy.

Tryptophan

RL: Right. In fact, I'd take that a degree further. Not only do excessive nutrients produce expensive urine;

they can actually become part of the toxic burden because they have to be metabolized. It just loads up the liver system. For example, there's one area that we see routinely in looking at our laboratory data that illustrates that, and that is tryptophan. I've got a lot of mixed emotions about tryptophan status and how many people are still reluctant to deal with it. Certainly, the companies that handle amino acids, may be reluctant because of the old bugaboo that came up from the unfortunate incidence of some impure tryptophan that was produced. On the other hand, it produces these wonderful sleep effects and it also produces serotonin that helps mood disorders and so forth. There's a swing back to using tryptophan, but we see cases where tryptophan is being loaded at perhaps a gram or two a day, or just a gram or so at night. We monitor tryptophan pathway metabolites, particularly the kynurenineand serotonin pathways.

The Kynurenine Pathway
The kynurenine pathway is a fascinating system because it's the pathway that you first learn about in nutritional studies which allows tryptophan to be converted to niacin. You have to have B6 and then you can make niacin from tryptophan. It turns out that the intermediates of that pathway are wonderful markers for B6 insufficiency. We measure xanthurenic acid and it's a byproduct of the kynurenine pathway from tryptophan. If it goes high, it means you don't have enough B6; at least, that's one likely interpretation. We see cases where the patient has been loaded up with lots of B6, perhaps 100 mg or more in some cases, and this has gone on for quite a long time. Now, they've been monitored and they should be fairly well replete in B6. Then, we do a test and find a high xanthurenic acid. We have to go back and ask if they're taking tryptophan.

I had a case not too long ago that we're tracking now. The basic problem in this individual, who is a high-powered executive, was that he couldn't sleep. The practitioner was giving him L-tryptophan and it was loading up the kynurenine pathway so heavily that even with adequate B6, his xanthurenic acid was very high and, at one point, his quinolinic acid went high, which is a product of the macrophage kynurenine pathway that, it turns out, impacts the brain and can have counterproductive clinical outcome because it tends to induce insomnia. So, we have to be careful. When you see that, you need to back off on the tryptophan and deal with the other issues. For example, that patient had a low magnesium. When you see that red cell magnesium is low, maybe that's where you can focus the intervention.

My emphasis these days is to help practitioners understand that once they grasp the power of nutritional therapies in general, and when they focus those therapies, the power of the intervention goes up exponentially.

JB: That was a marvelous specific example. I think everyone could get their arms around that. For those individuals who have not been in the field as long as you have, you were referring to the eosinophillic myalgia syndrome, or EMS, that occurred in the late 1980s from the Showa Denko- produced tryptophan from Japan that unfortunately had unusual impurities in it—formaldehyde tryptophan dimers—that created an immune response that unfortunately led to death in about 37 people, and thousands of other people were adversely affected. It's always important for us to recognize what we're doing, how we're doing it, and the purity of the materials we are using.

I was also intrigued to hear you talk about the quinolinic acid story. We've heard a lot recently about neuroactive agents in methyl-D-aspartate, or NMDA receptor sites, and how that causes neuronal activation leading to hyper-excitability. Quinolinic acid is one of those compounds that serves as a mimetic of NMDA activation. When we talk about hyper-arousal or neuroexcitotoxicity, we have to be

very mindful that these compounds we consider as food-derived materials, like tryptophan or phenylalanine, based upon their metabolism and the sensitivity that individuals may have, can have a variety of effects, from beneficial to not-so-beneficial, in fact even deleterious. I think you've made that point very clear. Let's not shoot in the dark. If we're doing metabolic medicine, let's have the right objective markers to know what we're doing.

For the people getting into this field, sometimes there is a level of confusion with the literally hundreds of different tests that can be done. From your experience, how would you recommend starting? Would it be organic acid testing to look at Krebs cycle intermediates? Would it be fatty acid testing? Would it be amino acid testing? Normally, a doctor will probably not order a full metabolic profile because of the expense to the patient. They have to pick their way through the discovery process.

What Lab Tests to Order

RL: That's a question we get constantly here at Metametrix. Which tests should I order? Which one is the best test that you have? Of course, that can be answered in a variety of ways. In a general sense, the widest spectrum of information that you are likely to get would be, for example, the organic acids, if you wanted a single profile of testing where a single specimen would be sent and we would do a profile. The range of information you get from organic acids is broader than probably any other test you could order. We understand that you'd like to investigate the entire network of nutrient interactions. But, as you say, you can't always do that. However, you can make certain decisions, depending on the patient you're asking the question about. For example, if the patient is in mid-life, and a depressive, bi-polar type patient (they are fairly common), I tend to lean toward doing amino acid testing. In interventions with amino acids (depending on the other aspects of the history), we recommend doing free-form, custom-blended amino acids because this has had such a wonderful history of helping that kind of patient.

That's not to say that you don't want to go ahead and investigate things like a specific biotin deficiency marker, dysbiosis markers, and that sort of thing, but the amino acids rise on the scale of importance for that type of condition. If you have evidence that it's a recent onset of symptomatology and the patient was working around paint or other toxic substances, you might want to do some toxic metal testing. You can use history and symptoms to guide you to specific testing. That's a little better than just generally asking the question, what's the best test?

JB: That's a very salient bit of information and really helpful guidance. When the listener has a chance to read your book, if they haven't already done so (Laboratory Evaluations in Molecular Medicine), I think it would help them to see where differing tests, or panels of tests, can give different kinds of information so they can, as you said, match the patient, symptoms, history, and antecedents with what questions they'd like to ask, based upon what insight those various tests can provide. I think that's a good guide—to make sure you understand the patient before you start calling for the tests so that you can align the two strategically.

RL: Exactly. Then, of course, frequently, once you make a decision and you order, let's say, the amino acids and that scenario, and you get it back and let's say phenylalanine is high and tyrosine is low. Well, then you'd like to go and investigate factors that might pertain to BH4. Currently, there's no direct test for that cofactor, but there are tests for the oxidative status parameters that are so strongly affected. You might go ahead and start the BH4.

Another scenario with amino acids would be to start arginine, because you see arginine/citrulline are way out of balance and you have a patient with hypertension in which you'd start arginine on anyway. In the case of phenylalanine/tyrosine imbalance, you might decide to investigate oxidative stress and lipid peroxides. You might assess the 8-OHDG oxidative damage markers, or measure serum vitamin E, CoQ10, and so forth. In the case of arginine, you might look at ADMA to see if that's a problem, and then folic acid, if that's causing the ADMA. You wind up being able to pursue specific lines of investigation through the testing, depending upon what you initially see.

JB: You can hear Dr. Lord speak with great fluency about things that, for most of us, still probably sound like new words—like 8-OHDG, which is hydroxydeoxyguanosine, and is a measurement of oxidative damage to DNA, or asymmetrical demethylarginine, ADMA as a way of indirectly assessing endothelial nitric oxide sufficiency. When you're dealing with someone that has 30 years of experience like Dr. Lord, these patterns come easily. What he and I are both advocating is that the only way to really start down this road to develop a level of competency is to learn by doing. You really have to start asking some of these questions about metabolism and be able to deal with your fear about not knowing everything. I don't believe there's anyone in the world, no matter how brilliant, who understands the whole metabolomic web. It's still emerging before our eyes, and it's doing so in real time. It's not a time-lapse photograph as a two-dimensional chart on the wall; it's a three-dimensional, time-dependent phenomenon that is happening with our age and with our environment. It's always in dynamic change, so it is a challenge.

Carnitine and CoQ10 Markers

RL: The really cool thing about my job, Jeff, is that we'll get the question about which tests, and we respond that the organic acid testing has the most powerful and widest range. A doctor out there will say OK, and a lot of times they'll still start treating organic acids as their new metabolic functional medicine serum chemistry. They'll run it on new patients and call in, and if they see something they can't figure out, we'll do consultations with them. We start by advising them to look at carnitine and Q10 markers, and they may be high. There may be a real problem with Q10 and there's not just one, but four or five markers confirming over and over again that Q10 is a metabolic issue in that particular patient. So, we advise them to definitely put Q10 on the list. We go through the whole thing, looking at biotin, B12, folic acid, neurotransmitters, and the detox markers you see in dysbiosis. After we do a few cases like that, what happens so often is that the doctor will pauseand then say, "Wow! You can really see inside the patient, can't you!?" At that point, you grasp their excitement and it renews your conviction that this is such a powerful and understandable tool. Once you look at it that way, you just have to learn the associations. The compounds you didn't know how to pronounce last week you now see if they're high, the patient is in need in CoQ10, or biotin, or whatever. And now you can see that and focus the intervention.

Dosage of Supplements

Let me go back to your supplement-dosing question. At that point, I sense that even with experienced practitioners, some confusion lingers when we start talking about dosing and when to go to high-level dosing. I have to point out that if you're talking about the general population and what level of CoQ10 everyone should take, well, you can put a limit on what's generally safe for people to take, but that's really not the question you are asking. When you have information on your desk that says the patient sitting in front of you has a specific biotin depletion state, you want to go up to that very aggressive supplementation for a given interval of time. The rule of thumb is, let's say, 90 days. I always advise a reevaluation after 90 days. Don't just keep them there, tell them to take a certain regimen, and that's the end of it, because they may simply become depleted if it's not a genetic condition. They can taper off of

it; tell them what foods to eat, and they're on their way. You've done your optimization of their health.

JB: You have given us insight that is absolutely invaluable. For many people who may be new to this field, the whole concept of doing metabolic evaluation may appear to be outside the scope of what they'd even considered to be part of their assessment toolkit. You've opened up the door for learning in a way that hopefully has shed some light in the corners. A lot of people turned off the lights in the corners of metabolism after they got through the course, and now you've turned the lights back on. Your advocacy about how this can open up potential solutions to complex problems that appear untenable and intractable, is a great advocacy. I want to thank you, Dr. Lord, for your years of work, and for sharing your insight with us. No doubt, you have helped to get a few other people started down the path to using these tools effectively in managing some of their complicated patients.

RL: You're more than welcome, Jeff. It's great to be working alongside of you and your wonderful history and contributions to the field.

JB: Thanks a million and we'll talk to you soon.

Markers of Dysbiosis

In his discussion, Dr. Lord alluded to dysbiosis markers. I want to add a couple of thoughts at the end of this month's discussion that tie back to the detoxification and biotransformation topic for our symposium next April. That is, the endogenous bacteria that constitute two-and-a-half to three pounds of highly-metabolically active living organisms in the colon, and even in the small intestine, have their own metabolic personalities, and they produce secondary metabolites that our bodies have to manage and detoxify. Some of them may be trophic and immune-stimulating. Others may be toxic and require activity of the detoxification pathways to eliminate them from the body.

The gut is tied to a whole series of potential neuroactive metabolites. We certainly can see that in patients with hepatic encephalopathies. One would necessarily call that gastrointestinal hepatic encephalopathy, where patients develop hallucinations as a consequence of an overload of these metabolites coming from the gut that are not properly cleansed by the liver through the detoxification systems, and end up crossing the BBB and having an effect on neurochemistry. We used to think these hallucinations were a consequence of hyperammonia, but it turns out that they are not very closely correlated with gut ammonia levels. They are more closely correlated with the concentration of middle molecular-weight amino acid molecules in the blood, or things like spermidine, cadaverine, and putrecine. The names alone suggest their origin.

These particular bioactive amines, which are derived from proteins, can induce significant changes in brain biochemistry. There are specific protein fragments called peptides that are partially digested and can be absorbed reasonably intact, or they may directly affect receptors on the GI mucosa that influence the gut-brain signaling process. As Dr. Gershon told us in his book, *The Second Brain*, the gut has a tremendous propensity and capability to generate neuroactive molecules. In fact, the brain, which produces about one third of the body's serotonin, is also influenced by the gut, which produces two thirds of the body's serotonin. We have a second brain, that which is associated with gut physiology.

Genes, the Gut, and Schizophrenia

This has been beautifully discussed and evaluated by Gwynneth Hemmings of the Schizophrenia Association of Great Britain, Institute of Biological Psychiatry. Her work is seminal in understanding the connection between genetic uniqueness, gut physiology, and various types of mental disorders, including schizophrenia. In an article that appeared in *Medical Hypothesis*, Gwynneth Hemmings and her colleague, Dr. Wei, talk about the relationship between schizophrenia and celiac disease, which both involve a genetic component.[9] They indicate that there are several lines of evidence that have shown a genetic relationship between these two conditions.

"Celiac disease is characterized by damage to the microscopic finger-like projections called villi, which line the small intestine and play a significant role in digestion, due to an inflammatory condition caused by a reaction to wheat gluten or related rye and barley proteins."

This may induce various types of alterations in gut function and what has often been called a "leaky gut," or changes in intercellular junctions that lead to middle molecular-weight molecules passively diffusing across the gut mucosal barrier and gaining entry to the systemic circulation, which could influence CNS function. To support this hypothesis, which Hemmings and Lei propose, a conditional test was conducted to look at the combined effect of the CLDN5 gene, which is involved in forming intestinal barriers and the DQB1 gene that is associated with celiac disease. In looking at these linkage studies, Hemmings and Lei suggest that these two genes may work together in conferring a susceptibility to schizophrenia, and this gut connection to brain biochemistry seems to be very real, particularly related to specific genotypes.

When Dr. Lord was talking about dysbiosis, he was referring to metabolic byproducts of certain types of bacteria—gut flora—that induce altered neurotransmission or function, which can result in systemic effects, not just regional effects, in the GI system. This is a dramatic example of what we call the web in functional medicine. You cannot look at just a single point. If any one component of the web is distorted, the whole of the web is distorted. You have to look at distant sites to see what the impact might be.

I believe the Hemmings' contribution to our understanding is a very important part of our model of how bioactive agents from foods may work through a metabolic profile to ultimately induce what appear to be entirely unrelated symptoms. Their model is that permeability alteration in the gut, which may be caused by infection, or physical, chemical, or genetic reasons, induces the intake across the permeable membrane of various antigen-inducing substances, such as an epitope from gluten, which then binds to certain HLA class-2 molecules, like the DRB1 or DQB1, on antigen-presenting cells, and then induces CD4 T cell response, activating the Th1 cells that induce inflammation and the production of mediating molecules called the inflammatory cytokines—TNF-α, IL-1, and so forth. This leads to destruction of the villous structure of the small intestine, ultimately leading to malabsorption syndromes and malnutrition, and one starts getting alteration in the metabolism of these bioactive amines that may induce brain biochemical disturbances, categorized as affective or behavioral disorders, or schizophrenia.

Models such as this, which are now testable, are tied together by the underlying concept of genetic uniqueness, and have started to open the door for a better cross-discipline understanding of the origin of various complex conditions. Psychiatry does not own schizophrenia. It is, in part, a metabolic disorder; it is a genetic disorder; it is a gastrointestinal disorder; and it is an immunoneurological disorder. Therefore, it is a functional disorder that requires a functional approach built on a gene-environment interactions. It is an interesting example of the connections between genomics, proteomics, metabolics, and phenomics. The phenome, or the phenotype, is schizophrenia. The origin of that phenotype develops by the

interaction of genomics, proteomics, and metabolomics with the environment. This is a different approach toward managing an individual patient, rather than to put him or her on a class of drugs known to block the endpoint of specific neurochemical function and induce what some people would call a metabolic disturbance in their brain biochemistry that brings the signs and symptoms of the condition under control, probably without ever addressing the origin, the triggers, or the mediators of the condition, in and of itself.

I always find it interesting when people talk about biological psychiatry, when they are really talking about the use of psychotrophic drugs, rather than looking biologically at the psychiatric manifestations from the origin at a functional level—the genomic, proteomic, and metabolomic levels. That is what Gwynneth Hemmings is talking about in her paper and why I think this is such important part of our emerging understanding.

Gilbert's Syndrome

If we were to take this model that I have been describing and map it back against the question of detoxification, a case in point might be Gilbert's syndrome. Gilbert's is a genetic-related condition. When I learned about it in school some 30 years ago, I was taught that it was a hard-wired condition. People either had it or they did not. It had to do with glucuronidation defects. People with this condition were not properly detoxifyiong bilirubin, because it was not being correctly glucuronidated and people got easily jaundiced. It was called a benign condition with no physiological concerns. Everybody called it a "genetic anomaly."

Over the years, however, things have changed dramatically, because now it is recognized that glucuronosyl transferase polymorphisms are many, not just a single gene mutation. There are varied forms with different degrees of severity of Gilbert's, in some cases fairly severe. Simple sleep disturbances or alterations in the diet can lead to jaundice. In other cases, it is much milder in its penetrance. People who have defects in the glucuronidation of bile may have insufficiencies of glucuronidation of other endogenous and exogenous molecules. Therefore, their level of detoxification function for many substances may be modified, affecting more than just the bile.

Recent studies by researchers like Joanna Lampe at the Fred Hutchinson Cancer Research Center have demonstrated that diet can play a role in modifying glucuronidation. In a 2005 *Journal of Nutrition* study, Lampe and coworkers found that individuals with a specific polymorphism in the glucuronidation gene called UGT1A1, had reduced bilirubin concentrations with increased intake of cruciferous vegetables, whereas those individuals with the most common genotype of UGT1A1 did not. This result suggests that the individuals with this polymorphism may be at greater risk of cancer from toxic substances that should be removed via this pathway, but may also have greater opportunity to decrease that risk through dietary intervention.[10]

What I have talked about in this issue is the connection between detoxification and biotransformation with metabolic effects in the diet-gene interaction. This is the nutritional phenotype I referred to at the beginning of this discussion, and which Dr. Lord so eloquently discussed. I hope I have given you some food for thought, as we start moving toward the 13thsymposium next April, in defining what biotransformation and detoxification really mean in the age of nutritional phenomics.

Thank you, and we look forward to being with you next month.

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